Investigation and synthesis of alkyl cyanoacrylates and modification of X-ray contrast agents for incorporation into alkyl cyanoacrylate for use in medical devices

by

Lauren Halliwell

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Contents

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Declaration

The work presented in this thesis is the work of the author. References to previous related results and idea have been fully acknowledged. All work was performed in the Department of Chemistry at the University of Warwick between October 2008 and October 2012 and has not been submitted for a degree at any other institution.

Lauren Halliwell

Abstract

The work in this thesis involves the development of a protected transesterification route for the production of novel cyanoacrylate monomers. As well as the modification of iodinated contrast agents to increase their solubility in cyanoacrylate, to enable monitoring of the adhesive within the body for possible use in the treatment of brain aneurysms. Chapter 1 provides an introduction to biological adhesives, in particular alky 2-cyanoacrylates and how they degrade to release formaldehyde. Details into iodinated X-ray contrast agents, their structure, uses and synthesis, as well as the current treatments for brain aneurysms.

Chapter 2 focuses on the modification of several iodinated contrast agents in order to increase solubility in ethyl cyanoacrylate. Three existing contrast agents were protected using a variety of different protecting groups and tested for solubility in ethyl cyanoacrylate. Partition coefficients were calculated for the successfully modified compounds. Chapter 3 outlines the development of the anthracene protected route for the synthesis of cyanoacrylate monomers, utilising the Diels-Alder and retro-Diels-Alder reactions of anthracene. This route was subsequently used to synthesis a range of cyanoacrylate monomers. Polymerisation of these monomers gave a range of polymers which were tested to determine their rate of degradation through formaldehyde detection. Chapter 4 further details the first and final step of the anthracene protected route developed in chapter 3. It involved ^{1}H NMR experiments to determine how substitution at the 9 and 10 position of anthracene affects the rate of reaction of the forward and retro-Diels-Alder reaction.

Abbreviations

Ac	Acetyl
Ac_2O	Acetic anhydride
aq.	Aqueous
Ar	Aryl
Bn	Benzyl
$B(OH)_3$	Boric acid
b.p.	Boiling point
br	Broad
*n*Bu	*n*-Butyl
*i*Bu	*iso*-Butyl
*s*Bu	*sec*-Butyl
^{t}Bu	*tert*-Butyl
^{t}BuOH	*tert*-Butanol
COSY	Correlation spectroscopy
DBU	1,8-Diazabicycloundec-7-ene
d	Doublet
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
ddt	Doublet of doublet of triplets
dt	Doublet of triplets
d_8 tol	Deuterated toluene
DCM	Dichloromethane
DMA	Dimethylacetamide

DMAP	Dimethylaminopyridine
DMF	Dimethylformamide
DSC	Differential Scanning Calorimetry
EI	Electron ionisation
eq.	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
Et_2O	Diethyl ether
EtOAc	Ethyl acetate
EtOH	Ethanol
h	Hours
HMBC	Heteronuclear multiple-bond correlation spectroscopy
HMQC	Heteronuclear multiple-quantum correlation spectroscopy
HPLC	High Performance Liquid Chromatography
Hz	Hertz
ICl	Iodine monochloride
ICP-MS	Inductively Coupled Plasma Mass Spectrometry
IR	Infra-red
m	Multiplet
Me	Methyl
MEHQ	4-methoxy phenol
MeOD	Deuterated methanol
MeOH	Methanol
min	minutes
m.p.	Melting point

M*w*	Molecular weight
NEt_3	Triethylamine
NMR	Nuclear Magnetic Resonance
PEG	Polyethylene glycol
Petrol	Petroleum ether 40-60
P_{ow}	Partition coefficient
Ph	Phenyl
ppm	Parts per million
py	Pyridine
q	Quartet
r.t.	Room temperature
s	Singlet
sat.	Saturated
sec	seconds
SEM	Scanning electron microscopy
SM	Starting material
t	Triplet
Tg	Glass transition temperature
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMS	Trimethylsilyl
TsOH	*para*- toluenesulfonic acid
WBS	Wound busting strength
VT NMR	Variable Temperature Nuclear Magnetic Resonance

1.0 Introduction

1.1 Biological adhesives

Biological adhesives have been around in some form since the introduction of bandages. The earliest material used in hospitals were natural rubber based, these have since been superseded by synthetic alternatives. The first commercial example was the use of medical bandages consisting of a pressure-sensitive adhesive and a backing, which is a carrier for the adhesive, first marketed to hospitals by Johnson & Johnson in 1899.[1] There are case reports in the literature for some patients experiencing an allergic contact dermatitis (ACD) to the chemicals in either the adhesive or the backing in these medical bandages. These reports do not adequately correspond to the frequency that patients report having an "allergy" to medical adhesive bandages.[2]

A  B 

Figure 1.1: A) Adhesive bandage, B) Allergic reaction experienced by some patients

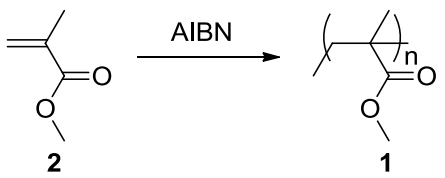
The chemicals in medical bandages include adhesives such as hydroabietic acid (an industrial derivative of colophony),[3] glycerol esters of hydrogenated abietic acid[4] wood rosin derivatives[5] and *p-tert*-butylphenol formaldehyde resin, an acrylate polymer used as a contact adhesive owing to its flexibility, strength, and rapid onset of action.[6,7] Other agents added include dodecyl maleamic acid, octadecyl maleamic acid,[8] and tetrahydrofuryl acrylate.[9] Plasticisers such as tricresyl phosphate found in

the vinyl backing[10] are added and used to increase the stretch potential of some adhesive tapes.[11] A range of initators (benzoyl peroxide) and/ or antioxidants and preservatives (2,5-di(tertiary-amyl)hydroquinone or diethyldithiocarbamate)[12] are added to initiate adhesion or increase stability depending upon the formulation. Epoxy resins have also been used as adhesives for contact bandages.[13]

Many other bio-adhesives have been developed since the introduction of medical bandages, these include synthetic polymeric materials, such as poly(methyl methacrylate)s, epoxy resins, polyurethanes and cyanoacrylates. These can be used directly in wound closure, as well as in dentistry and even in some surgical procedures.[14] All biological adhesives, whether light wound liquid adhesives such as poly-vinylpyrrolidone or deep wound cyanoacrylate glues, have the same objectives; a) fixture of the structures and surfaces to be bonded; b) microbial protection of the wound to avoid sepsis; c) filling of cavities; d) regulation of the moisture content; e) promote the natural healing process.[15]

1.1.1 Poly(methyl methacrylate) resin

Poly(methyl methacrylate) (PMMA) **1** is the synthetic polymer of methyl methacrylate **2** (Scheme 1.1) and has been used as a bone cement in orthopaedic procedures such as hip replacements.[16]



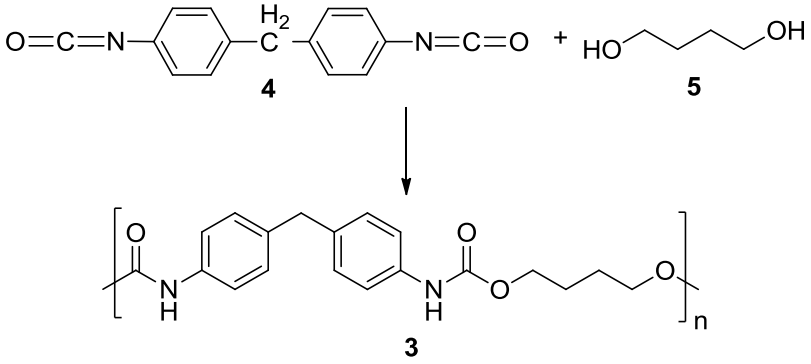
2 **1**

Scheme 1.1: Synthesis of poly(methyl methacrylate) PMMA 1

Methyl methacrylate monomers used in adhesive systems are conventionally cured by radical polymerisation initiated either by the addition of radical initiators or irradiation with light. For *in-situ* curing of methyl methacrylate monomers an initiator that works at body temperature is added, such as *N*,*N*-dimethyl-p-toluidine, this gives a curing time of 2-10 mins.[15] PMMA bone cement is more like a grout than glue, although sticky it does not bond to the bone or implant, it fills the space between the prosthesis and the bone preventing motion.[17] PPMA has revolutionised orthopaedic procedures, especially for large joint replacements but there are draw backs to its use. Although PMMA is biologically compatible it breaks down to methyl methacrylate which is an irritant and possible carcinogen. It is the release and subsequent absorption of the monomer and/ or additives (such as *N*,*N*-dimethyl-p-toluidine) that is thought to lead to side effects such as hypotension.[18]

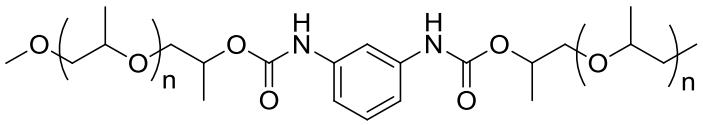
1.1.2 Polyurethane composites

Polyurethane polymers **3** are formed by reaction of an isocyanate **4** with a diol **5** (Scheme 1.2).



Scheme 1.2: Synthesis of polyurethane 3 from 4,4'-methylene diphenyl isocyanate 4 and 1,4-butanediol 5

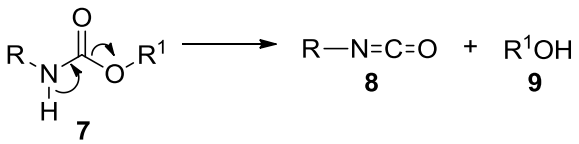
Polyurethanes have played a major role in the development of many medical devices such as cardiovascular devices, artificial organs and tissue replacements.[19] The mechanical properties of polyurethanes have shown them to be well suited for usage in a number of bio-medical devices; they have been shown to be durable, have good elasticity and are tolerated in the body during healing.[20–23] Polyurethanes have also been successfully modified; for example the hydrolytically unstable polyester polyurethane has been replaced by the more resistant oxidation-sensitive polyether based polyurethanes **6** (Figure 1.2), biologically active species such as anticoagulants have also been added.



6

Figure 1.2: Poly(propylene oxide) polyether based polyurethane 6

These modifications are designed to enhance the acceptance of the polyurethane composites within the body and promote healing, aiming to mimic natural tissue as closely as possible.[24] However *in-vivo* instability has been observed for prolonged implantation, causing major limitations for bio-medical applications by limiting the time such devices can be left in the body. Over time the polymer degrades *via* a depolymerisation mechanism (Scheme 1.3) to give the starting materials; one of which is an isocyanate, a known irritant that has been observed to give adverse effects.[25]



7 **8** **9**

Scheme 1.3: Degradation of the polyurethane linker *via* a depolymerisation mechanism

1.1.3 Fibrin sealants

Fibrin sealants are biological adhesives derived from blood. Fibrinogen is the main structural protein in blood, and is responsible for forming blood clots (Figure 1.3).[26]

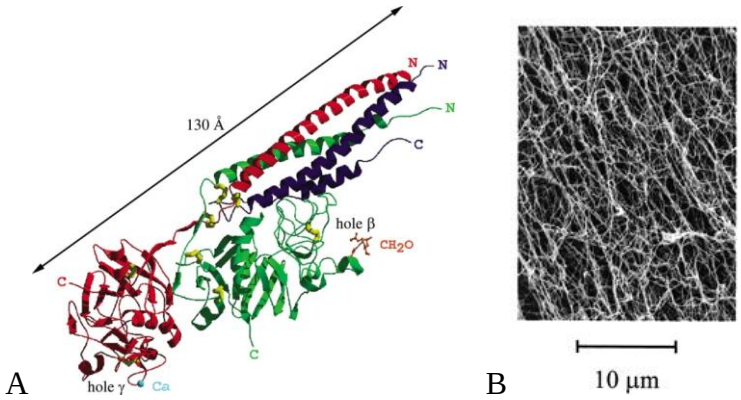


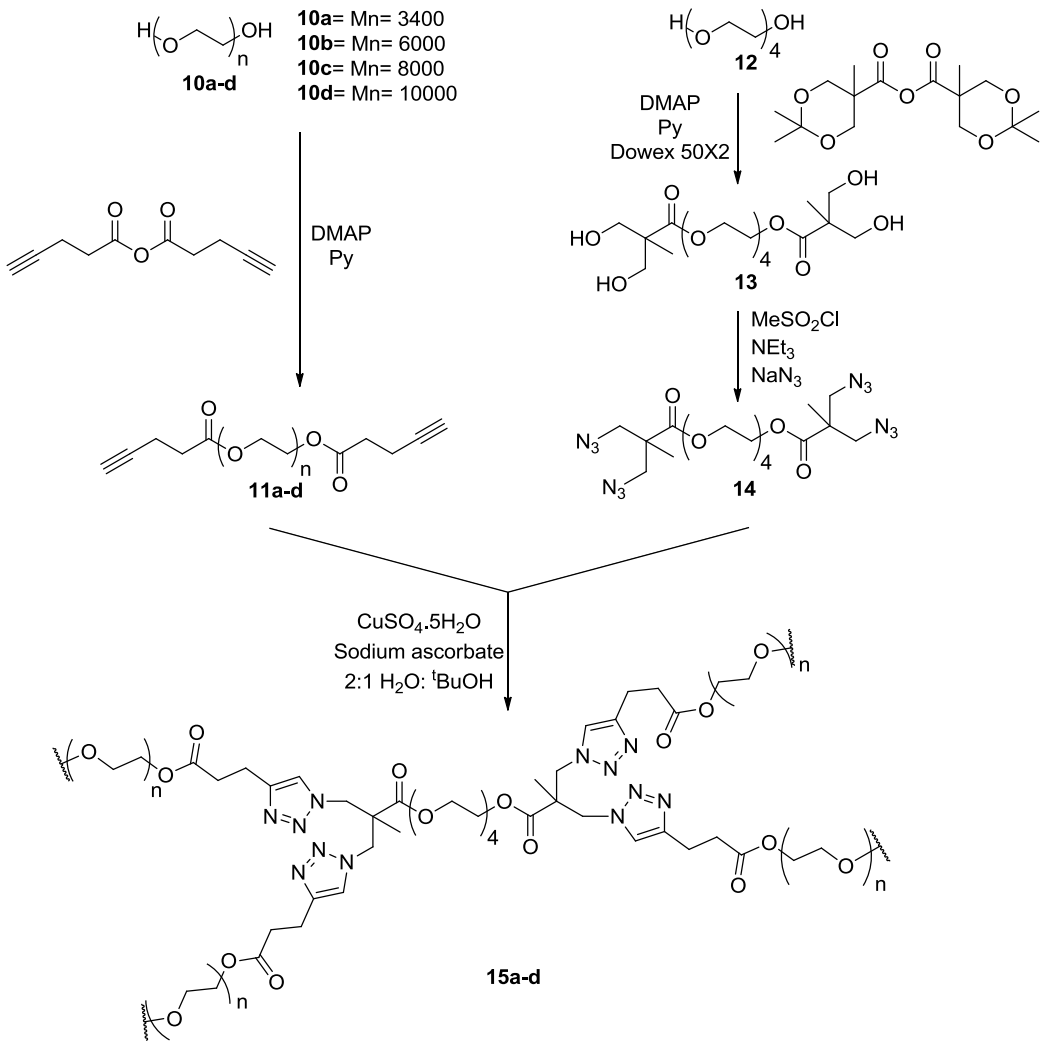
Figure 1.3: A) Ribbon model of human fibrinogen, B) Fibrinogen clot examined by scanning electron microscopy (SEM)

Fibrinogen is converted to strands of fibrin, in the presence of calcium ions, by thrombin, a serine protease. The fibrin monomers assemble in fibrils, forming a three dimensional network of fibres; a blood clot (Figure 1.3)[27]. Fibrin sealants are a formulation made up of fibrinogen and thrombin, used to create a fibrin clot.[28] The components may be applied sequentially or simultaneously to the site of repair by either syringe or spray. Prior to polymerisation fibrin sealants act as a spray-able "sticky" liquid that can readily adhere to wet surfaces. After the addition of thrombin, the fibrin glue polymerises *in-situ*, and becomes a semi-rigid, fluid tight adhesive capable of holding tissue or materials in place. Applications of fibrin sealants include repairing dura tears or bronchial fistulas, as well as in 'no suture' corneal transplantation. The first recorded use of fibrinogen as a tissue adhesive was in 1942, when it used for peripheral nerve repair in animal models.[29] In recent times fibrin glues have been used in successfully cardiovascular surgery for bypass

surgery, vascular graft, sinus rupture and repair of septal defects.[30–33] Fibrin glue has many advantages that make it a good bioadhesives; for example fast curing times (10-60 secs) and biodegradability. However it has a relatively poor adhesion and tensile strength, wounds closed *in-vivo* by a fibrin sealant are normally coupled with a few sutures to reinforce the repair. Use of fibrin glues also involves the risk of blood–borne disease transmission and potential for allergic reactions in patients.[34]

1.1.4 Polyethylene glycol (PEG) glues

In recent years PEG-based hydrogels have been investigated for the sealing of sutured wounds, in particular, as a safe watertight closure, used in addition to sutures for dural repair during cranial surgery. The hydrogel is applied to the tissue as a two-component system; eosin based primer and polymer sealant. The sealant consists of water soluble polyethylene glycol, a biodegradable polyacetic acid, trimethylene carbonate and a polymerisible acrylic ester. The eosin based primer penetrates the tissue, cross-links with itself and provides a mechanical interlink to the sealant; the two component work together to provide tissue penetration (primer) and the desired elastic properties (sealant) resulting in a cross-linked gel which degrades in the body after 8 weeks. PEG hydrogels can be synthesised using ‘click’ chemistry to give highly cross linked structures (Scheme 1.4). PEG-based sealants have been shown to stop cerebral spinal fluid leakage after neurosurgical dural repair.[35]



Scheme 1.4: PEG hydrogel construction 15a-d based on 'click chemistry'[36]

1.1.5 Cyanoacrylate adhesives

The most commonly used bio-adhesive for direct wound closure on the market today is Alkyl 2-cyanoacrylate **16** (Figure 1.4). Widely used in the closure of superficial wounds,[37] they have superseded the used of sutures for external wound closure.

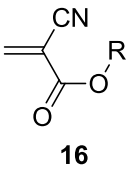
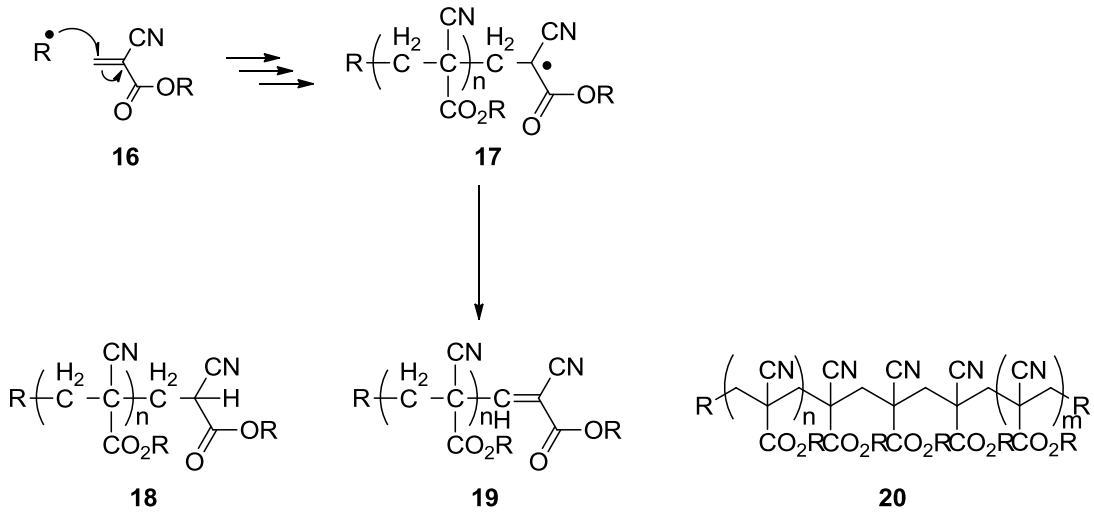


Figure 1.4: Alkyl 2-cyanoacrylate monomer 16

1.2 Alkyl 2-cyanoacrylates as biological adhesives

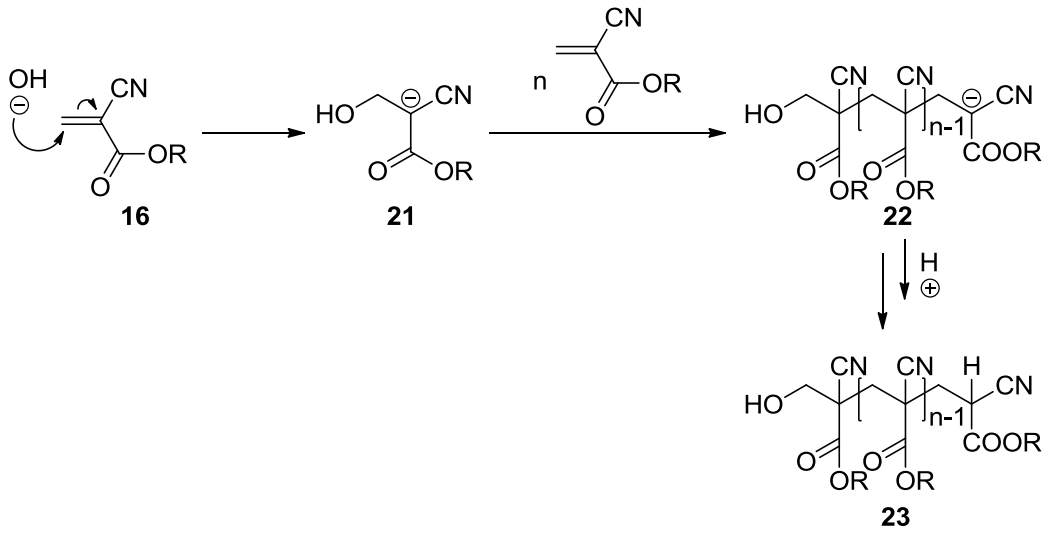
Alkyl 2-cyanoacrylates **16** (Figure 1.4) are liquid monomers that rapidly polymerise in the presence of a basic catalyst (pH 7 or above) such as water or alcohol.[38] The adhesive properties of the alkyl 2-cyanoacrylates **16** were discovered in the 1950s by the Tennessee Eastman Company.[39] Cyanoacrylate monomers can polymerise *via* two different mechanisms; free-radical (Scheme 1.5) or anionic (Scheme 1.6).[40] For free-radical polymerisation there are two different modes of termination; coupling and disproportionation, which give way to three different end groups.



Scheme 1.5: Free-radical polymerisation of cyanoacrylate[40]

In practice the anionic route is favoured because it is rapidly initiated at ambient temperature; polymerisation occurs in the presence of even a weak base such as water or alcohol, due to the electron withdrawing CN and COOR groups.[41] Thus polymerisation can be initiated quickly by contact with the surface of hydrophilic substrates, avoiding the need for catalysts or heating.[42] It is because of its excellent wetting properties and ability to bind to a number of substrates that have resulted in the successful application and marketing of alkyl-cyanoacrylates as "superglue".[43]

Cyanoacrylate monomers have been shown to be highly susceptible to anionic polymerisation.[44,45] Polymerisation proceeds by initial addition of an anion (amides, alkoxides, hydroxides, cyanides, phosphines, amines etc.) to the strongly activated carbon, carbon double bond. This is followed by linear chain elongation as further cyanoacrylate monomers are added with eventual termination of the growing chains by uptake of a proton.[46]



Scheme 1.6: Anionic polymerisation mechanism of cyanoacrylate[46]

Polymerisation is rapid and can be difficult to control; studies have determined temperature has a limited affect on the average molecular weight (M_W) of the resulting polymer. However pH and the R group of the ester have been shown to influence the average M_W. This is demonstrated by the differences between ethyl and octyl cyanoacrylate at pH 2, 7 and 11 (Table 1.1).[47] Poly(ethyl cyanoacrylate) showed the highest average M_W at pH 11; however the opposite was true for poly(octyl cyanoacrylate), the highest average M_W was achieved at pH 2.

pH	Average M_W (Da) ECA	Average M_W (Da) OCA
2	2.21×10^5	4.15×10^5
7	2.94×10^5	3.42×10^5
11	3.05×10^5	3.30×10^5

Table 1.1: Average Molecular Weight of ECA and OCA polymers at 25 ^{o}C at pH 2, 7 and 11, measured by GPC

Due to its ready ability to polymerise at room temperature, methyl-2-cyanoacrylate **16** (R=Me) was introduced as a rapid setting adhesive across a number of industries, (metal, glass, electronics and medicine).[48] Cyanoacrylates are desirable to the medical industry because they are liquid monomers (easy to apply) and polymerise in protic or moist environments (living tissues).[49] Cyanoacrylate adhesives cure on the skin surface within 5-60 seconds, sealing the wound instantly and forming a waterproof barrier.[50] Cyanoacrylates can be used on various parts of the body, from the mouth to the foot.[51] They have also been investigated for use in dental fields for pit and fissure sealants, exposed dental pulp and direct bonding of orthodontic brackets. Despite rapid setting of cyanoacrylate the major disadvantages were polymerisation shrinkage, brittleness, and erratic polymerisation set times.[52]

1.2.1 Skin adhesive *vs*. stitches

Each year in the US between 26 and 90 million lacerations occur, and over 7 million surgical incisions require closure.[53] There are several methods for wound closure; stitches, staples, surgical tape and skin adhesives such as alkyl cyanoacrylate. Cyanoacrylates continue to retain their adhesive qualities even in the presence of

moisture.[50] This is important for medical applications as human skin presents a huge variation of presentable substrates, for example wet, dry, oily, wrinkly, hairy.[54] Cyanoacrylates adhesives are currently the standard wound closure method for the repair of superficial lacerations[55] (Figure 1.5).

Figure 1.5: Head closure using cyanoacrylate adhesive

Tissue adhesives have several benefits over traditional sutures; they are more cost effective as they require less instrumentation, no suture kits, dressings or removal kits.[56,57] They also have cosmetic advantages as they prevent the formation of suture marks on either side of the wound and therefore reduce scarring.[58,59] There is no need for removal,[60] and there are no foreign bodies such as stitches or staples within the wound that may increase risk of infection.[61] Biological adhesives remove the risk of injuries from suture needles and therefore the risk of transmission of infectious diseases.[50] Due to the lack of instrumentation required skin adhesive is a much faster closure method, it is also less painful than sutures.[58,62,63]

Skin adhesives are a popular wound closure method, with most patients preferring them to stitches or staples.[64] There are several advantages to the patient; no anaesthesia is required, the procedure is non-invasive and painless and there is no need for follow up care.[65]The simplicity and speed of this application is especially useful in military conditions, or in remote locations where general practitioners are

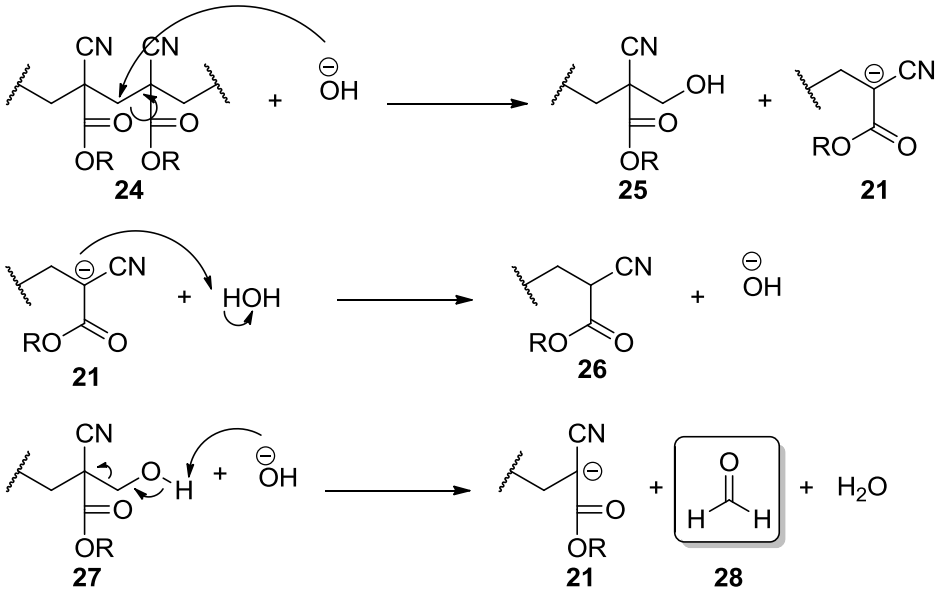
not always ready available.[66] When cyanoacrylate skin glues were first introduced it was thought there was a high risk of allergic reactions occurring in patients. Studies into the potential for allergic reaction were conducted. One such study monitored 43 patients over a three month period after the closure of surgical incisions.[67] The patients, representing a cross section of gender, age and health status, were divided into two groups; wounds closed with either sutures or ethyl cyanoacrylate adhesive. No patient experienced any allergic reaction, this result agreed with other results[68,69] and thus it was determined that the risk of allergic reaction was low and was outweighed by the advantages of cyanoacrylate adhesive over sutures.

Surgical tape, containing zinc oxide, offers many of the same advantages as skin adhesives: easy to use, rapid, painless, comfortable, does not require removal and cost effective. However, because of low bursting strength and tendency to fall off, the use of surgical tapes is limited to simple very low tension wounds.[70] It can however be used in conjunction with cyanoacrylate adhesive for the closure of long wounds. The tape holds the edges of the wound in place while the adhesive is applied (Figure 1.6).

Figure 1.6: Use of surgical tape to aid closure of long wound[71]

1.2.2 Degradation of poly(cyanoacrylate)s

The main drawback of using poly(cyanoacrylate)s as biological adhesives is that upon biodegradation they liberate formaldehyde.[72] The degradation process is initialised by the random addition of water molecules into the polymer chain **24**, which further degrades into a polymer fraction **21** and formaldehyde **28**. The process is accelerated by alkaline conditions, and is started by the initial attack of the hydroxyl ion, leading to a reverse Knoevenagel reaction[73] (Scheme 1.7).



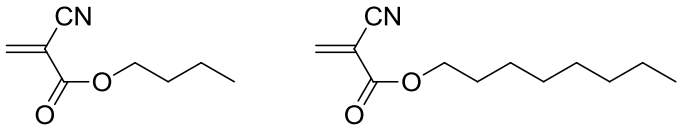
Scheme 1.7: Degradation of poly(alkyl cyanoacrylate) 24

The production of formaldehyde is an undesirable effect of a biological sealant as it leads to irritation and inflammation of adjacent tissues. Methyl cyanoacrylate was shown to cause tissue inflammation and cell necrosis in experimental animals.[74,75] Due to its rapid degradation methyl cyanoacrylate is no longer used as a skin adhesive.[76] Both butyl and octyl cyanoacrylates show a decrease in the inflammatory response and a slower degradation rate than methyl cyanoacrylate. This is thought to

be due to steric reasons.[77] Both butyl **29** and octyl cyanoacrylates **30** are licensed for use as skin adhesives, trade names Liquiband and Dermabond.

1.2.3 Octyl cyanoacrylate

Octyl cyanoacrylate **30** has many advantages over butyl cyanoacrylate **29** (Figure 1.7), including higher breaking strength, flexibility and resistance to splintering after drying. The wound busting strength (WBS) was measured for octyl and butyl cyanoacrylate, as well as surgical tape. The mean WBS of octyl-cyanoacrylate (298 mm Hg) was significantly higher than that of butyl-cyanoacrylate (199 mm Hg) or the surgical tape (129 mm Hg). In context of the strain that is likely to be exerted on these wound closures during normal daily routine compare to intra-abdominal pressures of the following activities; standing (13 mm Hg), pain (44 mm Hg), pressing (59 mmHg), vomiting (110 mm Hg), cough (150 mm Hg), and jumping (252 mm Hg).[78]



29 **30**

Figure 1.7: Butyl cyanoacrylate 29 and octyl cyanoacrylate 30

Although both are licensed it is octyl cyanoacrylate **30** that is now used as standard for wound closure as it forms strong bonds across wound edges.[79] This bond provides a flexible water resistant coating as octyl chains are hydrophobic, creating a barrier to microbial penetration[69] thus providing a natural healing environment.[80] Cyanoacrylates have also been shown to have anti-microbial properties both *in vitro* and *in vivo* in animal models,[81] in particular against Gram-Positive organisms that

are responsible for most wound infections. This anti-microbial barrier may be particularly important in the treatment of surgical incisions where a trend towards decreased wound infection rates were found in comparison with sutures.[82] In general, there have been many examples of both butyl **29** and octyl cyanoacrylates **30** being used in a wide variety of clinical settings.[65,68,83,84] For example, general plastic and paediatric surgery, neurosurgery, gynaecology, ophthalmology etc. Alternative applications of cyanoacrylates are under investigation including use internally in the vascular system and for the treatment of gastric varices (dilated submuscosal veins in the stomach which can led to gastrointestinal hemorrhage).[85]

1.3 Properties of cyanoacrylate polymers

There are a number of qualities required of an adhesive in its final cured state in order for it to be serviceable. It must have good tensile strength in order to withstand the stresses upon it without being brittle. Adhesive strength is important and can be measured by three different components; peel adhesion, tack strength and sheer strength.[54] Peel adhesion is the force needed to remove the adhesive material from a substrate. The peel strength of methyl, ethyl and propyl cyanoacrylate at room temperature is 183, 159, 95 psi respectively. The peel strength decreases as the chain length increases; this may be due to the increased flexibility of the longer chained monomers. Tack strength is used to gauge the strength and ease of formulation of the adhesive bond. Shear strength is a measurement of the cohesive strength of an adhesive; cyanoacrylates have been shown to form strong bonds at room temperature, methyl and ethyl cyanoacrylate give valves of 710-720 psi.[86]

The thermal properties of poly(ethyl cyanoacrylate) have been studied previously in order to determine the thermal behaviour of the cured adhesive. Thermal degradation of poly(ethyl cyanoacrylate) has been measured by thermal gravimetric analysis (TGA), which measures the % weight loss of the polymer with increasing temperature. The polymer starts to lose weight at approx. 160 ^{o}C and is at its maximum rate between 225 and 250 ^{o}C, it is completely degraded by 300 ^{o}C (Figure 1.8).

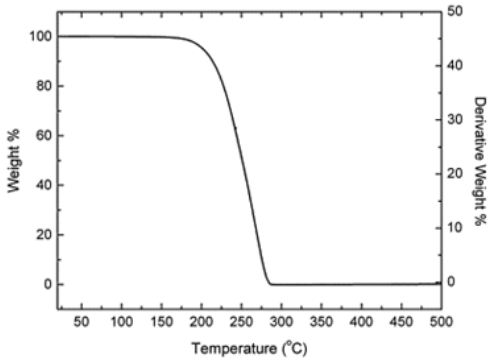
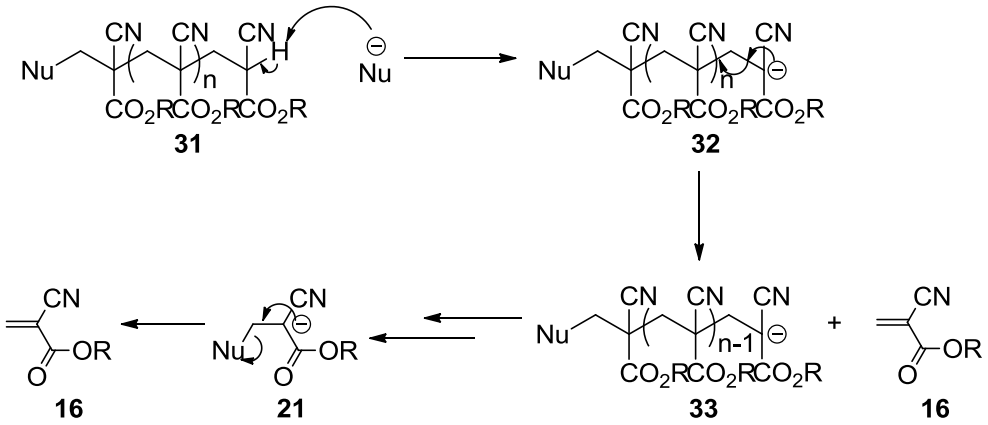


Figure 1.8: TGA of poly(ethylcyanoacrylate)[43]

The TGA clearly shows one mechanism for degradation; as the polymer is heated it degrades *via* an 'unzipping' mechanism, releasing cyanoacrylate monomer from the polymer backbone (Scheme 1.8).



Scheme 1.8: Thermal degradation of cyanoacrylate *via* an 'unzipping' mechanism

TG curves for the thermo destruction of poly(ethyl cyanoacrylate) under isothermal conditions at 140 ^{o}C have also been recorded (Figure 1.9). Isothermal conditions are used as a model for the aging process of an adhesive bonded joint. The degradation of poly(ethyl cyanoacrylate) proceeds vigorously and in an almost exponential course, reaching 45% weight loss within the experimental time of 3 h. This shows that the polymer degrades at a steady ready rate over time.

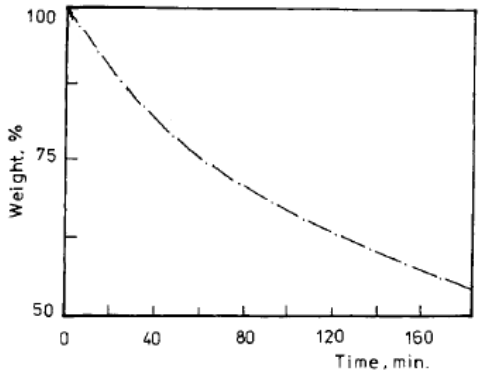


Figure 1.9: TG Curve of poly(ethyl cyanoacrylate); conditions: isothermal mode (3 h/ 140 ^{o}C)[87]

Differential scanning calorimetry (DSC) is a measure of amount of heat required to increase the temperature of a sample. DSC can be used to determine thermal transitions of polymers; such as melting point and glass transition temperature. The glass transition (Tg) is the temperature that a material undergoes a reversible transition from brittle state into a molten or rubber-like state. DSC of poly(ethyl cyanoacrylate) gives a Tg of approximately 140 ^{o}C, hugely above room and body temperature (Figure 1.10). Up until the Tg, in this case 140 ^{o}C, the polymer is brittle; it is possible to lower the Tg by adding plasticisers, or by making the alkyl chain longer resulting in a more flexible polymer. The Tg of poly-butyl and -octyl cyanoacrylate are lower; 86 ^{o}C and 40 ^{o}C respectively (Figure 1.11).[49]

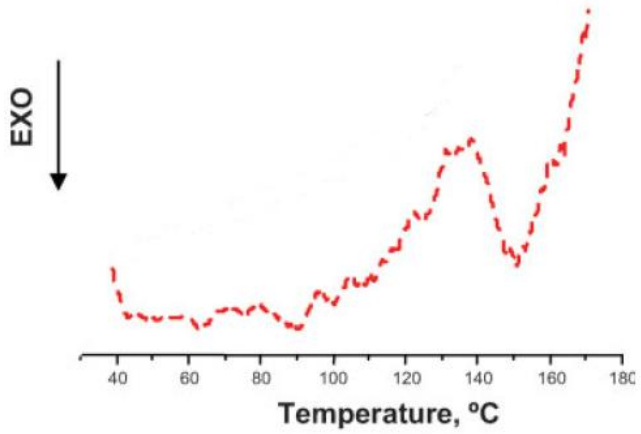


Figure 1.10: DSC curve of poly(ethylcyanoacrylate); conditions: 10 °C/min[49]

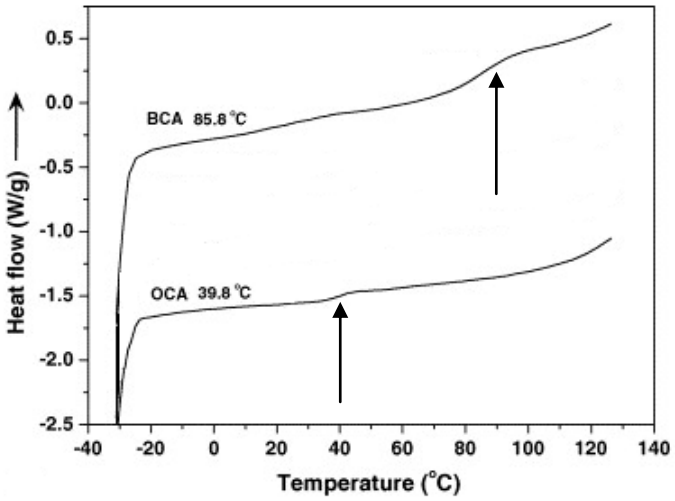


Figure 1.11: DSC thermograph of poly-butyl and –octyl cyanoacrylate; conditions: 10 °C/min

Poly(cyanoacrylate)s have been used extensively as adhesives across a number of industries, however they have a number of other applications.

1.3.1 Alternative uses of cyanoacrylate polymers

An alternative use of cyanoacrylates is for the detection of latent fingerprints on non-porous surfaces.[88] This was first demonstrated by the Japanese Criminal identification Division in 1978.[89] Since then the cyanoacrylate fuming method has

gained wide popularity and is used for development of prints on surfaces such as metals, electrical tape, glass, leather and plastics.[80,90–92] The cyanoacrylate fuming method involves exposure of the evidential object to cyanoacrylate fumes in an enclosed cabinet. The cyanoacrylate monomer vapours polymerise on the ridges of the fingerprints, producing a white deposit. A number of improvements have been made to this technique in order to accelerate the fuming process and minimise background development.[93–95] Traditionally detection of fingerprints on bank notes is extremely difficult. Figure 1.12 shows a white light image of a successfully imaged fingerprint on an Australian $5 note treated with ethyl 2-cyanoacrylate.[96]

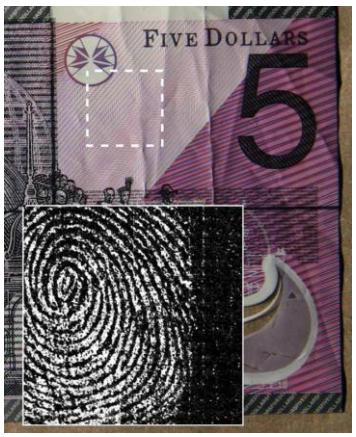


Figure 1.12 Fingerprint treated with ethyl 2-cyanoacrylate on banknote

For the past 30 years there has been interest in poly(alkyl cyanoacrylate)s for drug delivery systems; the polymers are biocompatible and approved for human use.[63,97] Since the first attempt in 1979[98] emulsion polymerisation has been applied for entrapment of various drugs in poly(alkyl cyanoacrylate)s nanoparticles under various different conditions[99–104] (Figure 1.13).

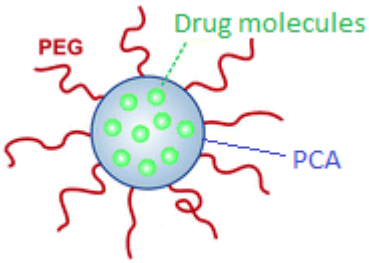


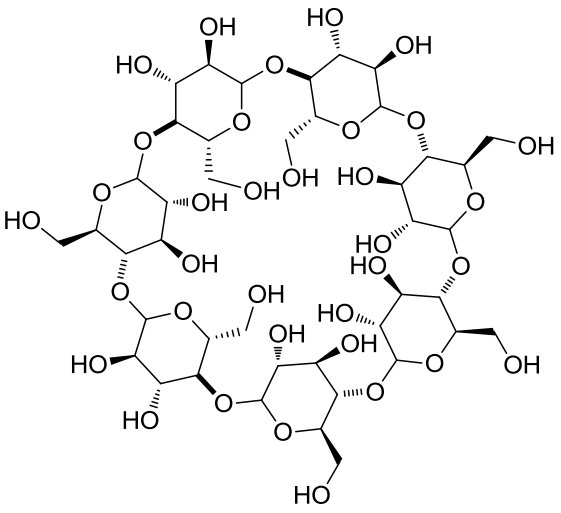
Figure 1.13: Poly(alkyl cyanoacrylate) nanoparticles

Over the years there has been an increase in the number of reports using mini-emulsion polymerisation for the engineering of poly(alkyl cyanoacrylate) nanoparticles[105–109] and nanocapsules.[110–112] Functionalisation of particle surface and adjustment of particle size can be accomplished by this technique.[113] Today poly(alkyl cyanoacrylate) nanoparticles are considered one of the most promising polymer colloidal drug carriers, in particular for use in cancer therapy.[114] However there are a number of limitations; molar masses of the formed polymer and nanoparticles size are strongly affected by the conditions of polymerisation, and can sometimes be difficult to control.[115–117]

Initial studies into mini-emulsion polymerisation of poly(alkyl cyanoacrylate)s focused on anionic polymerisation. This resulted in quite low molar masses, usually below 8 000 $gmol^{-1}$, which were dependent upon pH and concentration. Investigations have compared both radical and anionic mini-emulsion polymerisation in the formation of nanoparticles of poly(*n*-butyl cyanoacrylate).[40] Particle sizes were measured as a function of the pH, temperature and method of polymerisation, the final molar mass and the degradability of the polymer were recorded. The two different methods of polymerisation displayed differences in the rate of complete monomer conversion (radical: 20 min, anionic: 1 h) at pH 2. This effect is more

pronounced at pH 1, when it takes about 7 h for anionic polymerisation to fully convert monomer to polymer. Thus anionic polymerisation could be effectively slowed by changing the acid concentration.[46] In the case of anionic polymerisation the molar mass of poly(*n*-butyl cyanoacrylate) was observed to vary even after the monomer has been used up. This phenomenon is observed because the anionic polymerisation of butyl cyanoacrylate is a reversible process. On the other hand radical polymerisation gives a constant distribution of molar masses once the monomer has been used up, and this distribution has been shown to be stable for at least 5 days at pH 2.[118] Complete degradation of both materials occurred between 24-48 h, making these systems suitable for *in vivo* applications, but those derived anionically degraded faster.

Poly(*i*-butyl cyanoacrylate) nanoparticles have been prepared by anionic polymerisation under acidic conditions in the presence of cyclodextrin[119] (Figure 1.14). The size of the nanoparticles depended on the type of cyclodextrin used. Smaller particles were obtained with hydroxypropyl-β- **34** or hydroxypropyl-γ-cyclodextrin **35**, 103 and 87 nm respectively.



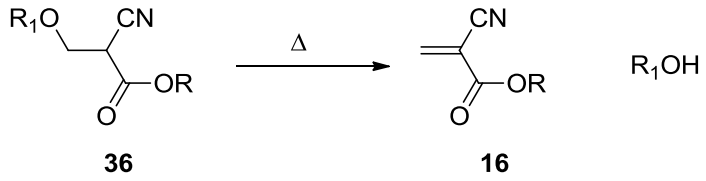
34

Figure 1.14: Hydroxypropyl-β-cyclodextrin 34

IR and ^{1}H NMR of nanoparticles prepared in the presence of hydroxypropyl-β-cyclodextrin **34** suggests the products are associated by weak bonds, not covalent coupling. Poly(*i*-butyl cyanoacrylate) nanoparticles including hydroxypropyl-β-cyclodextrin **34** and those without cyclodextrin were loaded with a series of steroids. The nanoparticles including cyclodextrin were between 100 – 200 nm smaller than those made solely from *i*-butyl cyanoacrylate. Despite this the nanoparticles that included hydroxypropyl-β-cyclodextrin **34** showed a significant increase in loading capacity; 7 times more for spironolactone up to 130 times more for prednisolone. DSC analysis of the combined nanoparticles loaded with progesterone showed the loss of the endothermic peak at 130 ^{o}C that is characteristic of progesterone melting. It was replaced by a broad endothermic transition in the region of 130-170 ^{o}C, suggesting progesterone is molecularly dispersed in the nanoparticles.

1.4 Synthesis of cyanoacrylate monomers

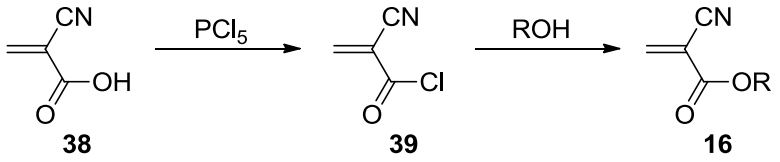
Alkyl 2-cyanoacrylates **16** were first synthesised by the pyrolysis of alkyl-3-alkoxy-2-cyanopropionates **36**[120] (Scheme 1.9).



Scheme 1.9: Pyrolysis of alkyl-3-alkoxy-2-cyanopropionates 36

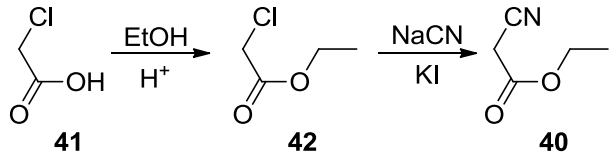
Thermolysis of ethyl cyanoacrylate **37** was later achieved to give free 2-cyanoacrylic acid **38**. This allowed preparation of some cyanoacrylates *via* the acid chloride **39** (Scheme 1.10).[121] This is a simple route for the production of cyanoacrylate,

however it has been shown to have limited applications as only a small number of monomers have been successfully synthesised this way.



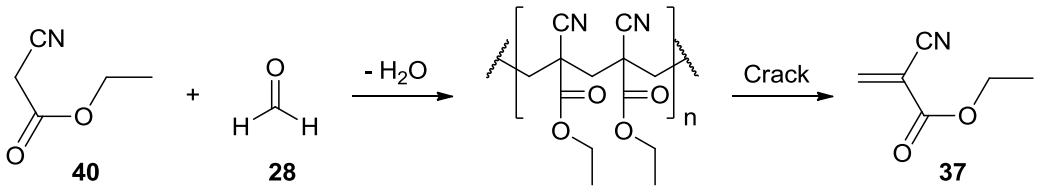
Scheme 1.10: Synthesis of alkyl 2-cyanoacrylate 16 from 2-cyanoacrylic acid 38

Cyanoacrylates have also been synthesised by condensation of cyanoacetate **40** and formaldehyde **28** in the presence of heat and vacuum.[122] This method first requires the synthesis of the necessary cyanoacetate; this can be achieved in two steps from mono-chloroacetic acid **41** (Scheme 1.11).



Scheme 1.11: Synthesis of ethyl cyanoacetate 40 from mono-chloroacetic acid 41

The cyanoacetate **40** can then be condensed together with formaldehyde **28** to form the cyanoacrylate oligomer. This is then depolymerised, or 'cracked' at high temperatures and reduced pressure, to give the cyanoacrylate monomer **37** (Scheme 1.12).

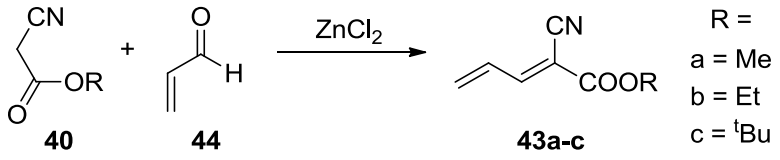


Scheme 1.12: Synthesis of ethyl cyanoacrylate 37 from cyanoacetate 40 and formaldehyde 28

Several improvements have been made to this reaction, including: a) using non-aqueous solvent during the condensation stage to enable quick and easy removal of

water from the reaction media,[123] b) closely regulating the pH of the first step as it is base catalysed[124] and then neutralising any remaining base before moving onto the depolymerisation stage,[125] c) regulating the mole ratio of formaldehyde and cyanoacetate to provide a readily polymerising cyanoacrylate oligomer,[126] d) providing a dry atmosphere[127] and using phosphoric acid as a heat transfer media for the final step.[128] The optimisation of this reaction has made this process industrially viable for the production of a range of simple cyanoacrylate monomers with low boiling point. However due to these monomers undergoing rapid polymerisation in the presence of moisture, stabilisers are needed during the synthesis and in the storing of the monomers in order to prevent premature polymerisation.

The above condensation method has also been used to synthesise alkyl 2-cyano-2,4-pentadienoates **43a-c** from the corresponding cyanoacetate **40** and acrolein **44** in the presence of a zinc chloride catalyst (Scheme 1.13).

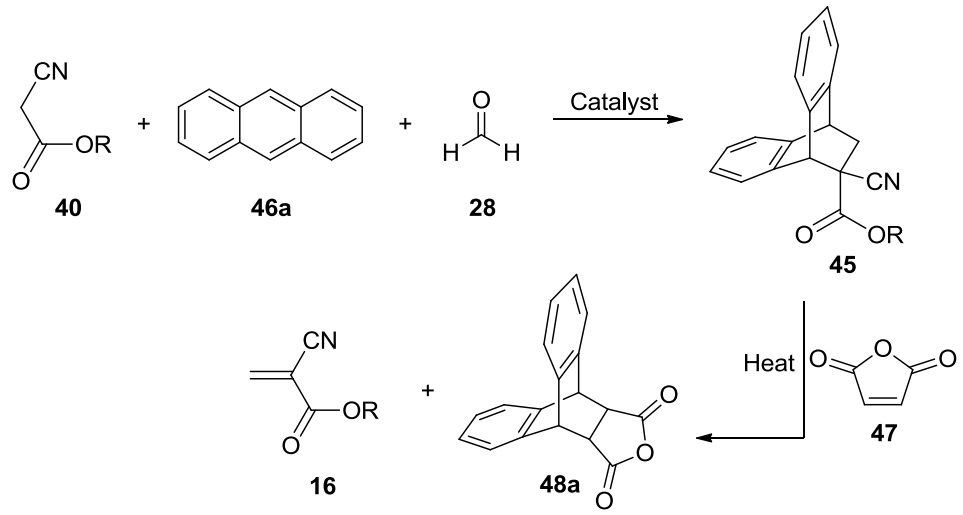


Scheme 1.13: Synthes/is of alkyl 2-cyano-2,4-pentadienoates 43a-c

The resulting alkyl 2-cyano-2,4-pentadienoates **43a-c** all polymerised in the presence of water. Addition of the alkyl 2-cyano-2,4-pentadienoates **43a-c** to cyanoacrylate increased the adhesive strength compared to cyanoacrylate alone. Addition of ethyl 2-cyano-2,4-pentadienoate **43b** increased the bond strength between stainless steel surfaces considerably to 22.8 and 25.0 MPa at 100 and 125 ^{o}C, respectively compared to 8.00 and 6.42 MPa. Cyanoacrylate adhesives modified with alkyl 2-

cyano-2,4-pentadienoates can be used to join together surfaces that are exposed to temperatures in the range of 100 to 150 ^{o}C.

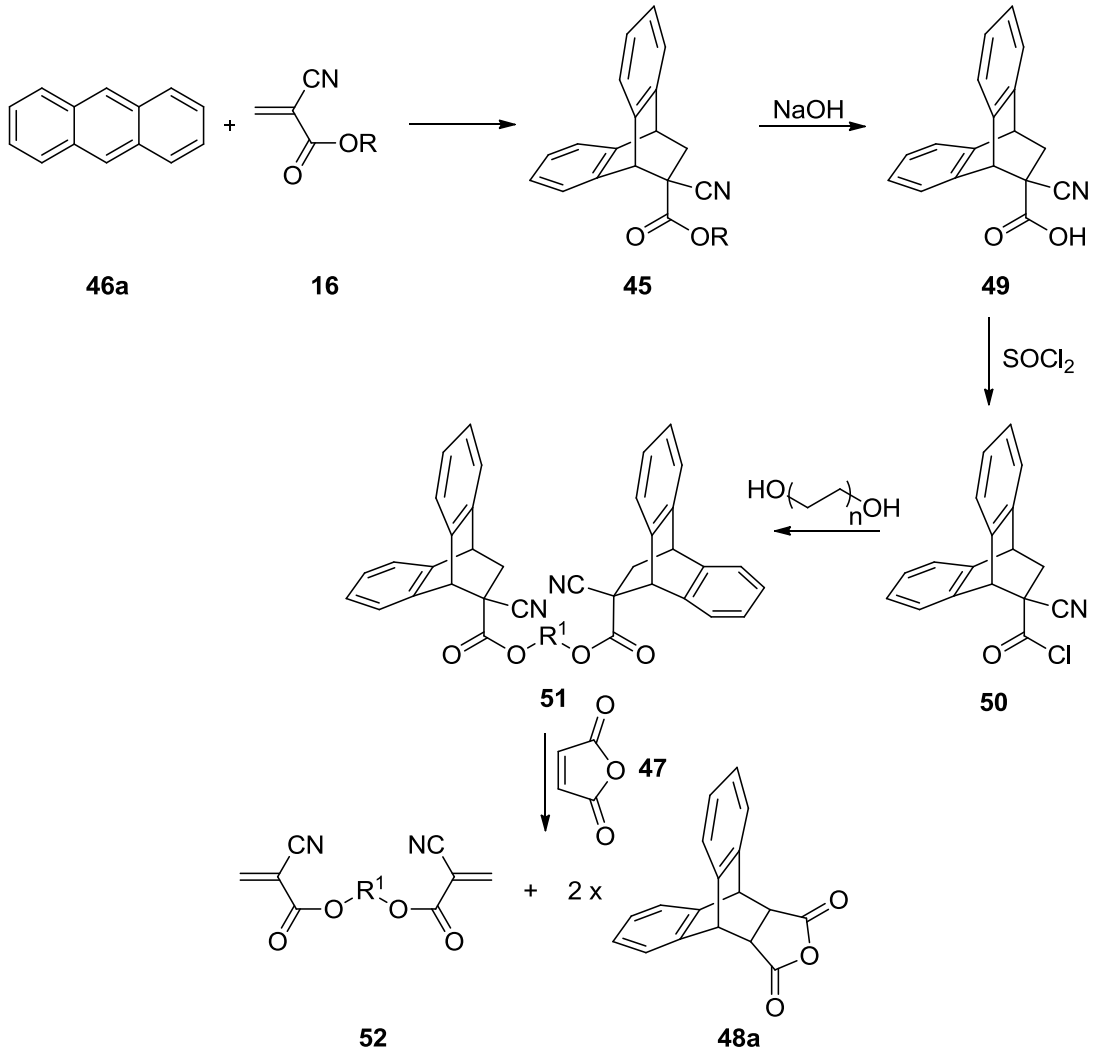
Previous studies of the synthesis of cyanoacrylate monomers have also investigated the possibility of protecting the reactive double bond. It has been previously reported that anthracene adducts **45** can be used for the synthesis of cyanoacrylates.[129] The Knoevenagel condensation of formaldehyde **28** and alkyl cyanoacetate **40** was carried out in the presence of anthracene **46a**. The resulting cyanoacrylate monomer was trapped by **16** *in situ* to give a stable anthracene adduct **45**. This when heated in the presence of maleic anhydride **47** undergoes a retro-Diels-Alder reaction and collapses to give the cyanoacrylate monomer **16** (Scheme 1.14). This approach has only been used to prepare a small palette of monomers.



Scheme 1.14: Synthesis of cyanoacrylates 16 using anthracene 46a

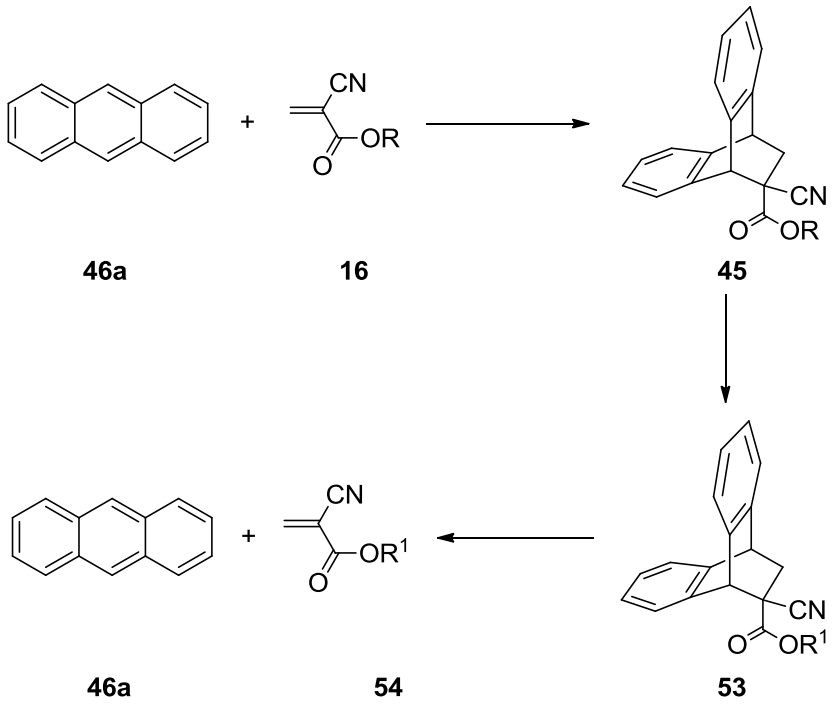
An alternative approach is to use anthracene **46a** to react with cyanoacrylates directly to give a stable anthracene adduct **45** to which modification of the ester moiety can be undertaken without polymerisation occurring. Anthracene **46a**, which has been acting as a protecting group can then be removed *via* a retro-Diels-alder

reaction yielding a new cyanoacrylate monomer. Previous work in this area includes the development of a multi-step synthesis for bis(2-cyanoacrylate) monomers **52** from the Diels-Alder adducts of alkyl 2-cyanoacrylate and anthracene,[130–133] (Scheme 1.15). Anthracene adduct **45** was prepared by Diels-Alder reaction of anthracene **46a** with alkyl cyanoacrylate **16**.[134] This was then hydrolysed with NaOH to the corresponding carboxylic acid **49**, before conversion to the acid chloride **50**. Two equivalents of the acid chloride were then reacted with the appropriate diol furnishing bis-anthracene adducts **51**. A retro-Diels-Alder reaction using maleic anhydride to trap the freed anthracene **46a** was then required to complete the synthesis and yield the bis-cyanoacrylate monomer **52**.



Scheme 1.15: Synthesis of bis(2-cyanoacrylate) 52

In principle, this chemistry can be adapted for the synthesis of a range of novel 2-alkyl cyanoacrylates **16**; due to the anthracene starting material being regenerated it may be possible to apply continuous flow techniques to this route. This will be re-visited in Chapter 3, (Scheme 1.16).

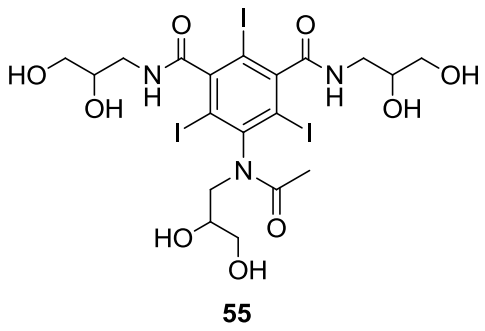


Scheme 1.16: Proposed anthracene protected synthesis of cyanoacrylates

1.5 X-ray contrast agents

A contrast agent is a substance used in medical imaging to enhance structures or fluids within the body. X-rays provide good visualisation of bone structure because there is a natural contrast between electron dense bones and the surrounding soft tissue. However, contrast between the different soft tissues in the body is so small that unenhanced X-ray images cannot differentiate between them.[135] To differentiate soft tissue areas such as the cardiovascular system, X-ray contrast agents are used. Iodine and barium are the most common types of contrast medium for enhancing X-

ray-based imaging methods. Barium sulphate is an insoluble white powder and has been used for radiographic imaging of the GI tract since 1910. It is still widely used for detection of conditions such as ulcers, inflammatory bowel disease and gastric cancer.[136] Barium sulphate is mixed with water, thickeners and de-clumping agents, to make the contrast agent. It is usually swallowed or administered as an enema, after examination the contrast agent leaves the body with the faeces. Iodinated contrast agents are water soluble compounds that are administered intravenously as a solution. They can be used anywhere in the body and are the most commonly used contrast media in medical imaging, an example of an iodinated contrast agent is iohexol **55** (Figure 1.15).



55

Figure 1.15: X-ray contrast agent iohexol 55

Contrast agents work by absorbing X-rays and creating contrast between substrates. Different tissues within the body affect the X-ray beam to different degrees. The degree to which the X-ray beam is affected by an element is complex. One of the many variables is the number of electrons in the path of the beam with which it can interact with. This is dependent upon three factors; i) the thickness of the substance being studied, ii) the density of the substance, iii) the number of electrons per atom of the element *i.e.* atomic number.[137] If two organs have similar densities and similar average atomic numbers, then it is not possible to distinguish between them on an X-ray because no natural contrast exists.

The average atomic number of a structure can be artificially altered by adding a medium with a much higher average atomic number, *e.g.* a contrast agent. The purpose of a contrast agent is to absorb X-rays and thus create a distinction between the vessel of interest and the surrounding tissue,[138] (Figure 1.16).

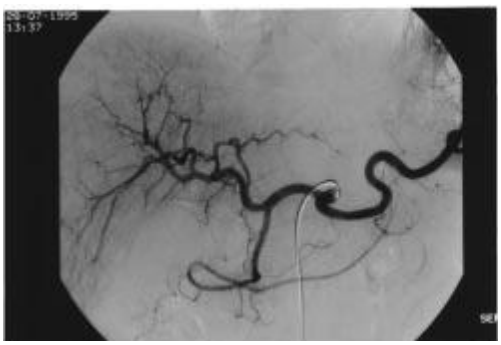


Figure 1.16: Angiogram of the celiac trunk and portal system with contrast[135]

Contrast agents are used in diagnostic tests in order to visualise organs or blood vessels. Heavy metals such as barium and iodine are used as they allow significant contrast between blood vessels and organs due to high atomic number. Although there are many compounds with higher atomic numbers than iodine, none provide as good a compromise between contrasting power, safety due to reduced toxicity and cost.[137,139]

1.5.1 Iodinated contrast agents

Iodinated contrast agents are among the most widely used intravascular pharmaceuticals. Worldwide over 600 million X-ray examinations are carried out annually, and approximately 75 million of those will require use of iodinated contrast media.[138] There are several types of iodinated contrast agents, however all are metabolically stable in the body and are rapidly eliminated *via* urine or faeces. All contain several iodine molecules as they are responsible for absorption of X-

rays.[140] Modern iodinated agents are based around a 1,3,5-triiodinated benzene ring which first appeared in diatrizoic acid **56** in 1954.[135] There are four different class of iodinated contrast media based on this ring (Figure 1.17).

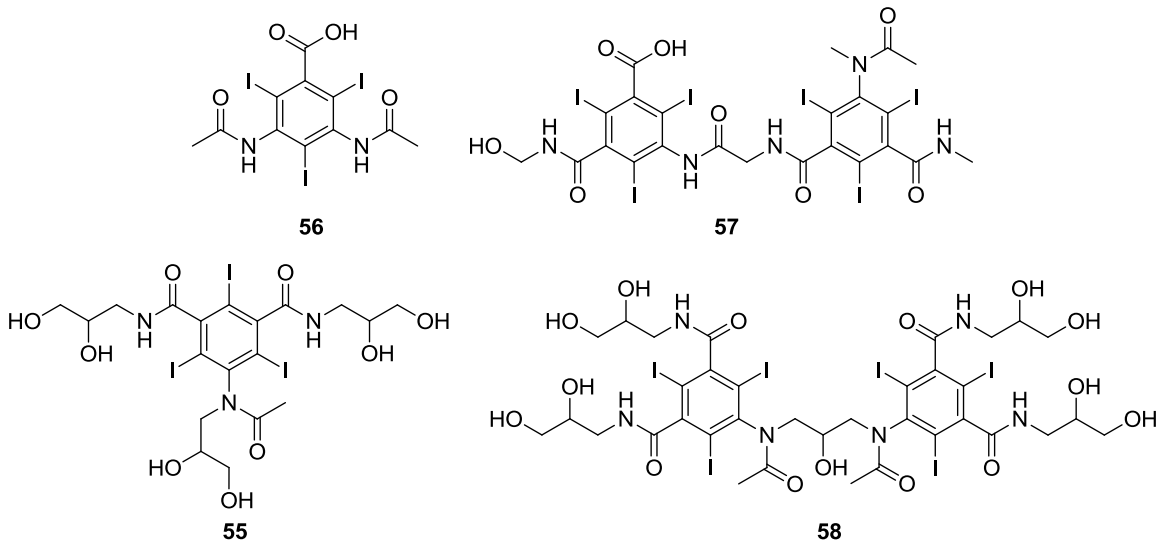


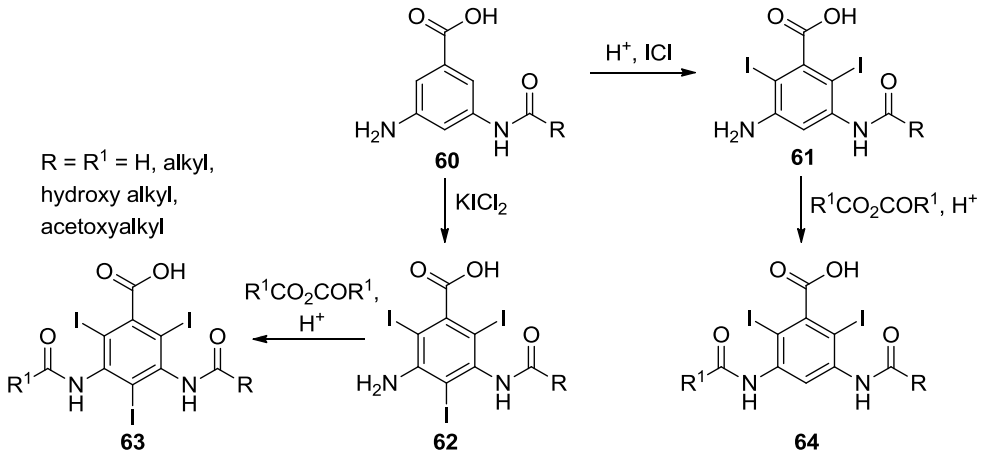
Figure 1.17: Iodinated contrast agents: diatrizoate acid **56** (ionic monomer), ioxaglate **57** (ionic dimer), iohexol **55** (non-ionic monomer), iodixanol **58** (non-ionic dimer)

The first generation were 'ionic' monomers such as diatrizoic acid **56**, which possess low toxicity and high water solubility. However these compounds can dissociate to give free iodide ions and can lead to cardiovascular, allergic and painful side effects and so have since been replaced.[141] The second generation of contrast agents are 'non-ionic' monomers, for example iohexol **55**, this class of compound is still one of the most commonly used in X-ray imaging. Non-ionic compounds are preferred as the iodine remains covalently bound and hence biologically unavailable; they have lower osmolality and greatly reduced pain upon injection.[142] The third and fourth class are both dimers; ionic e.g. ioxaglate[143] **57** and non-ionic e.g. iodixanol[144] **58**. All four classes include the tri-iodinated ring **59** with different side chains attached, the aim of the side chains are to give the contrast agent high water solubility and low

toxicity. Non-ionic monomers such as iohexol **55**, consists of long side chains rich in hydroxyl groups evenly distributed around the benzene core. Two of these side chains are usually identical, giving the compound a divalent structure.[138]

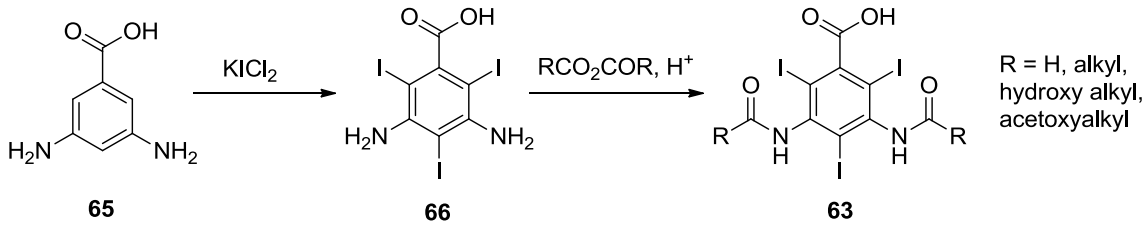
1.5.2 Synthesis of iodinated contrast agents

Diatrizoic acid **56** was the first commercially available iodinated contrast agent. After its introduction in 1955 investigations into other tri-iodo-3,5-diaminobenzoic acid derivatives as potential radiopaques were undertaken.[145] Two different synthetic approaches were employed for the preparation of these iodinated compounds. The first approach required one *N*-acyl group in place prior to iodination. Initial attempts to iodinate the starting material **60** using iodine chloride in dilute HCl resulted only in the di-iodo derivative **61**. Despite longer reaction times and increasing the amount of iodine chloride the tri-iodo compound **62** was not isolated. In order to successfully synthesise the tri-iodo derivative **62** it was necessary to reduce the acidity of the reaction by taking the amine salt of the starting material and reacting it with potassium iododichloride. The tri-iodo compound **62** was then successfully acylated to give a range of tri-iodo-3,5-diaminobenzoic acid derivatives **63** (Scheme 1.17).



Scheme 1.17: Preparation of 3,5-diacylamino-2,4,6-tri-iodobenzoic acid 63

The second approach involves iodination of 3,5-diaminobenzoic acid **65** using potassium iododichloride, followed by acylation of the tri-iodo derivative **66**, (Scheme 1.18).

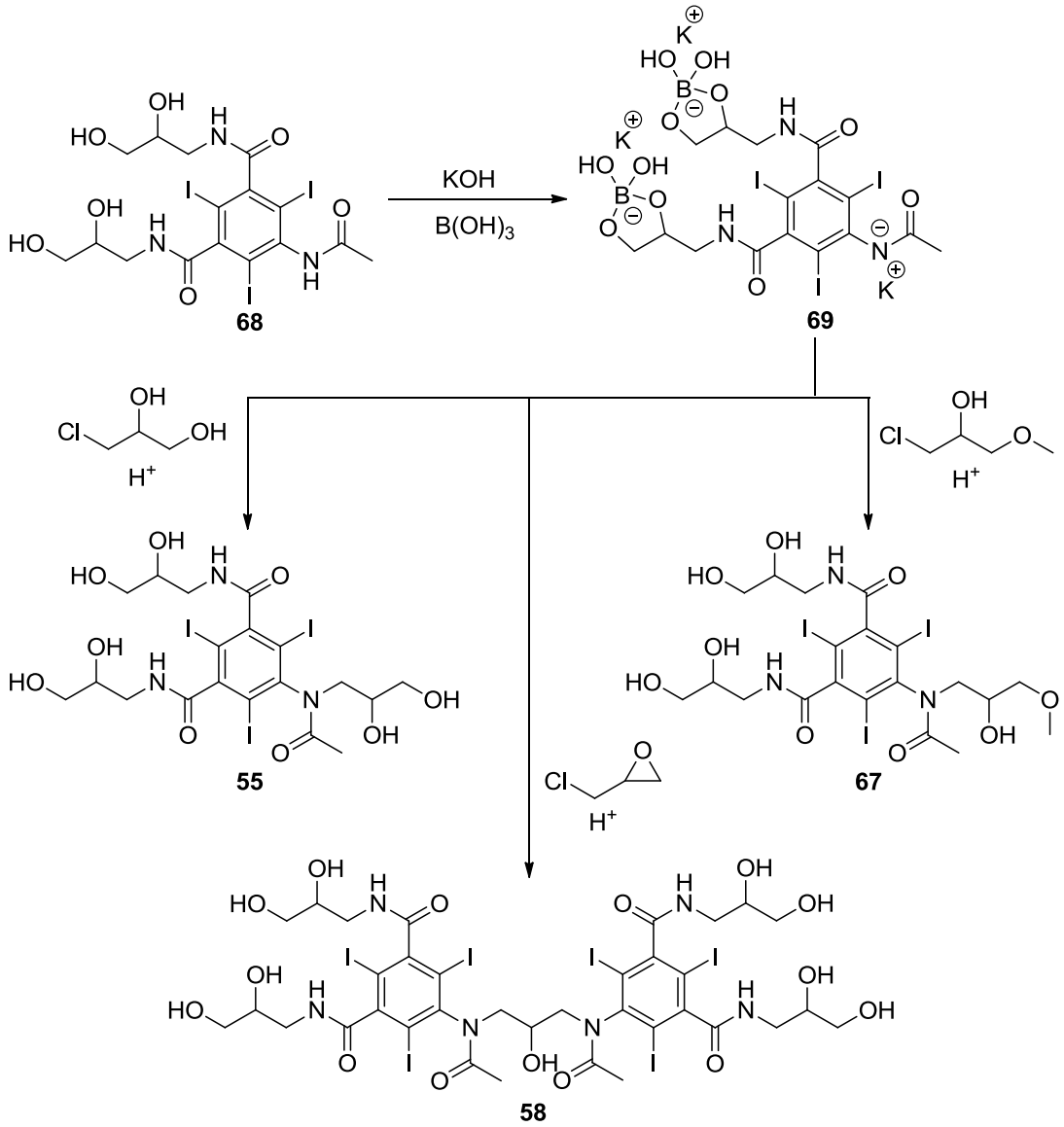


65 **66** **63**

Scheme 1.18: Preparation of 3,5-diacylamino-2,4,6-tri-iodobenzoic acid 63 from 3,5-dinitrobenzoic acid 65

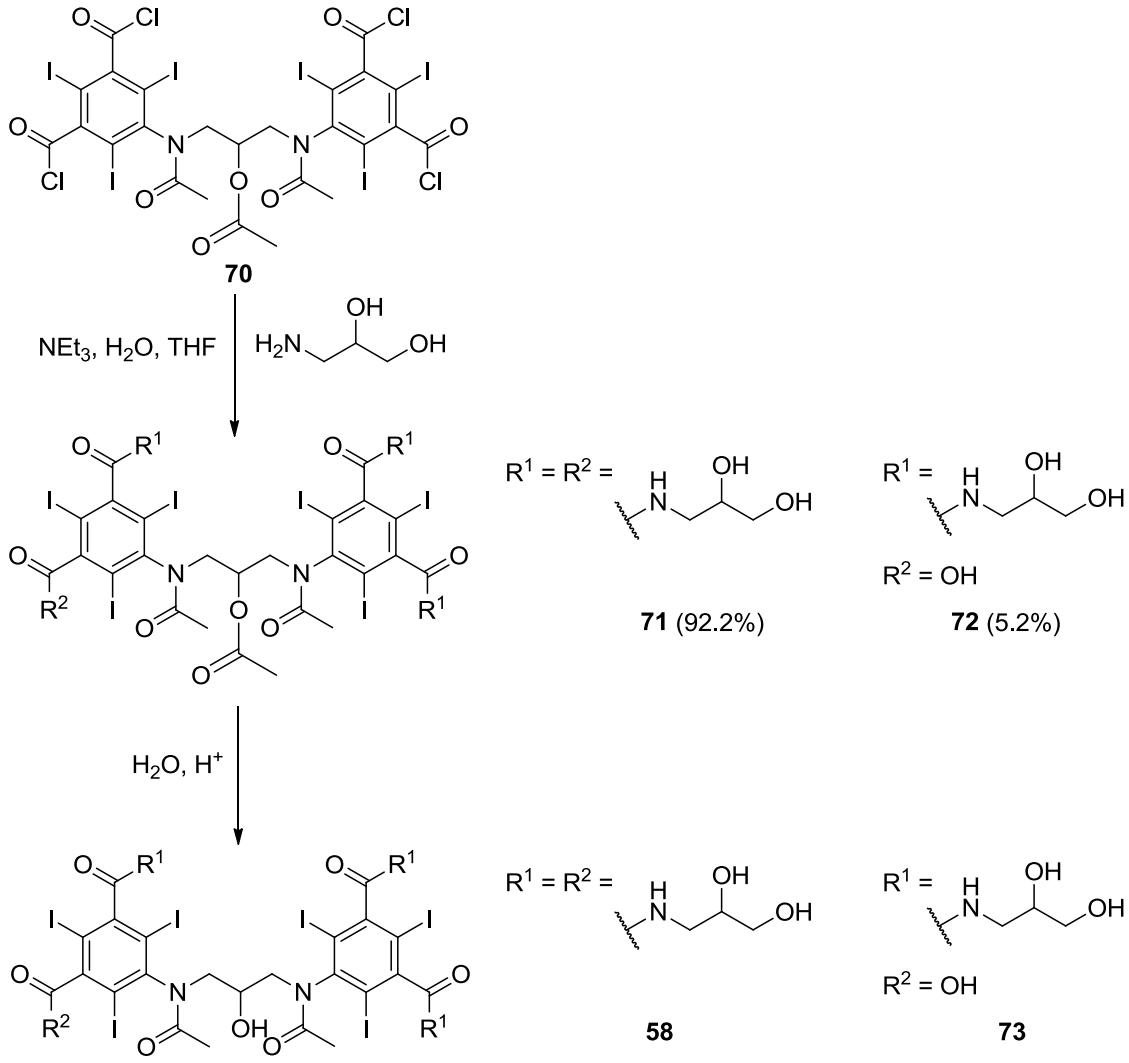
Diatrizoic acid **56** gave a toxicity of 13.4 g/kg when injected as an aqueous solution of the sodium salt in mice. Over the years there has been a move away from these first generation agents, e.g. diatrizoic acid **56** towards second and third generation agents such as iohexol **55** and iodixanol **58**. These agents are larger and more complex and require linear multistep procedures where different side chains (containing groups such as carboxylic acids, carboxamides, alcohols, and ethers) are successively introduced to the tri-iodinated benzene core. More nucleophilic sites are introduced to the molecule as the synthesis progresses, making promoting the desired alkylation over competing side reactions more challenging. Under the conditions needed for *N*-alkylation of the amide group, competing *O*-alkylation of the primary and secondary hydroxyl groups present on the side chains can occur. One way to prevent this is the use of protecting groups; however this strategy is not desirable to an industrial process as it involves two additional steps; application and removal of the protecting group. However exceptions can be made where a concatenated process may be established when the protection, the desired synthetic transformation, and the de-protection can all be performed in a one-pot procedure with cheap reagents and simple work-up. Scheme 1.19[146] illustrates one such method

using temporary protection of the 1,2-diol groups by boric acid, to allow selective *N*-alkylation in the synthesis of three known contrast agents iohexol **55**, iopentol **67** and iodixanol **58**. When the protection strategy was used the *N/O*-alkylation ratios were substantially improved resulting in increased yields of the target compounds **55**, **58** and **67**.



Scheme 1.19: Boric acid as a temporary 1,2-diol protecting group for selective *N*-alkylation in the synthesis of iohexol 55, iopentol 67 and iodixanol 58

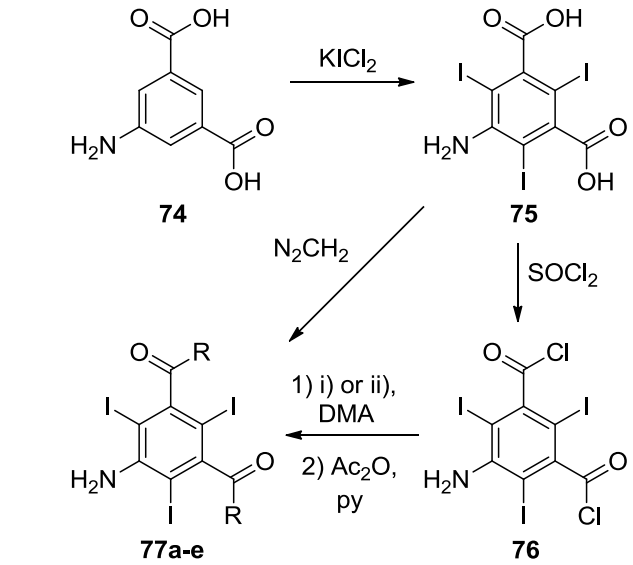
Iodixanol **58** can also be synthesised from the tetra-acid chloride **70**, adding the four side chains to give intermediate **71**. A simple procedure was developed to achieve selective *N*-alkylation by reacting acid chlorides with amines in a medium of THF and water. Due to the high rate of the *N*-alkylation reaction the competing process (hydrolysis of the acid chloride) to give side product **73** is only observed in low yields (Scheme 1.20).[147]



Scheme 1.20: Preparation of iodixanol 58 from tetraacid chloride 70

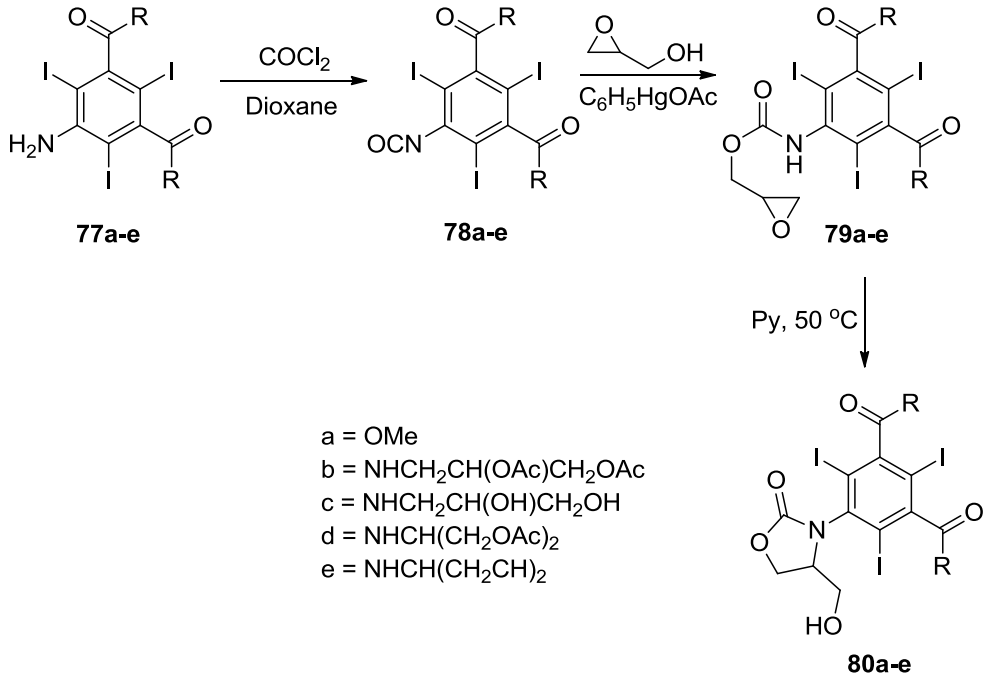
Iohexol **55** is a second generation contrast agent, non-ionic monomer, and is still used today in hospitals worldwide. Since the introduction of non-ionic monomers work has been conducted to improve the design of these compounds. For example

iohexol **55** displays hydrolytic instability of the ArN-(CO) bond leading to the corresponding aniline, during storage of the injectable solution. This is thought to arise from the anchimeric assistance to the cleavage of the amide bond by the neighbouring hydroxyl groups. To overcome this problem synthesis of compounds based on the oxazolidin-2-one moiety **80a-e** were investigated as they were expected to provide highly stable molecules at physiological pH ranges.[148] The starting materials for this synthesis were prepared from the aniline **74**; this was first iodinated using potassium iododichloride to give **75**. Diazomethane esterification of **75** gave **77a** in 98%. The synthesis of compounds **77b-e** was achieved by reaction with thionyl chloride to give the acid chloride **76**, which was reacted *in-situ* with the corresponding amino-diol. In the case of **77b** and **77d** this was followed by *O*-acetylation with acetic anhydride in pyridine (Scheme 1.21).



Scheme 1.21: Synthesis of starting materials 77a-e

The starting materials synthesised above were converted to the corresponding isocyanate **78a-e** by treatment with phosgene in dioxane. Addition of glycidol was achieved at room temperature in the presence of phenylmercuric acetate to give the glycidyl carbamate **79a-e** in 81% yield. Heating the glycidyl carbamate **79a-e** to 50 ^{o}C in pyridine for 2 h gave the desired products **80a-e** (Scheme 1.22).

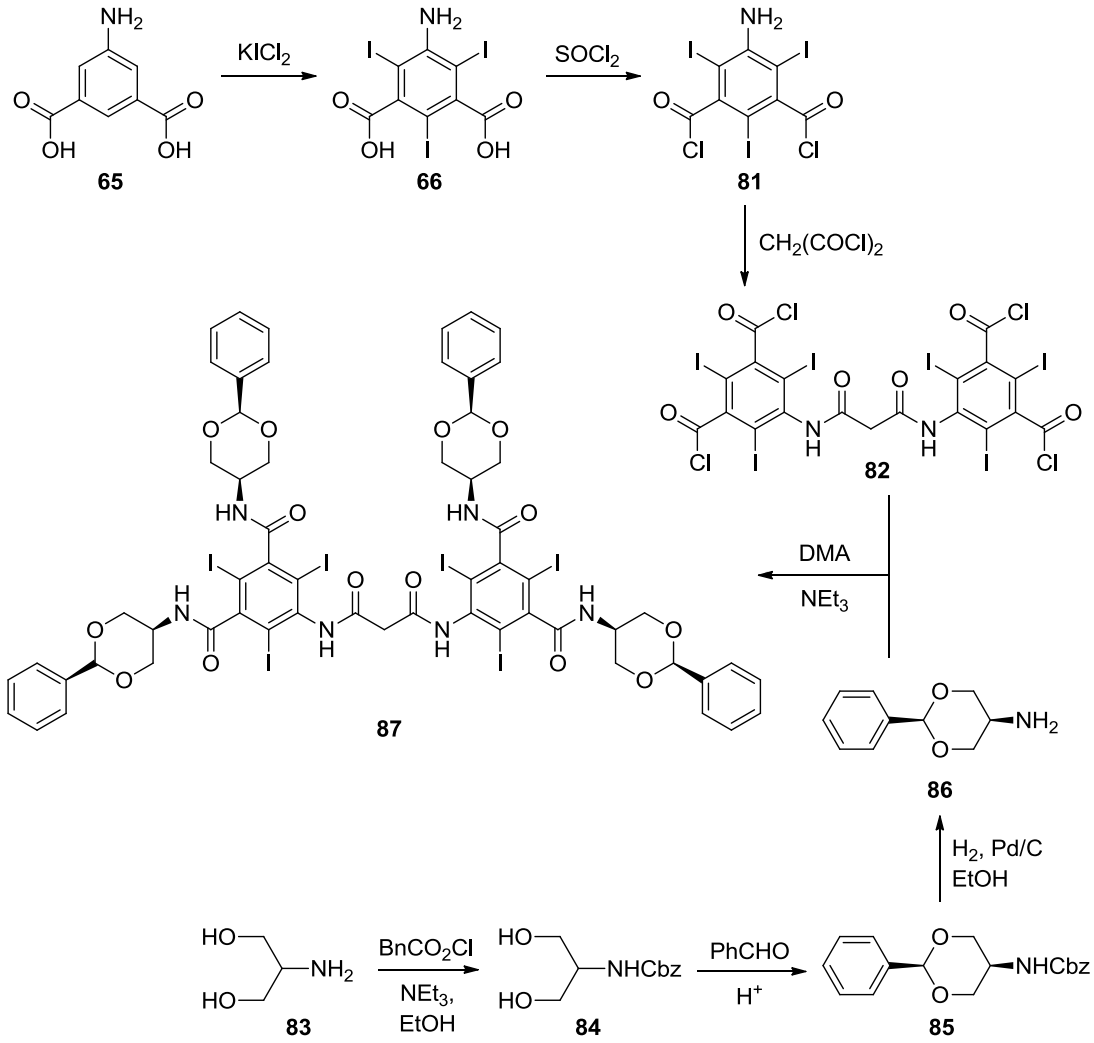


Scheme 1.22: Synthesis of oxazolidin-2-one derivatives 80a-e

The above oxazolidin-2-one derivatives **80a-e** were evaluated for their potential as X-ray contrast agents. Although they were hydrolytically more stable in aqueous solution, their relatively poor water solubility (~15%) prevented further consideration as contrast media, an application that requires 80% w/v.

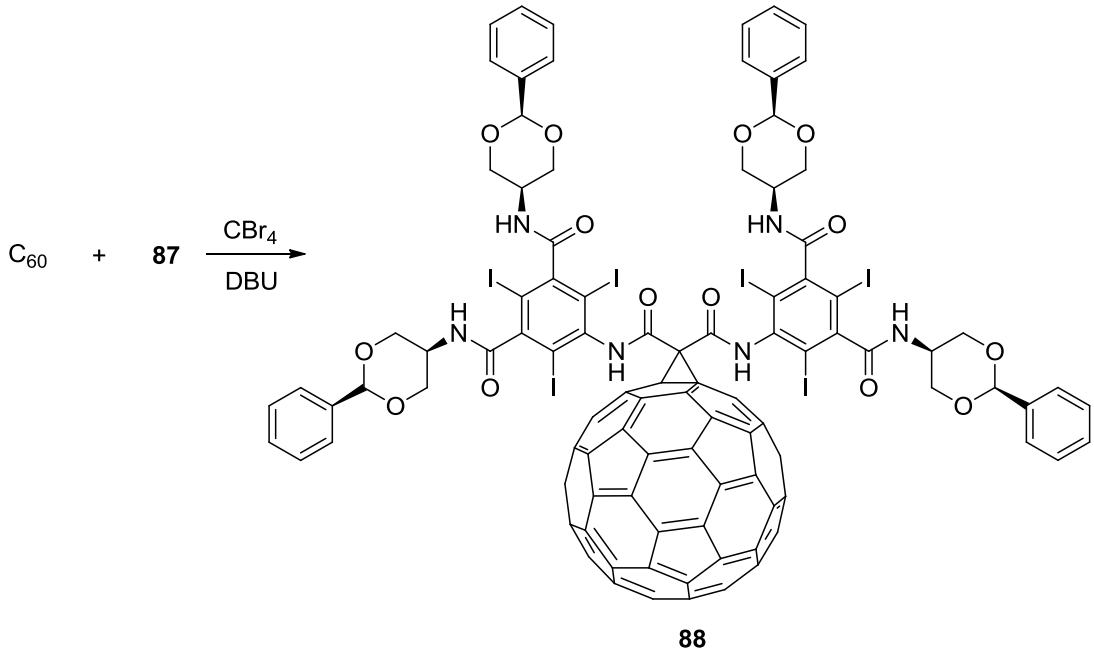
In order for new contrast agents to show significant improvement in tolerability or performance over existing ones novel classes of agent need to be considered. For example tungsten clusters,[149] metal chelates,[150] iodinated dicarbon carborane cages[151] or fullerenes, the latter of which are of interest as C_{60}-derived materials have

previously been utilised for biological applications. Investigations were undertaken to synthesise a C_{60}-based contrast agent,[152] first the highly-iodinated addend **87** was synthesised from 5-aminoisophhalic acid **65**. The first step was iodination using potassium iododichloride, followed by treatment with thionyl chloride to give diacid chloride **81**. The diacid chloride **81** was directly condensed with malonyl dichloride to give the tetrachloride **82** in 83% yield. Condensation of the tetrachloride **82** with 5-amino-2-phenyl-1,3-dioxane **86** in DMA at r.t. proceeded in 95% yield to give the hexa-iodinated, *O*,*O*'-protected malondiamide addend **87** (Scheme 1.23).



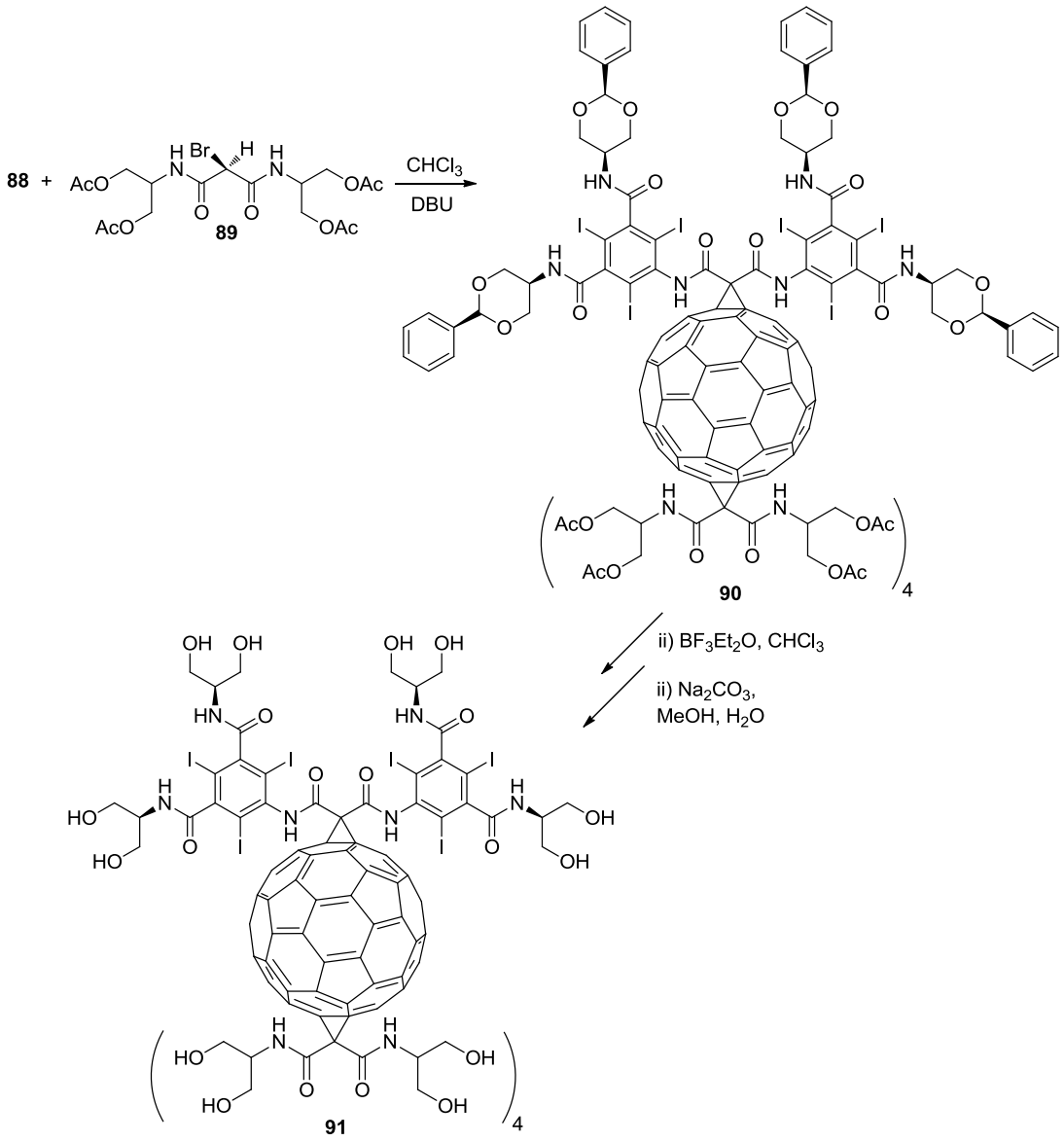
Scheme 1.23: Synthesis of the hexa-iodinated, *O*,*O*'-protected malondiamide addend 87

The reaction between the malonodiamide **87** and C60 proceeded at room temperature with CBr_4 and DBU in toluene/ pyridine, giving a surprisingly good yield of 77%, considering the steric bulk of addend **88** (Scheme 1.24).



Scheme 1.24: Synthesis of monoadduct 88

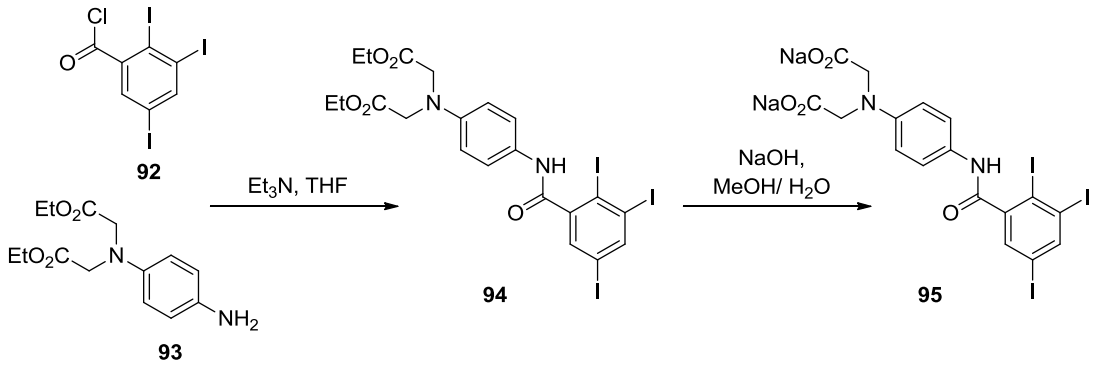
Initial deprotection of monoadduct **88** resulted in a material that was only sparely soluble in water. Therefore, given the high water solubility requirements for X-ray contrast agents, additional functionalisation of **88** was undertaken to improve its water solubilisation. This was achieved by addition of the smaller malonodiamide group $BrCH(COSer)_2$ **89** to the monoadduct **88**, followed by deprotection to give new contrast agent **91** (Scheme 1.25). Animal studies to determine the efficacy of the fullerene compound **91** as an X-ray contrast agent have not been published.



Scheme 1.25: Assembly and deprotection of X-ray contrast agent 91

While contrast agents have been used for the imaging of blood vessels, analysis of bone structures has not yet been achieved. Investigators[153] aimed to synthesise organic-iodine based conjugates that could 'lock' onto bone cracks. They proposed that to achieve this required structures with a receptor moiety conjugated into the iodine moiety with the aim of maximising the interactions with ions such as Ca(II) that are exposed on the surface of damaged bone. Three such first generation complexes to detect microcracks in bovine bones using CT imaging were

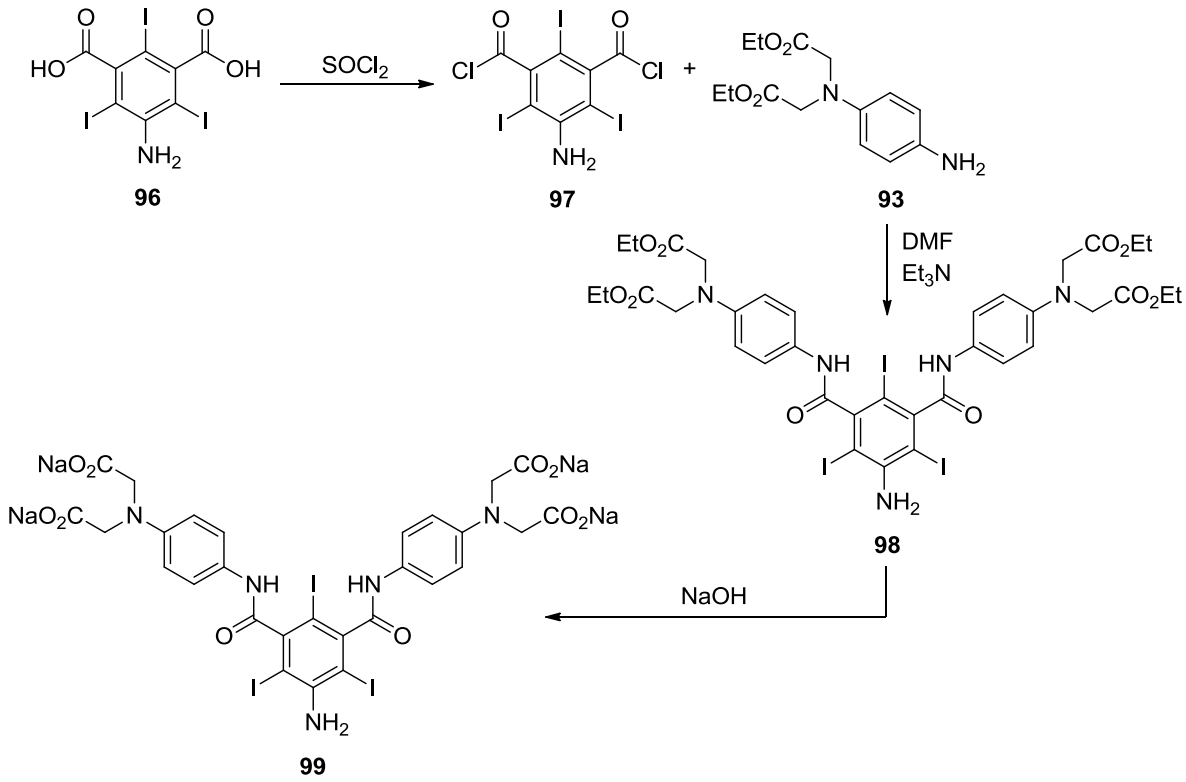
synthesised.[153] The first and the simplest of these compounds contains a single phenyliminodiacetate unit, attached to the iodinated aromatic ring *via* an amide spacer **95**. This target compound was synthesised by a coupling reaction between 2,3,5-triiodobenzoyl chloride **92** and the phenyliminodiacetate ethyl ester **93** (Scheme 1.26). The two starting materials were synthesised from commercially available substrates; 2,3,5-triiodobenzoyl chloride **92** from reaction of the carboxylic acid and thionyl chloride in an 85% yield. The phenyliminodiacetate ethyl ester **93** was formed from aniline in three steps; dialkylation using ethyl bromoacetate in the presence of K_2HPO_4, followed by nitration using nitric acid and finally hydrogenation using 10% Pd/C. Condensation of **92** and **93** was achieved in THF using Et_3N to give the diester **94** which was then hydroylised using NaOH to yield **95**.



Scheme 1.26: Synthesis of 95 from 2,3,5-triiodobenzoyl chloride 92

Compound **99** contained two phenyliminodiacetate moieties in a *meta* configuration in a bid to increase ionic interaction and stronger binding at the unsaturated lattice sites in damaged bone. Firstly, commercially available 5-aminoisophthalic acid was iodinated using potassium iododichloride to give starting material **96** which was converted to the acid chloride **97**. The condensation of the acid chloride **97** and the phenyliminodiacetate ethyl ester **93**, using Et_3N in DMA, resulted in the ethyl ester

intermediate **98**. This was hydrolysed using the same method as **95** to give target **99** (Scheme 1.27).

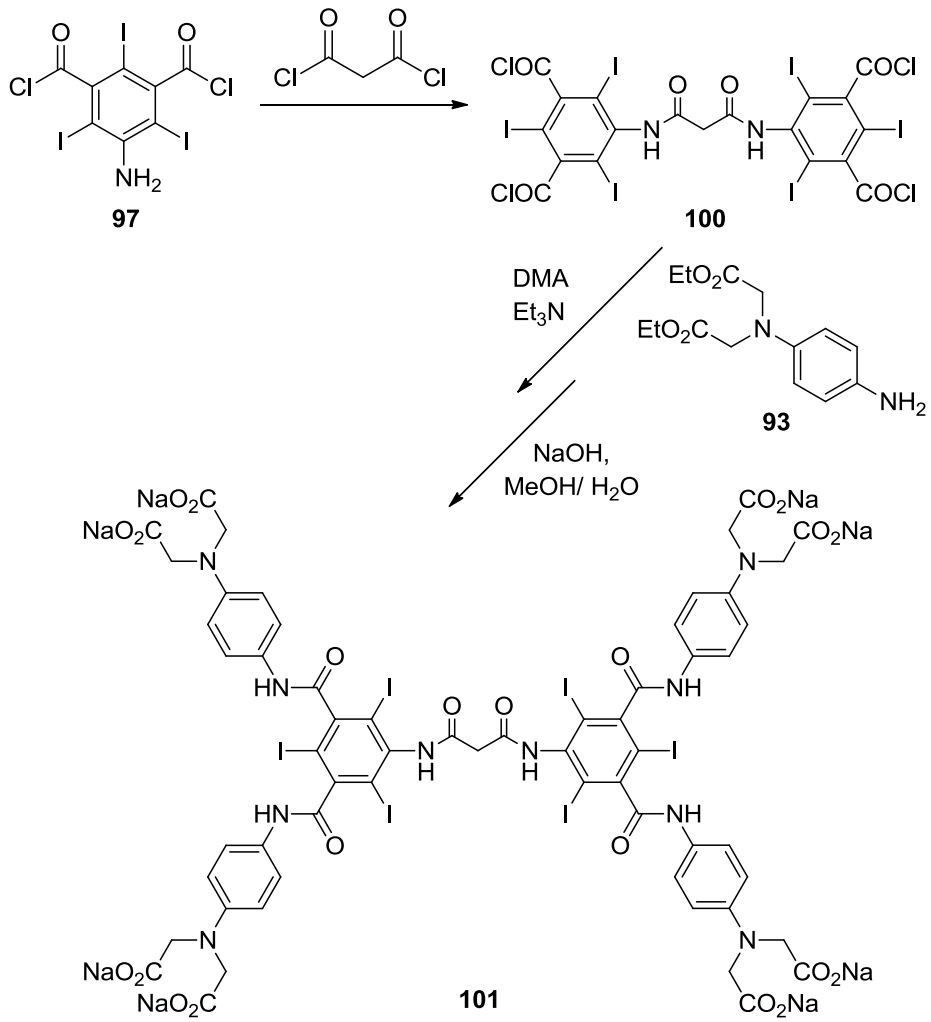


Scheme 1.27: Synthesis of 99 from 5-aminoisophthalic acid 96

The final compound **101** is a dimer, containing six iodine atoms and four chelator units in a *meta* configuration, and was expected to have the highest binding affinity. Compound **101** was synthesised from the bis-acid chloride **97** which was first reacted with malonyl dichloride to give the dimer **100** which using the same procedure as the previous two compounds gave **101** (Scheme 1.28).

Contrast agents **95**, **99** and **101** were subsequently used to label bone scratches on bovine tibiae and tested by CT imaging. The scratch was visible with all three contrast agents, however it was difficult to differentiate between bone and contrast agent in order to determine features such as scratch depth. This was thought to be due to the beam hardening effect, which masks the imaging from the agents.

However the results show that agents can bind to bone cracks and are important in future developments for bone-targeting CT imaging agents.



Scheme 1.28: Synthesis of 101 from bis-acid chloride 97

1.6 Current treatment of brain aneurysms

An aneurysm is an abnormality, a weakness in the wall of a blood vessel which causes dilation and ballooning of the arterial wall (Figure 1.18). This can occur in any vessel in the body. If an aneurysm in the brain ruptures it can lead to a stroke which can cause brain damage and death.

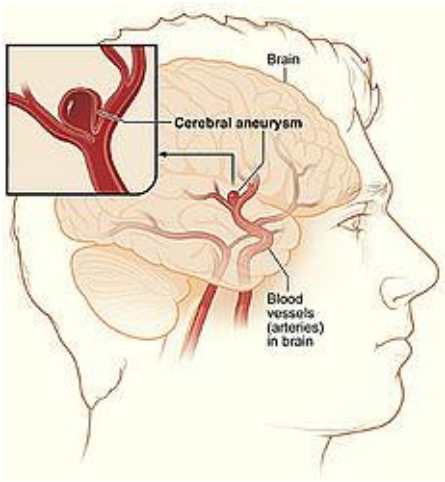


Figure 1.18: Brain aneurysm

It is not known for certain the cause of intracranial aneurysms or how they form, grow and rupture, however there is evidence to suggest that hypertension and smoking induced vascular changes play a major role.[154] Brain aneurysms are often discovered once they have ruptured, causing bleeding in the brain or the subarachnoid space. Treatment is focused on stopping the bleeding and hopefully preventing permanent brain damage. However it is possible to prevent brain damage by treating the un-ruptured aneurysm.

In the past intracranial aneurysms were normally only discovered after rupture and subsequent subarachnoid haemorrhage. Now increasingly aneurysms are detected before rupture due to improved sensitivity of imaging techniques. Once detected there are three treatment options:[155] firstly observation, this involves follow up imaging to monitor the aneurysm. The second option is surgical clipping, this is an open procedure and involves making an incision in the scalp, opening the bone and dissecting through the bone to place a clip across aneurysm where it arises from the blood vessel, thus preventing the blood flow from entering the aneurysm (Figure 1.19).

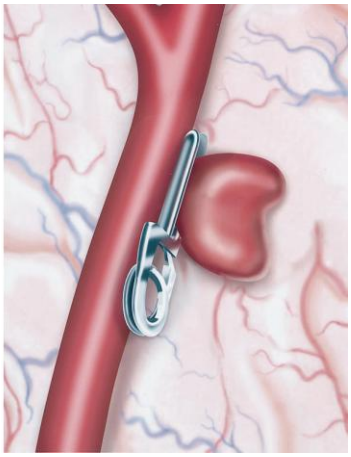


Figure 1.19: Surgical clipping[71]

The final option is endovascular "coiling" which involves inserting a catheter into a vessel in the groin and navigated through the blood vessels, with the aid of contrast media to visualise vessels, to the brain and into the aneurysm. Coils are then packed into the aneurysm until it arises from the blood vessel, stopping blood from entering,[156] (Figure 1.20). The treatment option selected depends on several factors included the size of the aneurysm and the patients age, both of which effect the risk of rupture.[157]

A **B** **C**

Figure 1.20: Coiling treatment of aneurysms A) before treatment, **B)** after coiling, **C)** X-ray image shows densely packed coils[154]

Previous to the availability of detachable coils, most intracranial aneurysms were surgically clipped to prevent rupture.[157] In recent years there has been a move towards "coiling" for treatment of aneurysms as it has been shown to give better outcomes than neurosurgical clipping for subarachnoid haemorrhage[158] It is also more popular with patients as it is less physiologically stressful and less invasive than clipping. Minor risks of coiling include, reaction to the contrast agent, groin hematomas and infection, similar risks to those of diagnostic catheter angiography.[159] Several studies comparing endovascular and surgical management of ruptured and un-ruptured intracranial aneurysms show significantly improved outcomes with coiling.[71,160] Coiling has been shown to give lower rates of patient mortality, shorter hospital stays and lower treatment costs.[161]

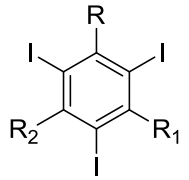
Endovascular coiling has been shown to effectively prevent re-bleeding of ruptured aneurysms.[162] It also shows better outcomes at 12 months and during follow ups extended to 7 years.[163] However it is not feasible to perform coiling for some aneurysms (approximately 10 – 15% of cases) due to difficult access or if the contours of the aneurysm do not allow for coils to fit safety inside.[155] Also several reports have shown that aneurysm recurrence or reopening is more frequent after coiling,[164, 165] and so is not always more preferable to clipping.

1.7 New applications of cyanoacrylate adhesives in combination with contrast agents

New applications for cyanoacrylate adhesives are currently being explored, in particular the internal use of cyanoacrylates. In theory cyanoacrylates could be used

to treat brain aneurysms in place of coiling. As with coiling a catheter could be inserted into the groin and navigated into the aneurysm. Instead of packing the aneurysm with platinum coils, cyanoacrylate adhesive could be dispensed into the aneurysm, sealing it off and stopping blood from entering. This would be less expensive than platinum coils and the adhesive can take any shape necessary to fill the aneurysm. Cyanoacrylate polymerises quickly within the body and would therefore form a solid barrier which would prevent blood from entering the aneurysm. In order to monitor the glue as it is inserted in the aneurysm and to ensure it polymerises and therefore seals off the aneurysm it needs to be visualised within the body. This involves the use of contrast agents as with conventional coiling. However after coiling treatment, the sealed aneurysm can be visualised by X-ray as the platinum coils are visible, this would not be possible with cyanoacrylate glue.

To overcome this problem a known contrast agent could be combined with the adhesive before application. This would allow the cyanoacrylate to be visualised as it was guided through the body to the brain. It would then be possible to check the position of the glue and that it had successfully sealed the aneurysm by X-ray. However X-ray contrast agents are water soluble, meaning that they will not dissolve in cyanoacrylate. The main group of X-ray contrast media are iodinated agents and are based around a 1,3,5-tri-iodinated benzene ring **59** (Figure 1.21).



59

Figure 1.21: 1,3,5-tri-iodinated benzene ring

They have long side chains rich in hydroxyl groups evenly distributed around the benzene core. It is these hydroxyl groups that make the compound highly water soluble. If these hydroxyl groups could be protected with simple protecting groups the compound could be modified to be more organic soluble. Any group added to the contrast media needs to be small, so as to not significantly increase the molecular weight and therefore significantly decrease the iodine concentration. It is the iodine molecules that absorb the X-rays and therefore create distinction between the vessel of interest and the surrounding soft tissue.

The following three chapters describe attempts to (a) chemically modify commercially available contrast agents so that they dissolve in cyanoacrylate adhesives, (b) the development of novel cyanoacrylates that are less susceptible to biodegradation and formaldehyde release and (c) the improvement and development of an industrial synthesis of cyanoacrylate monomers.

2.0 – Incorporation of Contrast Agents in Cyanoacrylate Adhesive

2.1 Introduction

Contrast agents are substances used to enhance the contrast of structures/fluids within the body during medical imaging, for example during X-ray or MRI imaging. Tri-iodophenyl derivatives **59** have long been established as X-ray contrast agents[166] (Figure 2.1).

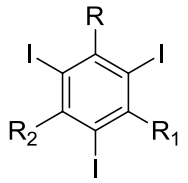


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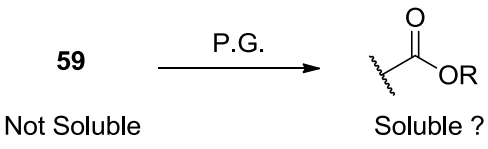
Figure 2.1: Triiodophenyl core of iodinated X-ray agents

The incorporation of an X-ray contrast agent into cyanoacrylate bioadhesives would allow the glues to be imaged and their position in the body determined, which would be beneficial in the development of new applications, for example in the treatment of brain aneurysms. Currently brain aneurysms are treated by either surgical clipping or endovascular coiling.[167] In endovascular coiling a micro catheter is inserted into the femoral artery in the patients leg. Fluoroscopic imaging is used to navigate through the vascular system into the aneurysm to deploy a series of platinum coils to densely pack the aneurysm and exclude it from circulation and therefore rupture[168] (Figure 2.2).

(i) (ii)

Figure 2.2: Posterior inferior cerebella artery aneurysm before (i) and after (ii) treatment[168]

Cyanoacrylate adhesive would be a cheaper alternative to platinum coils; the monomer is flexible and would take the shape of the aneurysm, it polymerises quickly in the presence of moisture[42] to form a solid barrier that would block off the blood flow and prevent rupture. Currently cyanoacrylate adhesives cannot be followed/ imaged in the body. If an X-ray contrast agent could be incorporated into the mixture then the flow of adhesive could be monitored in the body and this approach would become a viable alternative to coiling. However typical X-ray contrast agents, such as tri-iodophenyl derivatives **59**, are highly insoluble in cyanoacrylates. By using simple protecting group chemistry it should be possible to alter the solubility of the contrast agents sufficiently that they will dissolve in the hydrophobic cyanoacrylates allowing for the positioning of the adhesives to be followed by X-ray (Scheme 2.1).



Scheme 2.1: Use of protecting group chemistry to investigate effect on solubility

There are a number of known iodinated contrast agents commercially available. These can be classed into ionic or non-ionic reagents. Originally ionic reagents **56** (in the form of the sodium salt), were used, however in recent years there has been a move to non-ionic agents **55** and **58** as they may be administered in higher concentrations and have reduced side effects.[169] The ion charges resulting from the disassociation of compounds such as **56** can potentially disrupt the electrical charges in the brain and heart.[170] Examples of existing contrast agents include diatrizoic acid[171] **56** (ionic), trade name Hypaque, iohexol[172] **55** and iodixanol[173] **58** (non-ionic), trade names Omnipaque and Visipaque (Figure 2.3).

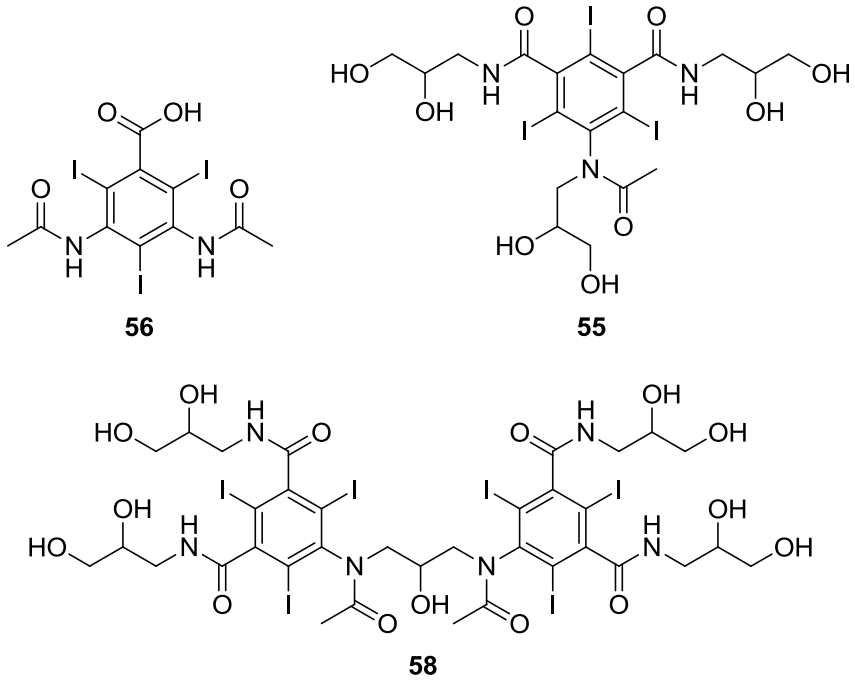


Figure 2.3: Contrast agents diatrizoic acid 56, iohexol 55 and iodixanol 58

If a particular chemical reaction needs to be carried out selectively at one site in a compound with multiple functional groups, other reactive sites need to be blocked, or protected. Over the years many different protecting groups for a range of different functional groups have been developed for this purpose.[174] Protection of acidic functionality (such as carboxylic acids and alcohols) within the contrast agents **55**,

56 and **58** would lead to more hydrophobic molecules which would have better solubilities within cyanoacrylate monomers and polymers. The contrast agent would require a solubility of approximately 10-15% by weight in any cyanoacrylate adhesive if it is to be easily observed in the body. It follows that contrast agents with higher percentages of iodine atoms within their structures would require less solubility within adhesives than those with lower percentages to achieve the same contrast. Protection of functional groups within the target contrast agents **55**, **56** and **58** will increase their molecular weights lowering the effective iodine concentration. In order to keep the effective iodine concentration as close to the commercial contrast agents as possible we will restrict our study to only the use of small protecting groups.

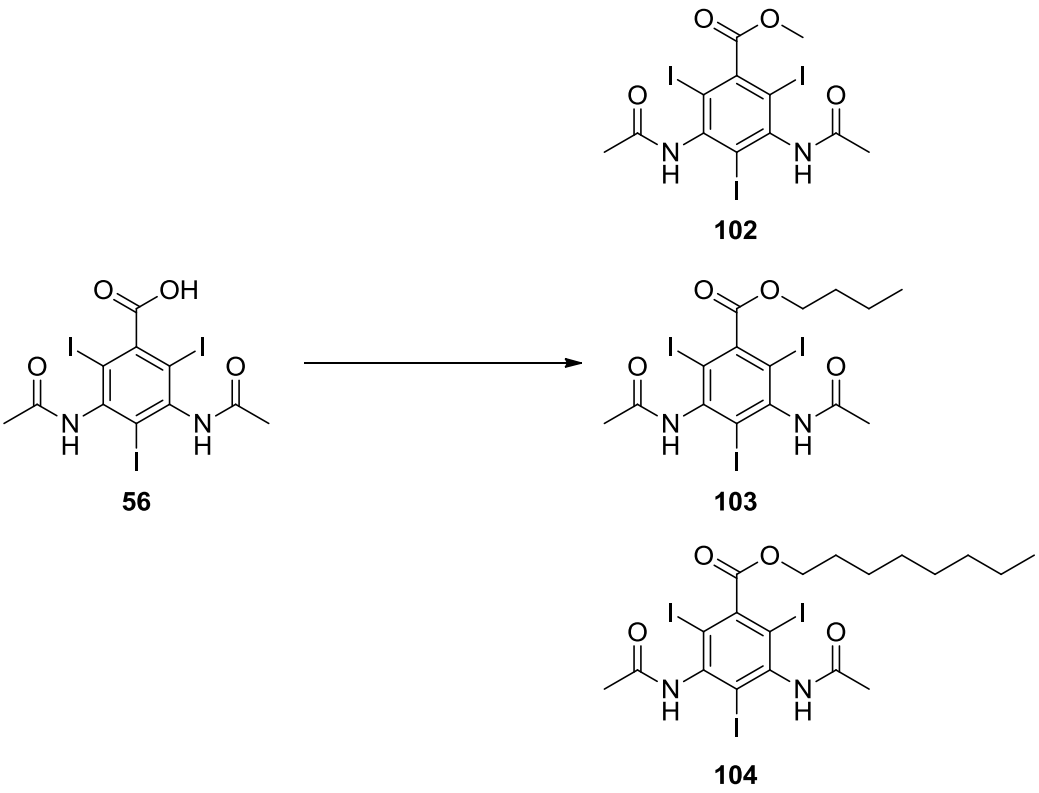
2.2 Chemical Protection of Contrast Agents 55, 56 and 58

*Aim: Protecting groups will be added to the free hydroxyl groups and the carboxylate group on the above X-ray contrast agents **55**, **56**, **58** in order to try and make them more hydrophobic and soluble in cyanoacrylate.*

2.2.1 Modification of diatrizoic acid 56

Diatrizoic acid **56** is the simplest of the above examples. The obvious choice for protection is the carboxyl acid functional group. As it has only one CO_2H group which was to be protected larger organic groups, *i.e.* long chains could be used as the effect on the 'iodine concentration' will be less than for the larger agents **55** and **58** with multiple hydroxyl groups. However the carboxylic acid to be protected is sterically hindered and therefore attaching bulky groups may be difficult. A series of

n-alkyl groups with increasing chain length were synthesised by conversion of the carboxylic acid **56** to the acid chloride which was further reacted with alcohols *in situ* to give the esters **102-104** (Scheme 2.2).



Scheme 2.2: Synthesis of diatrizoic acid ester series. *Reagents and Conditions*: i) diatrizoic acid (1 eq.), thionyl chloride (5 eq.), reflux, 6 h ii) ROH, pyridine (1.1 eq.), reflux, 36 h, **102** 2%, **103** 4%, **104** 2%.

The reactions were low yielding and the resulting products were still insoluble in most organic solvents. However mass spectroscopy of the crude reactions showed the relevant mass peaks (Figure 2.4, 2.5 and 2.6).

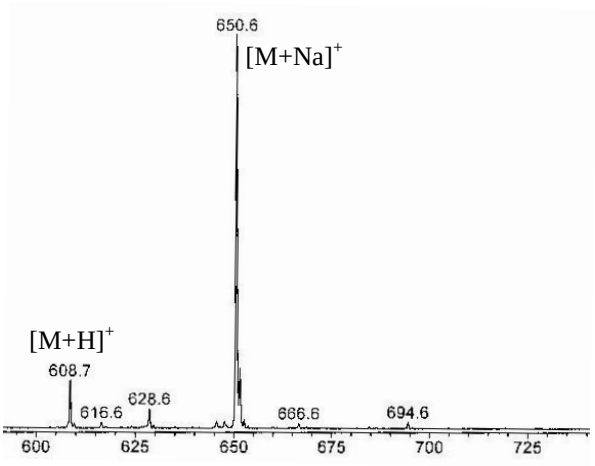


Figure 2.4: Crude mass spectroscopy of methyl 3,5-diacetamido-2,4,6-triiodobenzoate 102

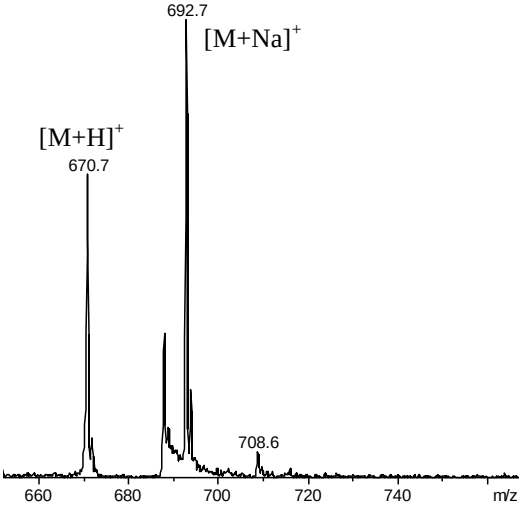


Figure 2.5: Crude mass spectroscopy of butyl 3,5-diacetamido-2,4,6-triiodobenzoate 103

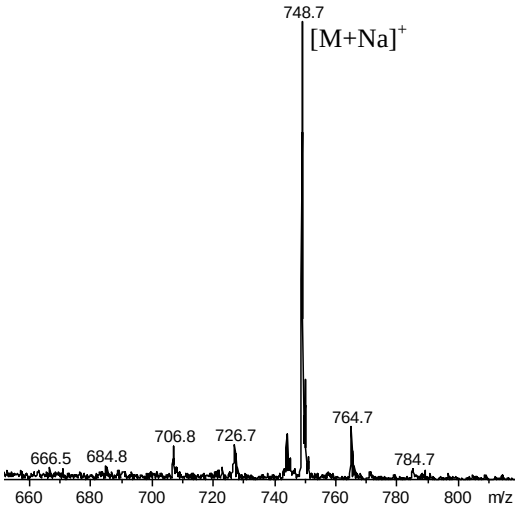
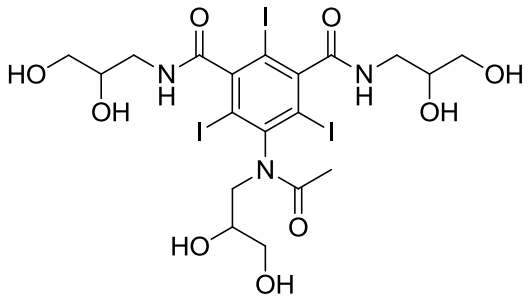


Figure 2.6: Crude mass spectroscopy of octyl 3,5-diacetamido-2,4,6-triiodobenzoate 104

Despite low yields and little solubility in organic solvents esters **102**, **103** and **104** were purified and tested for solubility in ethyl cyanoacrylate **37**. They displayed no solubility, therefore demonstrating that increasing the chain length had little effect. Hence it was concluded that diatrizoic acid **56** wasn't a suitable contrast agent to be incorporated into cyanoacrylates, and therefore the reactions were not optimised in order to improve the yields.

2.2.2 Modification of iohexol 55

Iohexol **55** (Figure 2.7) was considered a better candidate for incorporation into the adhesive as it has six hydroxyl groups, all of which can be protected to increase solubility in an organic medium. A range of different common alcohol protecting groups were studied (e.g. acetate, allyl, and acetonide.). Analysis of the reactions was difficult, due to the possibility of obtaining a mixture of mono-, di-, tri-, tetra-, penta- and hexa-protected products. In addition each product contained a mixture of diastereoisomers and the restricted rotation around the N-Ar and the N-CO bonds led to broadening of the peaks in the ^{1}H NMR, making them difficult to interpret. As a consequence we used mass spectrometry to monitor the progress of these reactions.



55

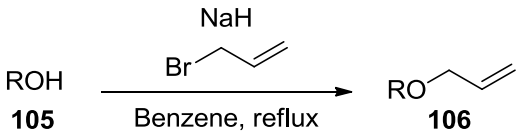
Figure 2.7: Contrast agent iohexol 55

The first issue to overcome was the limited solubility of iohexol **55** in the most common organic solvents. A quick investigation revealed useful solubility in methanol, DMF, pyridine and DMSO.

2.2.2.1 Hydroxyl protecting groups

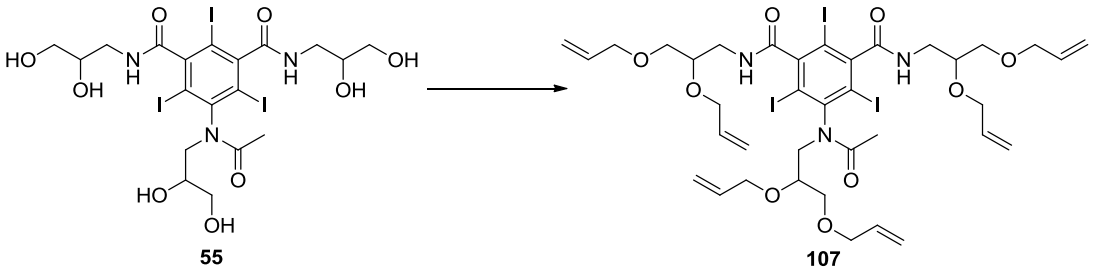
Allyl:

Allyl protection of alcohols is common in carbohydrate chemistry as allyl ethers are often compatible with the various methods for glycoside formation.[175] The fact that hydrophilic carbohydrates often have multiple alcohol functional groups to be protected (like iohexol **55**) suggested this was a useful protecting group to study. There are several methods for addition of this group, for example refluxing the alcohol with allyl bromide and a base[176] (Scheme 2.3).



Scheme 2.3: General method for allyl protection

Iohexol **55** was reacted with allyl bromide and NaOH in DMF[177] to give the hexa-allyl protected product **107** (Scheme 2.4).



Scheme 2.4: Attempted allyl protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), allyl bromide (7.5 eq.), NaOH (10 eq.), DMF, 50 ^{o}C, 24 h, 65% crude.

The crude ^{1}H NMR of **107** was difficult to interpret, because of the mix of protected products there were a large number of broad and overlapping peaks (Figure 2.8). Mass spectroscopy revealed peaks for penta- (**A)** and hexa-allyl **(B)** products, however peaks were also observed for the hepta- **(C)** and octa-allyl **(D)** compounds. Suggesting the two secondary amides had also reacted with the allyl bromide under the reaction conditions (Figure 2.9).

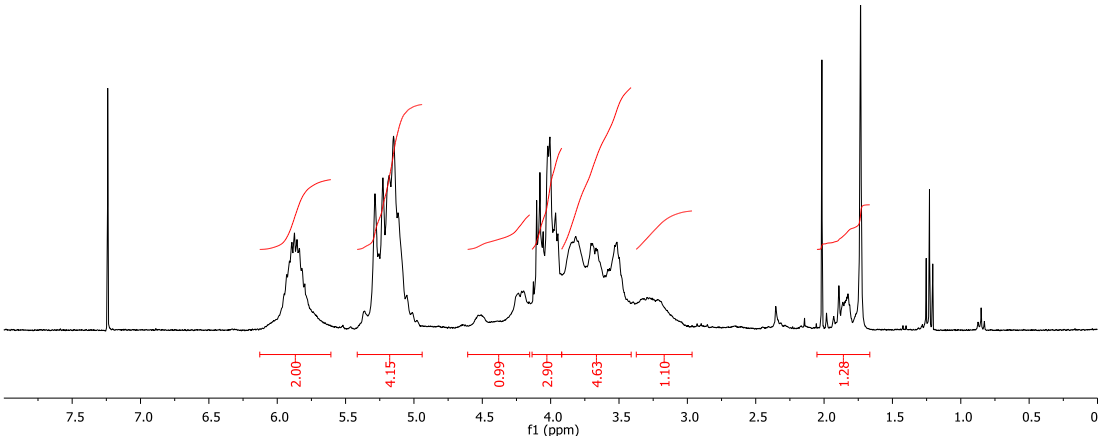


Figure 2.8: ^{1}H NMR of attempted allyl protection of iohexol 107

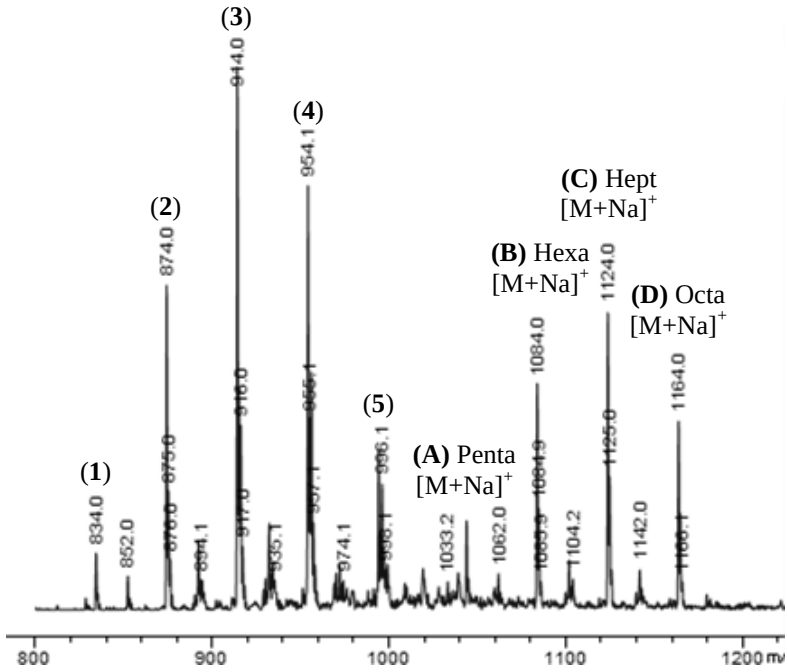
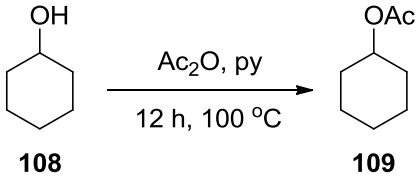


Figure 2.9: Mass spectrometry of crude allyl protection of iohexol 107

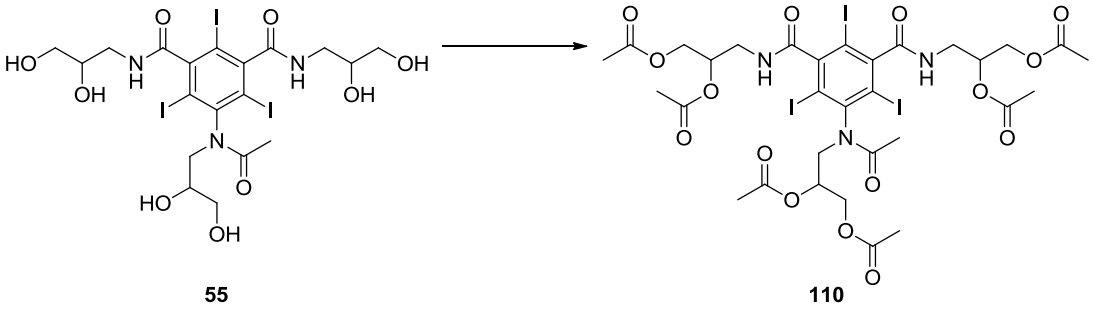
The penta-, hexa-, hepta- and octa-allyl peaks **(A-D)** give sequence with a repeating unit of 40 which corresponds to the addition of an allyl group. Another set of peaks with the same repeating unit of 40 was observed between 834 and 994 (labelled **1-5**). However the difference between the penta-allyl peak **(A)** and the last peak in this second series **(5)** is 50, suggesting they are two separate sequences. The mass peaks correspond to a loss of the *N*-acetyl group as well as a single iodine atom for each of the penta-octa allyl compounds (**A**-**D**) ($M+Na^+ -C_2H_3OI$). It was not possible to separate the mixture of allylated products by column chromatography; therefore the desired hexa-allyl product **107 (B)** was not isolated. Despite problems with purification the solubility of the crude mixture as a whole was tested in ethyl cyanoacrylate **37**. The mixture showed no solubility in ethyl cyanoacrylate **37** and therefore the allyl product was discounted without further optimisation.

Acetate:

The acetate protecting group seemed to be a viable candidate for the modification of iohexol **55** as it wouldn't significantly increase the molecular weight and therefore affect the contrast (by lowering the weight % of iodine in the compound significantly). Also hydrolysis of the acetate group under physiological conditions would release iohexol **55** and acetic acid, which the body can process without adverse effects. One of the most common methods for acetate introduction is reaction of acetic anhydride under basic conditions[178] (Scheme 2.5). As pyridine was found to be a suitable solvent for the dissolution of iohexol **55** we attempted reaction with acetic anhydride in pyridine[179] (Scheme 2.6).



Scheme 2.5: Acetate protection of cyclohexanol



Scheme 2.6: Acetate protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), acetic anhydride (8 eq.), pyridine, 50 °C, 48 h, 61%.

Following the reaction by mass spectrometry showed the fully acetate protected product **110** was formed (Figure 2.10).

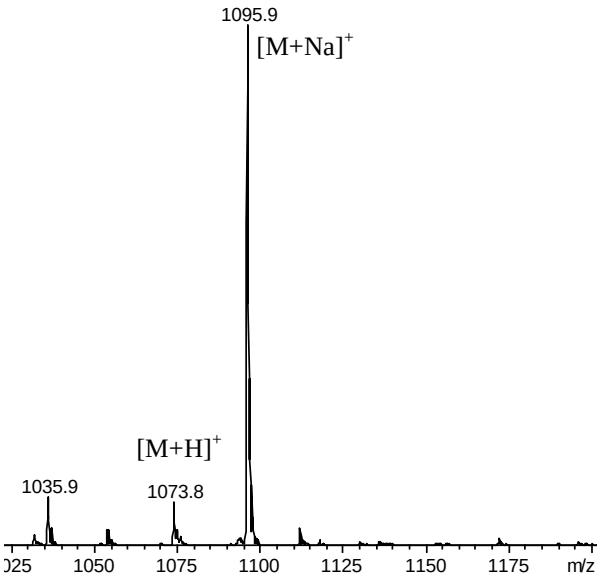
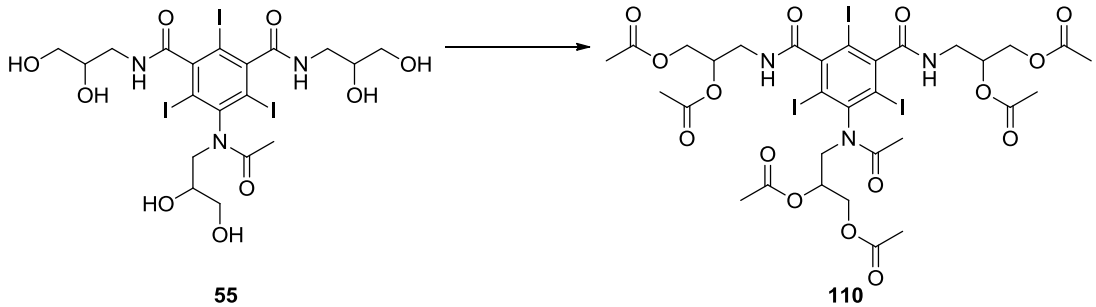


Figure 2.10: Mass spectrometry of hexa-acetate protected iohexol 110

The crude product was purified by column chromatography and the resultant white solid was tested for solubility in ethyl cyanoacrylate **37**. The product displayed approx. 15% solubility, however it also caused polymerisation of the ethyl cyanoacrylate **37** over a period of minutes. Polymerisation occurs in the presence of nucleophiles (e.g. water, alcohols) and nucleophilic bases (e.g. pyridine).[48] This suggested that basic/nucleophilic residues were left over from the protection reaction despite purification. Immediate polymerisation is not suitable for this product as it allows no application time. The contrast agent needs to be incorporated in the cyanoacrylate but without changing the properties of the adhesive. Thus it was concluded an alternative approach to make **110** using acidic conditions instead of basic conditions and lower temperatures would be more appropriate. The allyl-protected product **107** also caused the cyanoacrylate to polymerise, however since the product displayed no solubility in ethyl cyanoacrylate **37** it was ruled out without exploring alternative non-basic methods.

Iohexol **55** was combined with iodine[180,181] in acetic anhydride to form a paste, no solvent was added and the reaction mixture was stirred at r.t. for 5 days[182] (Scheme 2.7).



Scheme 2.7: Acetate protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), iodine (0.1 eq.), acetic anhydride (8 eq.), r.t., 5 days, 40%.

As the acetate groups start to add to the starting material it becomes more soluble and thus more reactive. After several days mass spectrometry showed the hexa-acetate product **110** [I_2] (Figure 2.11).

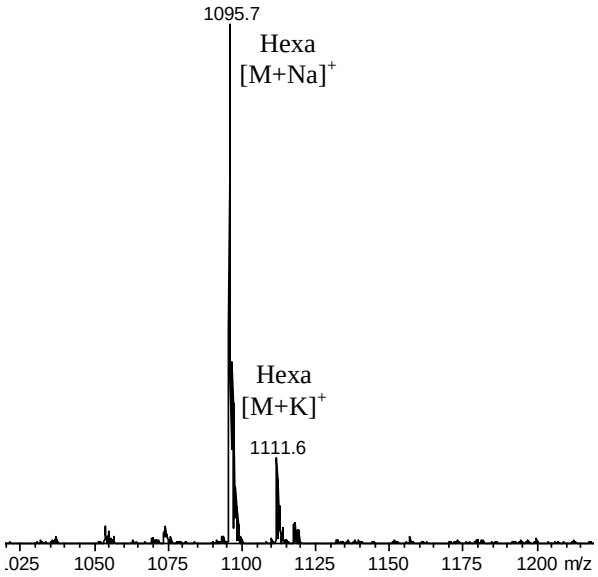


Figure 2.11: Mass spectrometry of acetate protected product 110 [I_2] *via* non-basic route

The acetate protected product **110** [I_2] showed 15% solubility in cyanoacrylate adhesive and unlike **110** [py] rapid polymerisation did not occur upon addition.

2.2.2.2 Stability of 110 [I_2] at pH 4, 7 and 10

In order to assess the stability of the acetate product **110** [I_2] in aqueous solution and to determine how it decomposes the reactions were monitored by mass spectrometry for a number of weeks. Neutral (pH 7), acidic (pH 4) and basic (pH 10) buffer solutions were used to see how the different conditions affect how **110** [I_2] hydrolyses.

pH 7:

The acetate product **110** [I_2] was combined with pH 7 buffer solution and a sample submitted for mass spectrometry within 1-2 hours. This showed mass peaks for the

hexa-, penta- and tetra-protected products (Figure 2.12), indicating a relative quick hydrolysis of the first two acetates. Interestingly, little further hydrolysis occurred over the next week.

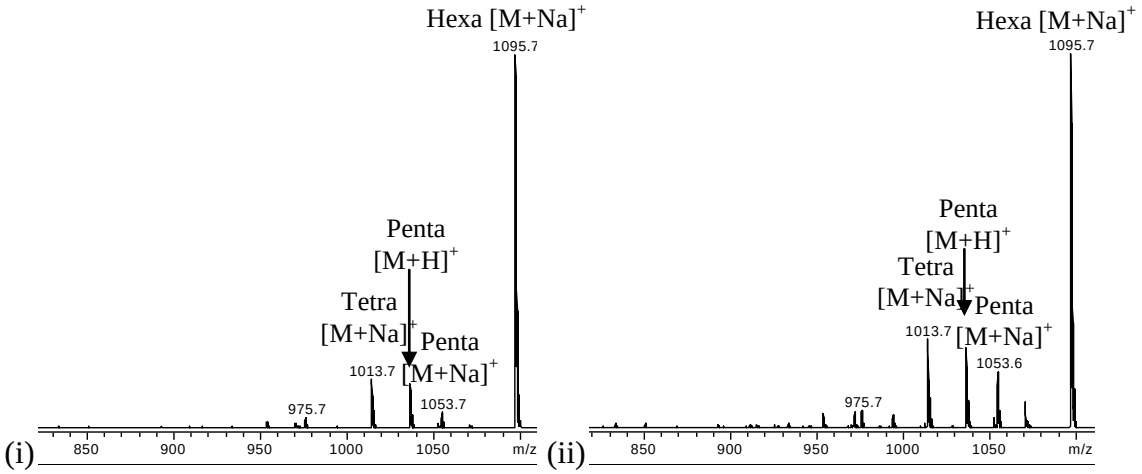


Figure 2.12: pH 7 buffer and acetate product 110 [I_2], (i) initial conditions, (ii) 1 week

The solution was monitored by mass spectroscopy for three weeks in total (Figures 2.13 and 2.14). After three weeks the number of mass peaks significantly increased and with peaks for the partially de-protected products, indicating that **110** [I_2] is broken down as expected by hydrolysis of the acetate groups particularly slowly.

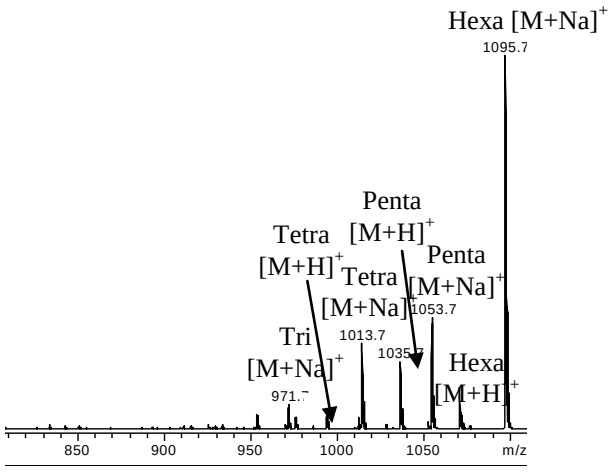


Figure 2.13: pH 7 buffer and acetate product 110 [I_2], 2 weeks

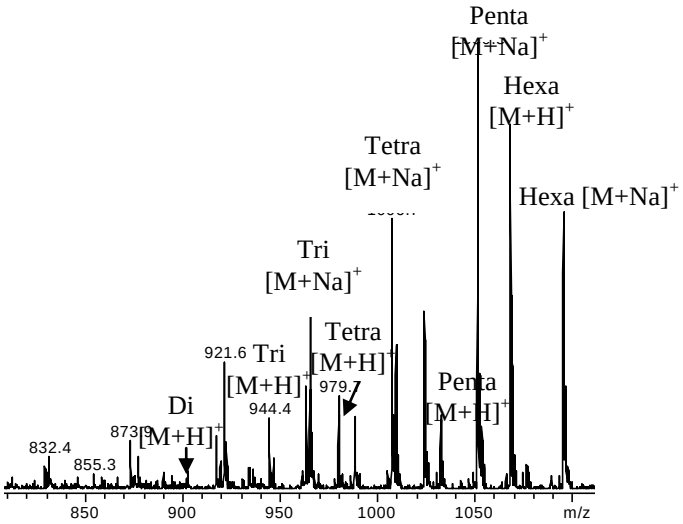


Figure 2.14: pH 7 buffer and acetate product 110 [I_2], 3 weeks

pH 10:

At pH 10 **110** [I_2] appears to be behave in a similar manner to the neutral solution. Comparison of the mass spectrometry shows an increase of mass peaks from initial conditions (Figure 2.15) to three weeks (Figure 2.16) as with pH 7. The mass spectrometry also shows the same peak pattern as the acetate groups are hydrolysed, suggesting **110** [I_2] is broken down in the same way.

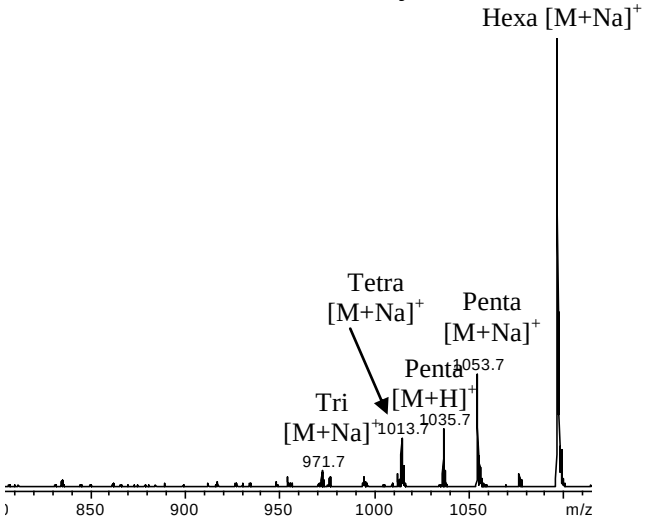


Figure 2.15: pH 10 buffer and acetate product 110 [I_2], initial conditions

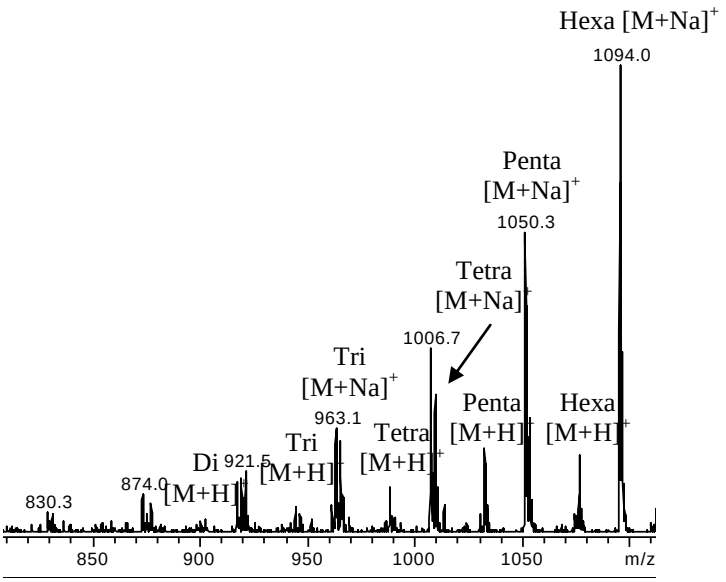


Figure 2.16: pH 10 buffer and acetate product 110 [I_2], 3 weeks

pH 4:

Under acidic conditions **110** [I_2] exhibits a somewhat different pattern. The hydrolysis appears to be relatively slow and even after three weeks the major hydrolysis product is only the penta-product with further hydrolysis products being minor components (Figures 2.17 and 2.18).

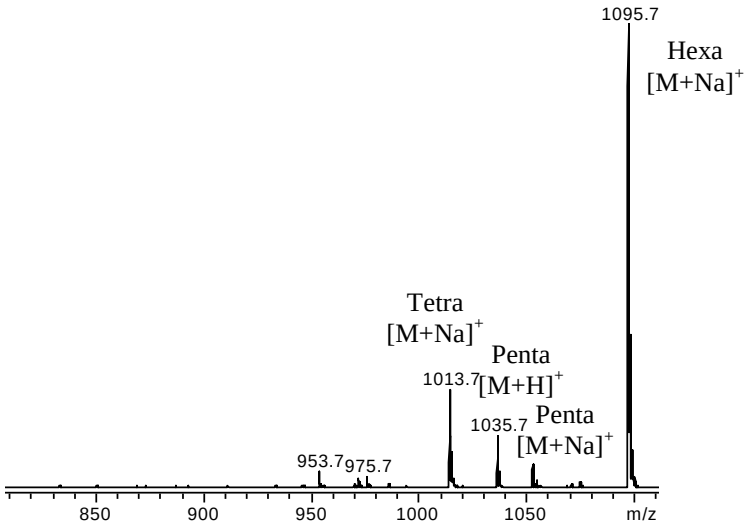


Figure 2.17: pH 4 buffer and acetate product 110 [I_2], initial conditions

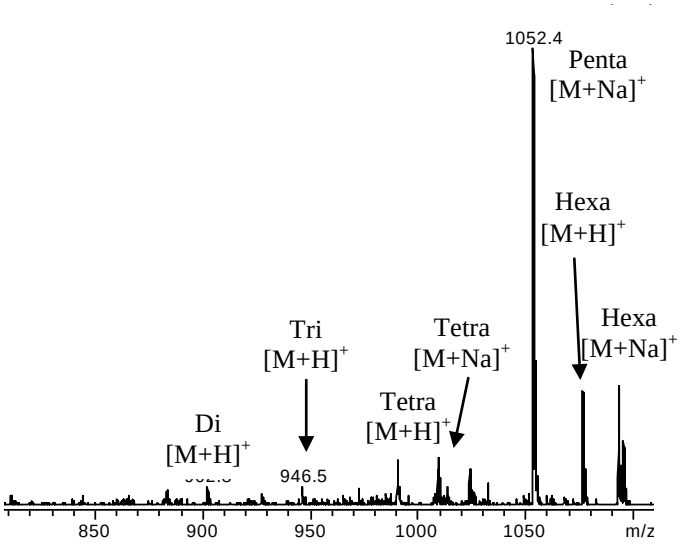
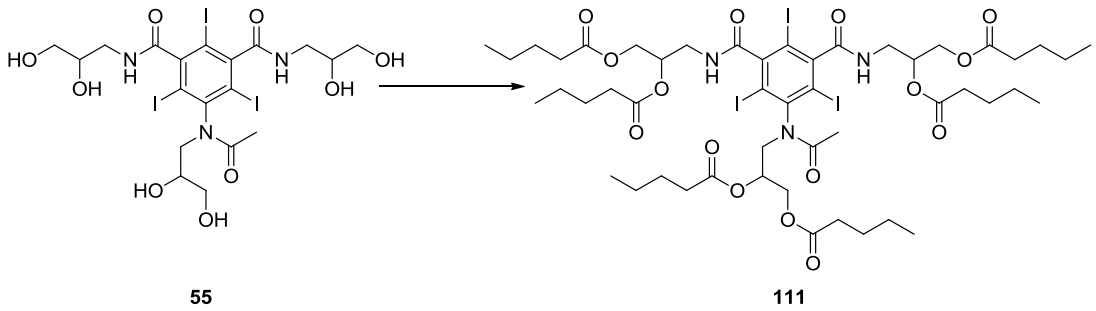


Figure 2.18: pH 4 buffer and acetate product 110 [I_2], 3 weeks

In conclusion the pH tests suggest that **110** [I_2] will break down in the body as expected, releasing by-products from iohexol **55** and acetic acid. Therefore given this and its solubility in ethyl cyanoacrylate **37** the acetate protected product **110** [I_2] is a viable candidate for incorporation into the adhesive for use within the body.

2.2.2.3 Affect of increasing the ester chain length

The incorporation of acetate groups increased the solubility of iohexol **55** in ethyl cyanoacrylate **37** by 15%. Would increasing the chain length increase the solubility further? Iohexol **55** was reacted with pentanoic anhydride under the same conditions to give **111** in 14% yield (Scheme 2.8). The pentanoate product **111** also shows some solubility in ethyl cyanoacrylate **37**; however this was less than 10%. Despite the larger protecting groups **111** showed less solubility than the acetate product **110**.



55 111

Scheme 2.8: Pentanoic acetate protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), iodine (0.1 eq.), pentanoic anhydride (8 eq.), r.t., 6 days, 14%.

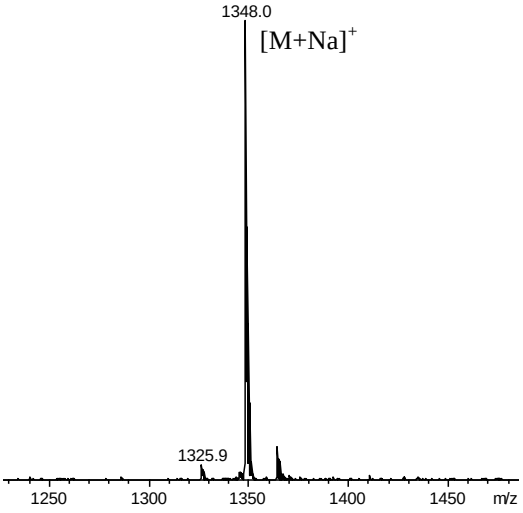


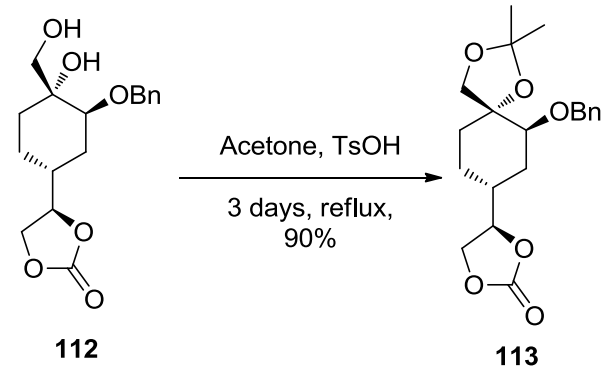
Figure 2.19: Mass spectrometry of pentanoic anhydride protected product 111

Increasing the number of carbons of the protecting groups did not further increase the solubility in ethyl cyanoacrylate **37**. Therefore despite both protected products **110** and **111** showing solubility it is the acetate protected product **110** that is the most suitable.

2.2.2.4 Acetonides as 1,2-diol protecting groups

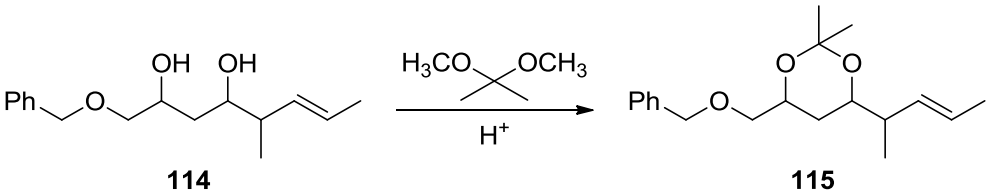
Due to the abundance of 1,2-diol functionality in natural products there are a number of 1,2- and 1,3- diol protecting groups. Acetonide protection is the most common form of 1,2- and 1,3-diol protection, and has been extensively used in carbohydrate

chemistry.[183] Acetone can be used under acidic conditions to form the acetonide group[184] (Scheme 2.9).



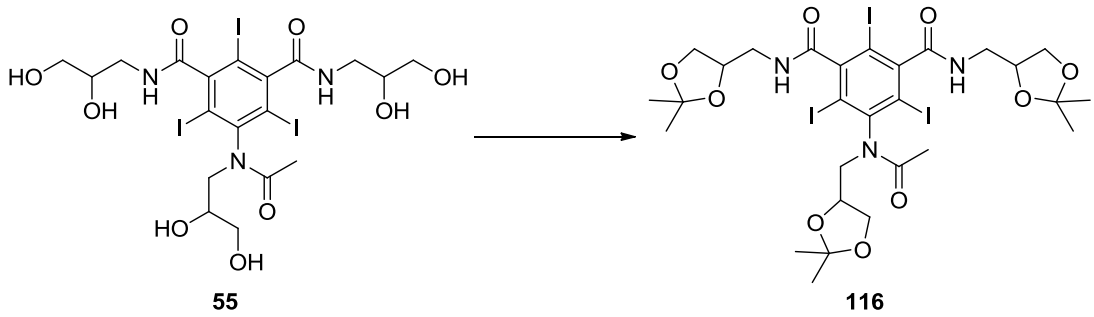
Scheme 2.9: Acetonide protection using acetone and TsOH

Dimethoxypropane can also be used under similar conditions to give the acetonide product,[185,186] (Scheme 2.10).



Scheme 2.10: Acetonide protection using dimethoxypropane

Iohexol **55** has three 1,2-diol systems, meaning diol protecting groups could be good targets. The advantage to this is the reduced number of possible protection products compared to hydroxyl protection (mono-, di- and tri-protected verses mono- to hexa protected). Experience from the previous protections indicated that picking reactions that occur under acidic conditions was preferred. Acetonide protection was undertaken using acetone and $CuSO_4/H^+$ (scheme 2.11).[187]



55 **116**

Scheme 2.11: Acetonide protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), acetone, $CuSO_4.5H_2O$ (2 eq.), TsOH (0.2 eq.), 50 ^oC, 48 h, 57%.

This resulted in a crude yellow solid which by mass spectroscopy was shown to contain S.M. as well as mono- **116a**, di- **116b** and tri-protected product **117c** (Figure 2.20).

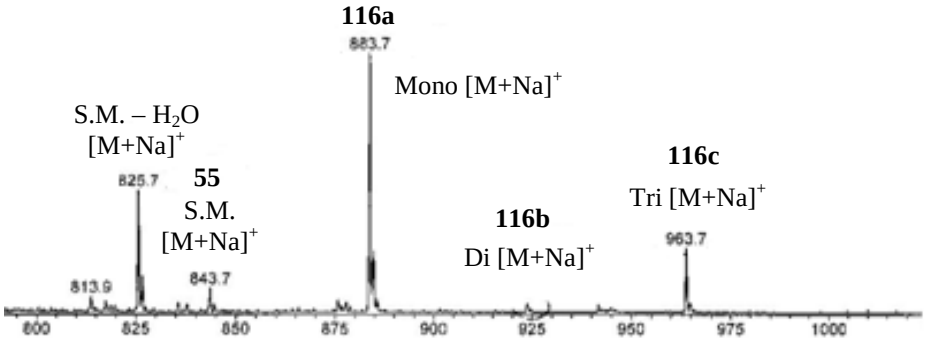


Figure 2.20: Crude mass spectrometry of acetonide protected iohexol 55

It was unclear how stable the protected products **116a-c** would be upon chromatography, so initially the product was purified by rapidly flushing through a plug of silica eluting with EtOAc. However this only removed the remaining S.M., leaving the mixture of products **116a**, **116b** and **116c**. Before effort was expended in finding appropriate purification protocols it was necessary to briefly explore whether the acetonide product **116c** was a viable candidate, thus the mixture was tested for solubility in ethyl cyanoacrylate **37**. The mixture of **116a**, **116b** and **116c** showed approximately 10% solubility in the adhesive and didn't cause rapid polymerisation.

This indicated that the presence of unreacted free hydroxyls are not themselves problematic in incorporation into cyanoacrylate and are not responsible for the polymerisation observed in **107**. The reaction was repeated on a larger scale (> 5 g), this time adding molecular sieves to the mixture in order to try and push the equilibrium towards product and increase the yield. In addition the $CuSO_4.5H_2O$ used was dried in a vacuum oven for 24 hrs at 60 ^oC to render it anhydrous, and the acetone solvent was dried over molecular sieves. This time no peak for S.M. **55** was observed in the mass spectroscopy (Figure 2.21). Interestingly, very little di-protection **116b** was indicated in either of the two mass spectras Figure 2.20 and Figure 2.21. While mass spectrometry is not quantitative the relative low abundance of the molecular ion for this product was puzzling.

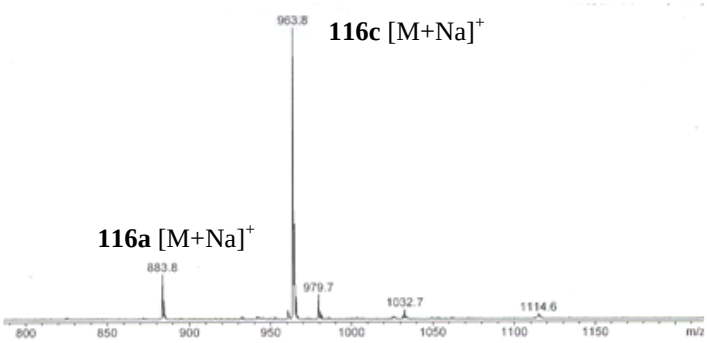


Figure 2.21: Crude mass spectroscopy for acetonide protected iohexol 55

Initial purification by flushing **116** through a silica plug suggested that **116** was stable to chromatography. Thus, **116** was purified by 'normal' flash column chromatography in order to attempt to isolate **116c** only. The main component from the column was analysed by LCMS, the UV trace showed one peak, suggesting only one product (Figure 2.22). However the mass spectrometry shows peaks for **116a** (mono-) and **116c** (tri-) for the LC peak at 11.2-12.0 minutes.

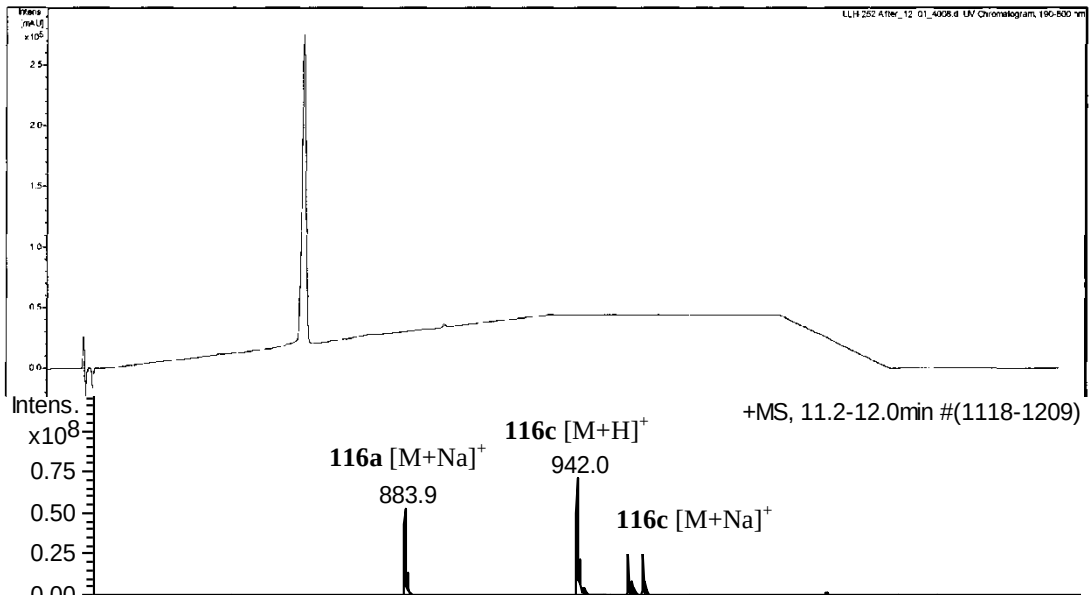
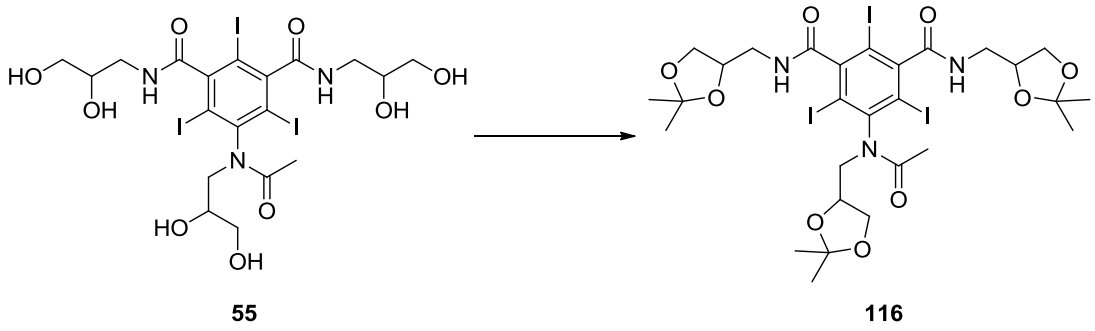


Figure 2.22: LCMS of purified acetonide protected iohexol 55

The purified product mixture was re-tested for solubility in ethyl cyanoacrylate **37**; it still displayed reasonable solubility, approx. 10%. Due to the mixture of compounds and the inability to separate them on chromatography, alternative methods of making **116** were investigated. An alternative route was tried using 2,2-dimethoxypropane,[185,186] and this gave the desired product **116** in 85% yield (Scheme 2.12). The reaction was run in DMF as solvent (as opposed to acetone) and the increased solubility of **116** under these reaction conditions furnished the reaction in only 24 hrs at r.t. (compared to 48 hours).



55 **116**

Scheme 2.12: Alternate acetonide protection of iohexol 55. *Reagents and Conditions*: iohexol (1 eq.), 2,2-dimethoxypropane (4 eq.), TsOH (0.1 eq.), DMF, r.t. 24 h, 85%.

The product was once again purified by column chromatography to give a white powder and as before the LCMS showed one peak on the UV trace (Figure 2.23) corresponding to the same peak observed from the previous reaction (Figure 2.22).

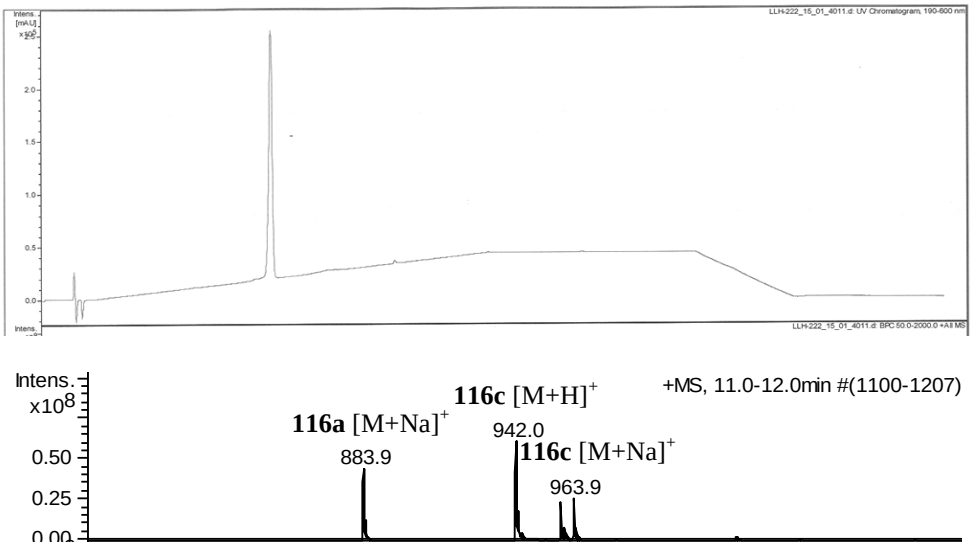


Figure 2.23: LCMS of purified acetonide protected iohexol 55 *via* alternative route

However once again the single peak in the UV showed molecular ions for both the **116a** (mono-) and **116c** (tri-) product in the mass spectra. This suggests one of two things; either that **116c** is breaking down to **116a** in the mass spectrometer. However this seems unlikely as electrospray ionisation was used which should prevent molecule fragmentation and one might also expect to see peaks for di-protection **116b**. Thus, it would appear that the traces from **116a** and **116c** are coalescing, which is why the UV shows only one peak. However, this too is unusual as it suggests that's very little di-protected compound **116b** is formed. This may be due to the increased solubility of the di-protected compound **116b** (relative to **116a**) under the reaction conditions, meaning that it rapidly reacts to tri-protect **116c** as soon as it is formed from the less soluble **116a**.

As before the product **116** was tested for solubility in ethyl cyanoacrylate **37**; however instead of 10% solubility as previously displayed for **116** ($CuSO_4$) this compound **116** (TsOH) did not dissolve but formed an emulsion. This behaviour was unexpected. The two products **116** ($CuSO_4$) and **116** (TsOH) were made *via* two different routes but the ^{1}H and ^{13}C NMR, mass spectroscopy and IR spectra appear identical. However because they behave very differently in ethyl cyanoacrylate there must be a difference-perhaps in morphology or minor contaminants. Elemental analysis showed both compounds to be authentic samples and equal in purity, (Table 2.1).

	Theory	Route A	Route B
C	35.7	35.4	35.3
H	4.1	4.0	4.0
N	4.5	4.3	4.4

Table 2.1: Elemental analysis of 116 from route A and B

Route A uses $CuSO_4$ in the reaction; if residual amounts of copper were still present in the product **116** ($CuSO_4$) they could be responsible for the solubility difference by initiating differing morphology. Therefore both samples were analysed for copper by ICP-MS. Analysis on the samples was carried out using an Aglient 7500cx ICP-MS. External single element calibrants and internal standards were used during the analysis which determined that any copper present was below the detection limit of the instrument (sub-ppb) for both samples. Thus copper contaminants are unlikely to be the reason for differential properties of the two compounds **116** ($CuSO_4$) and **116** (TsOH).

2.2.2.5 Thermal analysis of ethyl cyanoacrylate polymers with inclusion of 116 ($CuSO_4$) and 116 (TsOH) at varying levels

As the target protected contrast agent **116** is to be incorporated into the ethyl cyanoacrylate adhesive monomer it was important to determine how varying levels of incorporation of compound **116** would affect the properties of the polymer produced. If the properties were widely different to the parent ethyl cyanoacrylate polymer then they might not be useful for *in vivo* applications. We chose to investigate the thermal properties of the polymers, not because the polymers would be exposed to extreme temperature changes in the body but because analysis would allow differences in decomposition (and hence structural effects) to be easily determined. Thermal analysis is when the properties of materials are studied as they change with temperature. There are several different methods; in this case Thermogravimetric analysis (TGA) and Differential scanning calorimetry (DSC) were used. TGA measures the change in % mass as the material is heated to high temperatures, in this case 600^{o}C. DSC measures the heat flow as the material undergoes various phase transitions, *i.e.* melting point and glass transition.

Poly ethyl cyanoacrylate is known to decompose *via* depolymerisation[188] or by decomposition with loss of HCN[189] at temperatures between 180-260 ˚C. The TGA of poly ethyl cyanoacrylate shows this decomposition pathway as expected[43] (Figure 2.24). Next we compared the TGA of the two modified contrast agents **116** ($CuSO_4$) and **116** (TsOH) (Figure 2.24). Both modified contrast agents exhibited the same decomposition pathway (within experimental error). They both have a sharp degradation curve at just over 300^{o}C and then both slowly tail off. This shows that despite the differences in solubility, the thermal properties of the material are the

same. Initial decomposition leads to loss of about 60% weight, followed by two other decomposition pathways at higher temperature, the second occurring between 300-500 ˚C (leading to a further 20% loss) and the final pathway slowly causing decomposition above 500 ˚C. It is likely that loss of iodine and deprotection occurs first (equating to the 60% weight loss).

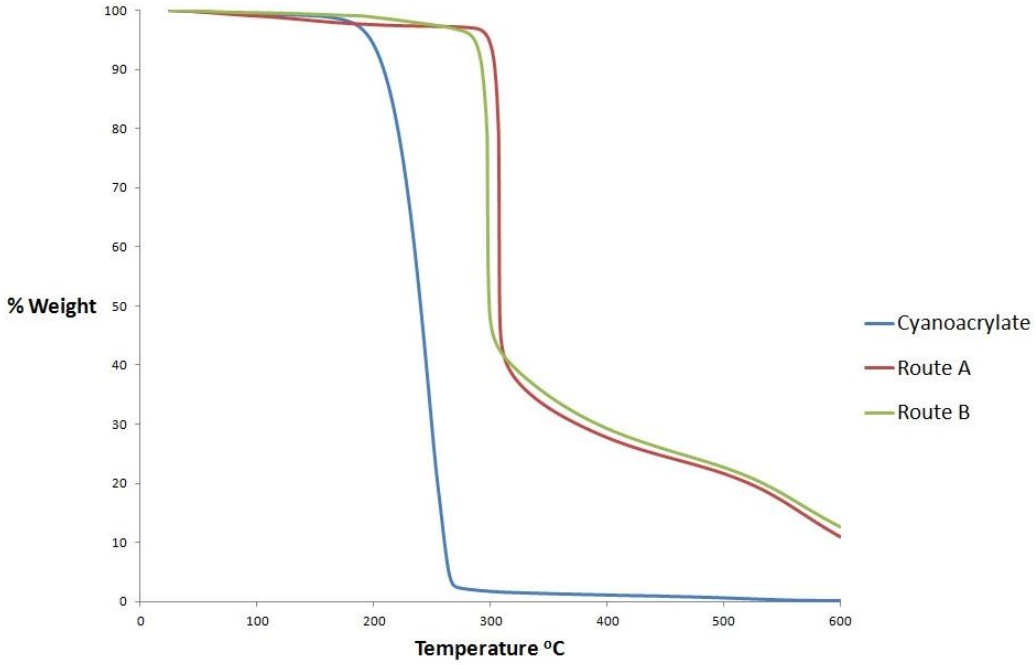


Figure 2.24: TGA of cyanoacrylate and 116 from route A and B

Despite **116** (TsOH) from route B not dissolving in ethyl cyanoacrylate **37** it did form a gel like emulsion which showed similar stability in the monomer to that of **116** ($CuSO_4$) from route A. Therefore both compounds were incorporated in the ethyl cyanoacrylate monomer **37** and the after polymerisation analysed by TGA. Two different loadings of **116** ($CuSO_4$) and **116** (TsOH) in the adhesive (5% and 20% w/w) were investigated (Figure 2.25). Unsurprisingly the major decomposition resembles that of the polymer. For the two 20% w/w samples decomposition starts about 10 ˚C earlier indicating higher % incorporations are affecting the materials properties.

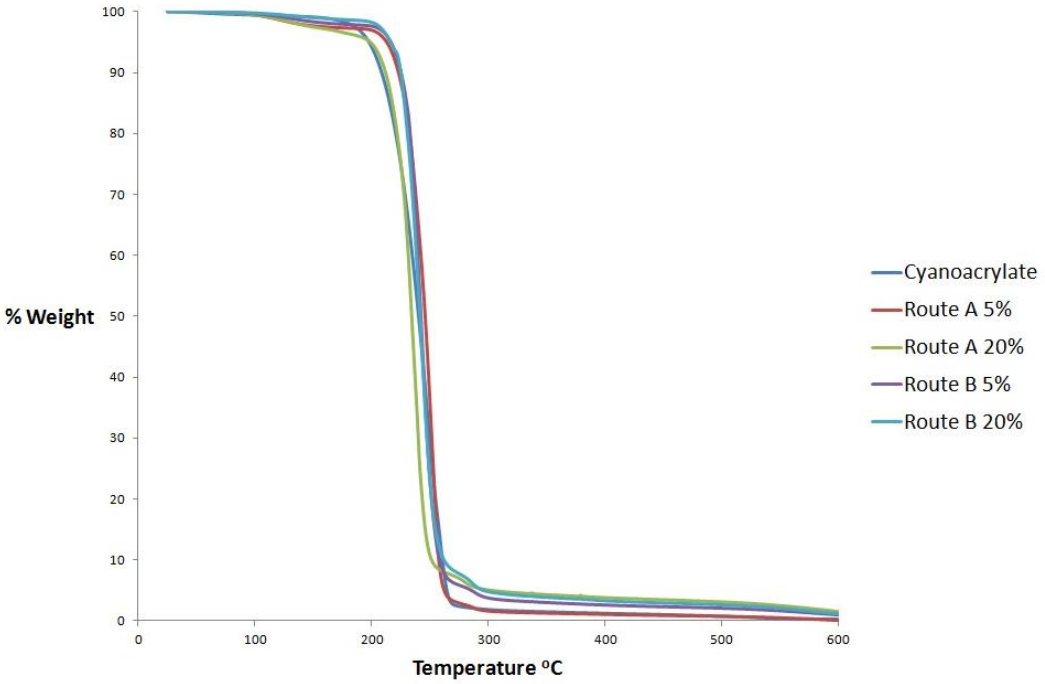


Figure 2.25: TGA of cyanoacrylate combined with 116 from route A and B

The TGA also shows that once incorporated in the cyanoacrylate adhesive whether the contrast agent has dissolved **116** ($CuSO_4$) or formed an emulsion **116** (TsOH) makes little difference. A minor second decomposition pathway at 260 ˚C (from the contrast agent) can be seen. The DSC further backs this up, by displaying very similar results for all combinations (Figure 2.26).

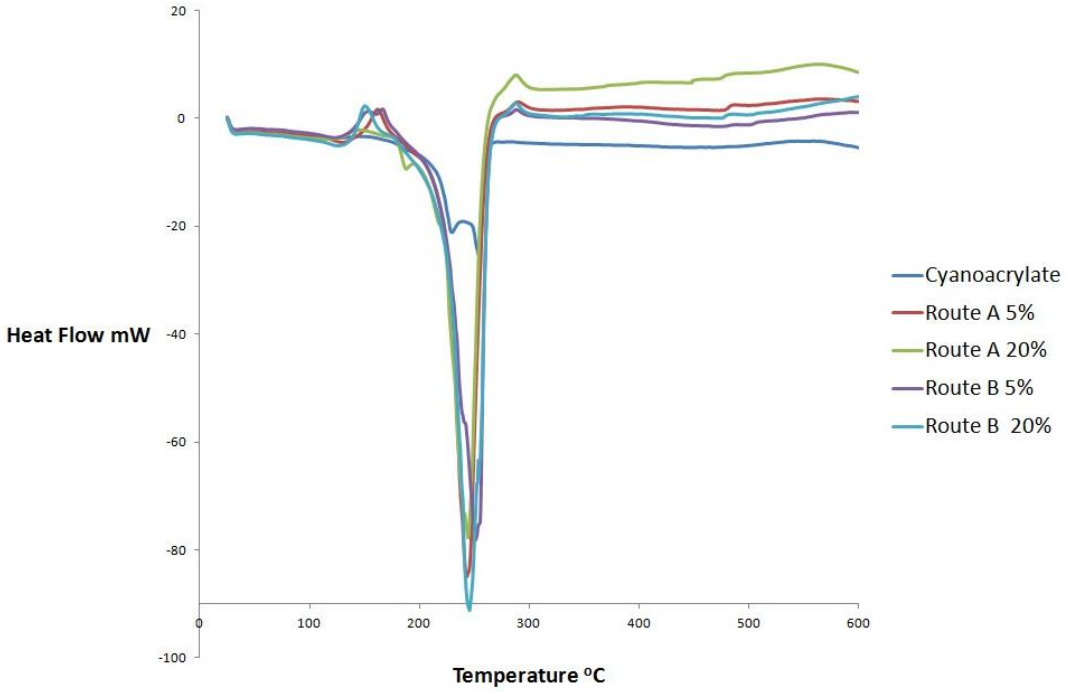


Figure 2.26: DSC of cyanoacrylate combined with 116 from route A and B

2.2.2.6 Variable temperature ^{1}H NMR of 116

The iohexol protected products **116** (TsOH) and **116** ($CuSO_4$) were difficult to analyse by ^{1}H NMR as in addition to a number of diastereomers the spectra were complicated by the slow rotation around the amide bonds and the potential atropoisomeric nature of the C-N bond in the anilide (due to the large iodine substituents). Variable temperature NMR is often used for similar compounds, by changing the temperature peaks can shift, sharpen, broaden and coalesce.[190] Variable temperature is often used to calculate the barrier to rotation about a bond. High barriers to rotation can lead to the existence of two separate rotamers, particularly at low temperatures. This can then lead to two sets of peaks in the ^{1}H NMR. As you heat up the sample you observe coalescence of these peaks to give one set of signals at high temperature. Using line shape analysis the rate of coalescence of the two sets of peaks can be measured allowing the barrier to rotation to be calculated. However

if the barrier is too high it can't be calculated by this method because coalescence is not observed at temperatures accessible for ^{1}H NMR experiments.

The two acetonide products **116** ($CuSO_4$) and **116** (TsOH) from routes A and B were analysed using variable temperature ^{1}H NMR in d_6-DMSO in an attempt to simplify the spectra and aid interpretation. Heating up the samples from r.t. to 100 ^{o}C caused the amide NH peaks to broaden and coalesce, and the peaks at 3.25-3.50 ppm to broaden, but no simplification of the spectra was observed. Both products behaved in the same way (only the spectra for **116** ($CuSO_4$) are shown Figure 2.27). Attempts to cool down the samples dissolved in $CDCl_3$ (r.t. to -59 ^{o}C) also led to unhelpful broadening for both samples (Figure 2.28). No useful information on barriers to rotation or significant simplifying of the spectra was observed.

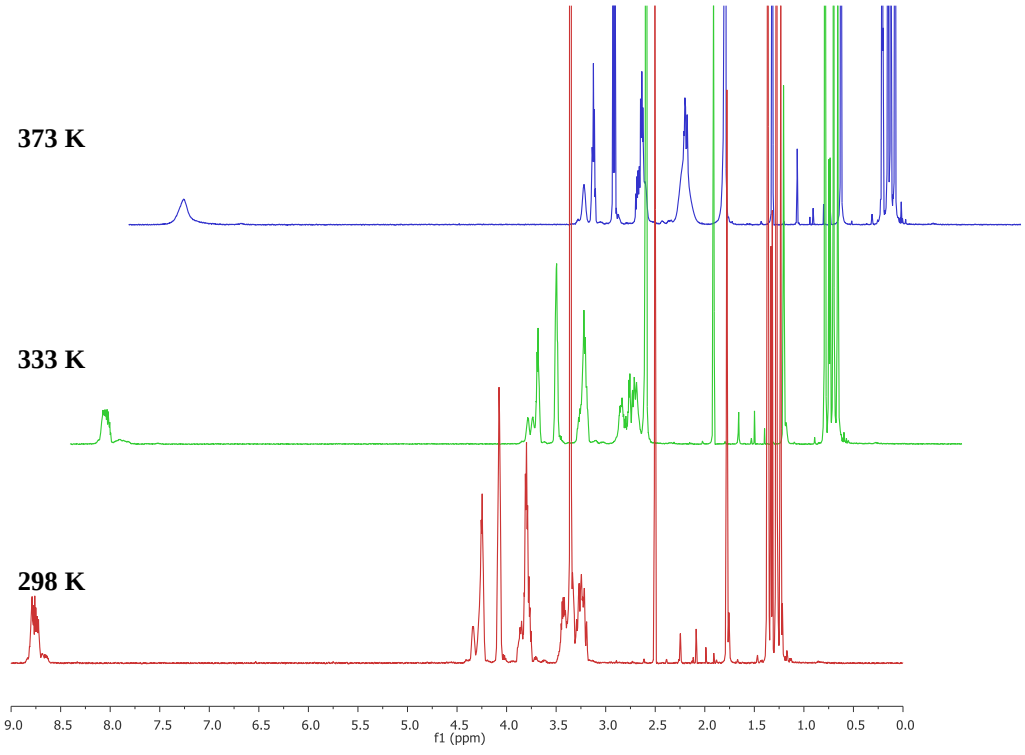


Figure 2.27: VT ^{1}H NMR of 116 ($CuSO_4$) from route A, 298 K – 373 K. The spectra for 116 (TsOH) were identical

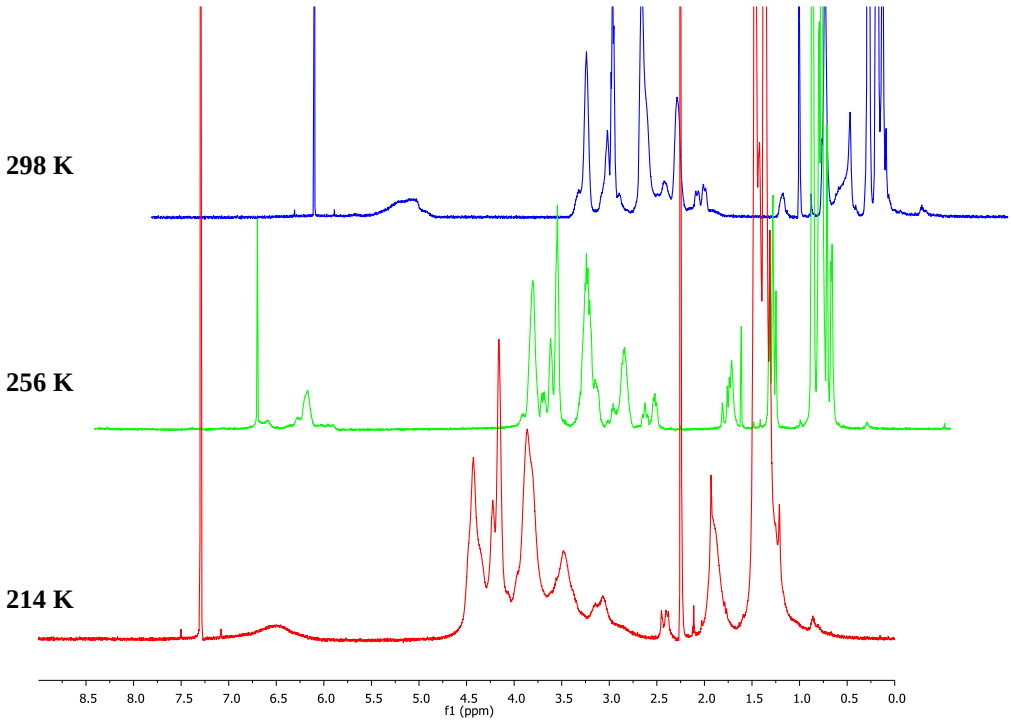


Figure 2.28: VT ^{1}H NMR of 116 ($CuSO_4$) from route A, 214 K – 298 K. The spectra for 116 (TsOH) were identical

A recent study into the rotational barriers of iodixanol **58** calculates the rotation around the phenyl-N bond to be between 28-33 kcal mol^{-1}.[191] This is sufficiently high to give rise to non-interconvertible rotamers at r.t., as iodixanol **58** is the dimer form of iohexol **55**, the same barrier to rotation would be expected, which is why VT ^{1}H NMR didn't yield any useful information.

2.2.2.7 X-ray diffraction of 116 ($CuSO_4$) and 116 (TsOH)

The two products **116** ($CuSO_4$) and **116** (TSOH), while appearing identical (^{1}H, ^{13}C NMR, IR, M.S, m.p., elemental analysis, TGA and DSC) were made *via* different methods (A and B) and exhibit differential solubility in ethyl cyanoacrylate **37**. The different preparation methods (including work-up), may lead to differences in the crystallisation patterns of the two solids. This could explain why two seemly

identical products have different solubility characteristics in the cyanoacrylate adhesive. **116** is a powder and therefore it was not possible to get a crystal structure of the two different products, for this reason both solids were analysed by X-ray diffraction (XRD). XRD is a powerful technique for studying powdered materials, as different materials produce distinctive diffraction patterns. By producing a diffraction pattern for each solid we the two samples could be compared, any significant differences could explain why they behave differently in the adhesive.

XRD works by the detector sitting at a certain position and counting the X-rays scattered from the sample in that position, before moving on to the next position and so on and so on. However no Bragg peaks were observed for either sample indicating that they both were amorphous solids. A Bragg peak is a pronounced peak on the Bragg curve which plots the energy loss of the X-ray as it travels through matter. This means that the sample is amorphous (effectively structureless or disordered) so all the molecules are packed together randomly, rather than in an ordered way. The lack of Bragg peaks lead to powder diffraction patterns for both samples which were mainly background noise (Figure 2.29 and 2.30. The only sharp peaks observed were at 39^{o} and 45^{o}, these are from the aluminium sample holder. Significant amounts of sample were analysed and so the low signal must be due to amorphous behaviour of both solids.

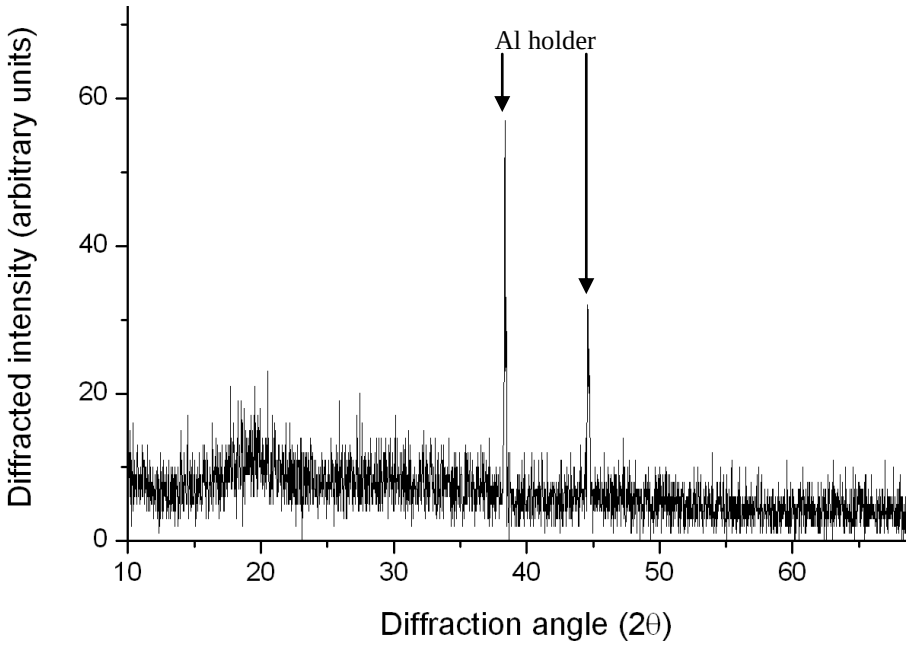


Figure 2.29: Powder diffraction pattern from 116 ($CuSO_4$) *via* Route A

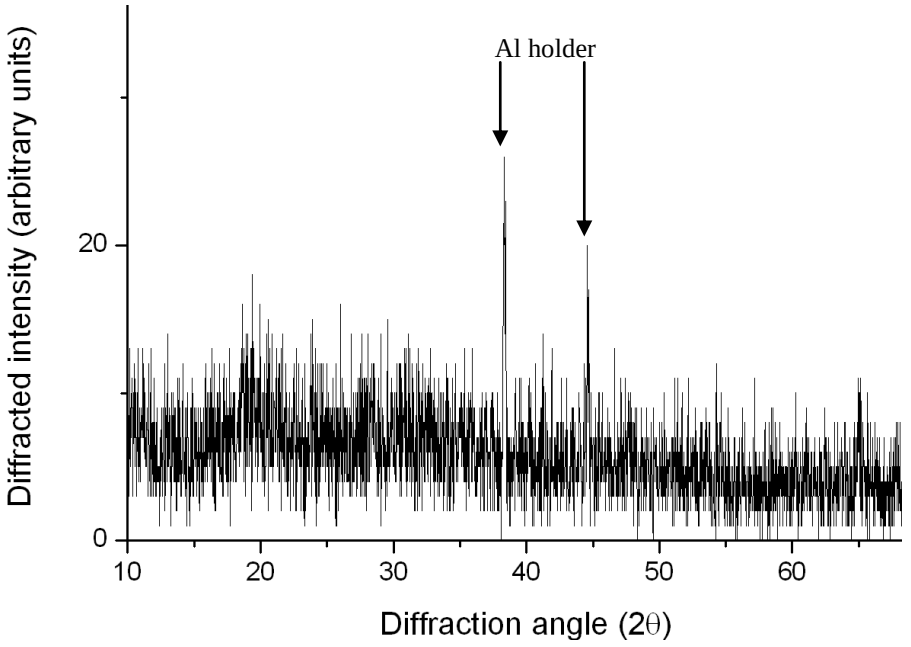


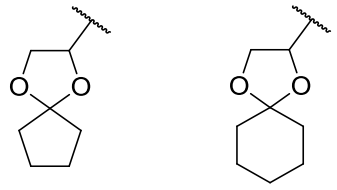
Figure 2.30: Powder diffraction pattern from 116 (TsOH) *via* Route B

It is still entirely possible that the differences in the properties of the two materials are due to a difference in the way the molecules are packed, but unfortunately because they are not crystalline this can't be observed by XRD. In summary after extensive analysis (^{1}H, ^{13}C NMR, mass spectroscopy, m.p., ICP-MS, IR, TGA, DSC,

XRD) both samples **116** ($CuSO_4$) and **116** (TsOH) appear identical apart from their solubility in ethyl cyanoacrylate **37**. Despite inconclusive results from XRD it seems likely that the difference in solubility is due to different morphologies, although it wasn't possible to prove this.

2.2.2.8 Cyclic 1,3-protecting groups

To probe the anomaly further, to produce more compounds for testing and to potentially increase solubility in ethyl cyanoacrylate **37** further cyclic protecting groups **117** and **118** (Figure 2.31) were investigated.



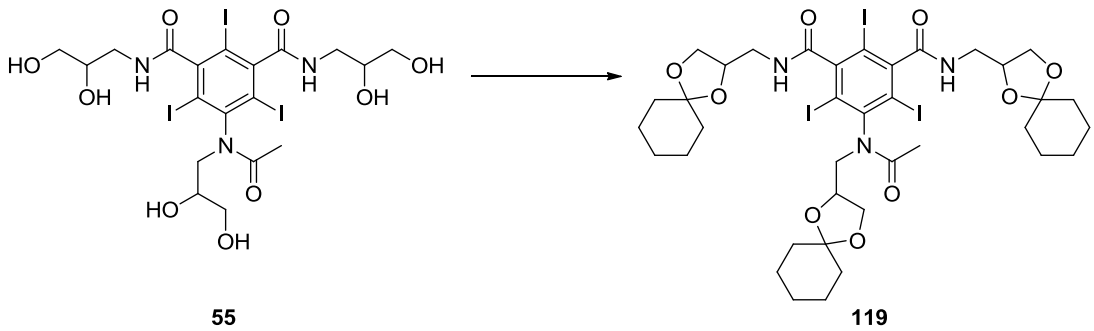
117 **118**

Figure 2.31: Cyclic 1,3-protecting groups

As before two routes of synthesis were chosen A (ketone, $CuSO_4/H^+$) and B (2,2-dimethoxyalkane, TsOH). Solubility of the identical compounds (produced by the two different routes) in ethyl cyanoacrylate **37** will be determined. This will illustrate if the differences in solubility between route A and B products are exclusive to the acetonide product **116** or are a general observation**.**

Six membered rings:

Firstly Route A was attempted using cyclohexanone (Scheme 2.13) to give the tri-cyclohexane protected protect **119**.



55 119

Scheme 2.13: Synthesis of 119 *via* route A. *Reagents and conditions*: iohexol (1 eq.), cyclohexanone, $CuSO_4$ anhydrous (2 eq.), TsOH (0.2 eq.), 85 ^oC, 6 days, 12%.

The reaction was followed by mass spectroscopy and took 6 days, longer than the acetonide reaction (2 days). Despite the longer reaction time the tri-cyclohexane protected product **119** was isolated pure after chromatography (Figure 2.32).

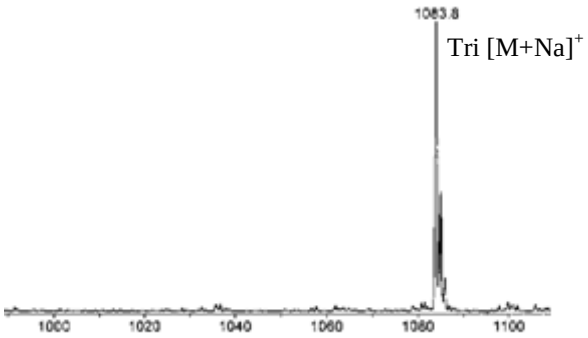
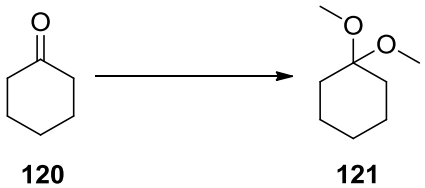


Figure 2.32: Mass spectroscopy of 119 *via* route A

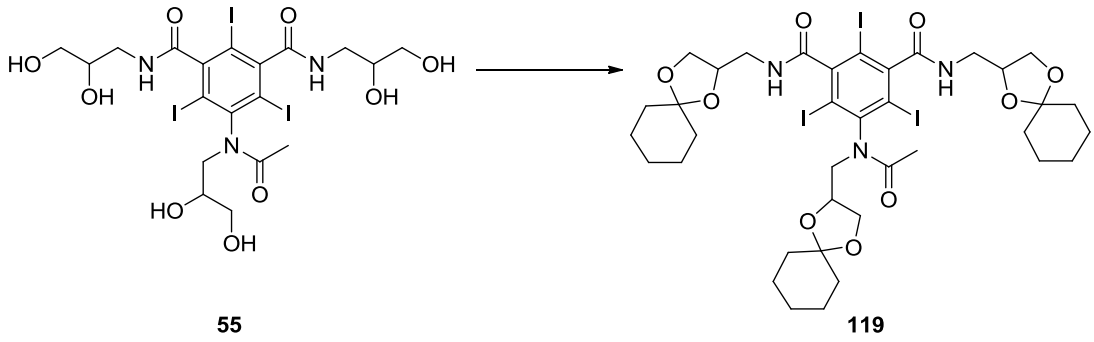
119 ($CuSO_4$) Was tested for solubility in ethyl cyanoacrylate **37**, however displayed none. For comparison **119** was also synthesised *via* route B, firstly 1,1-dimethoxycyclohexane was synthesised from cyclohexanone[192] (Scheme 2.14).



120 121

Scheme 2.14: Synthesis of route B starting material 121. *Reagents and Conditions*: cyclohexanone (1 eq.), trimethyl orthoformate (2 eq.), $ZnCl_2$ (0.1 eq.), methanol, reflux, 4 days, 73%.

The product **121** was reacted with iohexol **55** *via* route B to give **119** in 69% yield (Scheme 2.15). The reaction was complete in 24 h which is significantly faster than *via* route A. As before it was shown to be pure by mass spectroscopy of **119** (Figure 2.33), however the product still showed no solubility in cyanoacrylate.



Scheme 2.15: Synthesis of 119 *via* route B. *Reagents and conditions*: iohexol (1 eq.), TsOH (0.2 eq.), 1,1-dimethoxycyclohexane (4 eq.) DMF, r.t., 24h, 69%.

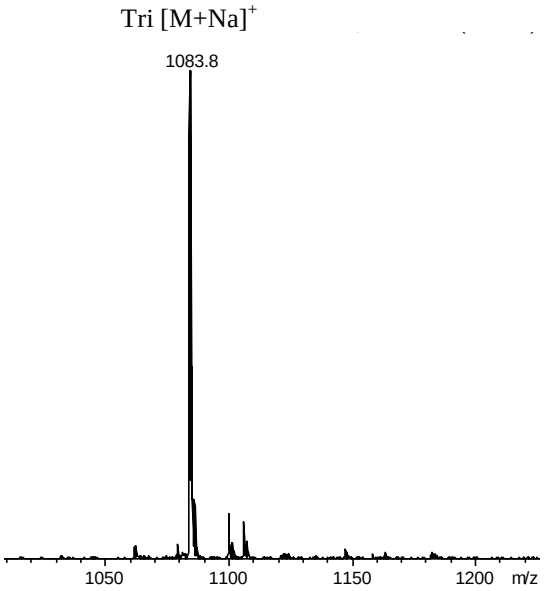
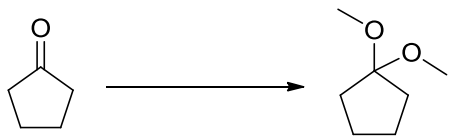


Figure 2.33: Mass spectroscopy of 119 *via* route B

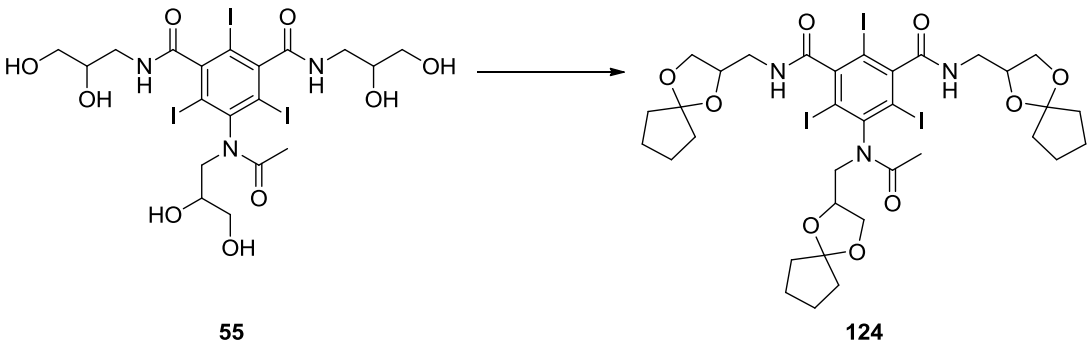
In this case the products from the different routes behaved similarly in their solubility in ethyl cyanoacrylate **37**. Therefore the difference between the two acetonide products **116** ($CuSO_4$) and **116** (TsOH) does not seem to be due to the method used to make them.

Five membered rings:

In order to see whether the difference in solubility for the acetonide reaction was an anomaly the cyclopentane protected product **124** was also synthesised *via* both routes. However, when route A ($CuSO_4$) was attempted using cyclopentanone none of the desired product **124** was produced. Several attempts with varying conditions were made including adding DMF to the reaction mixture to try and increase the solubility of the starting material **55**. It was possible to prepare **124** however, using method B. Firstly, 1,1-dimethoxycyclopentane was synthesised from cyclopentanone **122** using $ZnCl_2$ as a Lewis acid catalyst[192] (Scheme 2.16). Secondly, reaction with **55** and catalytic TsOH in DMF gave **124** in 38% yield after purification (Scheme 2.17).



Scheme 2.16: Synthesis of route B starting material 123. *Reagents and Conditions*: cyclopentanone (1 eq.), trimethyl orthoformate (2 eq.), $ZnCl_2$ (0.1 eq.), methanol, reflux, 4 days, 41%

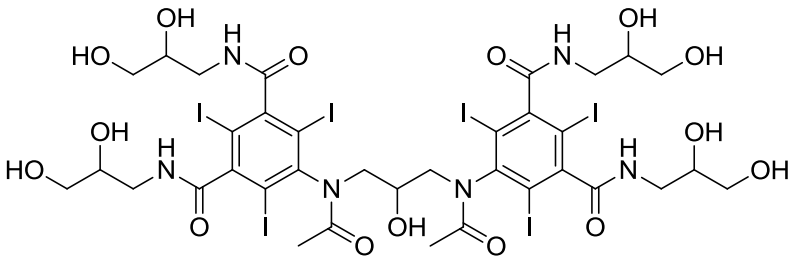


Scheme 2.17: Synthesis of 124 *via* route B. *Reagents and conditions*: iohexol (1 eq.), TsOH (0.2 eq), 1,1-dimethoxycyclopentane (4 eq.) DMF, r.t., 30h, 38%.

Disappointingly product **124** displayed no solubility in ethyl cyanoacrylate **37**. Neither of the cyclic protected products **119** and **124** were soluble in ethyl cyanoacrylate **37**, meaning that increasing molecular weight does not increase solubility. Overall the best candidate for the protection of iohexol **55** is the hexa-acetate product **110**.

2.2.3 Modification of iodixanol 58

Iodixanol **58** trade name Visipaque (Figure 2.34), is another known contrast agent, it is the dimer form of iohexol **55** and has nine free hydroxyl groups. This means there are more sites to functionalise, which will hopefully help to increase the solubility in cyanoacrylate further with comparison to iohexol **55**. However, the lack of solubility of the related cyclic compounds of iohexol (**119** and **124**) indicate that it is likely that that the amide and aryl iodide groups are also contributing to the insolubility in common organic solvents and that protection of the many hydroxyl groups themselves will not be sufficient to impart great solubility in organic solvents.

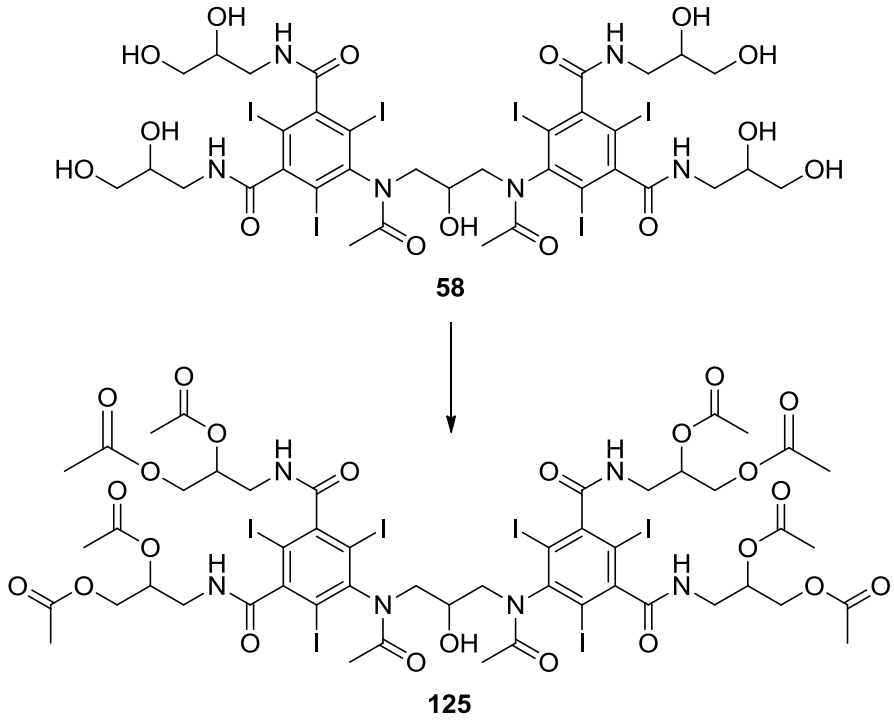


58

Figure 2.34: Contrast agent iodixanol 58

As acetate **110** and acetonide protection **116** of iohexol **55** resulted in an increase in solubility, both groups were added to iodixanol **58** in a bid to increase solubility

further. Firstly, **58** and iodine were combined in acetic anhydride at r.t. for six days to give **125** in 76% yield after purification (Scheme 2.18).



Scheme 2.18: Acetate protection of iodixanol 58. *Reagents and Conditions:* iodixanol (1 eq.), iodine (0.1 eq.), acetic anhydride, r.t., 6 days, 76%.

Mass spectroscopy (Figure 2.35) showed all nine hydroxyl groups had been functionalised. When tested **125** showed 5% solubility in ethyl cyanoacrylate **37** causing no polymerisation. This is less than the iohexol equivalent **110** (15%), suggesting that the increase in molecular weight and number of reactive sites is lowering solubility.

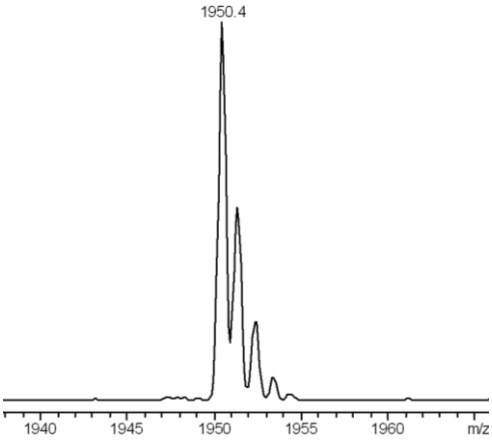
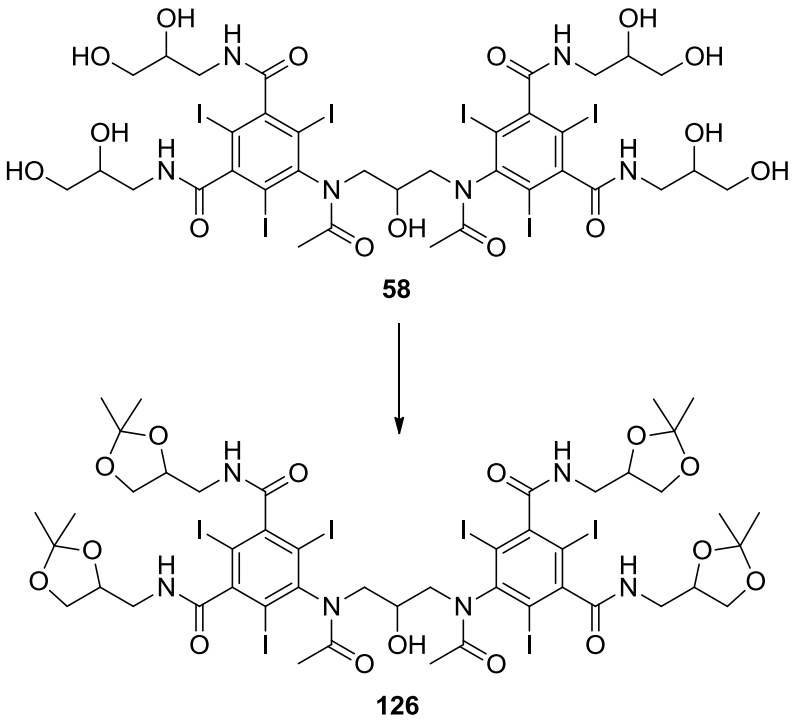


Figure 2.35: Mass spectroscopy of 125

Acetonide protection of iodixanol **58** was also attempted, *via* route A and B. However as with cyclopentanone attempts, route A failed to produce any of the desired product **126**, despite solubilising the starting material **58** with DMF and increasing the reaction times and temperature. Despite this **126** was successfully synthesised *via* route B (Scheme 2.19).



Scheme 2.19: Synthesis of 126 *via* route B. *Reagents and Conditions:* iodixanol (1 eq.), TsOH (0.5 eq.), 2,2-dimethoxypropane (6 eq.), DMF, r.t., 24h, 33%.

The product **126** however showed no solubility in ethyl cyanoacrylate **37**. Therefore overall it can be concluded that iodixanol **58** is not as good a candidate for modification than iohexol **55**. After much investigation it is clear that the acetate protected iohexol **110** is the only viable option for incorporation into cyanoacrylate adhesive for use in medical devices.

2.2.4 Partition Coefficient

So far all the solubilities have been judged by observing the maximum amount of contrast agent able to dissolve in ethyl cyanoacrylate monomer **37** by % weight; in order to quantify these values the partition coefficient for each contrast agent was calculated. The partition coefficient P_{ow} is the ratio of concentrations of a compound in two immiscible phases, commonly octanol and water. Therefore P_{ow} is a measure of the difference in solubility of the compound in the two liquids. In other words how hydrophobic or hydrophilic the compound is. The P_{ow} was calculated using the 'shake flask method' with octanol and water.[193] Analytical grade *n*-octanol and double distilled water were used, and both were first mutually saturated at r.t. by shaking equal amounts of both liquids on a mechanical shaker for 24 h. This was poured into a separating funnel and allowed to settle, water was let out the bottom and octanol poured out of the top to prevent contamination once separated.

To measure the P_{ow} for each sample 2 mL of water and 2 mL of octanol were added to a vial and 0.02 g of sample added before the sealed tube was shaken by hand for 10 minutes. After which the contents were allowed to settle for 1 h and then separated in the same way as the saturated liquids. The absorbance of each sample was measured in water and octanol at 240 nm. By using pre-determined calibration

graphs the concentration in each layer was calculated (See Appendix). P_{ow} is determined by dividing the concentration in octanol by the concentration in water. P_{ow} is dimensionless and is usually given in the form of log P_{ow}, a high P_{ow} is considered hydrophobic and a low P_{ow} is hydrophilic.

The shake flask method was applied to each of the protected contrast agents and then the absorbance measured for both the octanol and water layers so that the P_{ow} could be calculated, (Table 2.2).

Entry	Sample	Octanol		Water		P_{ow}	Log P_{ow}
		A	Conc.	A	Conc.		
	iohexol adducts						
1	acetate **110**	2.95	0.046	1.29	0.003	15.3	1.19
2	pentyl **111**	2.75	0.032	2.09	0.013	2.5	0.39
3	acetonide **116** ($CuSO_4$)	2.76	0.032	2.28	0.016	2.0	0.30
4	acetonide **116** (TsOH)	2.65	0.028	2.13	0.014	2.0	0.30
5	6 ring **119** ($CuSO_4$)	2.96	0.046	2.82	0.021	2.2	0.34
6	6 ring **119** (TsOH)	2.80	0.034	2.15	0.014	2.4	0.39
7	5 ring **124** (TsOH)	2.76	0.032	2.25	0.015	2.1	0.33
	iodixanol adducts						
8	acetate **125**	2.15	0.008	2.52	0.004	1.9	0.27
9	acetonide **126** (TsOH)	2.11	0.008	2.57	0.004	1.8	0.26
	diatrizoic acid adducts						
10	butyl ester **103**	0.86	0.001	1.58	0.007	0.2	-0.81
11	octyl ester **104**	1.00	0.001	1.08	0.003	0.4	-0.42
12	methyl ester **102**	1.11	0.002	1.29	0.005	0.3	-0.51

Table 2.2: Log P_{ow} of protected contrast agents 102 – 126

The only sample to give a high P_{ow} and therefore to be more hydrophobic than the others is entry 1, the acetate protected iohexol **110**. This follows the pattern of the solubility tests as **110** was the most soluble in ethyl cyanoacrylate. Entries 3 and 4 show the acetonide protected iohexol **116** ($CuSO_4$) and **116** (TsOH). These two

products, although appearing the same, gave differing results when tested for solubility in ethyl cyanoacrylate. However they each gave the same P_{ow} showing them to both be hydrophilic. This result is pleasing in one respect and not in another. Firstly, the fact that both give the same P_{ow} gives some credence to the theory that their differing solubility in ethyl cyanoacrylate is due to different morphologies. This difference would be negated once dissolved in the water used for the partition coefficient test. However, the fact that **116** ($CuSO_4$) was soluble in ethyl cyanoacrylate but has a relatively low P_{ow} value of 2.0 (lower than all the other ketal products that did not dissolve, entries 5-7) is worrying. This suggests that the octanol/ water P_{ow} isn't an exact model for how compounds will behave in ethyl cyanoacrylate. P_{ow} is used to tell how hydrophilic or hydrophobic a compound is and therefore suggests whether it will be soluble in organic media or water. However octanol is very different to ethyl cyanoacrylate adhesive and so can only be used as a guide.

The samples to give the lowest P_{ow} and therefore to be very hydrophilic, were the diatrizoic acid analogues **102**, **103** and **104**, entries 10-12. These compounds showed no solubility in ethyl cyanoacrylate or several organic solvents. The two iodixanol adducts **125** and **126**, entries 8 and 9, give the same low P_{ow} showing them both to be hydrophilic. However although the acetonide product **126** (entry 9) showed no solubility in ethyl cyanoacrylate, the acetate compound **125** (entry 8) showed 5% solubility. This difference isn't reflected in their P_{ow}, though it is only a small difference and the octanol/water model can only be used as a guide.

2.2.5 X-ray analysis of 110 in ethyl cyanoacrylate

Contrast agents diatrizoic acid **56**, iohexol **55** and iodixanol **58** were successfully modified with a number of different protecting groups. The most soluble in ethyl cyanoacrylate was the acetate protected iohexol **110**. This was the most viable candidate for incorporation into a cyanoacrylate medical product. However for it to be of use in the body, it needs to be able to be followed by X-ray. Proof was needed to show that **110** was an efficient X-ray contrast agent within the adhesive structure. The acetate protected product **110** was dissolved in ethyl cyanoacrylate (10-18% w/w in 1% gradations). Mixtures containing over 15% w/w of **110** did not fully dissolve in these tests and contain un-dissolved product. X-ray images of the vials were then taken (Figure 2.36).

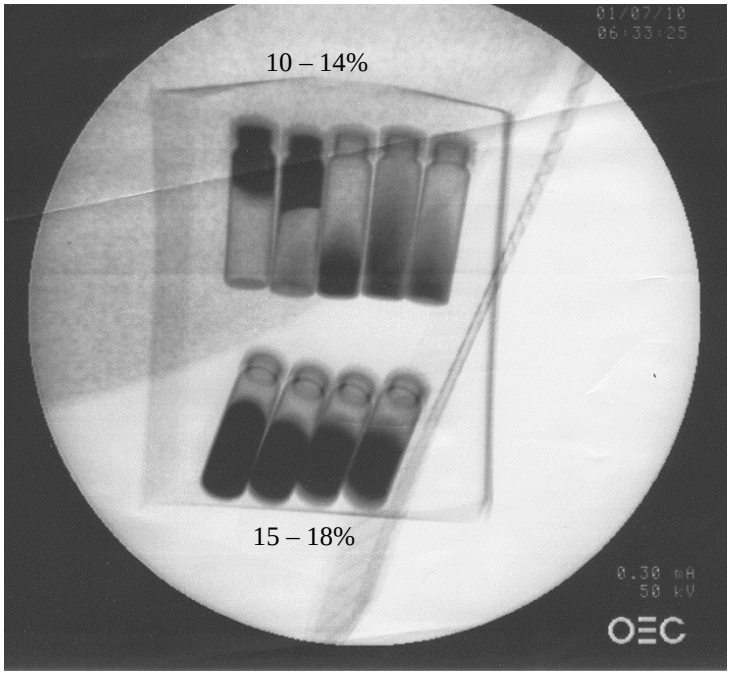


Figure 2.36 X-ray images of acetate product 110 in cyanoacrylate

The vials can be clearly seen on the X-ray, the darker the contents the more contrast the glue is displaying. The vials with 15% or more acetate product **110** show up

black in the X-ray, therefore **110** can be incorporating into the glue in sufficient amounts to give good contrast.

2.3 Conclusion

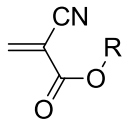
In conclusion, ethyl cyanoacrylate adhesive was proposed as an alternative to coiling for the treatment of brain aneurysms. In order to be able to dispense the adhesive in the correct location it needed to be visualised within the body. Hence the need to incorporate a contrast agent into the glue, however existing contrast agents do not dissolve in ethyl cyanoacrylate. Three existing imaging agents **55**, **56** and **58** were modified with a range of hydroxyl protecting groups with different degrees of success. Solubility testing revealed that iohexol **55** was the best agent for modification, with three protected products **110**, **111** and **116** showing significant solubility in ethyl cyanoacrylate. The best solubility was displayed by **110**, this also had the biggest P_{ow}. **110** was incorporated in ethyl cyanoacrylate monomer and this was allowed to polymerise. After polymerisation the material was tested for contrast with X-rays and it was shown that it would show up in the body. The product **110** gave good contrast and thus is a viable candidate to be used in the body for treatment of brain aneurysms.

Diatrizoic acid **56** and iodixanol **58** were discounted as they were more problematic to protect and the products that were successfully synthesised did not show enough solubility, if any in ethyl cyanoacrylate.

3.0 - Anthracene Protected Route for Synthesis of Cyanoacrylates

3.1 Introduction

Alkyl cyanoacrylates **16** (Figure 3.1) have been utilised as adhesives for a number of years, across a wide range of industries.[194] These compounds are highly adhesive and polymerise in the presence of a weak base such as water or alcohol due to the presence of two strong electron withdrawing groups.



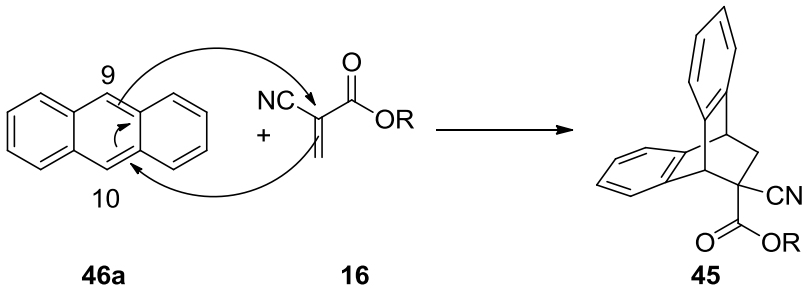
16

Figure 3.1: Alkyl cyanoacrylate 16

Alkyl cyanoacrylates **16** have been developed for use as biological adhesives, and are currently used in preference to stitches for superficial external lacerations.[61] However, cyanoacrylate skin glues have their disadvantages; cyanoacrylates degrade to release formaldehyde, and this can lead to irritation and inflammation of adjacent tissues. Previous studies have shown that poly(ethyl cyanoacrylate) P(ECA), degrades to give formaldehyde faster than poly(octyl cyanoacrylate) P(OCA) and poly(2-octyl cyanoacrylate) P(2-OCA).[48] Thus it has been suggested that the ester group of the cyanoacrylate **16** can directly affect the rate of degradation by steric hindrance at the ester. *By changing the R group it may be possible to slow the rate of degradation further and therefore decrease the amount of formaldehyde released in vivo. In this chapter this concept will be discussed.*

3.1.1 Synthesis of cyanoacrylates

There are a number of known routes for the synthesis of cyanoacrylate monomers, as described previously.[195] Anthracene **46a** has been used in previous syntheses as a protecting group, trapping the reactive cyanoacrylate monomer **16**. Anthracene **46a** undergoes a cycloaddition with the cyanoacrylate **16** to give a stable Diels-Alder adduct **45**. The anthracene protecting group can be easily removed from **45** *via* a retro-Diels-Alder reaction to release the cyanoacrylate monomer **16**, (Scheme 3.1).

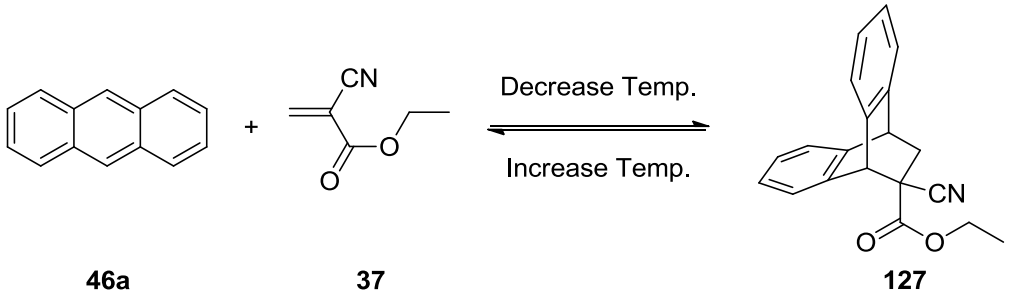


Scheme 3.1: Diels-Alder cycloaddition of anthracene 46a

3.1.2 Diels-Alder reactions of anthracene 46a

Anthracene **46a** is a polycyclic aromatic hydrocarbon and was first isolated from coal tar in 1833. It has since been utilised for a diverse range of applications including preparation of alizarin dyes to electroluminescent devices.[195] There has been a large amount of chemistry developed for the functionalisation and modification of anthracene's aromatic ring system, in particular cycloadditions. The stereochemistry of the reaction involves exclusive *cis* addition of the dienophile to the anthracene **46a** and retention of the dienophile stereochemistry in the product.[196] This retention of stereochemistry postulates a concerted mechanism, as for a two step mechanism to occur with retention of stereochemistry, the second step would have to be significantly faster than the rotation about the C-C σ bond formed in the

intermediate. The concerted mechanism involves forming two σ bonds simultaneously either by direct addition, or *via* an intermediate charge-transfer complex.[197] It has been observed by many studies that a transient colour is produced and disappears as the Diels-Alder reaction of anthracene **46a** proceeds. This has been attributed to the formation of a charge-transfer complex and therefore supports a concerted mechanism.[198] Several studies of Diels-Alder reactions of anthracene **46a** have investigated the solvent effect on the reaction rate.[199–201] In some cases electron accepting solvents have been shown to increase the rate of reaction by stabilising the electron rich transition state.[201,202] Aromatic solvents have been shown to produce an increase in reactivity with dienophiles that are capable of very strong charge-transfer interactions.[199] However in general the influence of solvent on rate of reaction is relatively small. The rate of the Diels-Alder reaction of anthracene **46a** appears instead to be governed more by temperature and substituent effects in the dienophile.[203,204] Lower temperatures and excess of dienophile can increase forward reactions rate, while higher temperatures favour the retro Diels-Alder, (Scheme 3.2).[205]



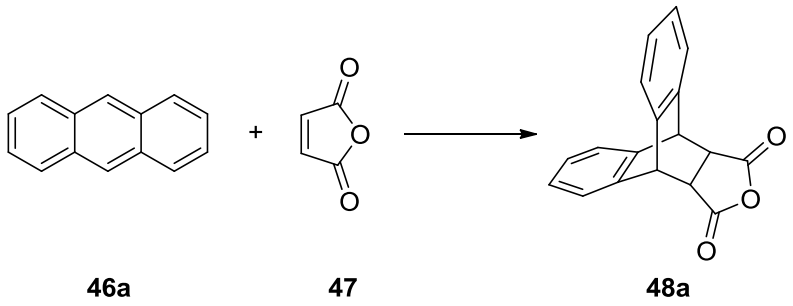
46a **37** **127**

Scheme 3.2: Equilibrium reaction between anthracene 46a and ethyl cyanoacrylate 37

9-10-Dimethyl anthracene has been shown to lead to a greater rate enhancement in the reaction with maleic anhydride than anthracene **46a** itself,[206] while electron withdrawing substituents on the dienophile can also effect the rate by lowering the

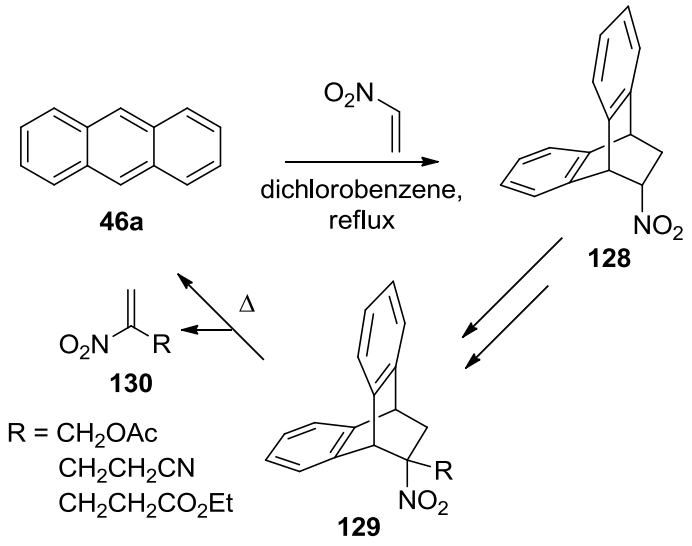
LUMO and changing its ability to accept π electrons.[207] The types of dienophiles used in Diels-Alder reactions of anthracene **46a** fall into four classes; (i) α, β-unsaturated carbonyls, (ii) alkenes attached to a heteroatom or halogen, (iii) alkenes and alkynes and (iv) heterodienophiles.

The first reported cycloaddition of anthracene **46a** was a fusion reaction (Scheme 3.3) between anthracene **46a** and maleic anhydride **47** in 1931,[208] later it was shown that the same adduct **48a** could be achieved by heating a solution of the two reactants in xylene.[209] Reaction of anthracene **46a** with various maleic anhydride type dienophiles is one of the most studied reactions of anthracene.[210–214]



Scheme 3.3: Fusion reaction between anthracene 46a and maleic anhydride 47

The first Diels-Alder reaction of anthracene with a monosubsituted alkene (Scheme 3.4) was carried out with 1-nitroethene. The reaction was used in the preparation of 1,1-disubstituted nitroalkenes **130** which were released after the decomposition of the modified adduct **129**.[215–217] The high reactivity of the nitro groups enabled the use of relatively mild conditions for these reactions; toluene, 110 ^{o}C, 3 h.[218]



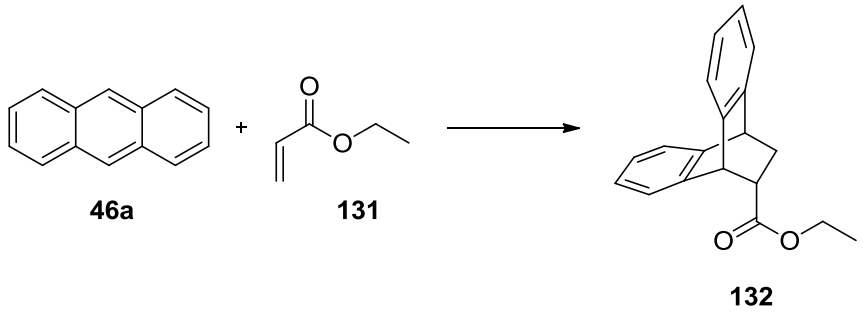
Scheme 3.4: Preparation of new highly substituted nitroalkenes 130[195]

This is an example of how the Diels-Alder reaction of anthracene **46a** can be used to functionalise reactive alkenes by 'trapping' the reactive functionality as stable cycloadducts. Subsequent release of the **130**, after modification can be carried out using a retro-Diels-Alder reaction.[219] Anthracene **46a** has been employed in a similar manner as a protecting group in the synthesis of natural products, in particular as protecting groups for benzoquinone, *N*-methyl maleimide and methyl acrylate.[211,220] *This approach will be used to prepare a range of novel cyanoacrylates for testing as adhesives and measure the degree of formaldehyde release during degradation as a function of structure.*

3.2 Development of anthracene protected route using ethyl acrylate 131

It was decided to prepare a range of novel cyanoacrylates differing in the ester group using an anthracene Diels-Alder protection/ chemical transformation/ retro-Diels-Alder deprotection strategy. The chemistry had to be amenable to a large scale process (small amounts monomers/ polymers initially would be sufficient for the

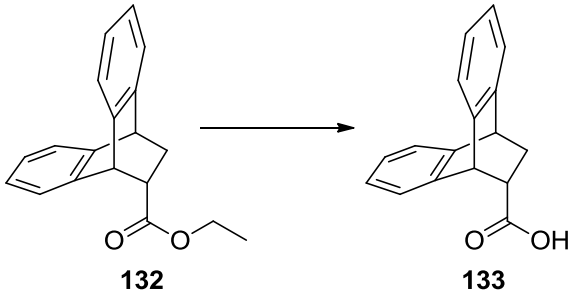
study but ultimately it needs to be amenable to a multi Kg batch process) and consequently, it was decided to keep chromatography to a minimum. Before embarking on chemistry with the highly reactive cyanoacrylates the protocols were optimised by examining the reaction of the easier to handle ethyl acrylate **131**. Once all steps were established the procedure could be applied to cyanoacrylates. Heating ethyl acrylate **131** with anthracene **46a** in refluxing xylene for 24 h furnished the protected anthracene adduct **132**, (Scheme 3.5).



Scheme 3.5: Synthesis of anthracene adduct 132. *Reagents and Conditions:* anthracene **46a** (1 eq.), ethyl acrylate **131** (1.1 eq.), MEHQ (0.1 eq.), xylene, reflux, 24h, 96%.

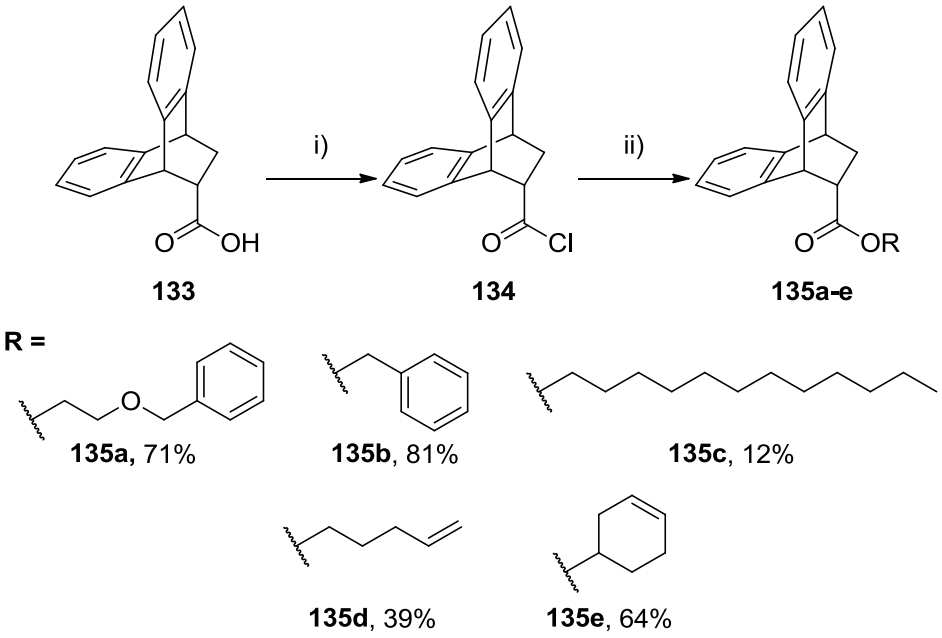
The crude 400 MHz ^{1}H NMR showed 10% un-reacted anthracene **46a**. Attempts to remove the excess anthracene by recrystallization using a variety of solvents (hexane, petrol, petrol/ EtOAc etc.) did not lead to pure **132**. As the left over anthracene **46a** was likely to be un-reactive in the further steps, the decision was taken to react **132** on crude. The next step undertaken was to hydrolyse the ester **132** to the corresponding carboxylic acid **133** in order to allow further functionalisation. The literature conditions[221] of a single equivalent of lithium hydroxide at r.t. gave no reaction, even after several days. Potassium carbonate in methanol and water was also tested as an alternative method however after four days heating at 65 ˚C there was still less than 50% conversion to **133**. Finally heating at reflux in THF: H_2O

with four equivalents of lithium hydroxide for 24 h proved successful, giving acid **133** in 68 % yield (Scheme 3.6).



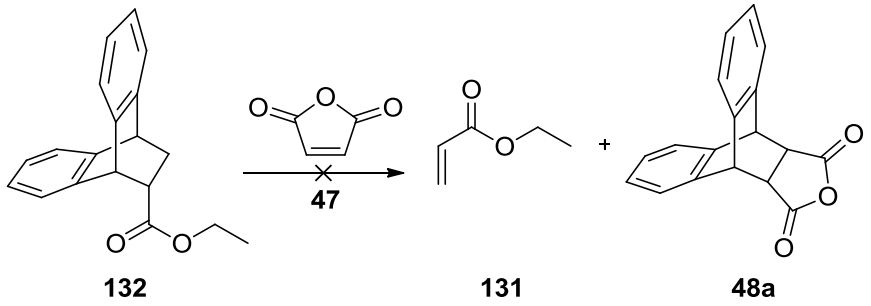
Scheme 3.6: Ester hydrolysis to give carboxylic acid 132. *Reagents and Conditions:* **132** (1 eq.), LiOH (4 eq.), THF: H_2O, 5: 4, reflux, 24 h, 68%.

The carboxylic acid **133** was then reacted with thionyl chloride at reflux for 6 h to give the crude acyl chloride **134** which was reacted *in-situ* with various alcohols in ether with pyridine as base to give a range of esters **135a-e** in 12-81% yield. (Scheme 3.7). These alcohols were chosen as they were readily available and represented various steric sizes.



Scheme 3.7: Esterification of carboxylic acid 133. *Reagents and Conditions*: i**) 133** (1 eq.), excess thionyl chloride, reflux, 6 h, ii) ROH (1.1 eq.), pyridine (1.1 eq.), Et_2O, r.t., 24 h, 12 – 81%.

The final step of the anthracene protected route is to remove the anthracene *via* a retro-Diels-Alder reaction and thus yield the new acrylate monomer. Two possible methods were identified for this reaction; firstly heating the anthracene adduct in the presence of maleic anhydride **47**.[39] This was tried on the anthracene adduct **132** as there was a large amount available, this was the crude sample that contained 10% un-reacted starting material **46a** (Scheme 3.8). The reaction was heated in xylene with an excess of maleic anhydride **47** (3 equivalents) in the presence of hydroquinone and phosphorous pentoxide and followed by 400 MHz ^{1}H NMR over 4 days.



Scheme 3.8: Retro-Diels-Alder reaction – maleic anhydride method. *Reagents and Conditions*: **132** (1 eq.), maleic anhydride **47** (3 eq.), hydroquinone (0.5 eq.), phosphorus pentoxide (0.5 eq.), xylene, reflux, 4 days.

During this time it was observed that the peaks for the un-reacted anthracene **46a** were disappearing from the NMR but the peaks for the adduct **132** remained. This suggests the maleic anhydride **47** was reacting with the un-reacted anthracene **46a** but not with any anthracene liberated from the retro-Diels-Alder reaction (Figure 3.2).

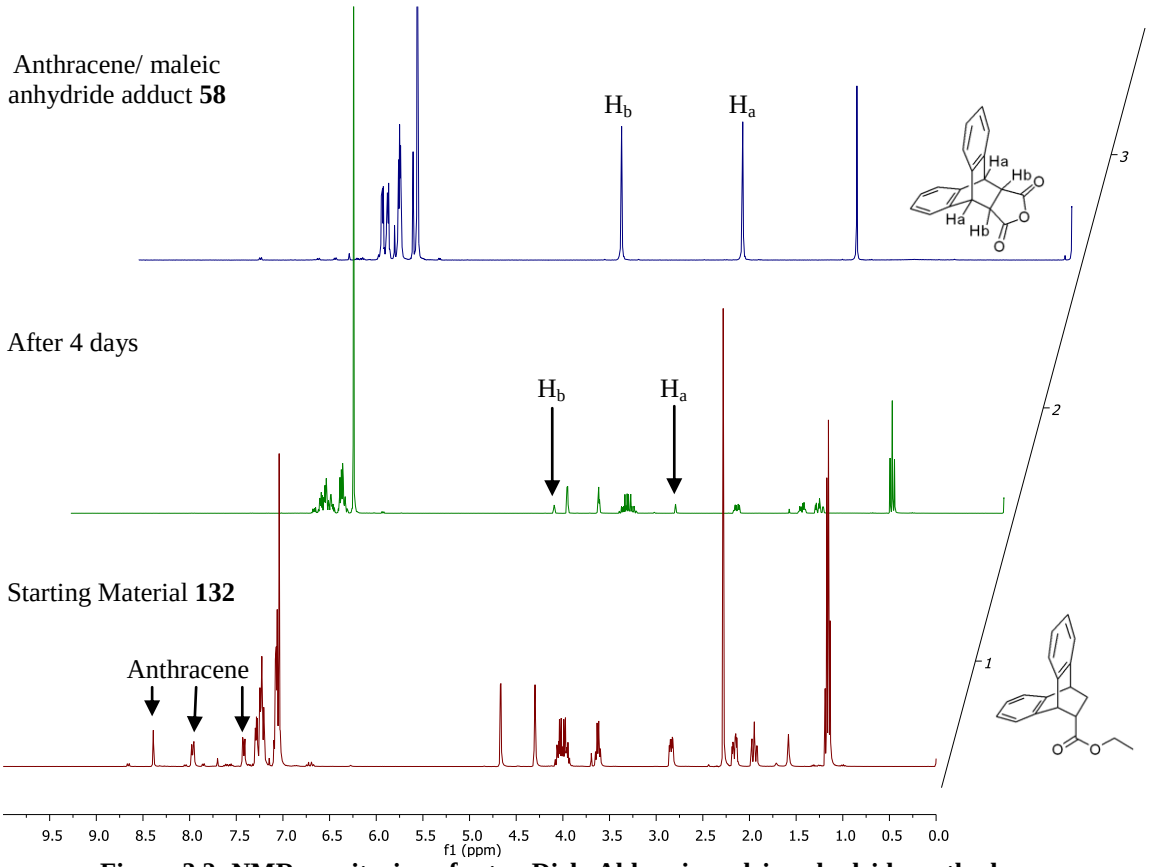
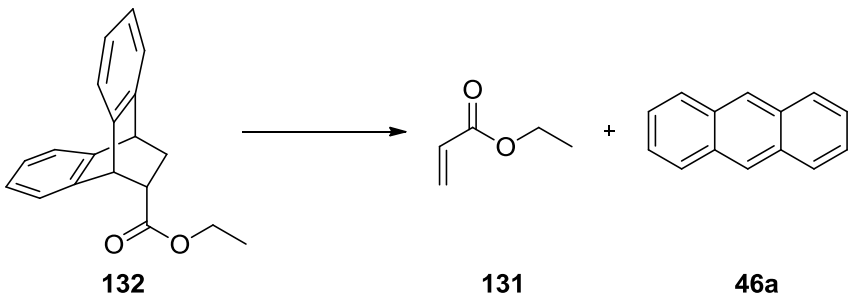


Figure 3.2: NMR monitoring of retro-Diels-Alder *via* maleic anhydride method

This suggested that refluxing xylene was not a high enough temperature to initiate an efficient retro-Diels-Alder process of **132**. The second method involved heating anthracene adduct **132** under vacuum to temperatures of 200 ^{o}C and above[222] (Scheme 3.9). This method has the advantage that the starting material **46a** is regenerated meaning the overall process may be suitable for continuous flow techniques.



Scheme 3.9: Retro-Diels-Alder reaction – heating method. *Reagents and Conditions*: **132** (1 eq.), heat under vacuum 200 ^{o}C+

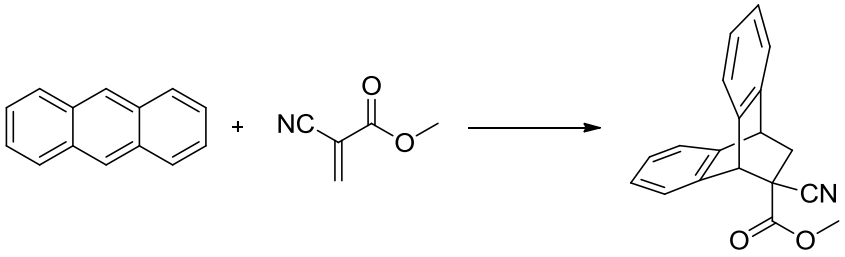
Several methods were examined including conventional vacuum distillation and Kugelrohr apparatus, but although this latter method showed signs of success it was also problematic. Due to the volatility of the acrylate monomer **131** liquid nitrogen was required to trap the product, but even this was not efficient and in general it was only possible to trap small quantities of ethyl acrylate **131**.

No acrylate monomer **131** was observed from the maleic anhydride method and only trace amounts were seen from the direct heating method. Problems with both methods were encountered due to the high volatility of ethyl acrylate **131** and the high temperature that it was formed at making efficient condensation difficult with the standard apparatus in the lab. However, cyanoacrylates themselves are less volatile than acrylates and so this last step should be less problematic with them. Having optimised the first four steps on ethyl acrylate **131** attentions turned to the desired cyanoacrylate monomers.

3.2.1 Anthracene protected route optimisation with cyanoacrylate

The previously established anthracene protected route can now be applied to the synthesis of novel cyanoacrylates. Methyl cyanoacrylate **136** was selected as the starting point due to its low cost and large scale availability. Heating a slight excess of methyl cyanoacrylate **136** (1.1 equivalents) with anthracene **46a** at reflux in xylene produced the Diels-Alder adduct **137**. However on a large scale (500 g) removing the xylene *in vacuo* proved extremely difficult and time consuming. In order to remove the xylene sufficiently it was necessary to concentrate *in vacuo* **137**, wash with hexane, filter and dry in a vacuum oven at 50 ^{o}C (10 mbar). However, this would not be viable on a large scale, thus xylene was substituted for toluene due to

its similar properties but lower boiling point, 110 ^{o}C, and this proved much easier to remove (Scheme 3.10). The lower temperature was still sufficient for efficient Diels-Alder reaction providing **137** in 92% yield after 24 hours at 110 ˚C.



46a **136** **137**

Scheme 3.10: Synthesis of anthracene adduct 137. *Reagents and Conditions*: anthracene **46a** (1 eq.), methyl cyanoacrylate **136** (1.1 eq.), MEHQ (0.1 eq.), toluene, reflux, 24 h, 92% crude.

As with ethyl acrylate **131** the reaction gave the anthracene adduct **137** in high yield but once again the crude material contained some un-reacted anthracene **46a**. However, with methyl cyanoacrylate **136** there was only approximately 5% anthracene **46a** remaining (by 400 MHz ^{1}H NMR) compared to the 10% with ethyl acrylate **131**. Thus the Diels-Alder / retro-Diels-Alder equilibrium favours the adduct **137** more for cyanoacrylate **136** than **132** with ethyl acrylate **131**. As before the synthesis was continued without removing the remaining anthracene **46a**. In an attempt to make the synthesis more industrially attractive, lowering the temperature of the Diels-Alder reaction was briefly investigated. The reaction between anthracene **46a** and methyl cyanoacrylate **136** was carried out at both r.t. and 40 ^{o}C in d_8-toluene and followed by ^{1}H NMR. At r.t. there was still 40% un-reacted anthracene **46a** after 7 days (Figure 3.3). While at 40 ^{o}C the reaction reached 95% completion in 3 days (Figure 3.4) compared to 24 h for the same result in refluxing toluene.

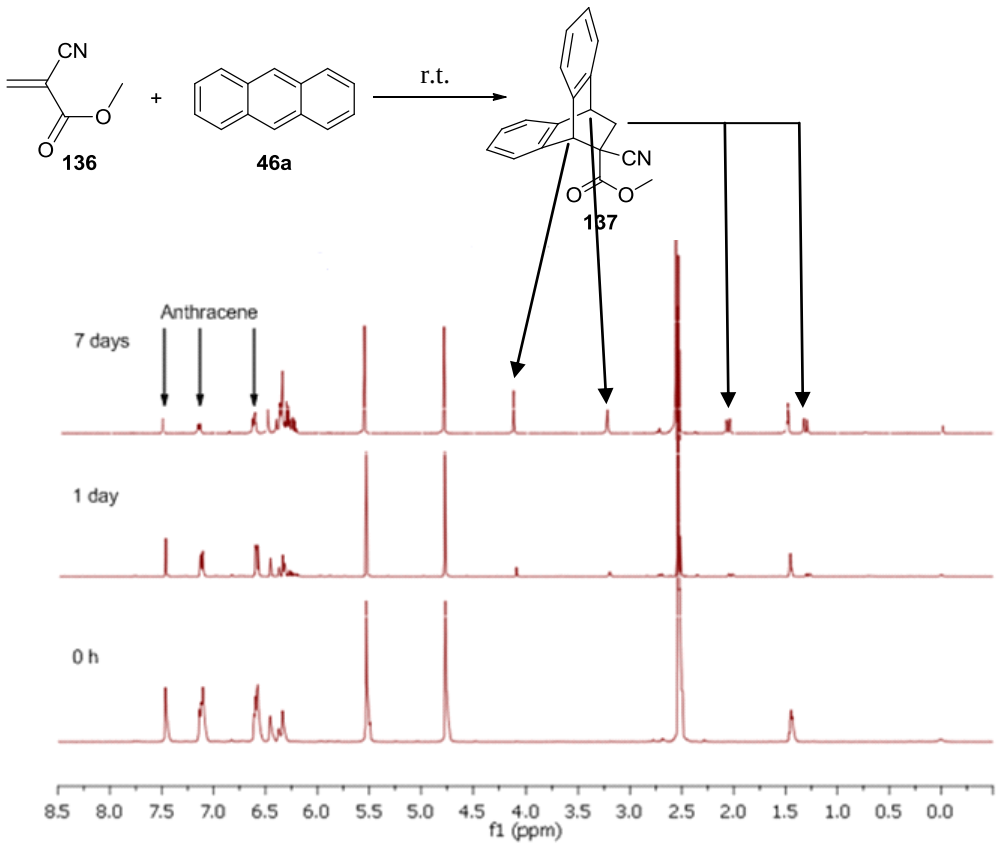


Figure 3.3: ^{1}H NMR of reaction between anthracene 46a and methyl cyanoacrylate 136 at r.t.

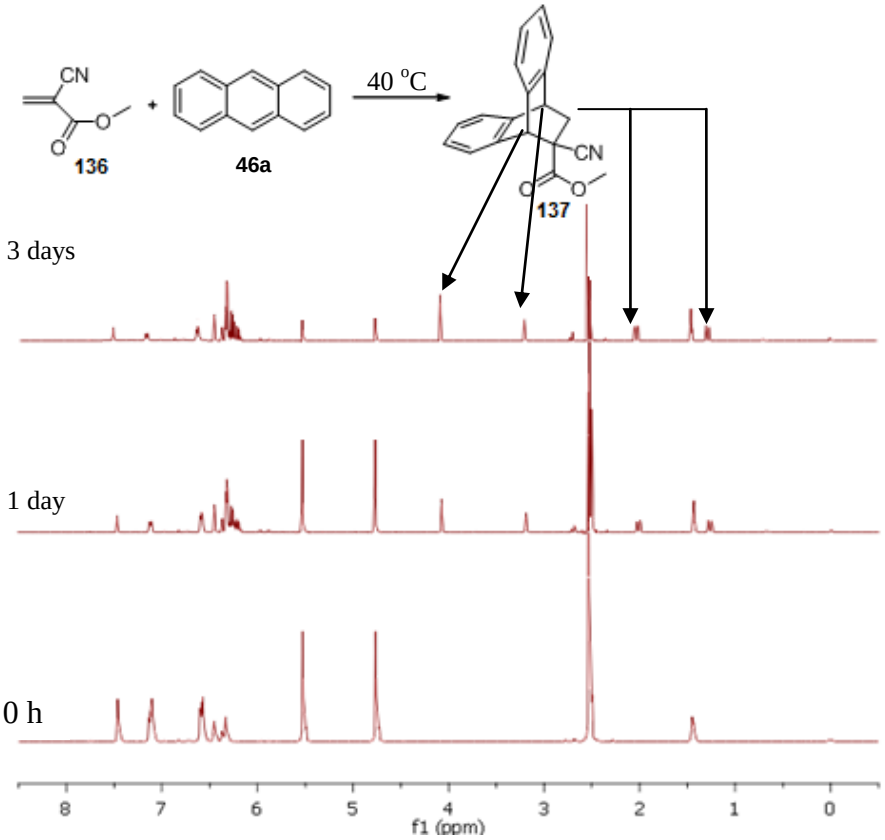


Figure 3.4: ^{1}H NMR of reaction between anthracene 46a and methyl cyanoacrylate 136 at 40 ^{o}C

With the desired adduct **137** in hand (780 g) next the hydrolysis reaction to give the carboxylic acid **49** was investigated. Using the protocol determined in the reaction of the ethyl acrylate derivative **131** gave the desired carboxylic acid **49** in 68% yield. However an alternative method,[39] KOH in refluxing ethanol, was found to give the desired product in 98% crude yield and with much shorter reaction times. This is much more suitable for an industrial process due to its shortened reaction time, increase in yield and simple filtration work-up.

3.2.2 Synthesis of anthracene esters

The carboxylic acid **49** was then reacted with various different alcohols to give a range of anthracene protected esters **138a-d**, **139a-f**, and **140a-c**. It was necessary to synthesise a series of anthracene esters in order to produce a series of cyanoacrylate monomers for direct comparison of formaldehyde release from their polymers. The first series of anthracene esters was the C_4 isomers **138a-d** chosen to assess the effect of steric congestion on the formation of formaldehyde, (Figure 3.5).

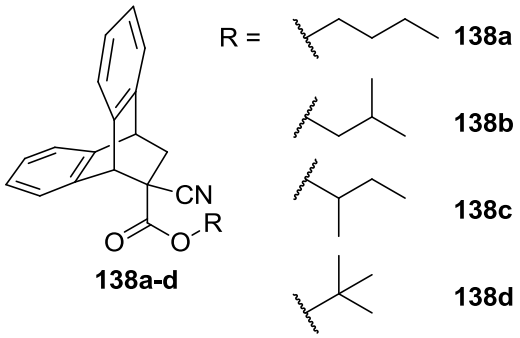


Figure 3.5: Anthracene esters 138a-d - C_4 isomer series

In addition, a range of phenolic esters **139a-f** were synthesised from *p*-substituted phenols (Figure 3.6). This series was chosen to incorporate both electron

withdrawing (Cl, NO_2, CF_3) and electron donating groups (CH_3, OMe) to probe the electronic effect on formaldehyde production.

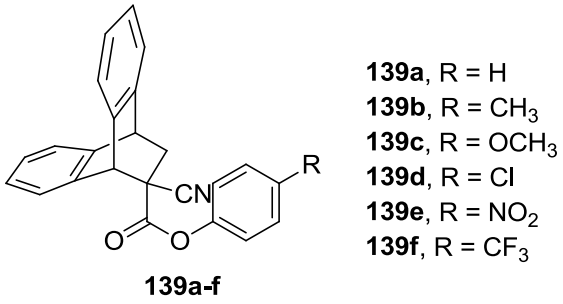


Figure 3.6: Anthracene esters 139a-f – *p*-substituted phenol series

Polymer adhesives can also theoretically decompose *via* hydrolysis of the ester groups to liberate poly(cyanoacrylic acid), although this is likely to be slow at physiological pH with alkyl ester derivatives **138a-d** it will be easier with phenyl ester derivatives **139a-f**. Also prepared was a range of simple sterically hindered esters that could liberate antiseptic molecules **140a-c** (e.g. 2,4,6-trichlorophenol and (-)-menthol), (Figure 3.7) upon hydrolysis. The 2,6-dimethoxy-6-methyl phenol derivative **140c** was also prepared as an electron rich version of **140a**.

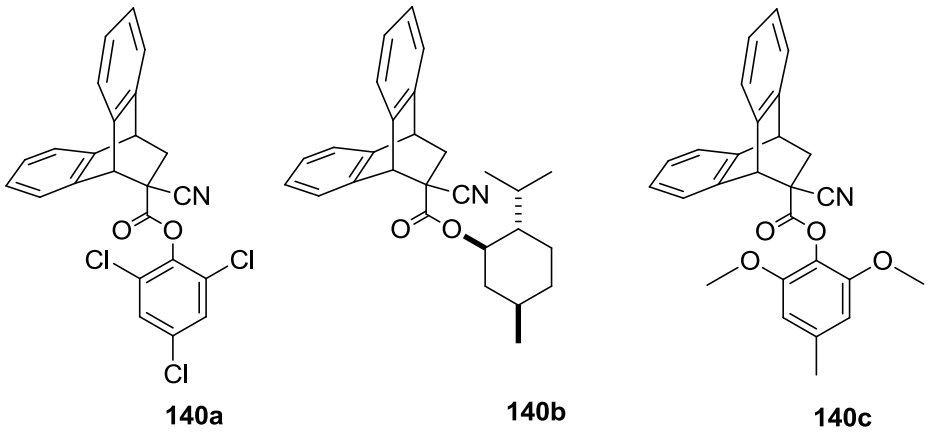
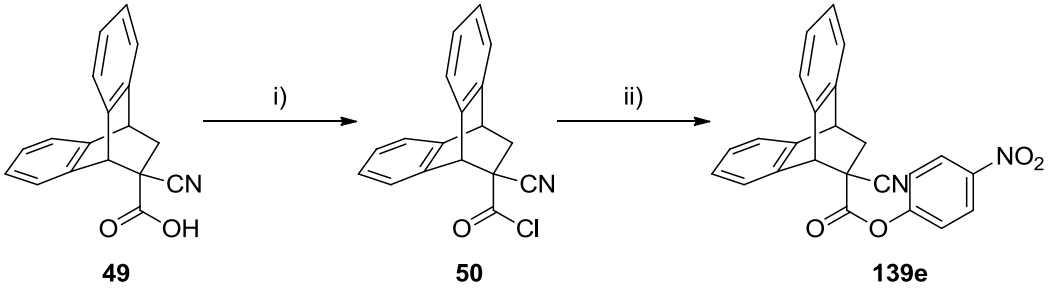


Figure 3.7: Anthracene esters 140a-c– tri-substituted phenols and antiseptic compounds

The esters were prepared as before. Hence, refluxing acid **49** with thionyl chloride for 6 h followed by the removal of excess thionyl chloride on a rotary evaporator

gave the crude acid chloride **50**. Addition of the appropriate alcohol or phenol to this acid chloride in chloroform furnished the desired adducts **138-140** in yields ranging from 6-65%, (Table 3.1), (Scheme 3.11).



Scheme 3.11: Esterification of carboxylic acid 49. *Reagents and Conditions:* i) **49** (1 eq.), $SOCl_2$, reflux, 6h, ii) *p*-nitro phenol (1.5 eq.), pyridine (1.1 eq.), chloroform, reflux, 36 h, 65%.

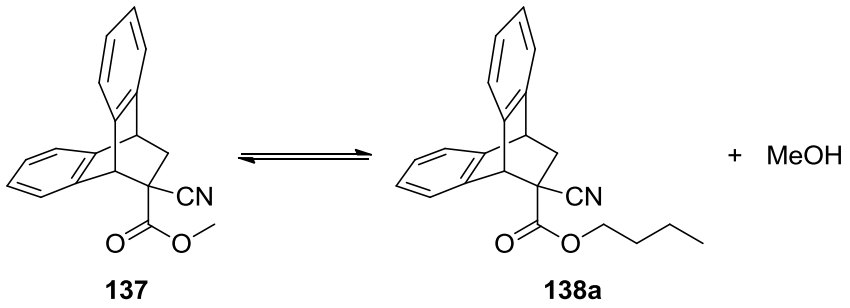
Anthracene ester	Reaction time (days)	% yield
138a	1.5	6
138b	1.5	25
138c	1.5	50
138d	7	23
139a	1.5	38
139b	1.5	48
139c	2	42
139d	3	37
139e	1.5	65
139f	1.5	50
140a	4	28
140b	1.5	38[a]
140c	4	31

Table 3.1: Reaction times and % yields for synthesis of anthracene esters 138-140

[a]compound as a mixture of two inseparable diastereisomers (1:1)

3.2.3 Direct *trans*-esterification method

While it was possible to prepare the desired esters using the 4 step protocol outlined, it would be industrially more attractive to transform the initial ester **137** to the desired esters **138a** by a one-step *trans*-esterification process rather than *via* the carboxylic acid **49**. This would shorten the route significantly. Initially the reaction between methyl ester **137** and *n*-butanol was investigated, using *p*-toluenesulfonic acid as an acid catalyst and an excess of *n*-butanol as solvent to drive the equilibrium towards the desired adduct **138a**. The reaction was undertaken using a distillation head to remove the methanol produced and thus push the equilibrium towards product **138a** (Scheme 3.12).



137 **138a**

Scheme 3.12: Direct trans-esterification of 137. *Reagents and Conditions*: **137** (1 eq.), TsOH (0.5 eq.), *n*-butanol (excess), reflux, 2 days 43%.

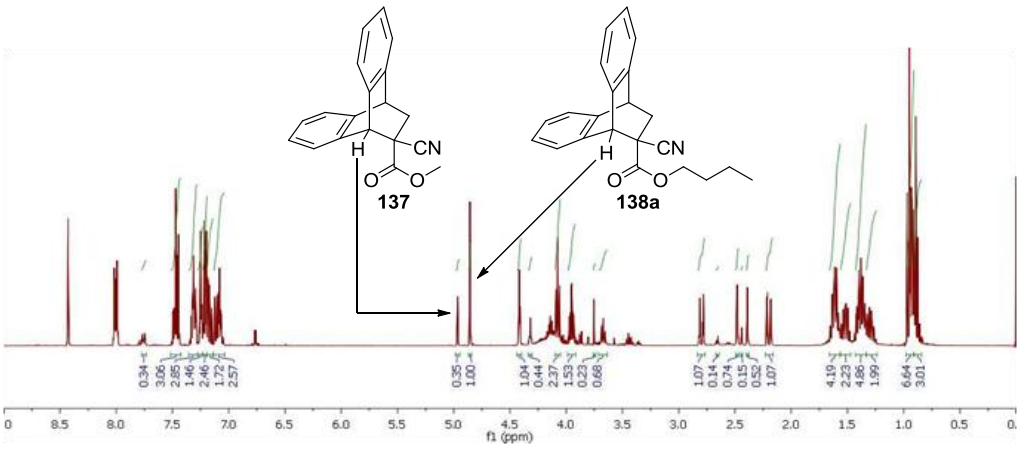


Figure 3.8: ^{1}H NMR of crude *n*-butyl anthracene adduct 138a produced *via* a *trans*-esterification approach

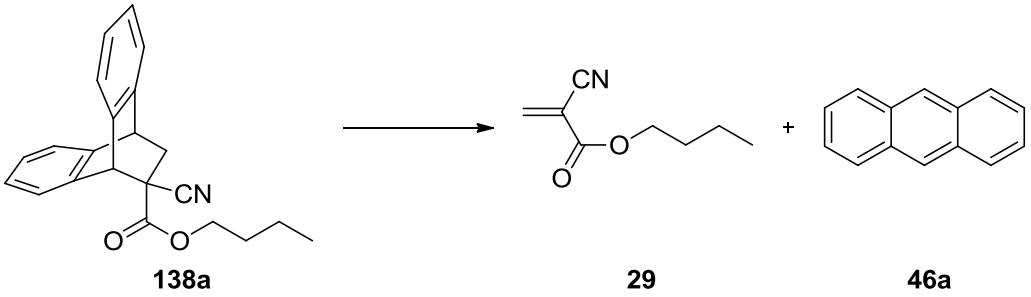
Although the method yielded the desired product **138a**, it was not possible to get the reaction to go to completion even after 2 days (35% starting material **137** remained as determined by 400 MHz ^{1}H NMR, Figure 3.8). In addition, while this example used *n*-butanol as both the reagent and solvent to help in developing a favourable equilibrium, for the other desired alcohols (many of which were solids) this would not be possible.

3.3 Retro-Diels-Alder

The first three steps of the anthracene protected route determined from the initial work with ethyl acrylate **131** transferred easily to the cyanoacrylates with only slight modifications. The final step is the retro-Diels-Alder to remove the anthracene **46a** protecting group and liberate the highly reactive novel cyanoacrylates **138-140**. The *n*-butyl protected ester **138a** was used to optimise this step as the butyl cyanoacrylate monomer **29** liberated is a known compound and therefore its physical properties such as boiling point are already in the literature allowing easy identification.[223] Once the final step had been successfully optimised this route would then be used to generate the complete series of cyanoacrylate monomers **141-143**.

The two methods used previously for the ethyl acrylate adduct **131** were re-investigated for cyanoacrylate adduct **138a**. Firstly the use of high temperatures and vacuum to activate the retro-Diels-Alder reaction (Scheme 3.13). Extreme temperatures were achieved by heating with a hot air pistol. At 138 ^{o}C (3 mbar) a colourless liquid distilled which was confirmed by 400 MHz ^{1}H-NMR to be the desired *n*-butyl cyanoacrylate **29**, thus the retro-Diels-Alder step can be carried out

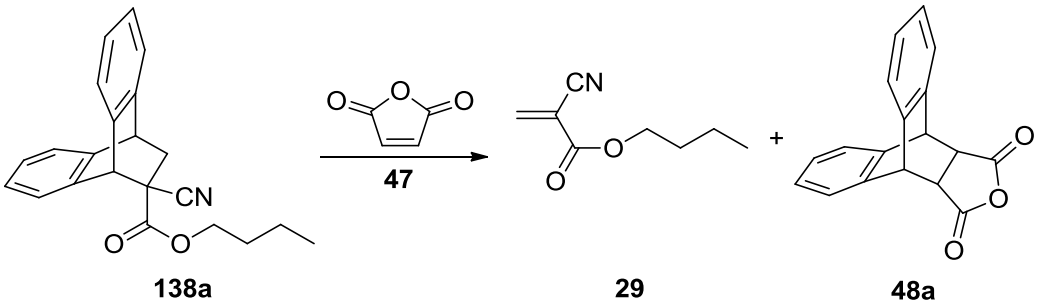
using only heat and vacuum. This would be beneficial for an industrial process as it has potential for use in a continuous flow reactor, with the anthracene starting material being regenerated and recycled.



138a **29** **46a**

Scheme 3.13: Retro Diels-Alder reaction – heating method. *Reagents and Conditions*: **138a** (1 eq.), heat under vacuum 200 ^{o}C +, 23%.

The second approach heats the anthracene adduct in the presence of maleic anhydride **47**. When this method was attempted with the ethyl acrylate adduct **131** none of the desired product was observed. For this reason the reaction was firstly carried out in d_6-benzene at 80 ˚C in order to monitor the reaction by ^{1}H NMR. Butyl anthracene adduct **138a** was refluxed in the presence of maleic anhydride **47** for four days, however it appeared that no reaction had occurred by ^{1}H-NMR. The reaction was repeated in xylene at 140 ˚C for 2 days in order to determine whether a higher reaction temperature was required for the substitution reaction to occur (Scheme 3.14). After 48 h the reaction was removed from the heat and benzene was added to precipitate out the anthracene maleic anhydride adduct **48a**, this was filtered off leaving butyl cyanoacrylate **29** in solution. The main impurity was small amounts of the anthracene maleic anhydride adduct **48a** that didn't precipitate out, this can be removed by distillation to give **29** as a colourless liquid (Figure 3.9).



Scheme 3.14: Retro Diels-Alder reaction – maleic anhydride method. *Reagents and Conditions*: **138a** (1 eq.), maleic anhydride **47** (3 eq.), hydroquinone (0.5 eq.), phosphorus pentoxide (0.5 eq.), xylene, reflux, 48 h, 10%.

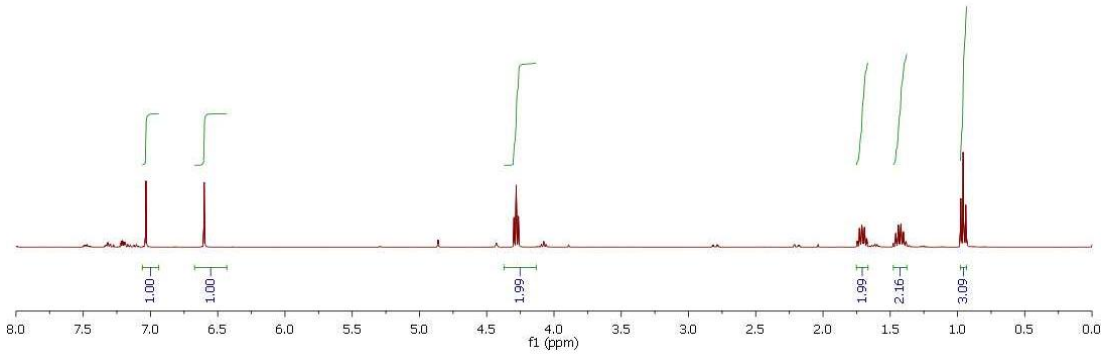


Figure 3.9: ^{1}H NMR of n-butyl cyanoacrylate 29

In this case while the anthracene starting material **46a** was not recycled and the reaction time was longer than the vacuum method it required less harsh conditions *e.g.* lower temperatures, and the majority of by-product **48a** was precipitated out from the desired cyanoacrylate monomer. Thus it was decided to carry out the retro-Diels-Alder reaction using the maleic anhydride protocol on all anthracene esters **138-140** yielding a variety of cyanoacrylate monomers **141-143** (Figure 3.10) in yields ranging from 18-63%.

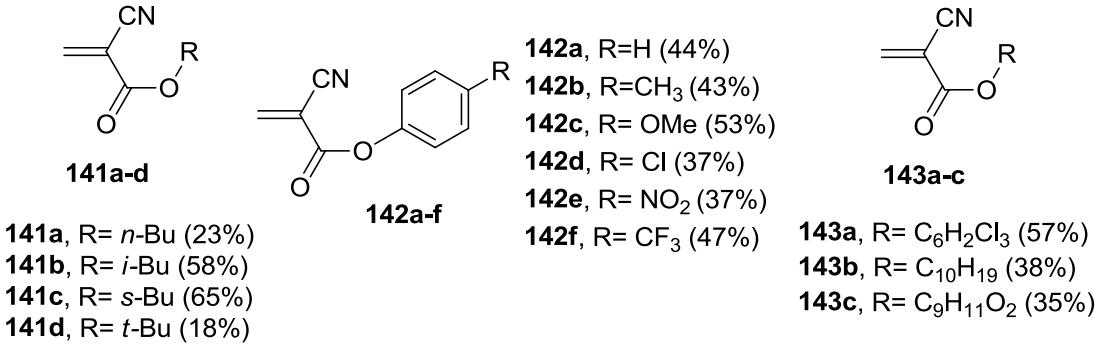
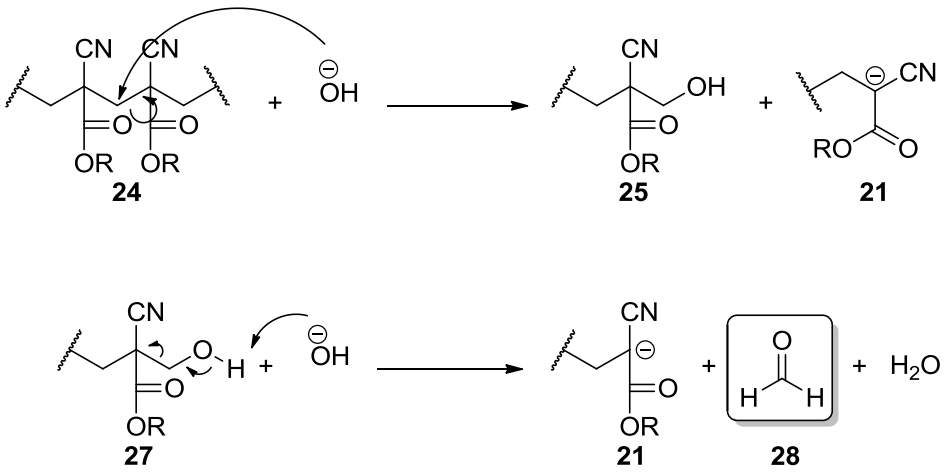


Figure 3.10: Cyanoacrylate monomers 141-143

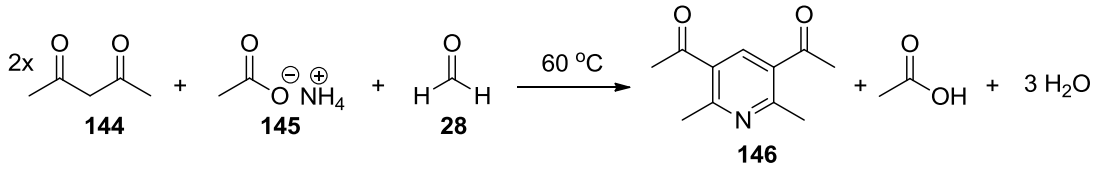
3.4 Polymer degradation

As previously stated, cyanoacrylate polymers **24** can degrade to liberate formaldehyde. Mechanistically this has been proposed to occur *via* nucleophilic displacement of a monomer group with hydroxide followed by base catalysed retro-Kneoevenagel reaction to give **25** and **21** (Scheme 3.15). It is likely that two factors can control the rate of this process. Firstly, the steric environment around the reacting carbon atom will affect the ability of hydroxide to mediate the first step and secondly the stability of the released anion **21** (pKa of malonic ester derivative) will be important in both steps.



Scheme 3.15: Degradation of cyanoacrylate polymer 24

The acetyl acetone (acac) method first published by Nash in 1953[224] is a widely applied standard procedure for the analysis of formaldehyde. The method is based on the Hansch reaction which involves the cyclisation of 2,4-pentanedione (acac) **144**, ammonium acetate **145** and formaldehyde **28** at 60 °C (Scheme 3.16). The resulting product is the highly fluorescent dihydropyridine 3,5-diacetyl-1,4-dihydrolutidine **146** which can be detected by UV-vis spectroscopy at 412 nm.[225]



Scheme 3.16: Reaction of formaldehyde 28 with 2,4-pentanedione 144

Release of formaldehyde from poly(ethyl cyanoacrylate) P(ECA), poly(octyl cyanoacrylate) P(OCA) and poly(2-octyl cyanoacrylate) P(2-OCA) have been studied previously using the acac method. It has been reported that higher alkyl poly-cyanoacrylates exhibited less tissue toxicity because they degrade and release formaldehyde slowly.[226] Degradation studies performed at 85 °C under accelerated conditions showed P(ECA) released significantly higher levels of formaldehyde than P(OCA) and P(2-OCA); 90 μg/mL over 7 days compared to 50 μg/mL (Figure 3.11).[227] P(OCA) and P(2-OCA) gave very similar results suggesting little difference between the secondary and the primary ester. The production of formaldehyde is accompanied by a decrease in the average molecular weight of the polymer. This was shown by the change in average molecular weight of P(ECA), from 1427 to 990 when the polymer was dissolved in 95% acetonitrile, 5% water solution and heated to 80 °C for 24 h.

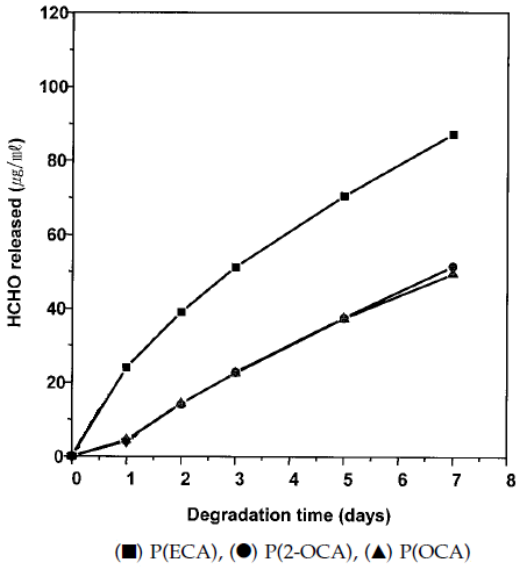
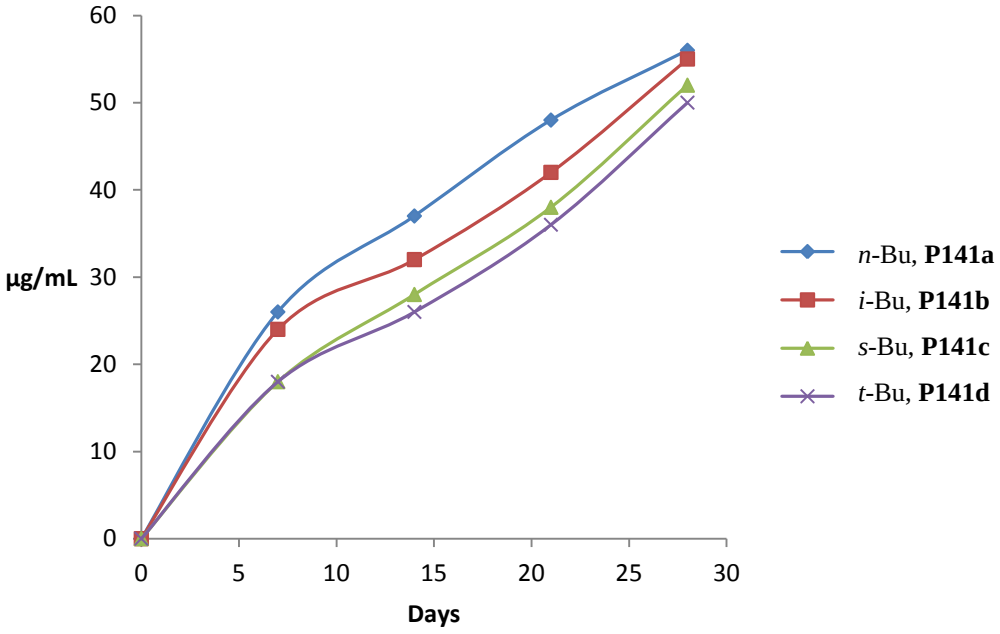


Figure 3.11: Release profile of formaldehyde from P(ECA), P(2-OCA) and P(OCA)[227]

3.4.1 Detection of formaldehyde in the decomposition of novel cyanoacrylate polymers P141-P143

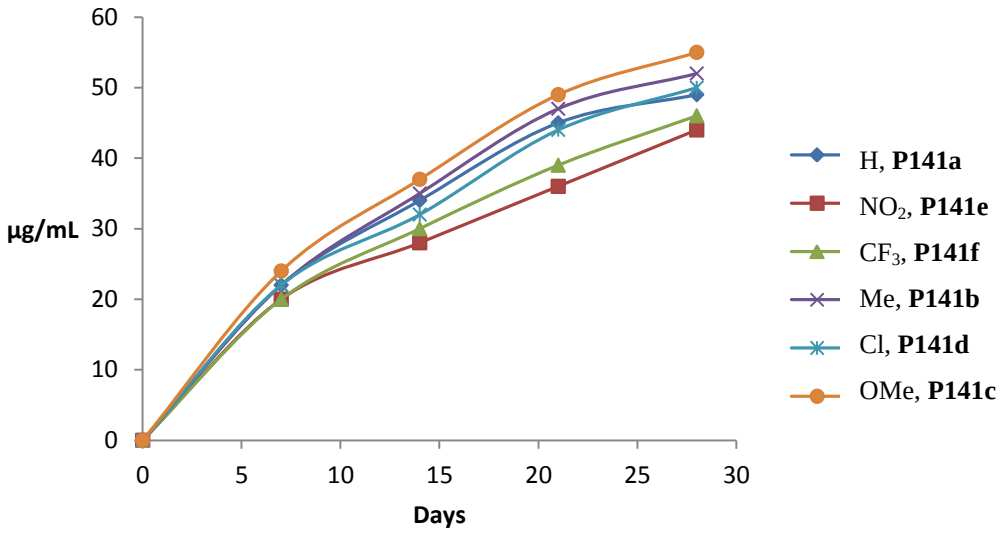
The monomers **141-143** produced in section 3.3 were polymerised by the addition of water (1-2 drops) to give polymers **P141a-d**, **P142a-f** and **P143a-c**. These polymers were suspended in water for 28 days at room temperature and the formaldehyde liberated measured every 7 days. The resulting polymers were added to pentane-2,4-dione reagent **144** (2 eq.), PBS extract solution (0.1 eq.) and PBS solution (0.9 eq.) in deionised water (0.05 M). The solution was heated to 60 ^{o}C for 10 min and then cooled in ice for 2 min. The UV absorption at 412 nm was recorded within 20 min of removal from the ice. This was carried out after 7, 14, 21 and 28 days from polymerisation. The amount of formaldehyde released was calculated using the pre-determined calibration graph (see appendix).

The first series of polymers to be compared were the C4 isomers **P141a-d** differing in their steric hindrance around the ester functionality. All four materials released between 50 – 56 µg/mL over the course of the four weeks (Graph 3.1). This was intermediate between the ethyl, P(ECA) 90 µg/mL and the octyl P(OCA) 50 µg/mL. There were however slight differences between the four polymers, the highest amounts of formaldehyde were released by *n*-Bu and *i*-Bu cyanoacrylate polymers **P141a** (56 µg/mL) and **P141b** (55 µg/mL). The lowest amount of formaldehyde and hence the slowest to degrade was the *t*-Bu polymer **P141d** (50 µg/mL). The order of stability (**P141d** > **P141c** > **P141b** > **P141a**) indicates that the steric environment around the ester is important in determining the rate of degradation and that the more hindered isomers **P141c-d** liberate formaldehyde more slowly (although the difference between all four materials **P141a-d** was relatively small). There appears to be a change in rate for all the substrates between week 1 and 2 but the low number of data points makes this uncertain.



Graph 3.1: Formaldehyde released from polymers P141a-d over 4 weeks

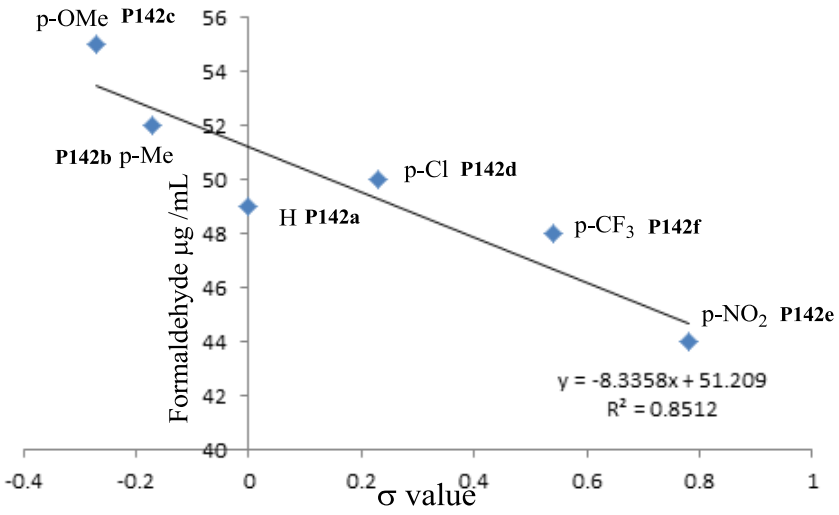
In order to monitor the electronic effect on the rate of degradation, a range of *para*-substituted phenol polymers **142a-f** were compared where the steric parameters were similar but the electronic effect on the stability of the malonitrile anion **21** produced was significantly different. As before there was relatively little difference between the amount of formaldehyde released (44 - 55 µg/mL) but there was an observable trend showing electron withdrawing groups provided the best stability towards degradation, (Graph 3.2).



Graph 3.2: Formaldehyde released from polymers P142a-f over 4 weeks

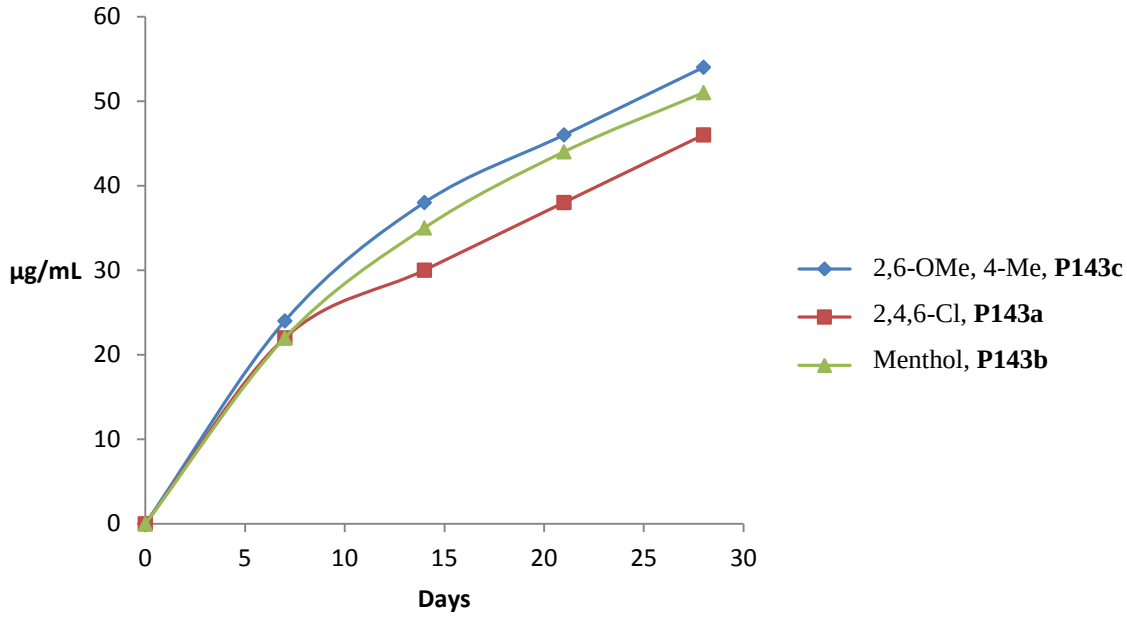
The degradation rate (**P142f** < **P142a** ~ **P142d** < **P142b** < **P142c** or NO_2 < CF_3 < H ~ Cl < Me < OMe) generally parallels the acidity of the malonitrile leaving groups in water and the Hammett σ para parameters.[228] The slowest degradation was observed by *p*-NO_2 (44 µg/mL) **P142e** and *p*-CF_3 (48 µg/mL) **P142f** polymers, two highly electronegative groups. The highest levels of formaldehyde were released by the electron donating *p*-OMe **P142c** (55 µg/mL) and *p*-Me **P142b** (52 µg/mL) polymers. However *p*-Cl (50 µg/mL) **P142d** and phenol (49 µg/mL) **P142a** gave very similar results, showing marginal differences in degradation rates. The order or degradation

rate is opposite to that expected based upon the leaving group ability of the malonitrile groups. As the polymer degrades the polymer chain is 'unzipped' generating an anion. The ability of the R group to stabilise this anion through delocalisation should affect the rate of degradation. As before there appears to be a difference in degradation rate occurring between 1-2 weeks with the electron withdrawing derivatives undergoing this change more obviously. This may indicate a change in mechanism. Hydrolysis of the ester groups on the polymers to carboxylic acids are more likely to occur with the electron poor phenol esters **P142e-f** than electron rich derivatives **P142b-c**. Once hydrolysis has taken place to give a cyanoacrylic acid group degradation to give formaldehyde is less likely to take place at this position on the polymer chain. In addition phenols are known to react with formaldehyde to produce phenol formaldehyde adhesives (PF resins) such as Bakelite. Liberated phenol could scavenge any formaldehyde produced and this might show up in a significant difference in rate of formaldehyde liberation over time depending upon the relative rates of hydrolysis verses formaldehyde generation. This may be one reason to explain the trend that formaldehyde formation decreases with the increasing leaving group ability of the phenol.



Graph 3.3: Formaldehyde released from polymers P142a-f verse Hammett σ-parameter

The final series of polymers **P143a-c** were those that included R groups with medicinal properties (Graph 3.4). The three polymers gave results between 45-55 µg/mL, this is within the same range as the above phenol series **P142a-f**.



Graph 3.4: Formaldehyde released from polymers 143a-c over 4 weeks

The slowest degradation was observed for the 2,4,6-trichlorophenol cyanoacrylate polymer **P143a (**45 µg/mL). This is similar to the *p*-nitrophenol analogue **P142e** (44 µg/mL) and slower than the related *p*-chlorophenol derivative **P142d** (50 µg/mL). This is again confirming the trend that more electron withdrawing substituents lead to a decrease in the loss of formaldehyde, (pKa of *p*-nitrophenol = 7.16, 2,4,6-trichlorophenol = 6.23, phenol = 9.98, *p*-chlorophenol = 9.38 and *p* -methoxyphenol = 10.21).[229] Comparison with the 2,6-dimethoxy-6-methyl phenol derivative **P143c** containing three electron donating groups confirms this but interestingly for the phenol derivatives the electronic effect was more pronounced than any steric effect. The rate of formation of formaldehyde from the menthol derivative **P143b** (50 µg/mL) parallels that of the *t*-Bu **P141d** (50 µg/mL) and *s*-Bu **P141c** (52 µg/mL)

derivatives. This is not surprising as steric congestion at the α- carbon of the ester alkoxy group is similar in **P143a** and **P141c-d**, as is their pKa's (*t*-BuOH = 18, Menthol = 19.5).[230]

3.5 Conclusion

A synthetic route using anthracene as a protecting group has been applied to the synthesis of acrylate and cyanoacrylate monomers. The proposed route was successfully used for the production of novel cyanoacrylate monomers **141a-d**, **142a-f**, **143a-c** differing in the steric and electronic nature of the ester substituents. These monomers were allowed to polymerise in the presence of hydroxyl ions and the degradation of the resulting polymers **P141a-d**, **P142a-f**, **P143a-c** was monitored using a formaldehyde assay.

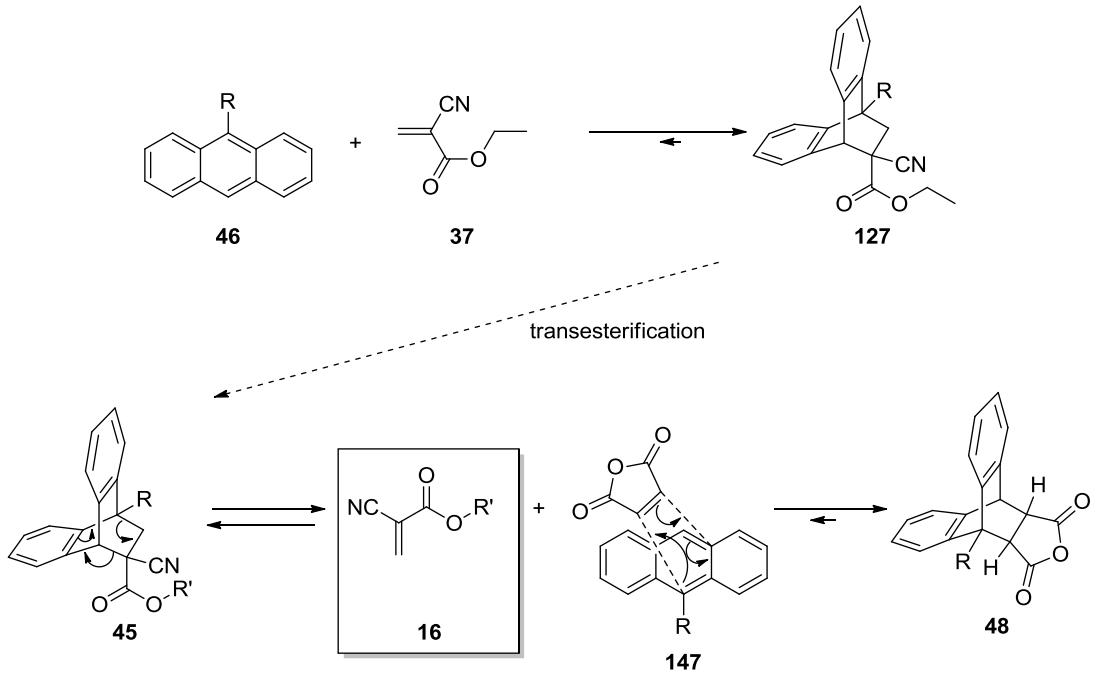
Formaldehyde monitoring showed the slowest degradation was observed for the *p*-NO_2 **P142e**, *p*-CF_3 **P142f** and the 2,4,6-trichlorophenol derived **P143a** polymers containing strongly electron withdrawing groups. While polymers with strongly electron donating groups e.g. *p*-methoxy **P142c** and 2,6-dimethoxy-4-methylphenol **P143c** showed the opposite effect. Interestingly for phenol derivatives the electronic effect was more pronounced than any steric effect and was the reverse to that expected for the accepted mechanism of formaldehyde formation by retro-Knoevenagel reaction. Instead the data hints that for esters with good leaving groups (e.g. pKa of phenols between 6.2-7.2), competitive hydrolysis may occur over time which suppresses formaldehyde build-up by either decreasing the rate of retro-Knoevenagel reaction or scavenging liberated formaldehyde *in situ*. For alkyl ester

substituents **P141a-d** with poorer leaving group ability (pka 16-19) then steric parameters become dominant, presumably due to decomposition by the accepted retro-Knoevenagel pathway.

4.0 Substituted Anthracene Investigations: Finding a better anthracene derivative for a viable industrial cyanoacrylate process.

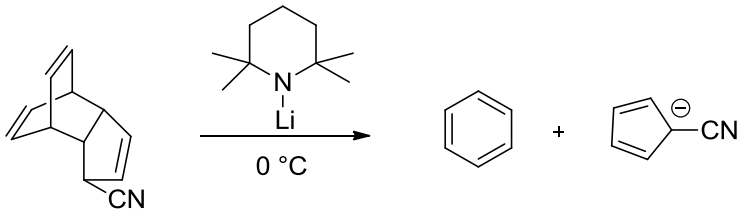
4.1 Introduction

Previous investigations have shown the anthracene **46a** (R = H) protected route for the synthesis of a range of cyanoacrylates **16** was a viable process (Scheme 4.1). However the forward Diels-Alder[208] (**46→127**) step requires long reaction times (depending upon the temperature) and the retro-Diels-Alder step (**45→16**) is slow, low yielding and also requires high temperatures. For any commercial industrial process these steps need to be optimised and temperatures lowered as much as possible to save on energy costs. For this route to be improved changes need to be made in both the first step and the final step.



Scheme 4.1: Route to cyanoacrylates

Cycloaddition/retro-cycloaddition sequences are equilibria. For [4+2] cycloadditions this equilibrium normally favours the Diels-Alder adduct because of thermodynamics, (lose two C=C π bonds and gain two C-C σ bonds).[231] Typically therefore retro-Diels-Alder reactions are carried out at high temperatures. Retro-reactions have been performed at low temperatures but only when one of the retro-products is either highly volatile or can be trapped out by another species (thereby removing it from the equilibrium). Many strategies have been used to facilitate retro-Diels-Alder reactions at low temperatures, for example the use of a base to strategically deprotonate one of the retro-products can bias the equilibrium,[232] (Scheme 4.2). The strategy used here employs an excess of maleic anhydride to trap out the anthracene product. Anthracene benefits from favourable re-aromatisation during the retro-reaction and also gives the insoluble maleic anhydride/anthracene adduct **52** which biases the equilibrium.

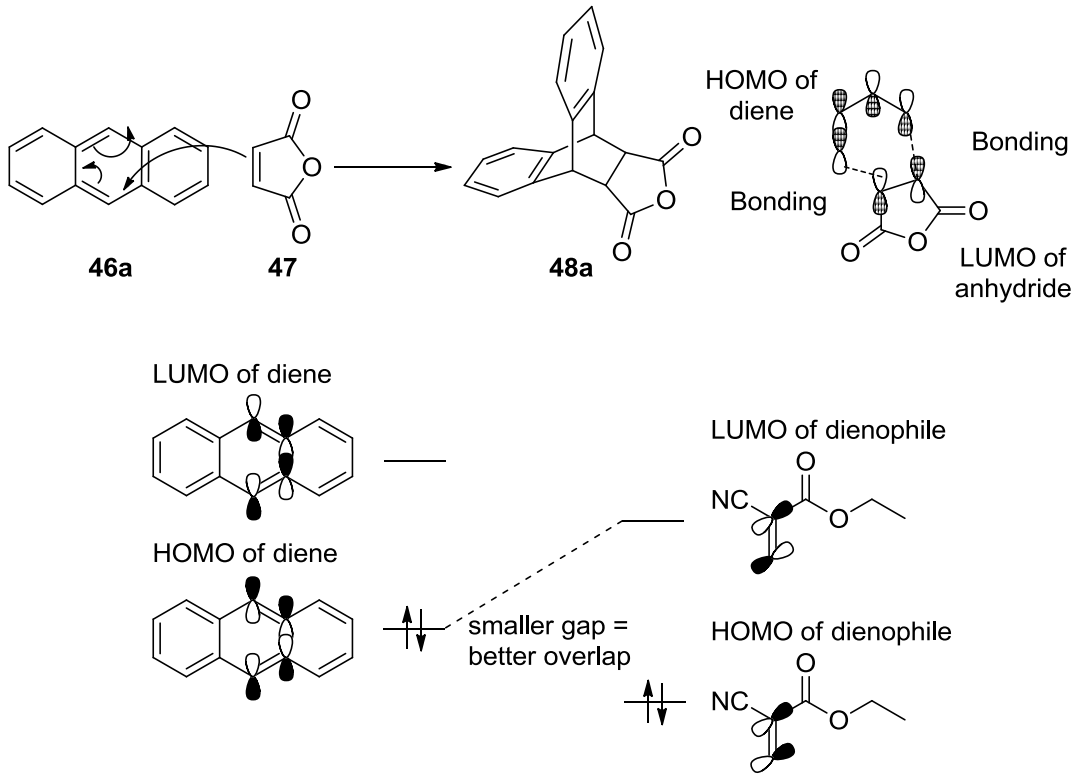


Scheme 4.2: Low temperature base mediated retro-Diels-Alder reaction

4.1.1 The rates of Diels-Alder and retro-Diels-Alder reactions

The rates of both forward and backward reactions can be controlled electronically by changing the structure of the diene or dienophile component. In cycloadditions orbitals need to be available with the correct symmetry in order for the reaction to proceed. During 'normal' Diels-Alder reactions the HOMO of the diene (e.g. anthracene) combines with LUMO of the dienophile (e.g. ethyl cyanoacrylate)

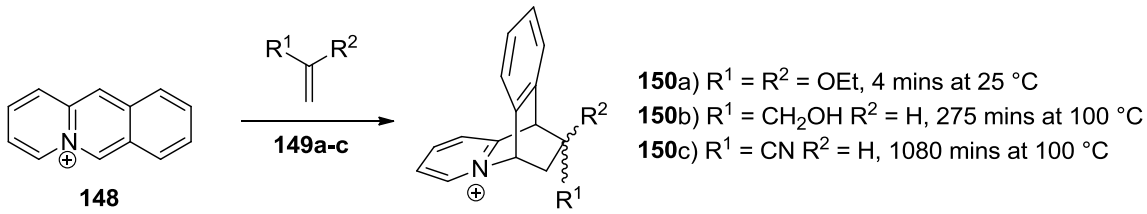
(Scheme 4.3). In order for the reaction to occur there must be a bonding interaction at each end and the rate of the reaction will be controlled by the HOMO/LUMO energy separation. Electron withdrawing substituents on the dienophile lower the LUMO and electron donating substituents on the diene raise the HOMO providing a lower energy gap between the reacting orbital's and a faster reaction as a consequence. For example, the Diels-Alder reaction between anthracene **46a** and maleic anhydride **47** readily occurs because the symmetry is correct and there is a good match between the energy of the anthracene HOMO and the maleic anhydride LUMO (due to two electron withdrawing groups on the dienophile).[233]



Scheme 4.3: Molecular orbitals of anthracene 46a reacting with maleic anhydride 47 and ethyl cyanoacrylate 48a

In reverse electron demand Diels-Alder reactions the opposite is true, it is the HOMO of the dienophile that is closer in energy to the LUMO of the diene. In these cases electron donating groups on the dienophile will increase the rate. Hence,

reaction of the iminium ion diene **148** with dienophiles **149a-c** shows increasing rates with increasing electron donation of the substituents (Scheme 4.4).

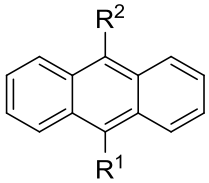


Scheme 4.4: Diels-Alder reaction between pyrido[1,2-b]isoquinolinium and dienophile 149a-c[234]

Few reports have emerged dealing with substituents effects in retro-Diels-Alder reactions.[222] Those have indicated that while electron donating substituents generally increase the rate of the backward reaction, electron withdrawing substituents can have the same effect. This was explained due to the movement towards a biradical mechanism.

4.1.2 Approach to improving first step (46→127)

The first step (**46→127**) could be improved by altering the electronic nature of the groups R^1 and R^2 on the anthracene **46a-l** (Figure 4.1).[235] It should be possible to alter the rate of both the initial Diels-Alder and the final retro-Diels-Alder reaction by tailoring this substituent (see section 4.1.4). Generally the forward reaction should be increased by electron donating groups at the 9-position.[195]



46a-l

Figure 4.1: 9, 10-substituted anthracene

4.1.3 Approach to improving the final step (45→16)

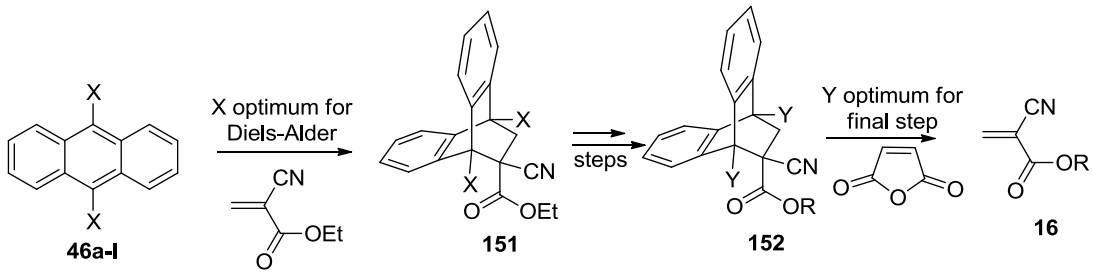
While the effect of different substitution at C-9 or C-10 of the anthracene dienes on the rate of the first step (**46→127**) is relatively simple to predict, the effect on the rate of the final step (**45→16**) is less certain. That is because the final step involves two separate processes, the retro-Diels-Alder reaction itself followed by the trapping of the anthracene derivative **46a-m** with maleic anhydride. Any change in substituent at the anthracene will change the rates of both these processes. As previously stated, other studies have shown that the rate of the retro-Diels Alder reaction can be accelerated by both electron withdrawing and donating substituents.[222]

Both cyanoacrylate and maleic anhydride are reactive dienophiles and there will be a competition between them for the anthracene derivative. Another approach to increase the rate of the final step would be to replace maleic anhydride with a more reactive (lower energy LUMO) dienophile such as 1,1,2,2-tetracyanoethene.

4.2 Aim

In order to identify an anthracene derivative **46a-l** that is better suited to an industrial synthesis of cyanoacrylate derivatives it was decided to study the effect of different substituents at the C-9 and C-10 position of anthracene upon the first step (conversion to give **127**) and in the last step (conversion to give **16**) of the process. Whether 1,1,2,2-tetracyanoethylene would be a better candidate as a anthracene trapping agent was also studied. If it was found that one substituent was optimal for the first step, but a different one for the last step it may be possible to interconvert

the anthracene substituents (**151→152**) midway in the overall synthetic strategy to take advantage of this (Scheme 4.5).



Scheme 4.5: Potential modification of anthracene protected route

4.3 Choice of anthracene derivatives

A number of substituted **46a-m** anthracenes were chosen which included a range of electron withdrawing and electron donating groups at C-9 and C-10 for comparison against the current model; anthracene **46a** (Figure 4.2).

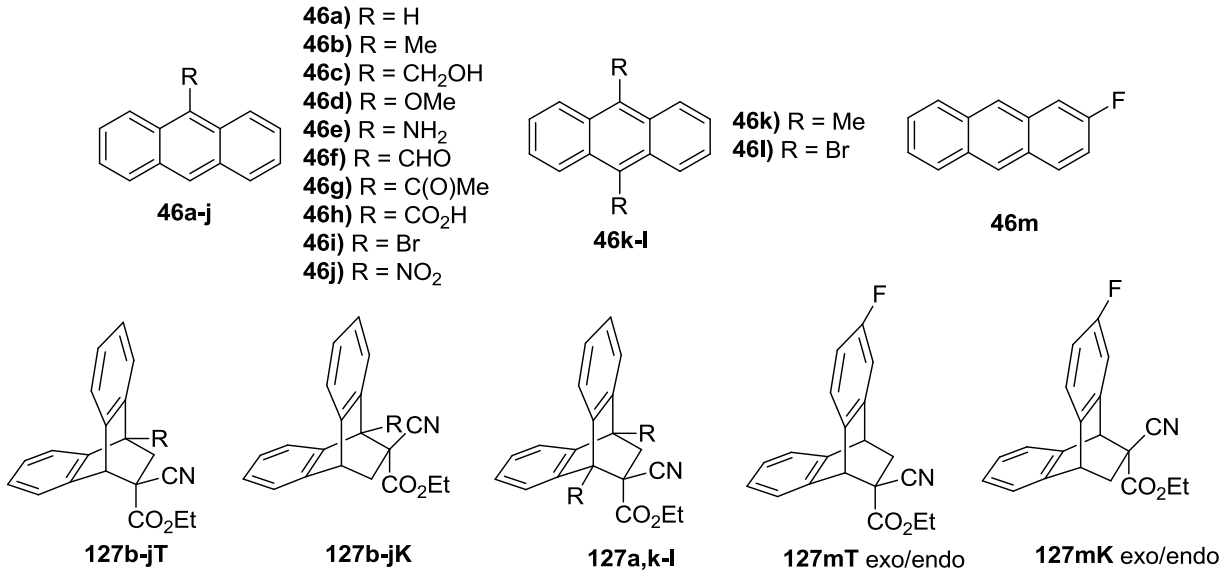


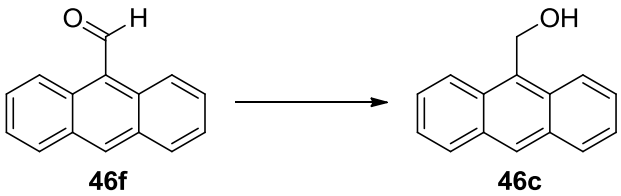
Figure 4.2: Substituted anthracenes 46a-m

Mono-substituted 9-anthracenes **46b-j** and fluorinated anthracene **46m** would lead to two possible regioisomeric products (**127b-jT**, **127b-jK** and **127mT, 127mK** respectively). However, any mixture of Diels-Alder adduct isomers would ultimately

be destroyed in the retro step meaning this was not necessarily a problem. The two 9,10-disubstituted products **46k** and **46l** would avoid this complication giving **127k-l** only (assuming both R groups were the same).

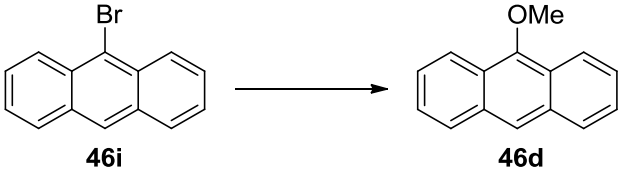
4.4 Synthesis of substituted anthracenes

Anthracenes **46a-b**, **f-i** and **k-m** were commercially available and were used without further purification. The commercially available 9-anthracenecarboxaldehyde **46f** was reduced with $NaBH_4$ to give 9-hydroxymethylanthracene[236] **46c** in 46% yield (Scheme 4.6).



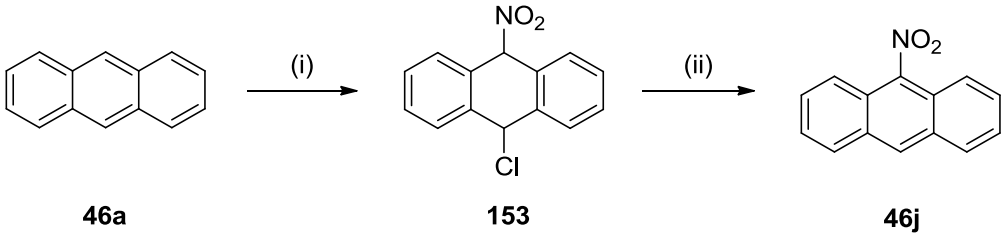
Scheme 4.6: Synthesis of 9-hydroxymethylanthracene 46c. *Reagents and Conditions:* 9-anthracenecarboxaldehyde **46f** (1 eq.), $NaBH_4$ (2 eq.), THF, 0 ^oC then reflux, 16 h, 46%.

A Buchwald-Hartwig[237] coupling between methanol and 9-bromoanthracene **46i** utilising palladium (II) acetate and X-Phos as ligand furnished 9-methoxyanthracene **46d** (Scheme 4.7). Careful chromatography was required to purify **46d** but it was impossible to remove 20% residual anthracene **46a** (from an incomplete coupling).



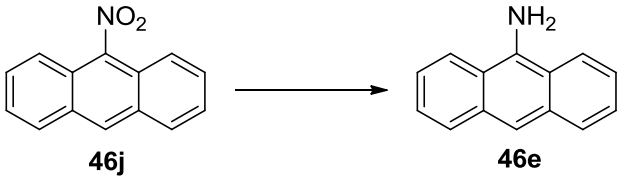
Scheme 4.7: Synthesis of 9-methoxyanthracene 46d. *Reagents and Conditions:* 9-bromoanthracene **46i** (1 eq.), methanol (2 eq.), Cs_2CO_3 (1.5 eq.), $Pd(OAc)_2$ (0.05 eq.), X-Phos (0.05 eq.), toluene, 90 ^oC, 3 days, 15%.

It was possible to make 9-aminoanthracene **46e** *via* a three step procedure from anthracene **46a**. Firstly, anthracene **46a** was treated with concentrated HNO_3/HCl in glacial acetic acid to give 9-nitro-10-chloro-9,10-dihydroanthracene **153** as a yellow precipitate. This was converted *in situ* with 10% NaOH[238] to give 9-nitroanthracene **46j** in 61% yield over the two steps (Scheme 4.8).



Scheme 4.8: Synthesis of 9-nitroanthracene 46j. *Reagents and Conditions*: (i) anthracene **46a** (1 eq.), HNO_3 (1.5 eq.), 1:1 CH_3CO_2H: HCl, (ii) NaOH 10%, 60-70 ^oC, 61% over two steps.

Reduction of 9-nitroanthracene **46j** with $SnCl_2$/HCl in acetic acid, followed by reaction *in situ* with 5% NaOH produced 9-aminoanthracene **46e** in 39% yield (Scheme 4.9).[239] This molecule was found to be unstable and had to be stored in the dark in a freezer. It was used in experiments immediately before it could degrade.



Scheme 4.9: Synthesis of 9-aminoanthracene 46e. *Reagents and Conditions:* 9-nitroanthracene **46j** (1 eq.), CH_3CO_2H, $SnCl_2$ (5 eq.), HCl, 30 min, 80 ^oC; 5% NaOH, 30 min, r.t. 39%.

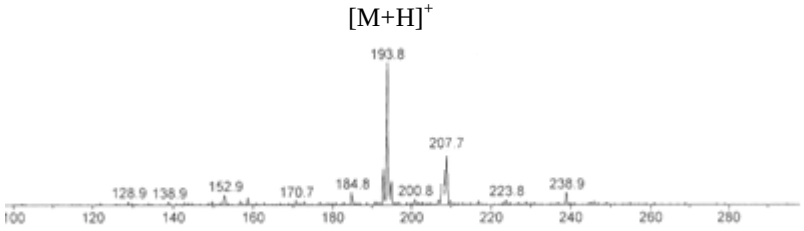


Figure 4.3: Mass spectroscopy of 9-aminoanthracene 46e

4.4.1 Comparison of rates for the forward Diels-Alder reaction

With a range of substituted anthracenes **46a-m** in hand it was possible to investigate their reactions with ethyl cyanoacrylate **37**. In order to gather data into the relative rates of reaction for each of the anthracene derivatives the conversion by ^{1}H NMR at a specific time point was measured as a direct comparison. Anticipating that some reactions would be faster than the parent anthracene **46a** and others slower, conditions which provided an intermediate conversion of 61% for anthracene itself were chosen (heating at 70 ^{o}C for 7 h in d_8 toluene as solvent with an 1.1 eq. excess of ethyl cyanoacetate). All the reactions were carried out at the same concentration (0.25 M) and an internal standard (anisole) was added (50 mol%) to each reaction to allow accurate ratios of products to be determined by ^{1}H NMR. The NMR standard anisole was subjected to reaction with ethyl cyanoacrylate **37** to check it was un-reactive under the standard reaction conditions. The reaction could be followed by the loss of the characteristic aromatic peaks for each anthracene derivative and the increase in peaks between at 1.7 ppm and 3.0 ppm corresponding to the diastereotopic CH_2 group in the bridge of the adducts. Figure 4.4 shows the corresponding regions for the 9,10-dimethyl anthracene **46k** reaction as way of illustration.

The majority of the reactions were successful in providing the desired adducts, however 9-aminoanthracene **46e** failed to give **127e** instead it appeared to decompose under the reaction conditions. Consequently, it was not possible to evaluate the 9-amino derivative **46e** any further. The Diels-Alder reaction of 9-methoxyanthracene **46d** also caused issues. Due to the 20% contamination with anthracene **46a** two Diels-Alder adducts were obtained in a 4:1 ratio.

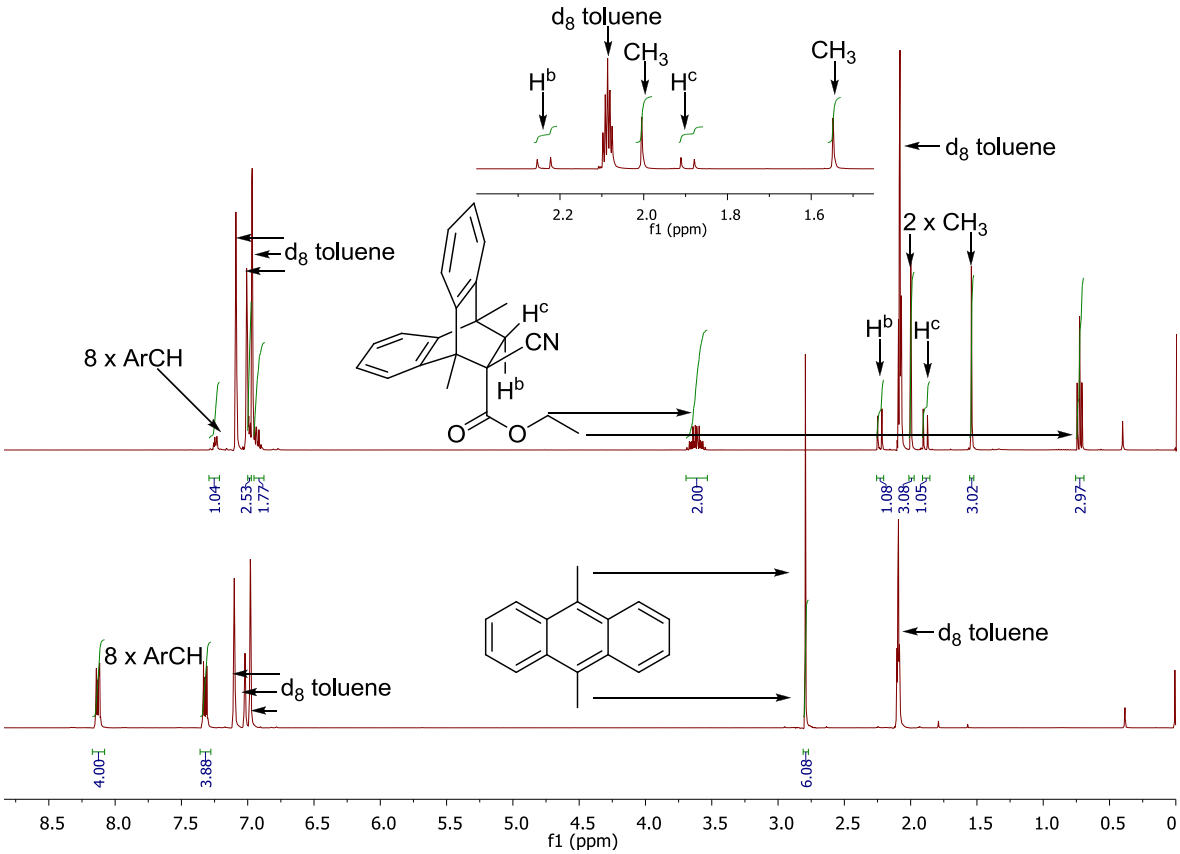


Figure 4.4: ^{1}H NMR of 9,10-dimethyl anthracene 46k and 9,10-dimethyl anthracene adduct 127k

Comp.	Subs.	Conversion to kinetic product K (7 h / 70˚C)[a]	Reaction time (days)	Yield of thermodynamic product T (time / 110˚C)
46a	H	61%	1	81%[b]
46b	Me	100%	0.33	88%[c]
46c	CH_2OH	43%	2	48%
46d	OMe	80%[d]	2	85%[d]
46e	NH_2	-	-	-
46f	CHO	38%	2	41%
46g	C(O)Me	43%[e]	2	10%
46h	CO_2H	0%	3	10%
46i	Br	63%[f]	2	26%
46j	NO_2	0%	3	9%

46k	Me	100%	0.33	87%[b]
46l	Br	25%	4	16%[b]
46m	F	60%[g]	2	68%[g]

[a]Ratio determined by 400 MHz ^{1}H NMR, estimated error ± 3%. [b]Only one product possible. [c]5:1 ratio of thermodynamic T: kinetic products K. [d]As a 4:1 inseparable mixture of **127dK** and **127a**, significant reaction to give **127dK** occurs at room temperature. [e]Both regioisomers were formed (ratio **K**:**T** = 2:1). [f]Both regioisomers were formed (ratio **K**:**T** = 16:1) [g]An inseparable mixture of four compounds in a 1:2:2:2 ratio was isolated (each regioisomer produces an *exo* and *endo* product). No further effort was undertaken to establish the identify of each isomer or separate the mixture.

Table 4.1: % conversion of anthracene's 46a-m for Diels-Alder step

With the exception of 9-amino **46e** the order of reactivity (Table 4.1) was found to be **46d>46k~46b>46i~46a~46m>46c~46f~46g>46l>46h~46j**. As expected the electron donating substituents **46b**, **46k** increased the rate of the reaction (it was not possible to get accurate values for **46d**, see later but significant formation of the desired adduct occurs at room temperature), while the electron withdrawing substituents slowed the reaction. The most electron withdrawing substituent **46j** (NO_2 Hammett σ-value = 0.78) exhibited the slowest rate. Intermediate rates were provided by **46f, 46g, 46c** with intermediate σ-values (CHO Hammett σ-value = 0.42, C(O)Me Hammett σ-value = 0.50, CH_2OH Hammett σ-value not available) and the fastest rate of an electron withdrawing substituent by **46i** with the lowest σ-value as expected (Br, Hammett σ-value = 0.23).[240]

The most convenient alternative substrates to anthracene for an industrial process therefore were both 9-methylanthracene **46b** and 9,10-methylanthracene **46k** which resulted in 100% conversion within the 7 h. This is clear due to the disappearance of

the anthracene starting material peaks between 7.0 and 8.5 ppm. Such was the reactive nature of **46k** that it was possible to prepare the adduct **127k** in 78% yield after 4 h at only 40 ˚C.

4.4.2 Kinetic verses Thermodynamic control

Interestingly, the products obtained from 9-monosubstituted anthracenes **46a-j** were dependent upon the reaction conditions. This can be illustrated by methyl substituted compound **46b** (Figure 4.5). At the lower temperature (70 ˚C) the expected kinetic product **127bK** was formed exclusively (the so called 'ortho' adduct), while at higher temperature the thermodynamic product **127bT** ('meta' adduct) was formed predominantly (5:1 after 8 h). The ^{1}H NMR of the thermodynamic product **127bT**, exhibits the signal for H^a as a singlet at 4.77 ppm while for the kinetic product **127bK** it is a triplet at 3.84 ppm due to coupling with the bridgehead methylene group (Figure 4.6). This coupling was readily observable in the COSY spectrum (Figure 4.7).

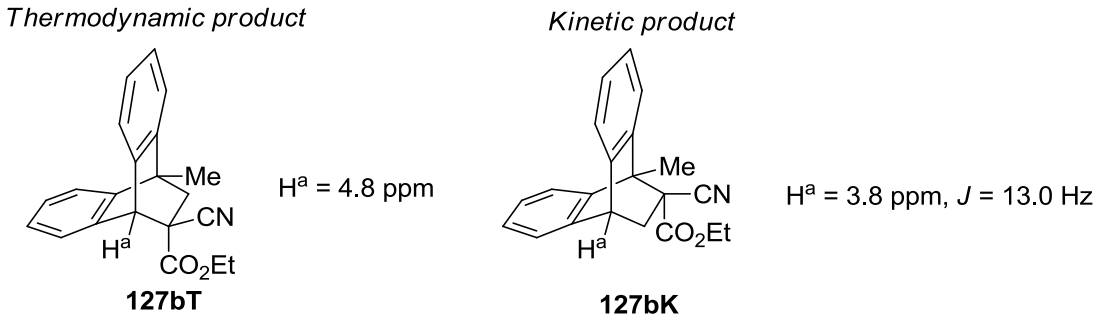


Figure 4.5: Thermodynamic and Kinetic products of 46b

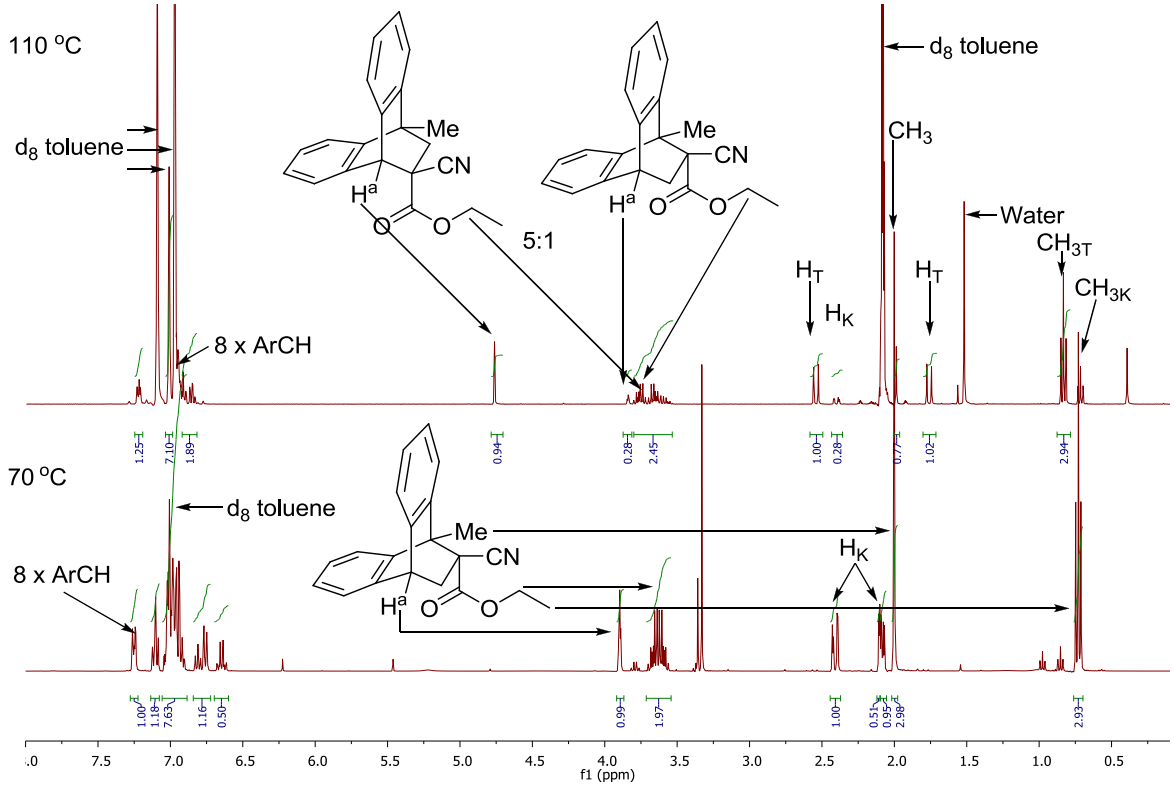


Figure 4.6: ^{1}H NMR of 9-methyl anthracene adduct 127b at 70 °C (kinetic product) and 110 °C (thermodynamic: kinetic product, 5:1)

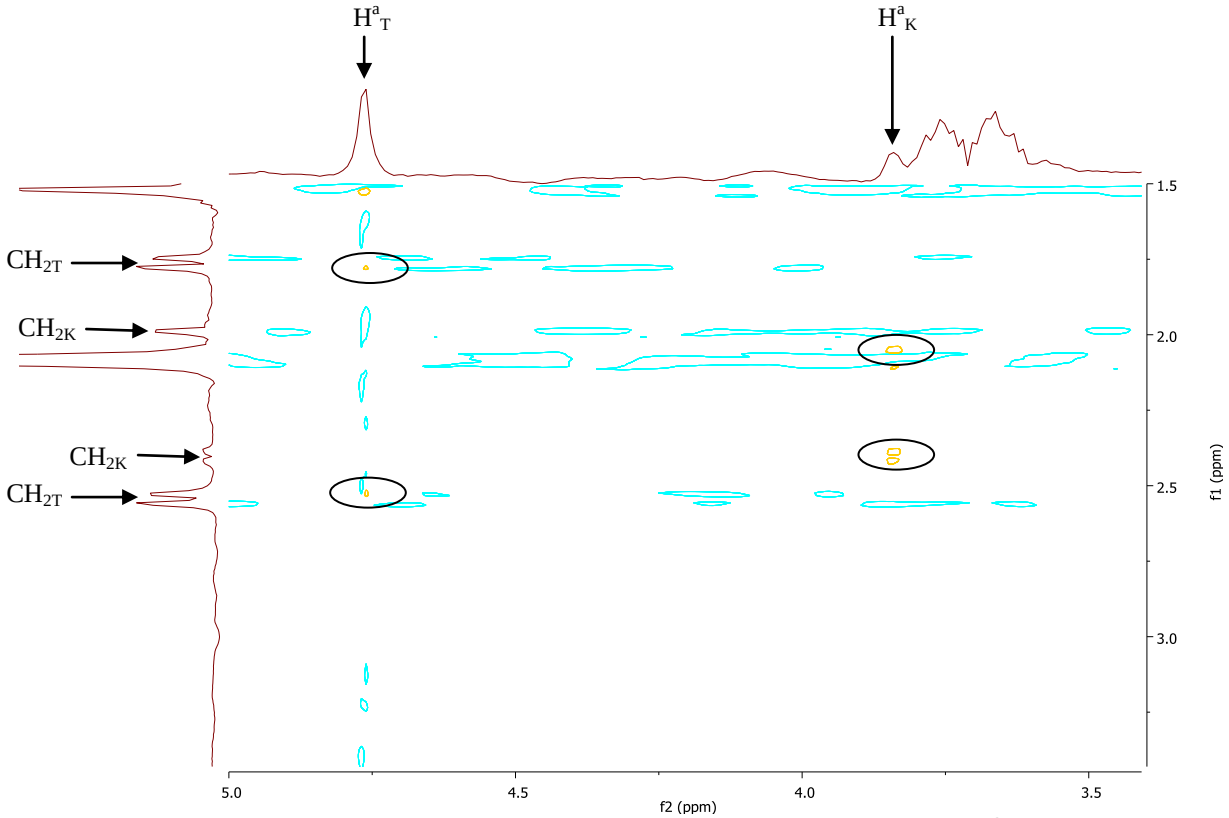


Figure 4.7: COSY of 9-methyl anthracene adduct 127b showing coupling between H^{a} and the methylene group in the thermodynamic and kinetic product

The formation of the thermodynamic product **127bT** when the reaction was carried out at 110 ˚C suggests that the Diels-Alder reaction is reversible under these conditions. The factors that control regiochemistry in Diels-Alder reactions are well known. For example, the reaction of methoxybutadiene **154** with acrolein **155** favours the 'ortho' adduct **156** and electron donating substituents at the 9-position of anthracene **46b-j** would be expected to do the same. The regioselectivity can be explained by analysing the energy gaps of the HOMO/LUMO molecular orbital combinations and the coefficients of the atomic orbitals on these HOMO's and LUMO's, (Figure 4.8). For **154** and **155** the most important interactions occur between the HOMO of the diene and the LUMO of the dienophile (8.5 eV difference in energy). The LUMO of the diene and HOMO of the dienophile energy gap is much higher (13.4 eV) and as such is less important in the analysis of regiochemistry. Best overlap occurs when orbitals of the similar size can interact. Thus for **154** and **155** the 'ortho adduct' is predicted and observed. Alternatively, the same regiochemical outcome can be predicted by a stepwise (non-concerted) mechanism.

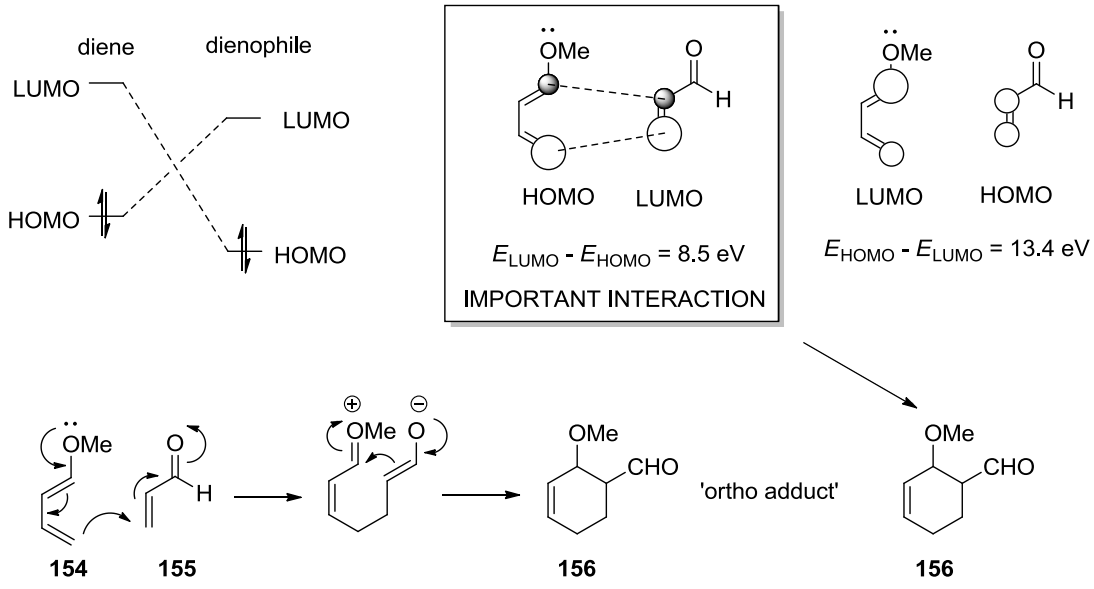


Figure 4.8: Interaction of molecular orbitals in Diels-Alder reactions

The reactions of **46b** (Me), **46c** (CH_2OH), **46f** (CHO), after 7 h showed formation of the products **127bK**, **127cK** and **127fK** respectively (kinetic) while **46d** (OMe), **46g** (C(O)Me), and **46i** (Br) showed mixtures of the two products **127 K:T** (**127d** = 4:1, **127g** = 2:1, **127i** = 16:1) and **127h** (CO_2H) and **127j** (NO_2) showed no products. Compounds **46a**, **46k** and **46l** only furnish one product (due to the symmetry of the molecule) while **46m** formed an inseparable mixture of regioisomers (each showing an *exo* and *endo* product) giving rise to a 1:2:2:2 mixture of isomers. Heating all the 9-monosubstituted substrates at 110 ˚C between 24-78 h furnished the thermodynamic products only **127b-jT**. For each substrate the two products could be easily distinguished by both the chemical shifts of protons H^a, H^b, and H^c and their coupling patterns. For the products **T**, H^a was typically 1.0 ppm higher than in **K**, while the bridge diastereotopic methylene protons were widely separated (0.6-0.9 ppm) in **T** compared to those in **K** (0.2-0.5 ppm) (Figure 4.9).

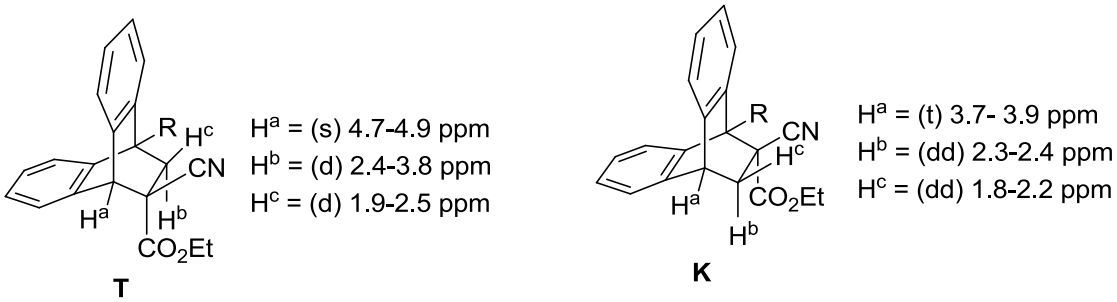


Figure 4.9: Thermodynamic T versus kinetic K products

Comp.	**Subs.**	**^{1}H NMR 127b-jK ppm[a]**	**$\Delta\delta$ of H^b-H^c ppm[a]**	**^{1}H NMR 127b-jT ppm[a]**	**$\Delta\delta$ of H^b-H^c ppm[a]**
46b	Me	H^b = 2.41, H^c = 2.09,	0.32	H^b = 2.60, H^c = 2.01,	0.59
46c	CH_2OH	H^b = 2.29, H^c = 2.00,	0.29	H^b = 2.71, H^c = 2.15,	0.56
46d	OMe	H^b = 2.30, H^c = 2.06,	0.24	H^b = 2.96, H^c = 2.17,	0.79
46f	CHO	H^b = 2.37, H^c = 2.21,	0.16	H^b = 2.94, H^c = 2.35,	0.59
46g	C(O)Me	H^b = 2.35, H^c = 2.22,	0.13	H^b = 3.08, H^c = 2.33,	0.75

46h	CO_2H	[b]	[b]	H^b = 3.14, H^c = 2.55,	0.59
46i	Br	H^b = 2.26, H^c = 2.18,	0.08	H^b = 3.26, H^c = 2.55,	0.71
46j	NO_2	[b]	[b]	H^b = 3.40, H^c = 2.79,	0.61

[a]Measured by 400 MHz ^{1}H NMR. [b]No product detected.

Table 4.2: Chemical shifts of H^b and H^c in 127b-jK and 127b-jT

In frontier molecular orbital terms there are two effects of placing an electron withdrawing substituent on a diene when reacting with an electron poor dienophile. Firstly, the energy gap between the most important HOMO/LUMO interaction is larger (meaning slower reaction) but the difference between the energies of the two different HOMO/LUMO interactions is less than for a conventional diene/dienophile interaction. For diene **46h** the gap is 9.5 eV and 10.4 eV respectively (compared with 8.5 and 13.4 eV for **154** and **155**). The closer difference in energy suggests that both interactions might become important in any analysis of regiochemistry of **46h**. The second is that the polarisation of the orbital coefficients will be significantly altered. Combining both of these effects can lead to loss of regiochemistry. For strongly electron withdrawing substituents, 'meta' compounds can become the fastest formed, with both kinetic and thermodynamic control providing the same product (Figure 4.10).

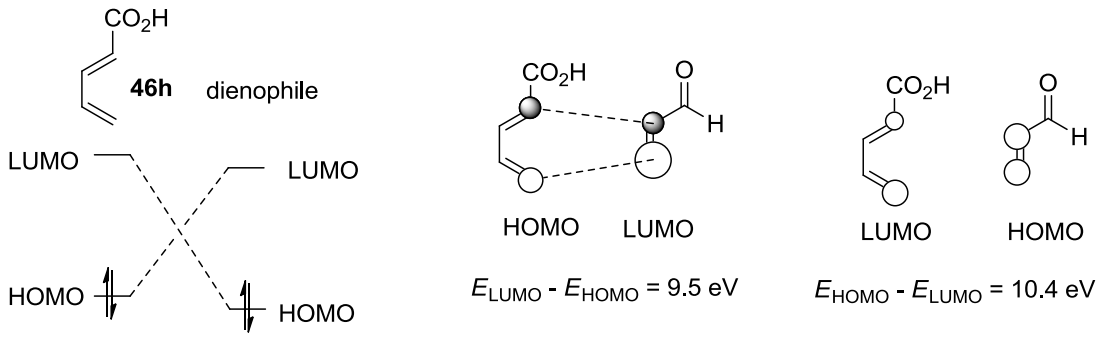


Figure 4.10: Molecular orbital interactions of 46h

Thus, the results (Table 4.2) can be explained by a combination of these factors. For the highly electron withdrawing groups (**46j**, NO_2) only 'meta' products are isolated after prolonged reaction times, for intermediate electron withdrawing groups (**46g**, C(O)Me or **46i**, Br) mixtures of regioisomers are detected at 70 ˚C (less selective reactions) but 'meta' products are detected at higher temperatures. For electron donating substituents (**46b**, Me) the reactions are fast and even after 8 h significant formation of the 'meta' adducts is occurring.

Special mention should be made of the reactions with 9-methoxyanthracene (**46d**) which was reacted 80% pure (contaminated with anthracene). The ^{1}H NMR of the reaction at 70 ˚C shows two adducts, the expected kinetic adduct **127dK** and the anthracene adduct **127a**. After prolonged heating at 110 ˚C the thermodynamic adduct **127dT** and anthracene adduct **127a** were isolated, (Figure 4.11). However, it proved impossible to separate the adducts **127a** and **127dT** by chromatography and as such this derivative was not pursued any further as it was unlikely to lead to efficiencies in any industrial process. However, significant reaction occurs at room temperature after only 10 minutes (40% conversion of **46d**) which indicates that the 9-methoxy anthracene derivative **127d** is the most reactive.

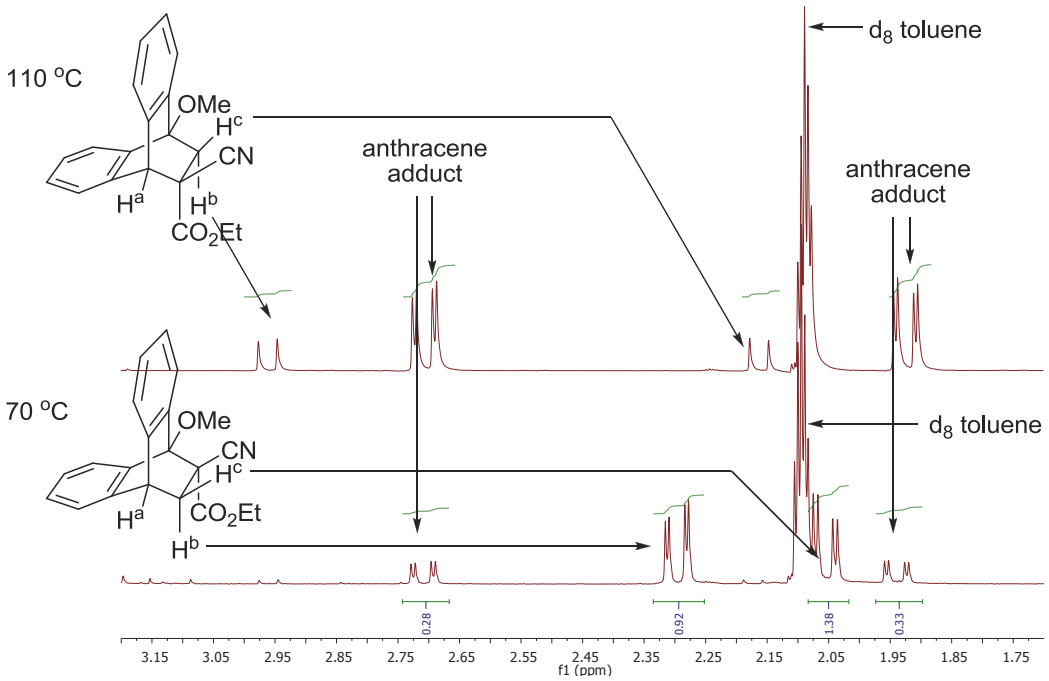


Figure 4.11: ^{1}H NMR of 9-methoxy anthracene adduct 127d at 70 °C and 110 °C

4.4.3 Diels-Alder reactions of 46k-m

The reactions of 9-substituted anthracenes lead to complications as two Diels-Alder products could be isolated. The addition of an identical group at the 10-position would alleviate this problem. Consequently the reactions of **46k-l** with ethyl cyanoacrylate were analysed at both 70 ˚C for 7 h and at 110 ˚C for 8 h (**46k**) and 4 days (**46l**) respectively. The derivatives were chosen because **46b** (9-Me) gave the best results of an electron donating group and **46i** (9-Br) gave the best results of an electron withdrawing group. Unsurprisingly the reaction of 9,10-dibromoanthracene **46l** was significantly slower than for 9-bromoanthracene. Pleasingly, the 9,10-dimethyl anthracene derivative **46k** gave high yields of isolated product **127k** at 70 ˚C and 110 ˚C in fact it was possible to run the forward Diels-Alder reaction in high yield (78%) at only 40˚C.

The only other substituted anthracene to be investigated was 2-fluoroanthracene **46m**. The fluorine substituent was not directly attached to one of the carbons of the 'diene' central anthracene ring but would exhibit a secondary electronic effect. The reaction gave a complicated mixture of regioisomeric products (each as a mixture of *exo* and *endo* isomers 1:2:2:2). While the rate was similar to the parent anthracene it did not provide any advantages in attempting to improve the industrial synthesis of cyanoacrylates over other derivative studied.

*In summary, the 9,10-dimethylanthracene **46k** was determined to be the best derivative to facilitate the Diels-Alder step of any industrial synthesis of ethyl cyanoacrylate derivatives. Its increased reactivity over the parent anthracene **46a** allowed the forward reaction to be undertaken at 40 ˚C, and the symmetrical nature of the derivative precluded regioisomer complications. In addition it is commercially available.*

4.5 Retro-Diels-Alder reaction investigations

The retro-Diels-Alder reaction is an important process that can be used to make reactive or strained molecules.[241] It is governed by the Woodward-Hoffman rules[241–244] and has found numerous applications in materials chemistry and synthesis.[245–248] The reaction is normally carried out thermally at high temperatures (>150 ˚C), but photochemical conditions also have been studied.[249] Having investigated the forward Diels-Alder reactions, it was now wished to explore the reverse process. In the reaction of 9-substituted anthracenes two regioisomers were produced depending upon the reaction conditions. These two regioisomers may have different retro-Diels-

Alder rates. While it was possible to furnish all the products **127b-jT** by heating at 110 ˚C in toluene, it was not possible to find conditions that lead to regioisomers **127b-jK** exclusively for all the substrates. Thus it was decided to compare the retro-Diels-Alder reactions of the thermodynamic adducts **127b-jT** only, acknowledging that this is a practically more difficult retro-process than if the reverse reaction of the kinetic products **127b-jK** were compared.

During the reaction the anthracene adducts **127a-m** undergo a retro-Diels-Alder reaction to give ethyl cyanoacrylate **37** and the anthracene liberated under these conditions forms a Diels-Alder adduct **48a** with maleic anhydride. The formation of **48a** affects the equilibrium of the reaction because the freed anthracene **46a-m** is not then able to react again with ethyl cyanoacrylate **37**. Therefore the equilibrium is pushed in favour of ethyl cyanoacrylate monomer **37** (Figure 4.12).

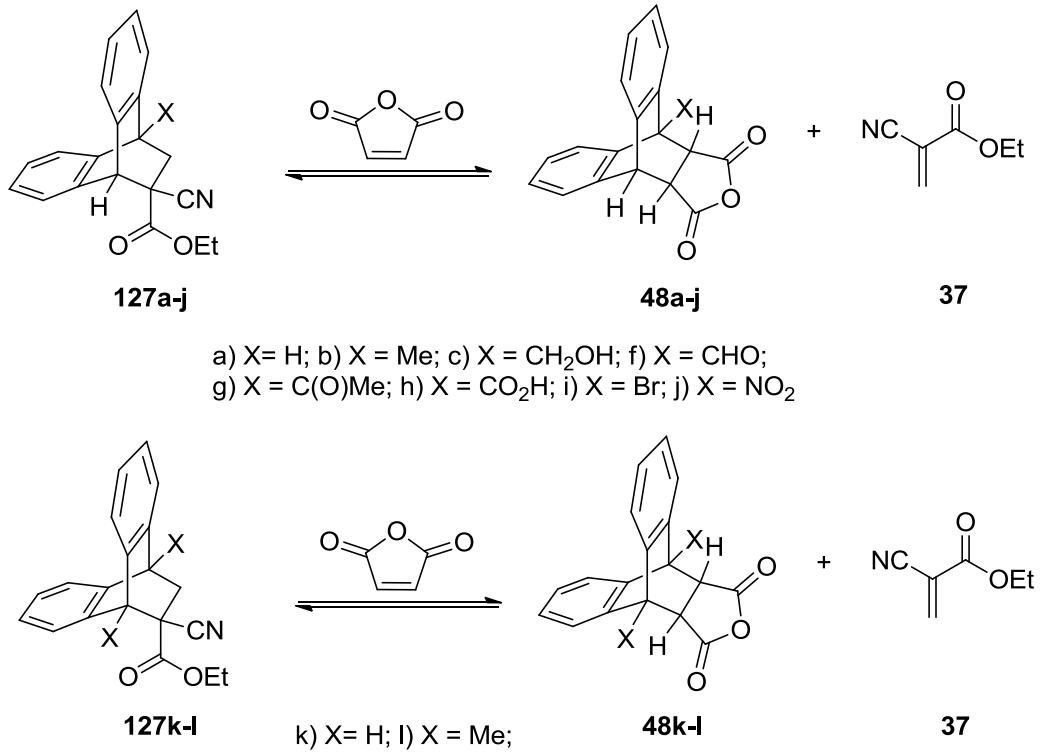


Figure 4.12: Reaction between freed anthracene and maleic anhydride to give adduct 48a-l

The production of the maleic anhydride adduct can be seen in the 400 MHz ^{1}H NMR; the two protons where the anthracene bridge and the maleic anhydride are joined come at approximately 3.5 ppm. When X=H the remaining proton/s on the bridge come around 4.8 ppm (Figure 4.13).

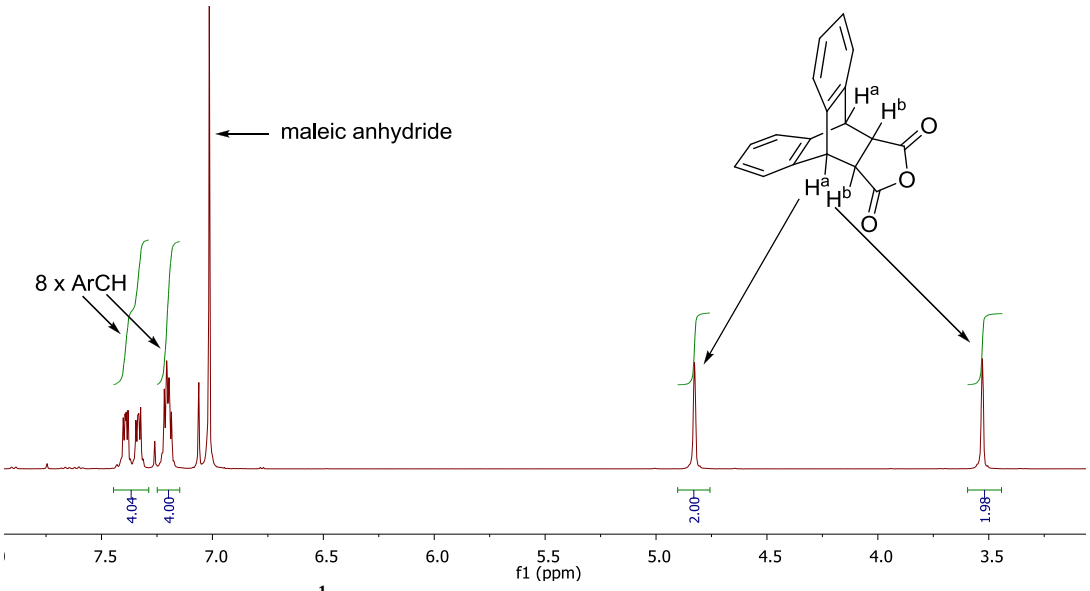


Figure 4.13: ^{1}H NMR of anthracene maleic anhydride adduct 48a

4.5.1 Measurement of conversion in retro-Diels-Alder reaction by ^{1}H NMR

All the anthracene adducts **127a-m** were combined with maleic anhydride (3 equivalents), hydroquinone (to suppress radical polymerisation of cyanoacrylate **37**) phosphorous pentoxide (to suppress water initiated polymerisation of cyanoacrylate **37**) and 1-methyl naphthalene (as an internal standard) and refluxed in xylene for 8 h at 140 ˚C in order to undergo a retro-Diels-Alder reaction. These conditions were chosen to mimic the industrial process where it is important to add the polymerisation inhibitors. Conditions were chosen so that the reaction of the anthracene adduct **127a** did not go to completion but progressed approximately 60%. After the reaction, all the volatiles (including ethyl cyanoacrylate) were removed on a vacuum pump and the crude mixtures analysed by ^{1}H NMR.

A typical ^{1}H NMR spectrum of an experimental run is shown in Figure 4.14 for the reaction of the 9-formyl derivative **127f**. It shows peaks for the starting material **127f**, the maleic anhydride adduct **48f** and 9-formyl anthracene **46f**. A certain level of 9-formyl anthracene **46f** (from the retro-reaction without trapping) builds up in the reaction mixture because the 'trapping' reaction with maleic anhydride is slow (due to electronically mismatched partners). The methyl peak at 2.7 ppm is for the NMR standard 1-methyl naphthalene (50 mol% added to the reaction). The amount of starting material **127f** remaining (61%) was calculated using the average of the clearly separated peaks at 10.84 (s), 4.89 (s), 2.94 (d) and 2.36 (d) ppm. The amount of maleic anhydride adduct **48f**, (35%) and 9-formyl anthracene **46f** (4%) was calculated in a similar manner; **48f** [peaks at 10.88 (s), 4.83 (d), 4.03 (d), 3.58 (dd)]; **46f** [(11.54 (s), 9.00 (d), 8.72 (s)]. The conversion to ethyl cyanoacrylate **37** is therefore 39% (Figure 4.14).

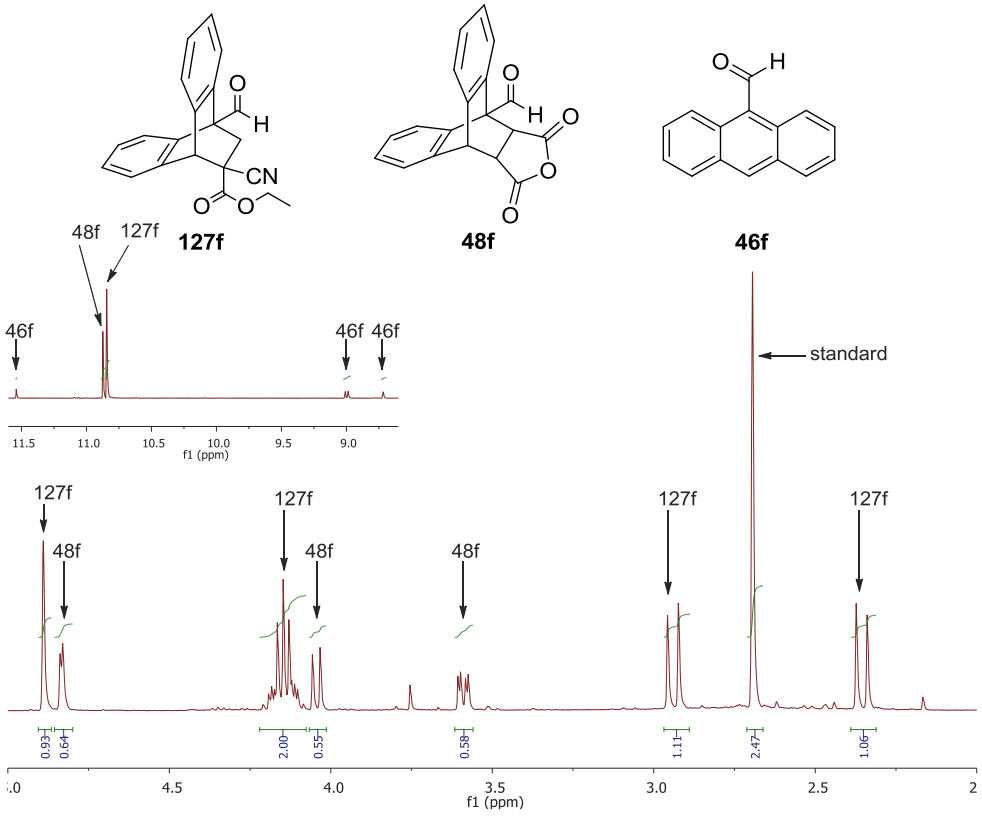


Figure 4.14: ^{1}H NMR of retro-Diels-Alder reaction of 9-formyl anthracene adduct 127f

Using this approach it was possible to measure the conversion by determining the levels of starting material remaining.

Comp.	Subs.	Conversion after 8 h[a]
127a	H	75%
127b	Me	54%
127c	CH_2OH	-[b]
127f	CHO	39%
127g	C(O)Me	52%
127h	CO_2H	-[c]
127i	Br	45%
127j	NO_2	0%
127k	Me	40%
127l	Br	70%
127m	F	56%

[a] Conversion determined by 400 MHz ^{1}H NMR, estimated error ± 3%. [b] Not studied in detail due to competing acylation of free hydroxyl group with maleic anhydride. [c] Not studied in detail as possible reactions with both maleic anhydride to give mixed anyhdride and dehydration with P_2O_5 possible. Trace amounts < 3% of maleic anhydride adduct identified in crude NMR.

Table 4.3: % conversion of retro-Diels-Alder reactions of 127a-m

Hydroxymethylene derivative **127c** was not studied in detail due to the inherent reactivity of the free hydroxyl towards maleic anhydride. Heating **127c** with maleic anhydride under the retro-Diels-Alder reaction conditions led to a relatively messy ^{1}H NMR spectrum. The acylated product **157** was tentatively identified from this crude spectrum, (Figure 4.15), but no further analysis was undertaken. No peaks corresponding to trapping of the retro-Diels-Alder product **48c** could be detected in this crude NMR.

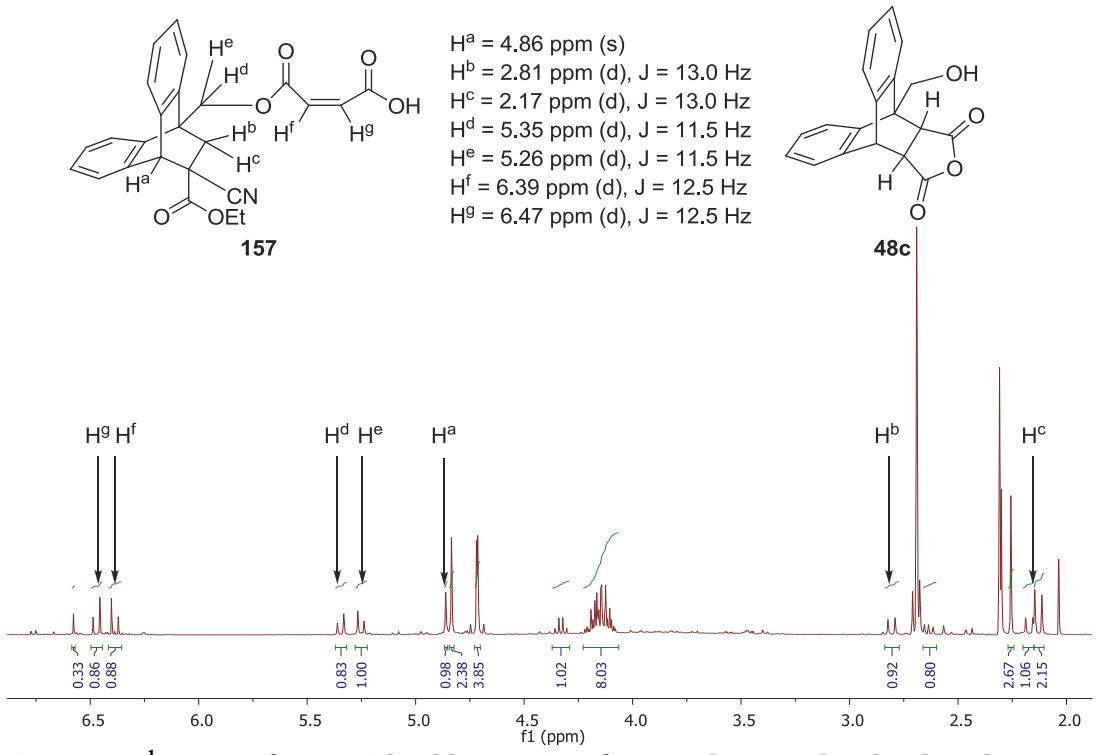
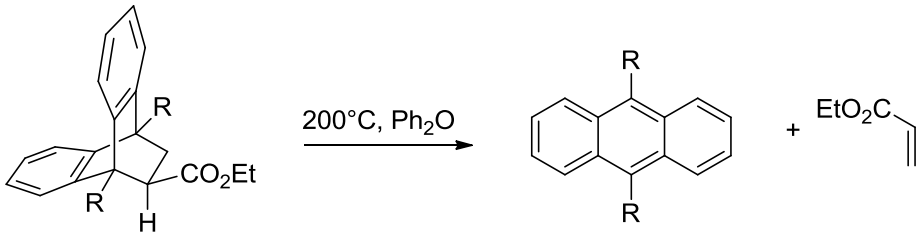


Figure 4.15: ^{1}H NMR of retro-Diels-Alder reaction of 127c and proposed acylated product 157

Reaction of the carboxylic acid derivative **127h** was also not studied in detail for similar reasons. Reaction of maleic anhydride with the carboxylic acid functionality could furnish a mixed anhydride and the P_2O_5 added to the reaction mixture could also cause dehydration of **127h** to give a symmetrical anhydride. This coupled with the low yield of **127h** produced in the forward reaction meant that **46h** was a poor candidate for further study.

The factors which affect the rate of retro-Diels-Alder reactions are known to be complicated. In the related retro-Diels-Alder reactions of di-substituted adducts **158a-e**[222] mildly electron withdrawing R-groups (R = C(O)Me, k = 3 x 10^5 s^{-1}) showed similar rates to mildly electron donating substituents (R = Me, k = 3 x 10^5 s^{-1}), halogen substituents were slightly slower (R = Br, k = 1 x 10^5 s^{-1}) and strongly electron donating (R = OMe, k = 7 x 10^6 s^{-1}) and strongly electron withdrawing (R =

NO_2, k = 3 x 10^3 s^{-1}) significantly faster and slower respectively. The effect of carboxylic acid and aldehyde functionality were not studied. They concluded that for mildly electron withdrawing groups the mechanism was moving towards a biradical process (rather than a concerted process). Other work[250] has provided evidence of a steric acceleration in the retro-Diels-Alder reaction as steric release for the substituents R occurs on going from **127a** to anthracene **46a** which increases the rate with larger substituents. In addition, R substituents that are potentially conjugating (e.g. CHO, C(O)Me) would gain conjugation in the anthracene which would be lacking in the Diels-Alder adduct. Our results are in broad agreement with those of Czarnik[251] on the retro-Diels-Alder of acrylate derivatives **158a-e** (Scheme 4.10) (**127b**~**127g**>**127f**~**127i**>>>**127j**).

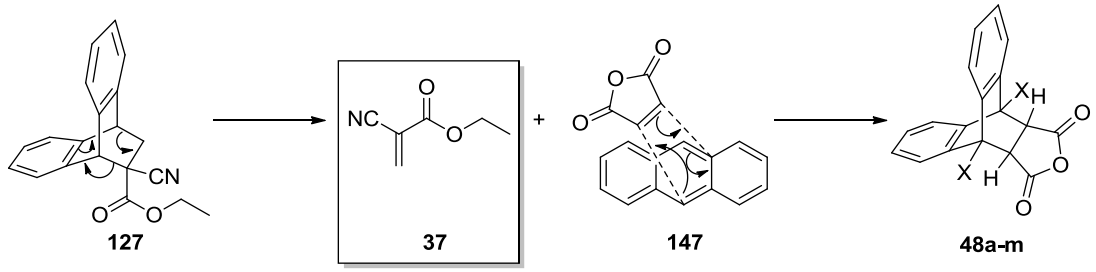


158a-e a) R = Me, b) R = C(O)Me, c) R = Br, d) R = OMe, e) R = NO_2

Scheme 4.10: Retro-Diels-Alder reaction of 158a-e

However, the reactions studied here are inherently more complicated because they are followed by another Diels-Alder reaction of the released anthracene derivatives with maleic anhydride to ultimately force the initial retro-Diels-Alder equilibrium in the desired direction (Scheme 4.11). Thus reagents which may undergo a faster retro-Diels-Alder sequence (e.g. **127g**, R = C(O)Me) may undergo a slower 'trapping' reaction with maleic anhydride. This was observed for a substrates **127f** (R = CHO) and **127g** (R = C(O)Me) as the corresponding free 9-substituted anthracene derivatives **46f** and **46g** could also be detected in the reaction mixtures after 8 h. The

best results were obtained with the parent anthracene **127a**, 9,10-dibromoanthracene **127k** and 2-fluoroanthracene **127m** adducts with intermediate results for the 9-methyl **127b** and 9,10-dimethyl anthracene **127k** derivatives. The relatively fast rate of the 9,10-dibromo derivative **127l** (faster than 9-bromo derivative **127i**) may be due to the release of extra steric strain during the reaction.



Scheme 4.11: Retro-Diels-Alder mechanism using maleic anhydride

4.5.2 Changing dienophile to 1,1,2,2-cyanoethylene

Changing the trapping agent from maleic anhydride to 1,1,2,2-tetracyanoethylene **159** in the retro-Diels-Alder reaction of the anthracene **127a** and 9,10-dimethylanthracene **127k** derivatives was briefly studied. The cycloaddition between **159** and anthracene **127a** is well documented. It is rapid and proceeds *via* an initial charge transfer complex due to the low lying LUMO of the dienophile component.[198] Kinetics and mechanistic studies also show that solvent effects are also important.[197,252] First authentic samples of the two adducts **160a,k** were prepared using a literature procedure.[253]

Then both **127a** and **127k** were subjected to the same reaction conditions as before but replacing maleic anhydride with 1,1,2,2-cyanoethylene. Upon addition of the dienophile a colour change (white to orange) characteristic of the diene/ dienophile charge transfer complex occurred indicating trapping of anthracene adducts.

However surprisingly conversion was lower for both **127a** (52% compared to 75%) and **127k** (32% compared to 40%) compared to with maleic anhydride. At this time it is unclear why this should be the case and further investigation is needed to probe these effects more deeply.

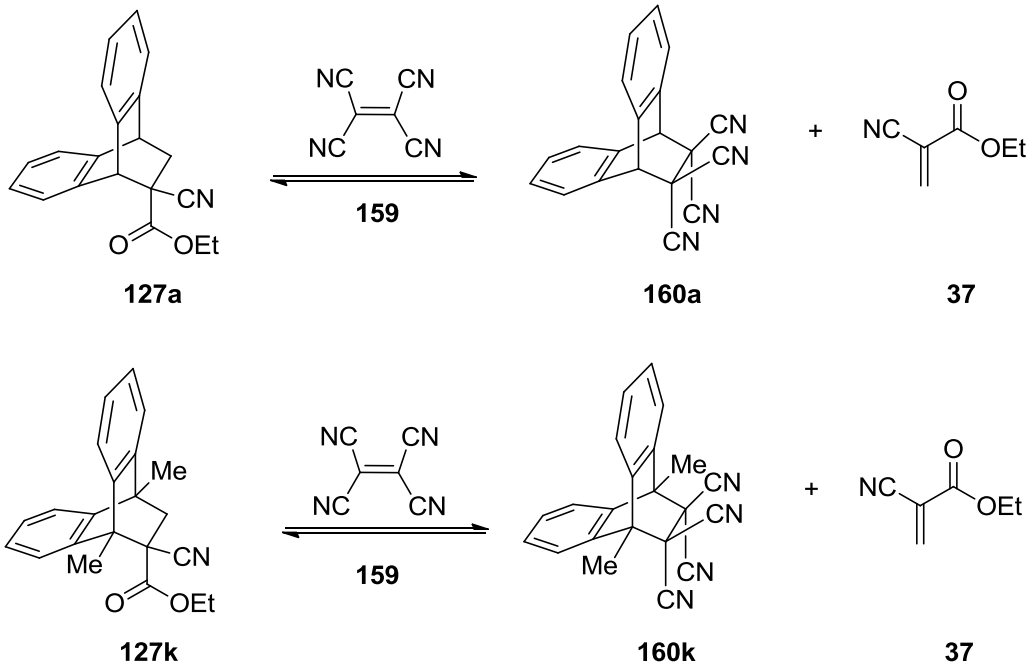


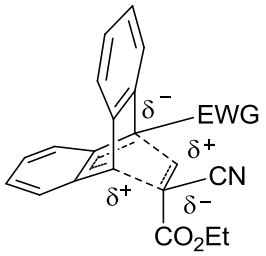
Figure 4.16: Retro-Diels-Alder reaction replacing maleic anhydride with 1,1,2,2-tetracyanoethylene

4.6 Conclusion

In conclusion, the forward and reverse reactions of a range of 9-substituted **46a-j** and 9,10-disubstituted anthracenes **46k-l** with ethyl cyanoacrylate **37** have been investigated. The rates of reactions and their initial regiochemistry could be predicted using a frontier molecular orbital approach. In general for 9-substituted derivatives, 'ortho' adducts **127a-jK**, (kinetic products) were obtained after reaction at 70 ˚C for 7 h, reflecting the polarisation of coefficients in the diene component, but 'meta' adducts (thermodynamic products) obtained after 1-4 days at 110 ˚C,

indicating the reactions were reversible at this temperature. For some substrates with strongly electron withdrawing groups (**46h**, **46j**) 'meta' adducts were the only products isolated whatever the conditions indicating that for these substrates the polarisation of coefficients in the diene was changed or that the HOMO (dienophile)/ LUMO (diene) interaction was now the dominant pathway. The most industrially useful substrates for the forward reaction were identified as 9,10-dimethyl anthracene **46k**, 9-methyl anthracene **46b** and anthracene itself **46a**. Due to the lack of regioisomeric products and their commercial availability both **46k** and **46a** were identified as viable candidates for an industrial synthesis, with the remaining determining factor the cost of the starting materials verses the cost of the energy required to facilitate the reaction.

In the retro-Diels-Alder reaction the relative conversions of substrates could not be predicted based upon electronic considerations alone. Both mildly electron donating and withdrawing groups showed similar reactivities. This was similar to other studies by Czarnik[222] on retro-Diels-Alder reactions of anthracene acrylate **158a-e** adducts. One possible explanation is that for the electron withdrawing adducts the reverse reaction is proceeding *via* a different mechanism (e.g. biradical, or one with significant build -up of charge separation **161**). The relatively fast rate of the 9,10-dibromo derivative **127l** (faster than 9-bromo derivative **127i**) may be due to the release of extra steric strain during the reaction compared to the 9-bromo analogue **127i** (Figure 4.17).



161

Figure 4.17: Effect of EWG on charge separation of 161

Combining the efficiencies of both the forward Diels-Alder and the retro-Diels-Alder steps together under the conditions studied it becomes clear that the most likely candidates for an industrial process are **46a**, **46b** or **46k** (Table 4.4).

Comp.	Subs.	Efficiency of both steps combined
46a	H	46%
46b	Me	54%
46f	CHO	15%
46g	C(O)Me	22%
46i	Br	28%
46j	NO_2	0%
46k	Me	40%
46l	Br	17%
46m	F	34%

Table 4.4: Overall efficiency of anthracenes 46a-m

5.0 Experimental

5.1 General Information and Procedures

The starting materials used in the syntheses were obtained from commercial suppliers and were used without further purification. All melting points were measured using a Gallenkamp variable heater melting point apparatus and are uncorrected. NMR spectra were obtained at 298 K unless otherwise stated. ^{1}H and ^{13}C-NMR were recorded on Bruker DPX-300, DPX-400 and DRX-500 instruments and are referenced to tetramethylsilane (TMS) 0.00 ppm. Chemical Shifts (δ_H) are quoted in parts per million (ppm), coupling constant *J* is quoted to the nearest half hertz (Hz), data is reported as (δ_H, integration, multiplicity). Proton and carbon NMR assignments were routinely confirmed by ^{1}H-^{1}H (COSY), ^{1}H-^{13}C (HMQC) and ^{1}H-^{13}C (HMBC) experiments.

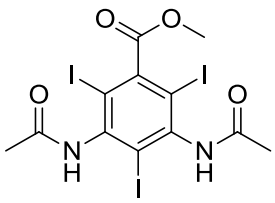
Low resolution mass spectra were recorded on Bruker Esquire 2000 for electro spray (ES) conditions, high resolution mass spectra was recorded on a Bruker MicroTOF. Only molecular ions, fractions from molecular ions and other major peaks are reported as mass/charge (*m/z*) ratios. Infrared spectra were recorded as solid state on Perkin-Elmer Avatar 320 FTIR spectrometer. Absorption maxima (ν_{max}) are recorded in wavenumbers (cm^{-1}). UV/vis spectra were recorded on Perkin Elmer Lambda 25 UV/vis spectrometer. Elemental analysis was performed by Warwick Analytical Services. TGA/ DSC were used to measure thermal properties of cyanoacrylate contrast mixtures using a Metler Toledo DSCI-Star.

Thin layer chromatography was performed on Merck silica gel 60 F-254 tlc sheets, the tlc plate was then visualized under a UV lamp and then stained with potassium permanganate. Flash column chromatography was carried out using Merck silica gel 60, 35-75μm as the stationary phase according to the procedure of Still et al.[254] Petrol refers to petroleum ether (40-60 ^{o}C) unless otherwise stated. All water used was deionised, solvents were evaporated on Büchi Re111 Rotavaporator equipped with a Büchi 461 water bath. All glassware was pre-dried in an oven (80 ^{o}C), cooled in a dry atmosphere before use.

5.2 Experimental procedures for substrates synthesised in Chapter 2

5.2.1 Diatrizoic acid (56) substrates

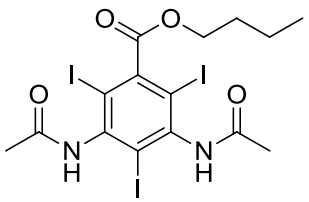
Methyl 3,5-diacetamido-2,4,6-triiodobenzoate (102)



Thionyl chloride (15.0 mL, 207 mmol) was added to diatrizoic acid **56** (10.0 g, 16.3 mmol) and heated to reflux for 5 h. Excess thionyl chloride was removed *in vacuo*. Methanol (25.0 mL, 617 mmol) and pyridine (1.45 mL, 17.9 mmol) were added and refluxed for 24 h. The methanol was removed *in vacuo* and the reaction taken up in EtOAc (50.0 mL) and water (50.0 mL). The product was subsequently extracted with EtOAc (3 x 50.0 mL) and the organic phase washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo*. This resulted in crude product **102** (0.83 g) as an orange solid, which was purified by column

chromatography (19:1 petrol/ EtOAc) to furnish the title compound **102** (0.22 g, 0.33 mmol, 2%) as a yellow/ orange solid. R_f (19:1 petrol/ EtOAc) 0.35; m.p.: 210 – 212 ^{o}C; v_{max}/cm^{-1}: 3258 (NH), 2998 (CH), 1717 (C=O), 1655 (NH-C=O); δ_H (700 MHz, MeOD) 3.94 (3H, s, COOC<u>H</u>$_3$), 2.15 (6H, s, NHCOC<u>H</u>$_3$); δ_C (175 MHz, MeOD) 170.3 (NH<u>C</u>=O), 169.7, 169.2 (<u>C</u>=O), 149.4, 147.2 (NH<u>C</u>CI), 142.7 (CO_2<u>C</u>CI), 85.9 (NHC<u>C</u>ICNH), 77.6, 75.3 (CO_2C<u>C</u>ICNH), 52.2 (COO<u>C</u>H$_3$), 23.0, 21.6 (NHCO<u>C</u>H$_3$); *m/z* (ES$^+$) 650.8 [M+Na]$^+$, found: 650.7750 [M+Na]$^+$ ($C_{12}H_{11}I_3N_2NaO_4$ requires 650.7751).

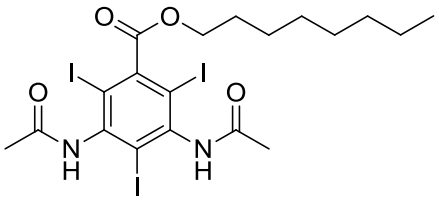
Butyl 3,5-diaacetamido-2,4,6-triiodobenzoate (103)



Thionyl chloride (10.0 mL, 138 mmol) was added to diatrizoic acid **56** (10.0 g, 16.0 mmol) and heated to reflux for 8 h. Excess thionyl chloride was removed *in vacuo*, butan-1-ol (50.0 mL, 546 mmol) and pyridine (1.45 mL, 17.9 mmol) was added and the reaction was heated to reflux for 30 h. The mixture was removed from the heat, water (50.0 mL) was added and the product was extracted with Et_2O (3 x 75.0 mL). The organic layers were washed with 2M aq. HCl (75.0 mL) and sat. aq. NaCl (75.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **103** (28.8 g) as a brown liquid. The crude product was purified by flash column chromatography (19:1 EtOAc/ petrol), followed by re-crystallisation (hexane) to yield the title compound **103** (0.41 g, 0.64 mmol, 4%) as an off-white solid. R_f (19:1 EtOAc/ petrol) 0.45; m.p. 256-257 ^{o}C; v_{max}/cm^{-1} 3320 (NH), 2968 (CH), 1718 (NH-C=O), 1663 (O-C=O); δ_H (400 MHz, MeOD) 4.58 (2 H, s, 2 x N<u>H</u>), 4.37 (2H, t, *J* 6.5,

$OC\underline{H}_2$-CH_2), 2.22 – 2.09 (6H, m, 2 x NH-CO-$C\underline{H}_3$), 1.84 – 1.69 (2H, m, OCH_2-$C\underline{H}_2$), 1.60 -1.44 (2H, m, CH_2-$C\underline{H}_2$-CH_3), 0.98 (3H, dd, *J* 8.0, 6.5, CH_2-$C\underline{H}_3$); δ_C (100 MHz, MeOD) 171.9, 171.5 (NH$\underline{C}$=O), 169.7 ($\underline{C}$=O), 149.9 (Ar$\underline{C}$-CO), 145.7, 145.6 (Ar$\underline{C}$-NH), 107.2 (NHC-$\underline{C}$I-CNH), 96.5, 96.3 (CO-C-$\underline{C}$I), 67.6 ($O\underline{C}H_2$-CH_2), 34.2 ($\underline{C}H_2$-CH_3), 31.5 (OCH_2-$\underline{C}H_2$), 23.1 (2 x NH-CO-$\underline{C}H_3$), 20.4 (CH_2-$\underline{C}H_2$-CH_3), 14.0 (CH_2-$\underline{C}H_3$); *m/z* (ES^+) 670.7 $[M+H]^+$, 692.7 $[M+Na]^+$, found: 692.8219 $[M+Na]^+$ ($C_{15}H_{17}I_3N_2NaO_4$ requires 692.8220); found C: 26.8, H: 2.4, N: 4.1, $C_{15}H_{17}I_3N_2O_4$ requires C: 26.9, H: 2.6, N: 4.2.

Octyl 3,5-diaacetamido-2,4,6-triiodobenzoate (104)

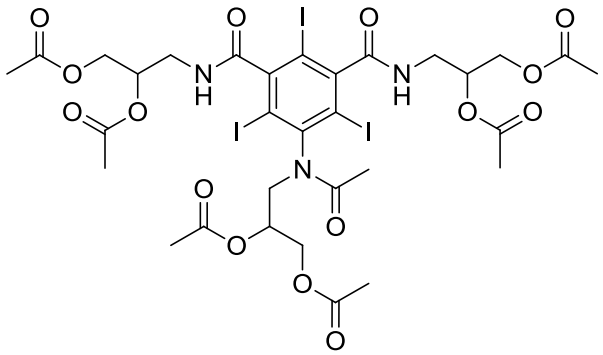


Thionyl chloride (10.0 mL, 138 mmol) was added to diatrizoic acid **56** (10.0 g, 16.0 mmol) and refluxed for 4 h. Excess thionyl chloride was removed *in vacuo*, octanol (30.0 mL, 191 mmol) and pyridine (1.45 mL, 17.9 mmol) were added and the mixture heated to reflux for 3 days. The reaction was removed from the heat, water (50.0 mL) was added and the product extracted with Et_2O (3 x 100 mL). The combined organic phases were washed with 2M aq. HCl (100 mL) and sat. aq. NaCl (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **104** (18.28 g) as a brown liquid. This was purified by flash column chromatography (19:1 DCM/ methanol) followed by re-crystallisation (hexane) to furnish the title compound **104** (0.28 g, 0.32 mmol, 2%) as an off-white solid. R_f (19:1 DCM/ methanol) 0.39; m.p. 269 – 270 ^oC; v_{max}/cm^{-1} 3210, 3166 (NH), 2923 (CH), 1731 (NH-C=O), 1666 (O-C=O); δ_H (400 MHz, MeOD) 4.59 (2H, s, 2 x N$\underline{H}$), 4.36 (2H, t,

J 6.5, OC<u>H</u>$_2$-CH$_2$), 2.20 – 2.16 (6H, m, 2 x NH-CO-C<u>H</u>$_3$), 1.53 –1.28 (12H, m, 6 x C<u>H</u>$_2$), 0.92 – 0.88 (3H, m, CH$_2$-C<u>H</u>$_3$); δ_C (100 MHz, MeOD) 171.9, 171.5 (NH<u>C</u>=O), 169.7 (<u>C</u>=O), 149.8 (Ar<u>C</u>-CO), 145.7, 145.6 (Ar<u>C</u>-NH), 107.2 (NH-C-<u>C</u>I), 96.5, 96.3 (CO-C-<u>C</u>I), 67.9 (O<u>C</u>H$_2$-CH$_2$), 33.0, 30.4, 30.3, 29.4, 27.3, 23.7 (6 x <u>C</u>H$_2$), 23.1 (2 x NH-CO-<u>C</u>H$_3$), 14.5 (CH$_2$-<u>C</u>H$_3$); *m/z* (ES$^+$) 748.9 [M+Na]$^+$, found 748.8848 [M+Na]$^+$ ($C_{19}H_{25}I_3N_2NaO_4$ requires 748.8846); found C: 31.5, H: 3.4, N: 3.9, $C_{19}H_{25}I_3N_2O_4$ requires C: 31.4, H: 3.5, N: 3.9.

5.2.2 Iohexol (55) substrates

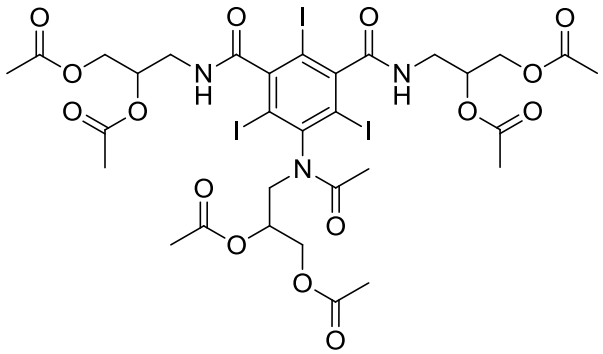
N^1,N^3-Bis(2,3-diacetoxy)propylcarbamonyl)-5-(N-(2,3-diacetoxy)propylacetamido)-2,4,6-triiodoisophthalamide (110) [py])



Iohexol **55** (10.0 g, 12.0 mmol) and acetic anhydride (9.00 mL, 96.0 mmol) were combined in pyridine (150 mL), warmed to 50 ^{o}C and left stirred for 48 h. Once the reaction had cooled water (100 mL) was added, the product was extracted with EtOAc (4 x 100 mL), washed with water (2 x 100 mL), 2M aq. HCl (2 x 100 mL) and sat. aq. NaHCO$_3$ (100 mL). The organic phase was dried (MgSO$_4$) and concentrated *in vacuo* to give the crude acetate **110 [py]** (10.3 g) as an off-white solid. The crude product was purified by column chromatography (EtOAc) to furnish the title compound **110 [py]** (7.90 g, 7.32 mmol, 61%) as a white solid. R$_f$ (EtOAc)

0.57; m.p. 92 – 93 ^{o}C; v_{max}/cm^{-1} 2996 (NH), 1731 (C=O), 1650 (N-C=O), 1543 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.85 (1H, m, NH), 6.51 (1H, m, NH), 5.40 – 5.19 (3H, m, CH_2-CH-CH_2), 4.49 – 4.33 (4H, m, OCH_2-CH and NHCH_2-CH), 4.33 – 4.16 (4H, m, OCH_2-CH and NHCH_2-CH), 3.98 - 3.87 (2H, m, NCH_2-CH), 3.77 - 3.60 (2H, m, OCH_2-CH), 2.10 (12H, s, CO_2-CH_3), 2.09 (3H, s, N-CO-CH_3), 1.91 (6H, s, CO_2-CH_3); δ_C (100 MHz, $CDCl_3$) 170.7, 170.6, 170.5, 170.4, 170.3, 170.2, 169.6, 169.3, 169.1 (C=O), 151.3, 151.1, 150.8 (ArC), 99.1 (CO-C-CI), 89.7, 89.6 (CN-CI), 70.2, 70.0, 69.9 (CH_2-CH-CH_2), 63.3, 63.0 (O-CH_2-CH), 46.2 (N-CH_2-CH), 40.1, 39.9 (NH-CH_2-CH), 22.8 (N-CO-CH_3), 21.4, 21.2, 21.1, 21.0, 20.8, 20.6 (CO_2-CH_3); *m/z* (ES$^+$) 1095.9 [M+Na]$^+$, found: 1095.9341 [M+Na]$^+$ ($C_{31}H_{38}I_3N_3NaO_{15}$ requires 1095.9335); found C: 34.3, H: 3.5, N: 3.9, $C_{31}H_{38}I_3N_3O_{15}$ requires C: 34.7, H: 3.6, N: 3.9.

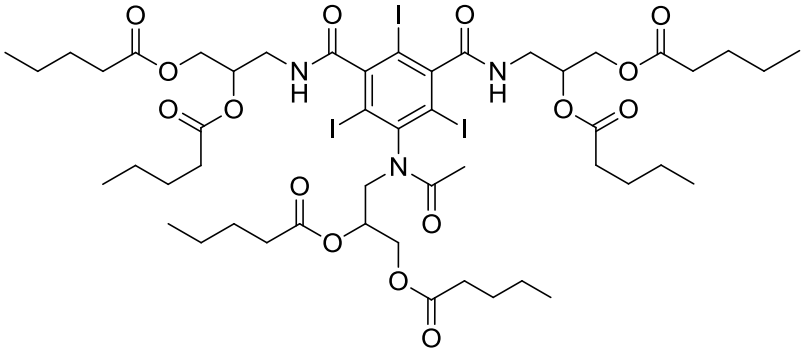
N^1,N^3-Bis(2,3-diacetoxy)propylcarbamonyl)-5-(N-(2,3-diacetoxy)propylacetamido)-2,4,6-triiodoisophthalamide (110 [I_2])



Iohexol **55** (7.50 g, 9.13 mmol) and iodine (0.23 g, 0.91 mmol) were combined in acetic anhydride (6.90 mL, 73.0 mmol) and left to stir at r.t. for 5 days. Water (10.0 mL) and sat. aq. Na_2SO_3 (20.0 mL) were then added and the product subsequently extracted with EtOAc (3 x 50.0 mL). The combined organic layers were washed with sat. aq. $Na_2S_2O_3$ (100 mL) and then sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and

concentrated *in vacuo* to yield crude acetate **110 [I_2]** (9.57 g) as a yellow solid. This was purified by column chromatography (EtOAc) to furnish the title compound **110 [I_2]** (3.90 g, 3.65 mmol, 40%) as a white solid. R_f (EtOAc) 0.39; m.p. 87-88 ^oC; ν_{max}/cm^{-1} 3280 (NH), 2910 (CH), 1729 and 1655 (C=O), 1541 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.86 – 6.76 (1H, m, N<u>H</u>), 6.51 – 6.36 (1H, m, N<u>H</u>), 5.33 - 5.16 (3H, m, CH_2-C<u>H</u>-CH_2), 4.38 – 4.26 (3H, m, OC<u>H_2</u>-CH), 4.23 – 3.91 (3H, m, OC<u>H_2</u>-CH), 3.87 – 3.68 (2H, m, NHC<u>H_2</u>-CH), 3.64 – 3.44 (4H, m, NHC<u>H_2</u>-CH and NC<u>H_2</u>CH), 2.02 – 2.00 (12H, m, CO_2-C<u>H_3</u>), 1.97 (3H, s, N-CO-C<u>H_3</u>), 1.89 – 1.80 (6H, m, CO_2-C<u>H_3</u>); δ_C (100 MHz, $CDCl_3$) 170.8, 170.7, 170.6, 170.5, 170.3, 170.2, 169.7, 169.4, 169.2 (<u>C</u>=O), 151.1, 150.8, 150.7 (Ar-<u>C</u>), 99.1 (CO-C-<u>C</u>I), 89.8, 89.6 (CN-<u>C</u>I), 70.1, 69.9, 68.4 (CH_2-<u>C</u>H-CH_2), 63.7, 63.0 (O<u>C</u>H_2-CH), 46.2, 46.1 (O<u>C</u>H_2-CH and N-<u>C</u>H_2-CH), 40.1, 39.9 (NH-<u>C</u>H_2-CH), 22.9 (NCO-<u>C</u>H_3), 21.2, 21.1, 21.0, 20.8, 20.6, 20.5 (CO_2-<u>C</u>H_3); *m/z* (ES^+) 1095.7 $[M+Na]^+$, found: 1095.9336 $[M+Na]^+$ ($C_{31}H_{38}I_3N_3NaO_{15}$ requires 1095.9335); found C: 34.3, H: 3.5, N: 3.9, $C_{31}H_{38}I_3N_3O_{15}$ requires C: 34.7, H: 3.6, N: 3.9.

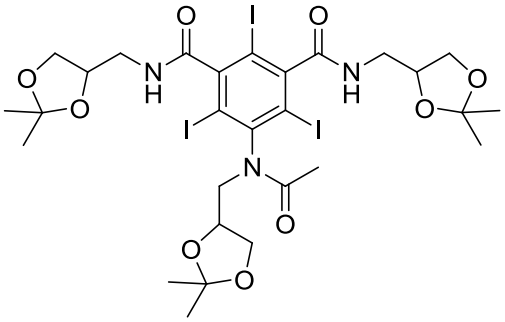
N^1,N^3-Bis(2,3-dipentanoyloxy)propyl)-5-(N-(2,3-dipentanoyloxy)propylacetamido)-2,4,6-triiodoisophthalamide (111)



Iohexol **55** (10.0 g, 12.2 mmol) and iodine (0.31 g, 1.22 mmol) were combined in valeric anhydride (19.2 mL, 97.4 mmol) and left to stir at r.t. for 6 days. Water (20.0

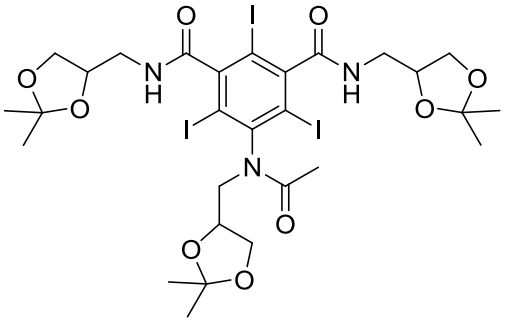
mL) was added and the product subsequently extracted with EtOAc (3 x 30.0 mL). The combined organic phase was washed with sat. aq. $Na_2S_2O_3$ (50.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield crude product **111** (23.5 g). This was purified by column chromatography (1:1 petrol/ EtOAc) to give the title compound **111** (2.20 g, 1.71 mmol, 14%) as a yellow oil. R_f (1:1 petrol/ EtOAc) 0.73; v_{max}/cm^{-1}: 3283 (N-H), 2957 (CH), 1736 (C=O), 1542 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 7.35 – 7.12 (1H, m, NH), 6.93 – 6.83 (1H, m, NH), 5.22 – 5.05 (3H, m, 3 x CH_2-CH-CH_2), 4.34 – 4.28 (2H, m, OCH_2-CH), 4.25 – 4.18 (1H, m, NCH_2-CH), 4.17 – 4.04 (4H, m, OCH_2-CH), 3.88 – 3.76 (1H, m, NCH_2-CH), 3.76 – 3.32 (4H, m, NH-CH_2-CH), 2.25 – 1.93 (12H, m, CO_2-CH_2), 1.73 – 1.66 (3H, m, N-CO-CH_3), 1.51 – 1.37 (12H, m, 6 x CH_2-CH_2-CH_2), 1.29 – 1.11 (12H, m, 6 x CH_2-CH_3), 0.77 (18H, tt, *J* 10.0, 5.0, 6 x CH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 174.2, 174.1, 173.3, 173.1, 173.0, 172.7, 169.7, 169.5, 169.1 (9 x C=O), 151.0, 150.5, 146.1 (3 x ArC), 99.3 (CCO-CI-CCO), 89.9, 89.6 (CN-CI-CCO), 69.8, 69.7, 68.0 (3 x CH_2-CH-CH_2), 63.6, 63.0, 62.8 (OCH_2-CH), 46.3, 46.2 (NH-CH_2-CH), 39.9 (N-CH_2-CH), 33.9, 33.8, 33.7, 33.5, 33.2, 33.1 (6 x CO_2-CH_2), 26.9, 26.8, 26.7, 26.5, 26.4, 26.2 (6 x CH_2-CH_2-CH_2), 22.8 (N-CO-CH_3), 22.4, 22.3, 22.1, 22.0, 21.9, 21.8 (6 x CH_2-CH_3), 13.8, 13.7, 13.6, 13.5, 13.4, 13.3 (6 x CH_2-CH_3); *m/z* (ES^+) 1348.0 $[M+Na]^+$, found: 1348.2160 $[M+Na]^+$ ($C_{49}H_{74}I_3N_3NaO_{15}$ requires 1348.2152).

N^1,N^3-Bis((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-(N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamido)-2,4,6-triiodoisophthalamide (116 [$CuSO_4$])



Iohexol **55** (7.50 g, 9.13 mmol), anhydrous $CuSO_4$ (2.91 g, 18.3 mmol) and TsOH (0.35 g, 1.83 mmol) were combined in acetone (100 mL) and heated to 50 ^oC for 3 days. The solution was dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **116 [$CuSO_4$]** (8.20 g) as a brown solid. This was purified by column chromatography (EtOAc) to give the title compound **116 [$CuSO_4$]** (5.50 g, 5.84 mmol, 64%) as a white solid. R_f (EtOAc) 0.66; m.p. 264-265 ^oC; ν_{max}/cm^{-1} 3268 (NH), 2983 (CH), 1686 (C=O), 1550 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.63 – 5.99 (2H, m, NH), 4.47 – 4.26 (3H, m, CH), 4.20 – 4.01 (4H, m, NCH_2-CH, OCH_2-CH), 3.80 – 3.60 (5H, m, $NHCH_2$-CH, OCH_2-CH), 3.46 – 3.30 (2H, m, $NHCH_2$-CH), 3.22 – 3.06 (1H, m, NCH_2-CH), 1.82 (3H, s, NCO-CH_3), 1.38 (6H, s, $CO_2(CH_3)_2$), 1.28 (9H, s, $CO_2(CH_3)_2$), 1.22 (3H, s, $CO_2(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 170.3 (N-C=O), 169.5, 169.4 (NH-C=O), 151.5, 151.2 (Ar-C-C=O), 148.9 (Ar-C-N), 109.7, 109.4, 109.3 ($CO_2(CH_3)_2$), 98.5 (CCO-CI), 89.8, 89.5 (CN-CI), 74.3, 73.8 (CH_2-CH-CH_2), 68.9, 67.1 (OCH_2-CH), 52.7 (NCH_2-CH), 42.4, 42.2 (NH-CH_2-CH), 27.1, 26.9, 25.5, 25.3 ($CO_2(CH_3)_2$), 22.9 (N-CO-CH_3)**;** *m/z* (ES^+) 963.8 $[M+Na]^+$, found 963.9641 $[M+Na]^+$ ($C_{28}H_{38}I_3N_3NaO_9$ requires 963.9640); found C: 35.5, H: 4.0, N: 4.2, $C_{28}H_{38}I_3N_3O_9$ requires C: 35.7, H: 4.1, N: 4.5.

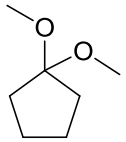
N^1,N^3-Bis((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-5-(N-((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)acetamido)-2,4,6-triiodoisophthalamide (116 [TsOH])



Iohexol **55** (7.50 g, 9.13 mmol) and TsOH (0.17 g, 0.91 mmol) were combined in DMF (75.0 mL), 2,2-dimethoxypropane (4.50 mL, 36.5 mmol) was added and the reaction left to stir at r.t. for 24 h. Water (50.0 mL) was added and the product extracted in EtOAc (3 x 100 mL). The combined organic layers were washed 2M aq. HCl (100 mL) and $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **116 [TsOH]** (10.1 g) as a yellow solid. This was purified by column chromatography (EtOAc) to yield the title compound **116 [TsOH]** (7.31 g, 7.76 mmol, 85%) as a white solid. R_f (EtOAc) 0.58; m.p. 271-273 ^oC; ν_{max}/cm^{-1} 3265 (NH), 2983 (CH), 1638 (C=O), 1546 (NH-C); δ_H (400 MHz, $CDCl_3$) 6.71 – 6.34 (2H, m, NH), 4.39 – 4.18 (3H, m, CH_2-CH-CH_2), 4.09 – 4.02 (1H, m, NCH_2-CH), 4.01 - 3.93 (2H, m, O-CH_2-CH), 3.76 – 3.49 (6H, m, NHCH_2-CH, OCH_2-CH), 3.39 – 3.21 (2H, m, NHCH_2-CH), 3.16 - 2.98 (1H, m, NCH_2-CH), 1.74 (3H, s, N-CO-CH_3), 1.30 (6H, s, CO_2(CH_3)$_2$), 1.21 (9H, s, CO_2(CH_3)$_2$), 1.13 (3H, s, CO_2(CH_3)$_2$); δ_C (100 MHz, $CDCl_3$) 170.3 (N-C=O), 169.4 (NH-C=O), 151.5, 151.2 (Ar-C-C=O), 148.8 (Ar-C-N), 109.7, 109.3 (CO_2(CH_3)$_2$), 98.4 (CO-CI), 89.9, 89.5 (CN-CI), 74.2, 73.8 (CH_2-CH-CH_2), 69.0, 67.2 (OCH_2-CH), 52.7 (NCH_2-CH), 42.4 (NHCH_2-CH), 27.1, 26.9, 25.5, 25.3 (CO_2(CH_3)$_2$), 23.0 (N-CO-CH_3); *m/z* (ES^+) 963.6 $[M+Na]^+$,

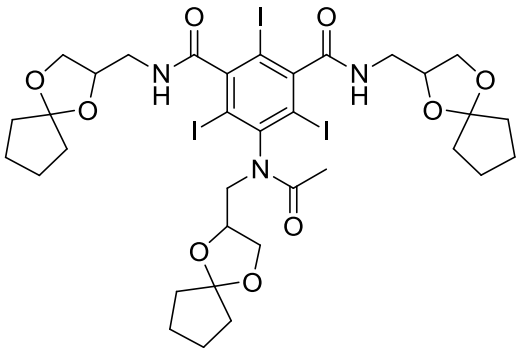
found: 963.9644 $[M+Na]^+$ ($C_{28}H_{38}I_3N_3NaO_9$ requires 963.9640); found C: 35.3, H: 4.0, N: 4.3, $C_{28}H_{38}I_3N_3O_9$ requires C: 35.7, H: 4.1, N: 4.5.

1,1-Dimethoxycyclopentane (123)



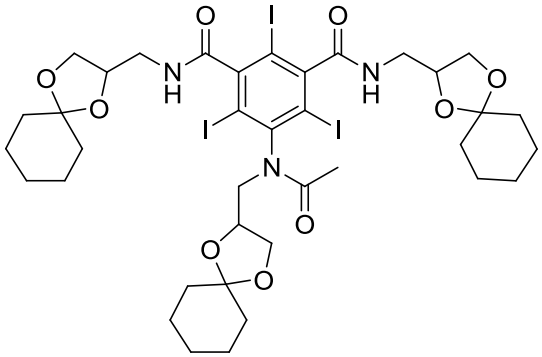
Cyclopentanone (15.0 g, 0.18 mol), trimethyl orthoformate (39.1 mL, 0.36 mol) and zinc chloride (2.40 g, 0.02 mol) were combined in anhydrous methanol (75.0 mL) and heated to reflux for 4 days. The resulting crude mixture was distilled under vacuum to yield the title compound **123** (29-32 ^oC, 9.45g, 0.07 mol, 41%) as a colourless liquid. R_f (9:1 petrol/ EtOAc) 0.45; b.p. 29-32 ^oC (8 mbar), lit.[255] b.p. 50 ^oC (27 mbar); ν_{max}/cm^{-1} 2950 (CH), 1450 (OCH_3); δ_H (400 MHz, $CDCl_3$) 3.13 (6H, s, $OC\underline{H}_3$), 1.72 – 1.65 (4H, m, $C(OCH_3)$-$C\underline{H}_2$), 1.62 – 1.55 (4H, m, CH_2-$C\underline{H}_2$)**;** δ_C (100 MHz, $CDCl_3$) 111.3 ($\underline{C}(OCH_3)_2$), 49.2 (2 x $O\underline{C}H_3$), 34.3 ($C(OCH_3)$-$\underline{C}H_2$), 23.3 (CH_2-$\underline{C}H_2$); *m/z* (ES^+) 153.1 $[M+Na]^+$, found: 153.088 $[M+Na]^+$ ($C_7H_{14}NaO_2$ requires 153.0888).

N^1,N^3-Bis(1,4-dioxaspiro[4.4]nonan-2-ylmethyl)-5-(N-(1,4-dioxaspiro[4.4]nonan-2-ylmethyl)acetamido)-2,4,6-triiodoisophthalamide (124)



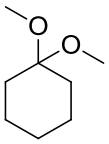
Iohexol **55** (7.50 g, 9.13 mmol), dimethyl cyclopentanone ketal (4.75 g, 36.5 mmol) and TsOH (0.35 g, 1.83 mmol) were combined in DMF (30.0 mL) and stirred at r.t. for 30 h. Water (50.0 mL) was added and the product extracted with EtOAc (3 x 50.0 mL). The combined organic layers were washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **124** (6.22 g) as an off-white solid. This was purified by flash column chromatography (1:2 petrol/ EtOAc) to yield the title compound **124** (3.50 g, 3.47 mmol, 38%) as a white solid. R_f (1:2 petrol / EtOAc) 0.36; m.p. 266-267 ^oC; ν_{max}/cm^{-1} 3250 (NH), 2934 (CH), 1638 (C=O), 1553 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.67 – 6.03 (2H, m, 2 x N<u>H</u>), 4.43 – 4.20 (3H, m, 3 x CH_2-C<u>H</u>-CH_2), 4.17 – 4.06 (1H, m, NC<u>H</u>$_2$-CH), 4.05 - 3.93 (3H, m, OC<u>H</u>$_2$-CH), 3.84 – 3.55 (5H, m, NHC<u>H</u>$_2$-CH, OC<u>H</u>$_2$-CH), 3.34 – 3.30 (2H, m, NHC<u>H</u>$_2$-CH), 3.24 – 3.08 (1H, m, NC<u>H</u>$_2$-CH), 1.82 (3H, s, N-CO-C<u>H</u>$_3$), 1.78 – 1.66 (12H, m, O_2C-C<u>H</u>$_2$-CH_2), 1.62 – 1.50 (12H, m, CH_2-C<u>H</u>$_2$); δ_C (100 MHz, $CDCl_3$) 170.3 (N-<u>C</u>=O), 169.5, 169.3 (NH-<u>C</u>=O) 151.5, 151.2 (Ar-<u>C</u>-C=O), 148.8 (Ar-<u>C</u>-N), 119.6 (O_2<u>C</u>-$(CH_2)_2$), 119.2 (O_2<u>C</u>-$(CH_2)_2$), 100.6 (CO-<u>C</u>I-CO), 98.5, 98.4 (CN-<u>C</u>I), 73.8, 73.4 (CH_2-<u>C</u>H-CH_2), 68.8, 67.1 (O<u>C</u>H$_2$-CH), 52.6 (N<u>C</u>H$_2$-CH), 42.5, 42.4 (NH-<u>C</u>H$_2$-CH), 36.7, 36.6, 36.2, 36.0 (O_2C-<u>C</u>H$_2$), 23.7, 23.6, 23.3, 23.3 (CH_2-<u>C</u>H$_2$), 23.0 (N-CO-<u>C</u>H$_3$); *m/z* (ES^+) 1041.8 $[M+Na]^+$, found: 1042.0104 $[M+Na]^+$ ($C_{34}H_{44}I_3N_3NaO_9$ requires 1042.0109); found C: 40.1, H: 4.4, N: 4.3, $C_{34}H_{44}I_3N_3O_9$ requires C: 40.1, H: 4.4, N: 4.1.

N^1,N^3-Bis(1,4-dioxaspiro[4.5]decan-2-ylmethyl)-5-(N-(1,4-dioxaspiro[4.5]decan-2-ylmethyl)acetamido)-2,4,6-triiodoisophthalamide (119)



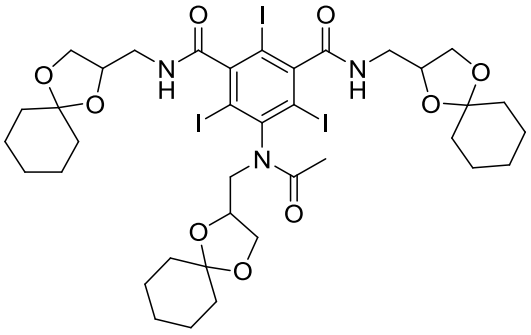
Iohexol **55** (7.00 g, 8.52 mmol), anhydrous $CuSO_4$ (2.72 g, 17.05 mmol) and TsOH (0.32 g, 1.70 mmol) were combined in cyclohexanone (30.0 mL), stirred and heated to 85 ^oC for 6 days. The solution was diluted with EtOAc (30.0 mL), filtered, dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **119** (12.3 g) as brown oil. This was purified by column chromatography (19:1 petrol/ EtOAc) to furnish the title compound **119** (1.03 g, 1.02 mmol, 12%) as an off-white solid. R_f (19:1 petrol/ EtOAc) 0.52; m.p. 157 – 158 ^oC; v_{max}/cm^{-1} 3274 (NH), 2930 (CH), 1648 (C=O), 1541 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.50 – 6.30 (2H, m, N<u>H</u>), 4.52 – 4.32 (3H, m, CH_2-C<u>H</u>-CH_2), 4.25 – 3.99 (3H, m, OC<u>H</u>$_2$-CH and NC<u>H</u>$_2$-CH), 3.84 – 3.71 (6H, m, OC<u>H</u>$_2$-CH and NHC<u>H</u>$_2$-CH), 3.51 – 3.37 (2H, m, NHC<u>H</u>$_2$-CH), 3.21 (1H, t, *J* 12.0, NC<u>H</u>$_2$-CH), 1.93 – 1.74 (3H, m, N-CO-C<u>H</u>$_3$), 1.67 – 1.46 (24H, m, C<u>H</u>$_2$ of cyclohexane ring), 1.38 (6H, s, C<u>H</u>$_2$ of cyclohexane ring); δ_C (100 MHz, $CDCl_3$) 173.5 (N-<u>C</u>=O), 169.4, 169.2 (NH-<u>C</u>=O), 151.5, 151.2 (Ar-<u>C</u>-C=O), 148.9 (Ar-<u>C</u>-N), 110.4, 110.1, 109.1 (O_2<u>C</u>-(CH_2)$_2$), 100.9 (CO-<u>C</u>I-CO), 98.5, 98.4 (CO-<u>C</u>I-CN), 73.6, 73.4 (CH_2-<u>C</u>H-CH_2), 68.4, 66.7 (O<u>C</u>H$_2$-CH), 52.7 (N<u>C</u>H$_2$-CH), 42.7, 42.5 (NH<u>C</u>H$_2$-CH), 36.7, 36.6, 35.0, 34.9, 34.7, 34.4, 25.1, 24.0, 23.8 (<u>C</u>H$_2$ of cyclohexane ring), 23.0 (N-CO-<u>C</u>H$_3$); *m/z* (ES^+) 1084.1 $[M+Na]^+$, found 1084.0573 $[M+Na]^+$ ($C_{37}H_{50}I_3N_3NaO_9$ requires 1084.0579).

1,1-Dimethoxycyclohexane (121)



Cyclohexanone (10.0 g, 102 mmol), trimethyl orthoformate (22.3 mL, 204 mmol) and zinc chloride (1.39 g, 10.2 mmol) were combined in anhydrous methanol (50.0 mL) and heated to reflux for 4 days. The resulting crude mixture was distilled under vacuum to give the title compound **121** (44-46 ^{o}C, 10.7 g, 74.5 mmol, 73%) as a colourless liquid. R_f (4:1 Petrol/ EtOAc) 0.63, b.p. 44-46 ^{o}C (8 mbar), Lit.[256] b.p. 66 ^{o}C (26 mbar); v_{max}/cm^{-1}**:** 2936 (CH), 1445 ($COCH_3$); δ_H (400 MHz, $CDCl_3$) 3.10 (6H, s, 2 x C-O-C$\underline{H}_3$), 1.60 – 1.52 (4H, m, C$(OCH_3)_2$-C$\underline{H}_2$), 1.43 (4H, dt, *J* 11.5, 6.0, C$(OCH_3)_2$-CH_2-C$\underline{H}_2$), 1.35 – 1.30 (2H, m, C-CH_2-CH_2-C$\underline{H}_2$)**;** δ_C (100 MHz, $CDCl_3$) 99.6 (C$(OCH_3)_2$), 47.3 (2 x C-O-C$\underline{H}_3$), 32.7 (C$(OCH_3)_2$-C$\underline{H}_2$), 25.6 (C-CH_2-CH_2-C$\underline{H}_2$), 22.8 (C$(OCH_3)_2$-CH_2-C$\underline{H}_2$); *m/z* (ES^+) 167.1 $[M+Na]^+$, found: 167.1043 $[M+Na]^+$ (requires $C_8H_{16}NaO_2$ 167.1048).

N^1,N^3-Bis(1,4-dioxaspiro[4.5]decan-2-ylmethyl)-5-(N-(1,4-dioxaspiro[4.5]decan-2-ylmethyl)acetamido)-2,4,6-triiodoisophthalamide (119)

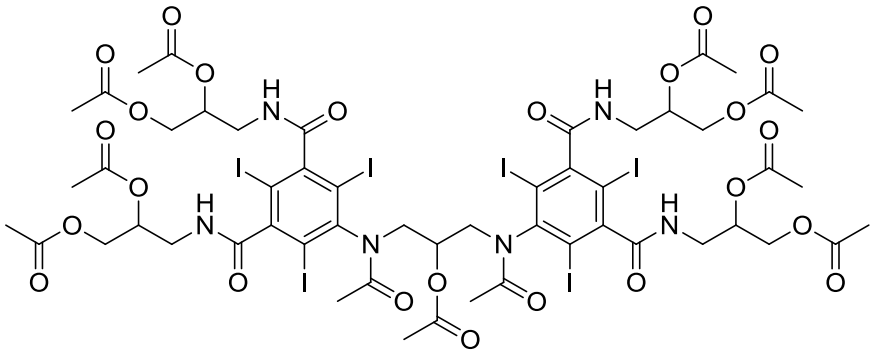


Iohexol **55** (7.50 g, 9.13 mmol) and TsOH (1.74 g, 1.83 mmol) and cyclohexanone dimethyl ketal (5.60 mL, 36.5 mmol) were combined in DMF (30.0 mL) and stirred at r.t. for 24 h. Water (50.0 mL) was added and the product extracted in EtOAc (3 x

100 mL). The combined organic layers were washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated in *vacuo* to give crude product **119** (9.29 g) as a white solid. This was purified by column chromatography (EtOAc) to yield the title compound **119** (6.71g, 6.30 mmol, 69%) as a white solid. R_f (EtOAc) 0.72; m.p. 154-156 ^oC; v_{max}/cm^{-1} 3283 (NH), 2931 (CH), 1743 (C=O), 1542 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 6.46 - 5.76 (2H, m, N<u>H</u>), 4.45 – 4.37 (1H, m, CH_2-C<u>H</u>-CH_2), 4.37 – 4.29 (2H, m, CH_2-C<u>H</u>-CH_2), 4.20 – 4.09 (1H, m, NC<u>H</u>$_2$-CH), 4.08 – 3.92 (3H, m, OC<u>H</u>$_2$-CH), 3.80 – 3.63 (5H, m, OC<u>H</u>$_2$-CH and NH-C<u>H</u>$_2$-CH), 3.45 – 3.30 (2H, m, NHC<u>H</u>$_2$-CH), 3.22 – 3.09 (1H, m, NC<u>H</u>$_2$-CH), 1.85 – 1.81 (3H, m, N-CO-C<u>H</u>$_3$), 1.61 – 1.40 (24H, m, C<u>H</u>$_2$ of cyclohexane ring), 1.33 (6H, bs, C<u>H</u>$_2$ of cyclohexane ring); δ_C (100 MHz, $CDCl_3$) 171.4 (N-<u>C</u>=O), 169.3, 169.1 (NH-<u>C</u>=O), 151.4, 151.2 (Ar-<u>C</u>-C=O), 148.9 (Ar-<u>C</u>-N), 110.4, 110.2, 109.8 (O_2<u>C</u>-$(CH_2)_2$), 100.4 (CO-<u>C</u>I-CO), 98.5, 98.4 (CO-<u>C</u>I-CN), 73.7, 73.6 (CH_2-<u>C</u>H-CH_2), 68.4, 66.9, 66.7 (O<u>C</u>H$_2$-CH), 52.7 (N<u>C</u>H$_2$-CH), 42.7, 42.0 (NH<u>C</u>H$_2$-CH), 36.9, 36.8, 36.7, 36.6, 36.2, 35.4, 35.0, 34.9, 34.7, 27.0, 25.0, 24.0, 23.9, 23.8, 23.0 (<u>C</u>H$_2$ of cyclohexane ring), 23.0 (N-CO-<u>C</u>H$_3$); *m/z* (ES^+) 1083.8 $[M+Na]^+$, found: 1084.0583 $[M+Na]^+$ ($C_{37}H_{50}I_3N_3NaO_9$ requires 1084.0579); found C: 42.1, H: 4.8, N: 3.8, $C_{37}H_{50}I_3N_3O_9$ requires C: 41.9, H: 4.8, N: 4.0.

5.2.3 Iodixanol (58) substrates

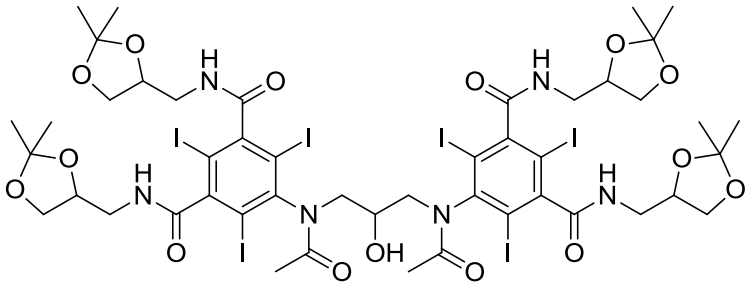
5,5'-(2-Acetoxypropane-1,3-diyl)bis(acetylazanediyl)bis(N^1,N^3-bis((diacetoxypropylcarbamoyl)-2,4,6-triiodoisophthalamide) (125)



Iodixanol **58** solution was concentrated *in vacuo* to remove water, resulting in a colourless solid that was crushed up to give a white powdered solid. The solid (5.65 g, 3.64 mmol) was combined with iodine (0.09 g, 0.36 mmol) in acetic anhydride (4.13 mL, 43.7 mmol) and stirred at r.t. for 6 days. Water (20.0 mL) was added and the product extracted with EtOAc (3 x 50.0 mL). The organic phase was washed with sat. aq. $Na_2S_2O_3$ (2 x 100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the title compound **125** (5.34g, 2.77 mmol, 76%) as a yellow solid. R_f (EtOAc) 0.14; m.p. 154-155 ^oC; v_{max}/cm^{-1} 3282 (NH), 2935 (CH), 1729 (C=O), 1541 (NH-C=O); δ_H (400 MHz, $CDCl_3$) 8.21 – 7.49 (2H, m, N<u>H</u>), 6.52 – 6.12 (2H, m, N<u>H</u>), 5.49 – 5.13 (5H, m, CH_2-C<u>H</u>-CH_2), 4.55 – 4.33 (4H, m, OC<u>H_2</u>-CH), 4.33 – 4.14 (4H, m, OC<u>H_2</u>-CH), 4.14 – 3.85 (4H, m, NC<u>H_2</u>-CH), 3.85 – 3.19 (8H, m, NHC<u>H_2</u>-CH), 2.18 – 1.97 (33H, m, 11 x CO-C<u>H_3</u>); δ_C (100 MHz, $CDCl_3$) 174.8, 171.4, 171.2, 171.0, 170.9, 170.8, 170.7, 170.6, 170.5, 170.4, 170.2, 170.1, 169.9, 169.6, 169.5 (<u>C</u>=O), 151.6, 151.5, 151.3, 151.2, 150.8, 150.7 (Ar<u>C</u>-CO and Ar<u>C</u>-N), 94.7, 94.0, 90.8, 90.6, 90.4, 90.0 (Ar<u>C</u>-I), 70.3, 70.1, 70.0, 69.9, 68.2 (CH_2-<u>C</u>H-CH_2), 63.3, 63.2, 63.1, 63.0 (O<u>C</u>H_2-CH), 40.2, 40.1, 40.0, 39.9, 39.8, 39.7 (N<u>C</u>H_2-CH and

NH<u>C</u>H_2-CH), 23.0, 22.9, 22.8, 21.4, 21.3, 21.3, 21.2, 21.2, 21.1, 20.8, 20.7 (CO-<u>C</u>H_3); *m/z* (ES^+) 1950.3 $[M+Na]^+$, found: 1928.8156 $[M+H]^+$ ($C_{53}H_{63}I_6N_6O_{24}$ requires 1928.8156); found C: 32.5, H: 3.1; N: 4.3, $C_{53}H_{62}I_6N_6O_{24}$ requires C: 33.0, H: 3.2, N: 4.4.

5,5'-(2-hydroxypropane-1,3-diyl)bis(acetylazanediyl)bis(N^1,N^3-bis((2,2-dimethyl-1,3-dioxolan-4-yl)methyl)-2,4,6-triiodoisophthalamide) (126)



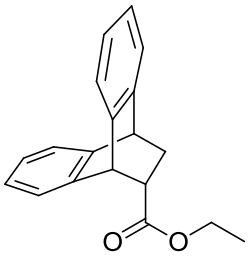
Iodixanol **58** (10.0 g, 6.45 mmol), TsOH (0.62 g, 3.24 mmol) and 2,2-dimethoxypropane (4.76 mL, 38.7 mmol) were combined in DMF (100 mL) and stirred at r.t. for 24 h. Water (100 mL) was added and the product extracted in EtOAc (3 x 100 mL). The combined organic layers were washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to furnish the crude product **126** (6.29 g) as a yellow oil. This was purified by column chromatography (9:1 DCM/ methanol) to yield the title compound **126** (3.63 g, 2.13 mmol, 33%) as a yellow solid. R_f (9:1 DCM/ methanol) 0.67; m.p. 167-169 ^oC; ν_{max}/cm^{-1} 3267 (NH), 2979 (CH), 1735 (C=O), 1542 (NH-C=O)**;** δ_H (400 MHz, MeOD) 4.61 – 4.36 (5H, m, CH_2-C<u>H</u>-CH_2), 4.28 – 4.13 (4H, m, OC<u>H_2</u>-CH), 4.08 – 3.87 (4H, m, OC<u>H_2</u>-CH), 3.60 – 3.41 (8H, m, NH-C<u>H_2</u>-CH), 3.34 (4H, dt, *J* 3.0, 1.5, NH-C<u>H_2</u>-CH), 1.97 – 1.86 (6H, m, N-CO-C<u>H_3</u>), 1.46 (12H, s, $CO_2(C\underline{H}_3)_2$), 1.37 (12H, s, $CO_2(C\underline{H}_3)_2$); δ_C (100 MHz, MeOD) 172.6, 172.5, 172.4, 172.3, 172.2, 172.1 (<u>C</u>=O), 153.0, 152.9, 152.8, 152.7, 152.6, 152.5 (Ar<u>C</u>-C and Ar<u>C</u>-N), 110.7

($\underline{C}O_2(CH_3)_2$), 91.4, 91.3, 91.2, 91.1, 90.7, 90.4 (Ar$\underline{C}$-I), 75.3, 75.2, 75.1, 75.1, 75.0 (CH_2-$\underline{C}$H-CH_2), 69.3, 69.1, 69.0, 68.9 (O$\underline{C}H_2$-CH), 44.0, 43.9, 43.8, 43.7, 43.7, 43.6 (NH$\underline{C}H_2$-CH and N$\underline{C}H_2$-CH), 27.5, 27.4, 25.8, 25.7 ($CO_2(\underline{C}H_3)_2$), 23.2, 23.1 (N-CO-$\underline{C}H_3$); *m/z* (ES^+) 1732.4 $[M+Na]^+$, found: 1732.8272 $[M+Na]^+$ ($C_{47}H_{60}I_6N_6NaO_{15}$ requires 1732.8282); found C: 32.9, H: 3.6, N: 4.9, $C_{47}H_{60}I_6N_6O_{15}$ requires C: 33.0, H: 3.6, N: 4.9.

5.3 Experimental procedures for substrates synthesised in Chapter 3

5.3.1 Substrates from the development of anthracene protected route using ethyl acrylate

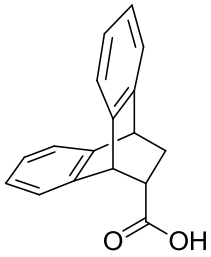
Ethyl-9,10-dihydro-9,10-endo-ethanoanthracene-11-(ethyl)-carboxylate (132)



Anthracene **46a** (15.0 g, 84.2 mmol), ethyl acrylate (9.27 g, 92.6 mmol) **131** and MEHQ (0.52 g, 4.21 mmol) were combined in xylene (100 mL) and heated to 130 ^oC for 24 h. The reaction mixture was allowed to cool to room temperature and then concentrated *in vacuo* to yield the crude product **132** (22.6 g, 96%, containing 10% starting material by ^1H NMR) as a pale yellow solid. The product was used without further purification. A small amount of the crude ester **132** (0.15 g) was purified by column chromatography (30:1 petrol/ EtOAc) to obtain the title compound **132** (0.10 g, 0.84 mmol, 1%) as a white solid. R_f (30:1 petrol/ EtOAc) 0.56; m.p. 101-103 ^oC; Lit[222] m.p. 98 - 99 ^oC; v_{max}/cm^{-1} 2961 (C-H), 1726 (C=O); δ_H (300 MHz, $CDCl_3$)

7.17-7.32 (4H, m, Ar-H), 7.02-7.12 (4H, m, Ar-H), 4.67 (1H, d, *J* 2.5, ArC-CH-CH), 4.32 (1H, t, *J* 2.5, Ar-C-CH-CH_2), 4.01 (2H, qq, *J* 11.0, 7.0, OCH_2-CH_3), 2.85 (1H, ddd, *J* 11.5, 5.0, 2.5, ArC-CH-CH-CO_2), 2.16 (1H, ddd, *J* 12.5, 5.0, 2.5, CH-CH_2-CH), 1.96 (1H, ddd, *J* 12.5, 10.5, 2.5, CH-CH_2-CH), 1.17 (3H, t, *J* 7.0, OCH_2-CH_3)**;** δ_C (75 MHz, $CDCl_3$) 172.9 (C=O), 143.4, 143.0, 141.9, 139.4 (Ar-C), 125.6, 125.5, 125.1, 125.1, 124.2, 123.1, 122.8, 122.7 (Ar-CH), 60.1 (OCH_2-CH_3), 46.3 (ArC-CH-CH), 43.4 (ArC-CH-CH-CO_2), 43.2 (ArC-CH-CH_2), 30.1 (CH-CH_2-CH), 13.7 (OCH_2-CH_3); *m/z* (ES^+) 301.0 $[M+Na]^+$, 279.0 $[M+H]^+$**,** found 301.1203 $[M+Na]^+$ ($C_{19}H_{18}NaO_2$ requires 301.1204). Found C: 81.9, H: 6.5, $C_{19}H_{18}O_2$ requires C: 82.0, H 6.5.

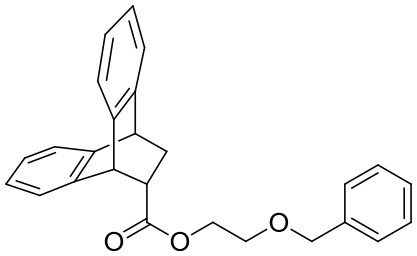
Ethyl 9,10-dihydro-9,10-endoanthracene-11-carboxylic acid (133)



The ethyl ester **132** (3.00 g, 10.8 mmol) and lithium hydroxide (1.00 g, 43.1 mmol) were dissolved in THF/H_2O, 5:4 (20.0 mL), heated to reflux and left stirring for 24 h. The reaction was removed from the heat and allowed to cool, water (30.0 mL) and DCM (30.0 mL) were added. The product was extracted with DCM (3 x 30.0 mL), the aqueous layer was acidified (2M aq. HCl) and then re-extracted with DCM (2 x 30.0 mL). The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo* to furnish the title compound **133** (1.83 g, 68%, containing 10% starting material by ^1H NMR) as a pale yellow solid. The product was used without further purification. A small amount of the crude acid **133** (0.10 g) was purified by re-

crystallisation, firstly in methanol followed by hexane to yield title compound **133** (0.08 mg, 0.32 mmol, 3%) as a white solid. R_f (20:1 petrol/ EtOAc) 0.66; m.p. 185-186 ^oC; Lit[222] m.p. 189 - 192 ^oC; v_{max}/cm^{-1} 3020 (O-H), 2910 (C-H), 1707 (C=O)**;** δ_H (400 MHz, $CDCl_3$) 7.24-7.32 (4H, m, Ar-H), 6.94-7.18 (4H, m, Ar-H), 4.67 (1H, d, *J* 2.5, ArC-CH-CH), 4.34 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.90 (1H, ddd, *J* 10.0, 5.0, 2.5, ArC-CH-CH-CO_2), 2.11 (1H, ddd, *J* 12.5, 5.0, 2.5, CH-CH_2-CH), 2.00 (1H, ddd, *J* 12.5, 10.0, 2.5, CH-CH_2-CH); δ_C (100 MHz, $CDCl_3$) 179.6 (C=O), 143.8, 143.7, 142.4, 139.7 (ArC), 126.3, 126.3, 125.8, 125.8, 125.1, 123.7, 123.6, 123.2 (ArC-H), 46.6 (ArC-CH-CH), 44.0 (ArC-CH-CH-CO_2), 43.8 (ArC-CH-CH_2), 30.6 (CH-CH_2-CH); *m/z* (ES^+) 273.1 $[M+Na]^+$, 251.1 $[M+H]^+$, found: $[M+Na]^+$ 273.0886 ($C_{17}H_{14}NaO_2$ requires 273.0891).

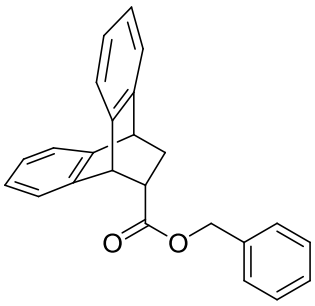
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-(benzyloxyethyl)-carboxylate (135a)



Carboxylic acid **133** (0.65 g, 2.60 mmol) was dissolved in thionyl chloride (3.00 mL, 41.4 mmol), and refluxed for 30 min before allowing to cool to r.t. The reaction was concentrated *in vacuo* to remove the thionyl chloride. Et_2O (1.00 mL), pyridine (0.25 mL, 2.86 mmol), and 2-benzyloxy ethanol (0.45 mL, 2.86 mmol) were added to the resulting acid chloride and the reaction was heated to 30 ^oC for 24 h. The product was extracted with Et_2O (2 x 10.0 mL), washed with 2M aq. HCl (2 x 10.0 mL) and sat. aq. $NaHCO_3$ (2 x 10.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give

crude product **135a** (0.71 g, 1.85 mmol, 71%) as an orange oil. The crude product was purified by column chromatography (10:1 hexane/ EtOAc) to obtain the title compound **135a** (0.32 g, 0.88 mmol, 34%) as a yellow oil. R_f (10:1 hexane/ EtOAc) 0.22; v_{max}/cm^{-1} 2947 (C-H), 2865 (C-O), 1729 (C=O); δ_H (500 MHz, $CDCl_3$) 7.22-7.41 (8H, m, Ar-H), 6.97-7.21 (5H, m Ar-H), 4.70 (1H, d, *J* 2.5, ArC-CH-CH), 4.56 (2H, s, OCH$_2$-ArC), 4.34 (1H, t, *J* 2.5, ArC-CH-CH$_2$), 4.21 (1H, ddd, *J* 12.0, 6.0, 3.5, CO_2CH_2-CH_2O), 4.13 (1H, ddd, *J* 12.0, 6.0, 3.5, CO_2CH_2-CH_2O), 3.51-3.71 (2H, m, CO_2CH_2-CH_2O), 2.92 (1H, ddd, *J* 10.5, 4.5, 2.5, ArC-CH-CH-CO_2), 2.18 (1H, ddd, *J* 12.5, 4.5, 2.5, CH-CH$_2$-CH), 1.99 (1H, ddd, *J* 12.5, 10.0, 2.5, CH-CH$_2$-CH); δ_C (100 MHz, $CDCl_3$) 173.5 (C=O), 144.1, 143.7, 142.5, 140.0, 138.0 (ArC), 129.8, 128.6, 127.9, 127.8, 126.3, 126.2, 125.8, 125.8, 124.9, 123.8, 123.5, 123.3, 122.8 (ArC-H), 73.2 (OCH$_2$-ArC), 68.1 (CO_2CH_2-CH_2O), 63.9 (CO_2CH_2-CH_2O), 46.9 (ArC-CH-CH), 44.1 (ArC-CH-CH-CO_2), 43.9 (ArC-CH-CH_2), 30.8 (CH-CH_2-CH)**;** *m/z* (ES^+) 407.2 $[M+Na]^+$, 385.1 $[M+H]^+$ found: $[M+Na]^+$ 407.1618 ($C_{26}H_{24}NaO_3$ requires 407.1623).

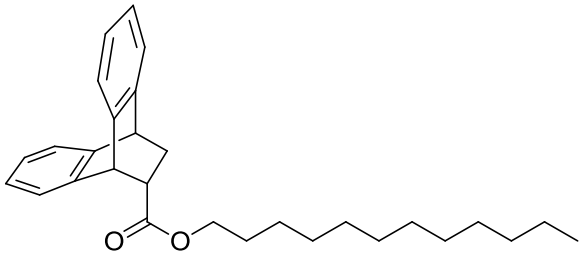
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-(benzyl)-carboxylate (135b)



Carboxylic acid **133** (0.50 g, 2.00 mmol) was dissolved in thionyl chloride (3.00 mL, 41.4 mmol), stirred and refluxed for 30 min before allowing to cool to r.t. The reaction was concentrated *in vacuo* to remove the thionyl chloride. Diethyl ether (1.50 mL), pyridine (0.18 mL, 2.2 mmol), and benzyl alcohol (0.23 mL, 2.2 mmol)

were added to the resulting acid chloride and the reaction was heated to 30 ^{o}C for 24 h. The product was extracted with Et_2O (2 x 10.0 mL), washed with 2M aq. HCl (2 x 10.0 mL) and sat. aq. $NaHCO_3$ (2 x 10.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **135b** (0.55 g, 81%) as an orange oil. The crude product was purified by column chromatography (hexane) to furnish the title compound **135b** (0.08 g, 0.26 mmol, 13%) as an off-white solid. R_f (hexane) 0.39; m.p. 76.2-78.3 ^{o}C; ν_{max}/cm^{-1} 3021, 2985 (C-H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 7.22-7.36 (8H, m, Ar-H), 6.99-7.11 (5H, m, Ar-H), 5.01 (2H, ABq, *J* 12.5, OCH_2-ArC), 4.67 (1H, d, *J* 2.0, ArC-CH-CH), 4.33 (1H, s, ArC-CH-CH_2), 2.92 (1H, m, ArC-CH-CH-CO_2), 2.22 (1H, ddd, *J* 12.5, 3.0, 2.5, CH-CH_2-CH), 1.99 (1H, m, CH-CH_2-CH); δ_C (100 MHz, $CDCl_3$) 173.5 (C=O), 144.0, 143.7, 142.4, 139.9, 135.9 (ArC), 128.6, 128.5, 128.3, 128.1, 126.3, 126.2, 126.0, 125.8, 124.8, 124.6, 123.7, 123.5, 123.3 (ArC-H), 66.6 (OCH_2-ArC), 46.9 (ArC-CH-CH), 44.1 (ArC-CH-CH_2), 43.8 (ArC-CH-CH-CO_2), 30.7 (CH-CH_2-CH); *m/z* (ES^+) 363.1 $[M+Na]^+$, found: $[M+Na]^+$ 363.1356 ($C_{24}H_{20}NaO_2$ requires 363.1361).

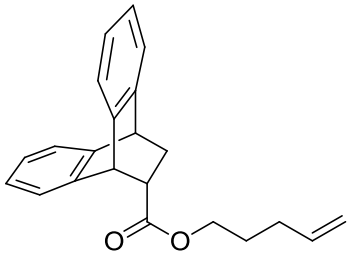
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-(dodecyl)-carboxylate (135c)



Carboxylic acid **133** (0.50 g, 2.00 mmol) was dissolved in thionyl chloride (3.00 mL, 41.4 mmol), stirred and refluxed for 30 min before allowing to cool to r.t. The reaction was concentrated *in vacuo* to remove the thionyl chloride. Et_2O (1.50 mL),

pyridine (0.18 mL, 2.2 mmol), and dodecanol (0.49 mL, 2.2 mmol) were added to the resulting acid chloride and the reaction was heated to 30 ^{o}C for 24 h. The product was extracted with Et_2O (2 x 10.0 mL), washed with 2M aq. HCl (2 x 10.0 mL) and sat. aq. $NaHCO_3$ (2 x 10.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **135c** (0.52 g, 62%) as red/brown crystals. The crude product was purified by column chromatography (hexane), followed by re-crystallisation in hexane to obtain the title compound **135c** (0.10 g, 0.24 mmol, 12%) as a pale yellow solid. R_f (hexane) 0.74; m.p. 68.1-69.7 ^{o}C; v_{max}/cm^{-1} 2917, 2850 (C-H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 7.21-7.33 (4H, m, Ar-H), 7.04-7.12 (4H, m, Ar-H), 4.67 (1H, d, *J* 2.5, ArC-CH-CH), 4.33 (1H, t, *J* 2.5, ArC-CH-CH_2), 3.90-4.01 (2H, m, OCH_2-CH_2), 2.87 (1H, ddd, *J* 10.0, 4.5, 2.5, ArC-CH-CH-CO_2), 2.17 (1H, ddd, *J* 12.5, 4.5, 2.5, CH-CH_2-CH), 1.98 (1H, ddd, *J* 12.5, 7.5, 2.5, CH-CH_2-CH), 1.28 (22H, s, CH_2 chain), 0.88 (3H, t, *J* 6.5, CH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 173.6 (C=O), 144.0, 143.7, 142.6, 140.0 (ArC), 126.2, 125.7, 125.6, 124.8, 123.7, 123.5, 123.3 (ArC-H), 64.9 (OCH_2-CH_2), 46.9 (ArC-CH-CH), 44.2 (ArC-CH-CH-CO_2), 43.9 (ArC-CH-CH_2), 31.9, 30.8, 29.9, 29.8, 29.7, 29.6, 29.4, 29.3, 28.7, 26.0 (CH-CH_2-CH), 22.7 (CH_2-CH_3); *m/z* (ES^+) 441.1 $[M+Na]^+$, 419.1 $[M+H]^+$, found: $[M+Na]^+$ 441.2764 ($C_{29}H_{38}NaO_2$ requires 441.2770); found C: 83.1, H: 9.2, $C_{29}H_{38}O_2$ requires C: 83.2, H: 9.2.

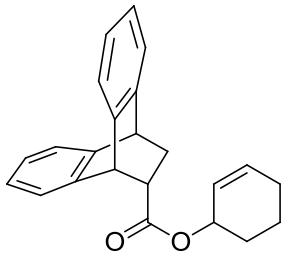
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-(pentenyl)-carboxylate (135d)



Carboxylic acid **133** (1.42 g, 5.68 mmol) was dissolved in thionyl chloride (4.0 mL, 55.1 mmol), stirred and refluxed for 30 min before allowing cooling to r.t. The reaction was concentrated *in vacuo* to remove the thionyl chloride. Et_2O (2.00 mL), pyridine (0.50 mL, 6.25 mmol), and 4-penten-1-ol (0.42 mL, 6.25 mmol) were added to the resulting acid chloride and the reaction was heated to 30 ^oC for 24 h. The product was extracted with Et_2O (2 x 10.0 mL), washed with HCl (2 x 10.0 mL) and $NaHCO_3$ (2 x 10.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **135d** (0.70 g, 39%) as an orange oil. The crude product was purified three times by column chromatography (30:1, 20:1 hexane/ EtOAc, 10:1 hexane/ Et_2O) to give the title compound **135d** (0.03 g, 0.11 mmol, 2%) as a yellow oil. R_f (10:1 hexane/ Et_2O) 0.32; v_{max}/cm^{-1} 2949 (C-H), 1730 (C=O), 1640 (C=C); δ_H (400 MHz, $CDCl_3$) 7.22-7.33 (4H, m, 4 x Ar-H), 7.05-7.11 (4H, m, 4 x Ar-H), 5.73-5.83 (1H, m, CH_2-CH=CH_2), 4.98-5.07 (2H, m, CH=CH_2), 4.67 (1H, d, *J* 2.0, ArC-CH-CH), 4.37 (1H, s, ArC-CH-CH_2), 3.98 (2H, m, q, *J* 10.5, 6.5, CH_2-CH_2-CH=CH_2), 2.87 (1H, dt, *J* 10.0, 3.5, ArC-CH-CH-CO_2), 2.13-2.19 (1H, m, CH-CH_2-CH), 1.96-2.08 (3H, m, CH-CH_2-CH and OCH_2-CH_2), 1.62-1.68 (2H, p, *J* 13.5, 7.0, OCH_2-CH_2-CH_2); δ_C (100 MHz, $CDCl_3$) 173.6 (C=O), 143.9, 143.7, 142.5, 140.0 (ArC), 137.5 (CH_2-CH=CH_2), 126.3, 126.1, 125.8, 125.7, 124.8, 123.7, 123.5, 123.3 (ArC-H), 115.3 (CH=CH_2), 64.2 (CH_2-CH_2-CH=CH_2), 47.0 (ArC-CH-CH), 44.2 (ArC-CH-CH-

CO_2), 43.9 (ArC-<u>C</u>H-CH_2), 30.8 (CH-<u>C</u>H_2-CH), 30.1 (O<u>C</u>H_2-CH_2), 27.9 (O<u>C</u>H_2-CH_2); *m/z* (ES^+) 341.1 $[M+Na]^+$, 319.0 $[M+H]^+$ found: $[M+Na]^+$ 341.1512 ($C_{22}H_{22}NaO_2$ requires 341.1517).

Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-(cyclohexenyl)-carboxylate (135e)

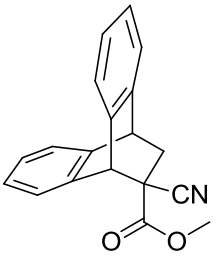


Carboxylic acid **133** (0.50 g, 2.00 mmol) was dissolved in thionyl chloride (3.00 mL, 41.4 mmol), stirred and refluxed for 30 min before allowing to cool to r.t. The reaction was concentrated *in vacuo* to remove the thionyl chloride. Et_2O (1.00 mL), pyridine (0.18 mL, 2.2 mmol), and cyclohexen-1-ol (0.22 mL, 2.2 mmol) were added to the resulting acid chloride and the reaction was heated to 30 ^oC for 24 h. The product was extracted with Et_2O (2 x 10.0 mL), washed with 2M aq. HCl (2 x 10.0 mL) and sat. aq. $NaHCO_3$ (2 x 10.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **135e** (0.42 g, 64%) as a yellow oil. The crude product was purified by column chromatography (10:1 hexane/ Et_2O), to yield the title compound **135e** (0.10 g, 0.30 mmol, 15%) as an off-white solid. R_f (10:1 hexane/ Et_2O) 0.29; m.p. 110-111 ^oC; ν_{max}/cm^{-1} 2905 (C-H), 1912 (C=C), 1732 (C=O)**;** δ_H (400 MHz, $CDCl_3$) 7.02-7.32 (4H, m, Ar-<u>H</u>), 7.04-7.12 (4H, m, Ar-<u>H</u>), 5.92-5.97 (1H, m, CH_2-C<u>H</u>=CH), 5.56-5.62 (1H, m, CH-C<u>H</u>=CH), 5.14 (1H, s, OC<u>H</u>-CH=CH), 4.68 (1H, d, *J* 1.0, ArC-C<u>H</u>-CH), 4.34 (1H, s, ArC-C<u>H</u>-CH_2), 2.87 (1H, ddd, *J* 10.0, 4.5, 2.5, ArC-CH-C<u>H</u>-CO_2), 1.92-2.22 (4H, m, CH-C<u>H</u>$_2$-CH and CH=CH-C<u>H</u>$_2$), 1.55-1.81

(4H, m, OCH-C<u>H</u>$_2$-CH$_2$ and OCH-CH$_2$-C<u>H</u>$_2$); δ_C (100 MHz, $CDCl_3$) 173.1 (<u>C</u>=O), 144.1, 143.7, 142.5, 139.9 (Ar<u>C</u>), 132.7 (CH=<u>C</u>H-CH$_2$), 132.6 (<u>C</u>H=CH-CH$_2$), 126.1, 125.8, 125.7, 125.6, 124.9, 124.7, 123.7, 123.4 (Ar<u>C</u>-H), 68.3 (O<u>C</u>H-CH=CH), 47.1 (ArC-<u>C</u>H-CH), 44.1 (ArC-<u>C</u>H-CH$_2$), 43.9 (ArC-CH-<u>C</u>H-CO$_2$), 30.6 (CH-<u>C</u>H$_2$-CH), 28.4 (CH=CH-<u>C</u>H$_2$), 28.2 (OCH-<u>C</u>H$_2$-CH$_2$), 24.9 (OCH-CH$_2$-<u>C</u>H$_2$); *m/z* (ES^+) 353.1 $[M+Na]^+$, found: $[M+Na]^+$ 353.1512 ($C_{23}H_{22}NaO_2$ requires 353.1517).

5.3.2 Anthracene protected esters from cyanoacrylate

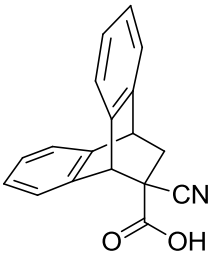
Ethyl-9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(methyl)-carboxylate (137)



Anthracene **46a** (10.0 g, 60.0 mmol), methyl cyanoacrylate **136** (8.90 g, 80.0 mmol) and MEHQ (0.4g, 3.00 mmol) were combined in toluene (100 mL) stirred and heated to reflux for 24 h. Once cool the reaction was concentrated *in vacuo* to give the crude product **137** (15.9 g) as a yellow solid. This was purified by column chromatography (9:1 petrol/ EtOAc) to yield the title compound **137** (12.3 g, 42.6 mmol, 71%) as a pale yellow solid. R_f (9:1 petrol/ EtOAc) 0.43; m.p. 95-97 ^oC, lit[257] m.p. 91-92 ^oC; ν_{max}/cm^{-1} 2975 (C-H), 2235(C≡N), 1751 (C=O); δ_H (400 MHz, $CDCl_3$) 7.04-7.52 (8H, m, Ar-<u>H</u>), 4.86 (1H, s, ArC-C<u>H</u>-CCN), 4.36 (1H, t, *J* 2.5, ArC-C<u>H</u>-CH$_2$), 3.60 (3H, s, OC<u>H</u>$_3$), 2.74 (1H, dd, *J* 13.0, 2.5, CH-C<u>H</u>$_2$-CCN), 2.14 (1H, dd, *J* 13.0, 2.5,

CH-C$\underline{H}_2$-CCN); δ_C (100 MHz, $CDCl_3$) 167.4 ($\underline{C}$=O), 143.1, 142.4, 138.1, 137.3 (Ar$\underline{C}$), 127.7 127.5, 126.7, 126.5, 125.9, 124.9, 124.0, 123.7 (Ar$\underline{C}$-H), 119.9 ($\underline{C}$N), 54.0 (O-$\underline{C}H_3$), 51.8 (ArC-$\underline{C}$H-CCN), 47.4 ($\underline{C}$CN), 43.2 (ArC-$\underline{C}$H-CH_2), 38.2 (CH-$\underline{C}H_2$-CCN)**;** *m/z* (ES^+) 312.0 $[M+Na]^+$, found: $[M+Na]^+$ 312.0995 ($C_{19}H_{15}NNaO_2$ requires 312.1000).

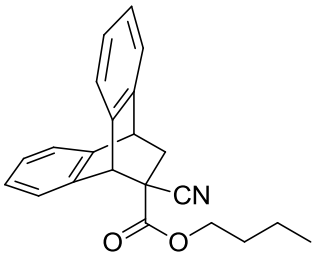
Ethyl 9,10-dihydro-9,10-endoanthracene-11-cyano-11-carboxylic acid (49)



Methyl ester **137** (468 g, 1.62 mol) was combined in KOH solution (181.5 g in 750 mL) and ethanol (750 mL), stirred and refluxed for 4.5 h. The reaction was allowed to cool; water (750 mL) was added followed by 2M aq. HCl acid until solid stopped crashing out of solution (approx. 1L). Suction filtration resulted in the crude carboxylic acid **49** (391 g) as a yellow solid. This was reacted on without purification, for analysis 1.50 g was purified by column chromatography (9:1 petrol/ EtOAc) to yield the title compound **49** (0.90 g, 3.24 mmol, 0.2% overall) as a white solid. R_f (9:1 petrol/ EtOAc) 0.03; m.p. 185-186 ^oC; v_{max}/cm^{-1} 3050 b (OH), 1716 (C=O); δ_H (400 MHz, $CDCl_3$) 7.49-7.07 (8H, m, Ar-$\underline{H}$), 4.85 (1H, s, ArC-C$\underline{H}$-CCN), 4.42 (1H, s, ArC-C$\underline{H}$-CH_2), 3.98 (1H, s, O$\underline{H}$), 2.68 (1H, dd, *J* 13.0, 2.5, CH-C$\underline{H}_2$-CCN), 2.20 (1H, dd, *J* 13.0, 2.5, CH-C$\underline{H}_2$-CCN); δ_C (100 MHz, $CDCl_3$) 170.6 ($\underline{C}$=O), 142.8, 142.5, 138.3, 137.3 (Ar$\underline{C}$), 127.6, 127.5, 126.6, 126.4, 125.8, 125.4, 123.7, 123.6 (Ar$\underline{C}$-H), 120.4 ($\underline{C}$N), 51.6 (ArC-$\underline{C}$H-CCN), 47.9 ($\underline{C}$CN), 43.2 (ArC-

C<u>H</u>-CH_2), 38.1 (CH-C<u>H</u>$_2$-CN); *m/z* (ES^+) 298.0 $[M+Na]^+$, found: 298.0838 $[M+Na]^+$ ($C_{18}H_{13}NNaO_2$ requires 298.0844).

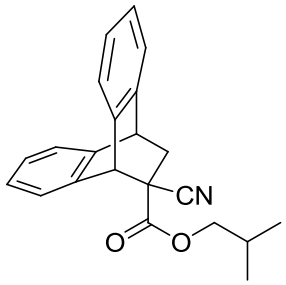
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(butyl)-carboxylate (138a)



Carboxylic acid **49** (20.0 g, 0.07 mol) and thionyl chloride (20.0 mL) were combined in chloroform (30.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, before butan-1-ol (10.1 mL, 0.11 mol), pyridine (6.40 mL, 0.08 mol) and chloroform (100 mL) were added and heated to reflux for 36 h. The reaction was allowed to cool to r.t., water (100 mL) was added and the product extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **138a** as an orange solid (11.0 g). This was purified by flash column chromatography (19:1 petrol/ EtOAc), followed by re-crystallisation (petrol) to furnish the title compound **138a** (1.52 g, 0.42 mmol, 6%) as a yellow solid. R_f (9:1 petrol/EtOAc) 0.58; m.p. 81 – 82 ^oC; ν_{max}/cm^{-1} 2957 (CH), 1743 (C=O); δ_H (400 MHz, $CDCl_3$) 7.52 – 7.42 (2H, m, Ar-<u>H</u>), 7.35 – 7.25 (2H, m, Ar-<u>H</u>), 7.24 – 7.07 (4H, m, Ar-<u>H</u>), 4.85 (1H, s, ArC-C<u>H</u>-CCN), 4.41 (1H, t, *J* 2.5, ArC-C<u>H</u>-CH_2), 4.07 (2H, td, *J* 6.5, 1.0, OCH_2-CH_2), 2.80 (1H, dd, *J* 13.0, 2.5, CH-C<u>H</u>$_2$-CCN), 2.19 (1H, dd, *J* 13.0, 2.5, CH-C<u>H</u>$_2$-CCN), 1.66 – 1.56 (2H, m, OCH_2-C<u>H</u>$_2$-CH_2), 1.46 – 1.32 (2H, m, CH_2-C<u>H</u>$_2$-CH_3), 0.94 (3H, t, *J* 7.5, CH_2-C<u>H</u>$_3$);

δ_C (100 MHz, $CDCl_3$) 166.9 (C=O), 143.0, 142.4, 138.0, 137.2 (Ar<u>C</u>), 128.2, 127.6, 126.6, 125.8, 125.4, 125.0, 123.9, 123.6 (Ar<u>C</u>-H), 119.9 (<u>C</u>N), 67.1 (O<u>C</u>H_2-CH_2), 51.8 (ArC-<u>C</u>H-CCN), 47.4 (<u>C</u>CN), 43.2 (ArC-<u>C</u>H-CH_2), 38.0 (CH-<u>C</u>H_2-CCN), 30.5 (OCH_2-<u>C</u>H_2-CH_2), 19.1 (CH_2-<u>C</u>H_2-CH_3), 13.7 (CH_2-<u>C</u>H_3)**;** *m/z* (ES^+) 354.0 $[M+Na]^+$, found: 354.1467 $[M+Na]^+$ ($C_{22}H_{21}NNaO_2$ requires 354.1470); found C: 80.1, H: 6.4, N: 4.1, $C_{22}H_{21}NO_2$ requires C: 79.7, H: 6.4, N: 4.2.

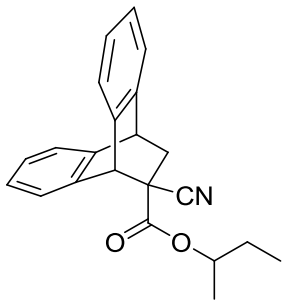
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(2-methylpropyl) carboxylate (138b)



Carboxylic acid **49** (20.0 g, 0.07 mol) and thionyl chloride (20.0 mL, 276 mmol) were combined in chloroform (30.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, 2-methyl-1propanol (10.1 mL, 0.11 mol), pyridine (6.40 mL, 0.08 mol) and chloroform (100 mL) were added and heated to reflux for 36 h. The reaction was allowed to cool to r.t., water (100 mL) was added and the product extracted with DCM (3 x 100 mL). The combined organic phase was washed with 2M aq. HCl and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **138b** as a brown solid (19.7 g). This was purified by flash column chromatography (19:1 petrol/ EtOAc), followed by re-crystallisation (petrol) to furnish the title compound **138b** (6.04 g, 0.02 mol, 25%) as a pale yellow solid. R_f (19:1 petrol/EtOAc) 0.36; m.p. 99 – 100 ^oC; v_{max}/cm^{-1} 2962 (CH), 1746 (C=O); δ_H (400 MHz, $CDCl_3$) 7.53 – 7.42 (1H, m, Ar-<u>H</u>), 7.34 – 7.27 (2H, m, Ar-<u>H</u>),

7.24 – 7.07 (5H, m, Ar-H), 4.86 (1H, s, ArC-CH-CCN), 4.41 (1H, t, *J* 2.5, ArC-CH-CH_2), 3.84 (2H, dd, *J* 10.5, 6.5, OCH_2-CH$(CH_3)_2$), 2.80 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.20 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 1.95 (1H, dp, *J* 13.5, 6.5, OCH_2-CH-$(CH_3)_2$), 0.95 (6H, dd, *J* 6.5, 4.5, CH-(CH_3)$_2$)**;** δ_C (100 MHz, $CDCl_3$) 166.8 (C=O), 143.0, 142.4, 138.0, 137.2 (ArC), 128.2, 127.6, 126.6, 126.4, 125.9, 125.0, 123.9, 123.6 (ArC-H), 119.9 (CN), 73.2 (OCH_2-CH-$(CH_3)_2$), 51.9 (ArC-CH-CCN), 47.5 (CCN), 43.2 (ArC-CH-CH_2), 38.0 (CH-CH_2-CCN), 27.7 (OCH_2-CH-$(CH_3)_2$), 19.1, 19.0 (OCH_2-CH-(CH_3)$_2$); *m/z* (ES^+) 354.0 $[M+Na]^+$, found: 354.1465 $[M+Na]^+$ ($C_{22}H_{21}NNaO_2$ requires 354.1470); found C: 80.0, H: 6.4, N: 4.2, $C_{22}H_{21}NO_2$ requires C: 79.7, H: 6.4, N: 4.2.

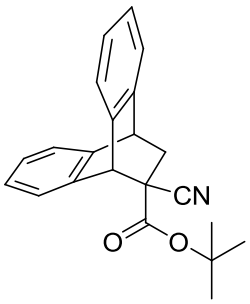
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(2-butyl)-carboxylate (138c)



Carboxylic acid **49** (20.0 g, 0.07 mol) and thionyl chloride (20.0 mL, 276 mmol) were combined in chloroform (30.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, butan-2-ol (10.1 mL, 0.11 mol), pyridine (6.40 mL, 0.08 mol) and chloroform (100 mL) were added and heated to reflux for 36 h. The reaction was allowed to cool to r.t., water (100 mL) was added and the product extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with 2M aq. HCl (100 mL) and $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **138c** as a brown oil (22.4 g). This was purified by

flash column chromatography twice (19:1 petrol/ EtOAc then 6:1 petrol/ EtOAc) to give the title compound **138c** (12.0 g, 0.035 mol, 50%) as an orange oil. R_f (6:1 petrol/ EtOAc) 0.37; v_{max}/cm^{-1} 2971 (CH), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.45 (1H, m, Ar-H), 7.34 – 7.28 (2H, m, Ar-H), 7.22 – 7.17 (3H, m, Ar-H), 7.17 – 7.07 (2H, m, Ar-H), 4.85 (1H, d, *J* 9.0, ArC-CH-CCN), 4.80 – 4.67 (1H, m, OCH-CH_3), 4.41 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.80 (1H, ddd, *J* 13.0, 8.0, 2.5, CH-CH_2-CCN), 2.18 (1H, ddd, *J* 13.0, 8.0, 2.5, CH-CH_2-CCN), 1.72 – 1.49 (2H, m, OCH-CH_2-CH_3), 1.19 (3H, ABq, *J* 6.5, OCH-CH_3), 0.92 (3H, ABq, *J* 7.5, OCH-CH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 166.4, 166.3 (C=O), 143.1, 143.0, 142.5, 142.4, 138.2, 138.1, 137.1, 137.0 (ArC), 127.6, 127.6, 127.5, 126.6, 126.3, 126.2, 125.8, 125.2, 123.9, 123.8, 123.6, 123.6 (ArC-H), 120.1, 120.0 (CN), 75.9, 75.8 (OCH-CH_3), 51.8, 51.7 (Ar-CH-CCN), 47.7, 47.3 (ArC-CH-CCN), 43.2 (ArC-CH-CH_2), 38.0, 37.8 (ArC-CH-CH_2), 28.7, 28.6 (OCH-CH_2-CH_3), 19.6, 18.8 (OCH-CH_3), 9.8, 9.6 (OCH-CH_2-CH_3); *m/z* (ES^+) 354.0 $[M+Na]^+$, found: 354.1465 $[M+Na]^+$ ($C_{22}H_{21}NNaO_2$ requires 354.1470).

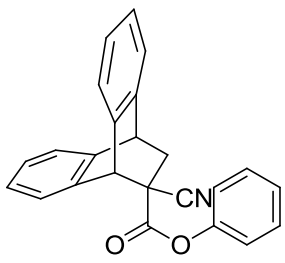
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(*tert*-butyl)-carboxylate (138d)



Carboxylic acid **49** (20.0 g, 0.07 mol) and thionyl chloride (20.0 mL, 276 mmol) were combined in chloroform (30.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, *tert*-butanol (10.5 mL, 0.11 mol), pyridine (6.40 mL,

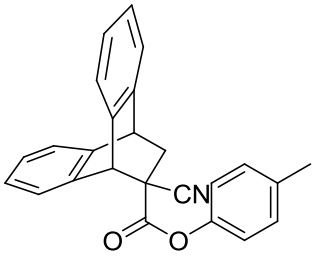
0.08 mol) and chloroform (100 mL) were added and heated to reflux for 7 days. The reaction was allowed to cool to r.t., water (100 mL) was added and the product extracted with Et_2O (3 x 100 mL). The combined organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **138d** as a yellow solid (13.60 g). This was purified by flash column chromatography (9:1 petrol/ EtOAc), followed by re-crystallisation (petrol) to furnish the title compound **138d** (5.10 g, 0.02 mol, 23%) as an off-white solid. R_f (9:1 petrol/ EtOAc) 0.54; m.p. 165 – 166 ^oC; v_{max}/cm^{-1} 2985 (CH), 1745 (C=O); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.44 (1H, m, Ar-H), 7.33 – 7.28 (2H, m, Ar-H), 7.24 – 7.13 (4H, m, Ar-H), 7.13 – 7.07 (1H, m, Ar-H), 4.81 (1H, s, ArC-CH-CCN), 4.40 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.76 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.14 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 1.40 (9H, s, C(CH_3)$_3$); δ_C (100 MHz, $CDCl_3$) 165.4 (C=O), 143.1, 142.4, 138.3, 137.2 (ArC), 127.6, 127.4, 126.5, 126.1, 125.8, 125.3, 123.8, 123.5 (Ar-C-H), 120.3 (CN), 84.1 (OC$(CH_3)_3$), 51.9 (ArC-CH-CCN), 48.0 (CCN), 43.2 (ArC-CH-CH_2), 37.8 (CH-CH_2-CCN), 27.7 (C(CH_3)$_3$); *m/z* (ES^+) 354.0 $[M+Na]^+$, found: 354.1465 $[M+Na]^+$ ($C_{22}H_{21}NNaO_2$ requires 354.1470); found C: 79.9, H: 6.4; N: 4.2, $C_{22}H_{21}NO_2$ requires C: 79.7, H: 6.4, N: 4.2.

Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(phenyl)-carboxylate (139a)



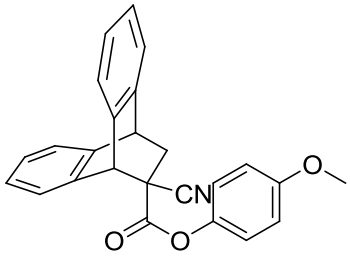
Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (5.00 mL, 68.9 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), phenol (1.03 g, 10.9 mmol) and pyridine (0.65 mL, 7.99 mmol) was added and the reaction refluxed for 36 h. Water (50.0 mL) was added and the product was extracted with Et_2O (3 x 50.0 mL). The organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **139a** (2.51 g) as a yellow solid. This was purified by column chromatography (9:1 petrol/ EtOAc), followed by recrystalisation (hexane) to yield the title compound **139a** (1.00 g, 2.76 mmol, 38%) as a white solid. R_f (9:1 petrol/ EtOAc) 0.33; m.p. 172 – 173 ^oC; ν_{max}/cm^{-1} 2320 (CN), 1774 (C=O); δ_H (400 MHz, $CDCl_3$) 7.57 – 7.51 (1H, m, Ar-H), 7.40 – 7.32 (5H, m, Ar-H), 7.27 – 7.14 (5H, m, Ar-H), 7.00 – 6.94 (2H, m, Ar-H), 5.09 (1H, s, ArC-CH-CCN), 4.47 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.91 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.29 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN); δ_C (100 MHz, $CDCl_3$) 165.6 (C=O), 150.4 (O-ArC), 143.0, 142.4, 137.7, 137.0 (ArC), 129.6, 127.9, 127.7, 126.8, 126.6, 126.5, 126.0, 125.2, 124.2, 123.7, 121.0, 120.6, 119.4 (ArC-H), 115.3 (CCN), 51.9 (ArC-CH-CCN), 47.6 (CN), 43.2 (ArC-CH-CH_2), 38.1 (CH-CH_2-CCN); *m/z* (ES^+) 374.1 $[M+Na]^+$, found 374.1148 $[M+Na]^+$ ($C_{24}H_{17}NNaO_2$ requires 374.1157); Found C: 81.9, H: 4.9, N: 3.9, $C_{24}H_{17}NO_2$ requires C: 82.0, H: 4.9, N: 4.0.

Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-methylphenyl)-carboxylate (139b)



Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (10.0 mL, 138 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), pyridine (0.65 mL, 7.99 mmol) and *p*-cresol (1.18 g, 10.9 mmol) were added and heated to reflux for 36 h. Water (50 mL) was added and the product extracted with Et_2O (3 x 50.0 mL). The combined organic layers were washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **139b** as yellow/ orange solid (3.28 g). This was purified by column chromatography (9:1 petrol/ EtOAc) to yield the title compound **139b** (1.25 g, 3.48 mmol, 48%) as a yellow solid. R_f (9:1 petrol/ EtOAc) 0.20; m.p. 169 – 170 ^oC; ν_{max}/cm^{-1} 2940 (CH), 1768 (C=O); δ_H (400 MHz, $CDCl_3$) 7.56 – 7.50 (1H, m, Ar-H), 7.37 – 7.32 (3H, m, Ar-H), 7.26 – 7.12 (6H, m, Ar-H), 6.87 – 6.82 (2H, m, Ar-H), 5.08 (1H, s, ArC-CH-CCN), 4.47 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.91 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.32 (3H, s, ArC-CH_3), 2.28 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN); δ_C (100 MHz, $CDCl_3$) 165.7 (C=O), 148.3, 143.1, 142.4, 137.7, 137.0, 136.3 (6 x ArC), 130.1 (2 x ArC-H), 127.9, 127.7, 126.7, 126.5, 126.0, 125.2, 124.2, 123.6 (8 x ArC-H), 120.6 (2 x ArC-H), 119.4 (CN), 51.9 (ArC-CH-CCN), 47.5 (CCN), 43.2 (ArC-CH-CH_2), 38.1 (CH-CH_2-CCN), 20.9 (ArC-CH_3); *m/z* (ES^+) 388.1 $[M+Na]^+$, found: 388.1308 ($C_{25}H_{19}NNaO_2$ requires 388.1313).

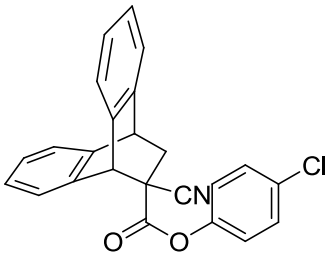
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-methoxyphenyl)-carboxylate (139c)



Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (5.00 mL, 68.9 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), pyridine (0.65 mL, 7.99 mmol) and 4-methoxyphenol (1.35 g, 10.9 mmol) was added and the reaction heated to reflux for 48 h. Water (50.0 mL) was added and the product extracted with Et_2O (3 x 50.0 mL). The organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **139c** (4.60 g) as an orange solid. This was purified by column chromatography (9:1 petrol/ EtOAc) to yield the title compound **139c** (1.16 g, 3.05 mmol, 42%) a yellow solid. R_f (9:1 petrol/ EtOAc) 0.14; m.p. 156 – 158 ^oC; ν_{max}/cm^{-1} 2964 (CH), 1748 (C=O); δ_H (400 MHz, $CDCl_3$) 7.56 – 7.50 (1H, m, Ar-H), 7.34 (3H, dd, *J* 8.0, 3.5, Ar-H), 7.26 – 7.13 (4H, m, Ar-H), 6.91 – 6.82 (4H, m, Ar-H), 5.08 (1H, s, ArC-CH-CCN), 4.46 (1H, t, *J* 2.5, ArC-CH-CH_2), 3.76 (3H, s, OCH_3), 2.90 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.28 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN); δ_C (100 MHz, $CDCl_3$) 165.9 (C=O), 157.8 (ArC-OCH_3), 143.9, 143.1, 142.4, 137.7, 137.0 (5 x ArC), 127.9, 127.7, 126.8, 126.5, 126.0, 125.2, 124.2, 123.6 (8 x ArC-H), 121.7 (CO_2-ArC-ArCH), 119.4 (CCN), 114.6 (ArCH-$COCH_3$), 55.6 (OCH_3), 51.9 (ArC-CH-CCN), 47.5 (CN), 43.2 (ArC-CH-CH_2), 38.1 (CH-CH_2-CCN); *m/z* (ES^+)

404.1 $[M+Na]^+$, found: 404.1262 $[M+Na]^+$ ($C_{25}H_{19}NNaO_3$ requires 404.1263); found C: 78.3, H: 5.0, N: 3.6, $C_{25}H_{19}NO_3$ requires C: 78.7, H: 5.0, N: 3.7.

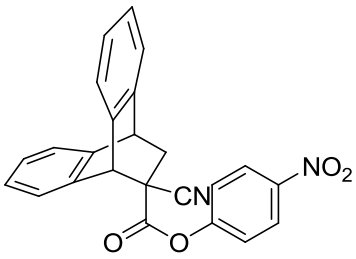
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-chlorophenyl)-carboxylate (139d)



Carboxylic acid **49** (2.00g, 7.26 mmol) and thionyl chloride (5.00 mL, 68.9 mmol) were combined in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, the resultant acid chloride was combined with 4-chlorophenol (1.40 g, 10.9 mmol) and pyridine (0.65 mL, 7.99 mmol) in chloroform (20.0 mL) and heated to reflux for 3 days. The reaction was quenched with water (20.0 mL) and the product was extracted with Et_2O (3 x 30.0 mL). The combined organic layers were washed with 2M aq. HCl (50.0 mL) and sat. aq. $NaHCO_3$ (50.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **139d** (2.26 g) as brown oil. This was purified by flash column chromatography (14:1 petrol/ EtOAc) to give the title compound **139d** (1.02 g, 2.69 mmol, 37%) as a white solid. R_f (14:1 petrol/ EtOAc) 0.81; m.p. 148-150 ^oC; ν_{max}/cm^{-1} 2960 (CH), 2243 (CN), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 7.55 - 7.51 (1H, m, Ar-H), 7.37 - 7.30 (5H, m, Ar-H), 7.26 - 7.15 (4H, m, Ar-H), 6.93 - 6.89 (2H, m, Ar-H), 5.06 (1H, s, ArC-CH-CCN), 4.48 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.91 (1H, dd, *J* 10.5, 3.0, CH-CH_2-CCN), 2.31 (1H, dd, *J* 10.5, 3.0, CH-CH_2-CCN);); δ_C (100 MHz, $CDCl_3$) 165.4 (C=O), 148.8 (ArC-Cl), 143.0, 142.3, 137.5, 136.9 (4 x ArC), 132.1 (ArC-O), 129.7 (O-C-

(C̲H)$_2$), 128.0, 127.8, 126.8, 126.6, 126.0, 125.4, 124.3, 123.7 (8 x ArC̲H), 122.4 (Cl-C-(C̲H)$_2$), 119.2 (C̲N), 51.9 (ArC-C̲H-CCN), 47.5 (CH-C̲-CN), 43.1 (ArC-C̲H-CH$_2$), 38.1 (CH-C̲H$_2$-CCN); *m/z* (ES$^+$) 407.9 [M+Na]$^+$, found 408.0762 ($C_{24}H_{16}ClNNaO_2$ requires 408.0767); found C: 74.6, H: 4.2, N: 3.7, $C_{24}H_{16}ClNO_2$ requires C: 74.7, H: 4.8, N: 3.6.

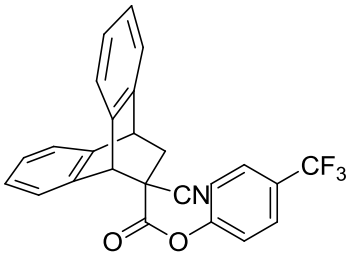
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-nitrophenyl)-carboxylate (139e)



Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (5.00 mL, 68.9 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), 4-nitrophenol (1.52 g, 10.9 mmol) and pyridine (0.65 mL, 7.99 mmol) was added and the reaction refluxed for 36 h. Water (50.0 mL) was added and the product was extracted with Et_2O (3 x 50.0 mL). The organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **139e** (5.06 g) as a yellow solid. This was purified by recrystallisation (petrol/ EtOAc) to furnish the title compound **139e** (1.87 g, 4.72 mmol, 65%) as an off-white solid. R_f (9:1 petrol/ EtOAc) 0.12; m.p. 124 – 125 ^oC; ν_{max}/cm^{-1} 1770 (C=O), 1523 (NO_2); δ_H (400 MHz, $CDCl_3$) 8.23 – 8.12 (2H, m, Ar-H̲), 7.56 – 7.48 (1H, m, Ar-H̲), 7.38 - 7.27 (3H, m, Ar-H̲), 7.27 – 7.13 (4H, m, Ar-H̲), 7.13 - 7.05 (2H, m, Ar-H̲), 5.09 (1H, s, ArC-CH̲-CCN), 4.49 (1H, t, *J* 2.5, ArC-CH̲-CH$_2$), 2.88

(1H, dd, *J* 13.0, 2.5, CH-C<u>H</u>$_2$-CCN), 2.29 (1H, dd, *J* 13.0, 2.5, CH-C<u>H</u>$_2$-CCN); δ_C (100 MHz, $CDCl_3$) 165.0 (<u>C</u>=O), 154.7, 145.9, 143.0, 142.3, 137.3, 136.8 (Ar<u>C</u>), 128.2, 128.0, 126.9, 126.7, 126.1, 125.5, 125.4, 125.0, 124.4, 123.8, 122.1, 122.0 (Ar<u>C</u>-H), 119.0 (<u>C</u>N), 52.0 (ArC-<u>C</u>H-CCN), 47.7 (<u>C</u>CN), 43.1 (ArC-<u>C</u>H-CH_2), 38.2 (CH-<u>C</u>H_2-CCN); *m/z* (ES^+) 419.1 $[M+Na]^+$, found 419.1004 $[M+Na]^+$ ($C_{24}H_{16}N_2NaO_4$ requires 419.1008); found C: 72.2, H: 4.0, N: 7.1, $C_{24}H_{16}N_2O_4$ requires C: 72.7, H: 4.1, N: 7.1.

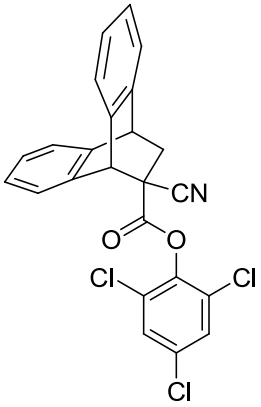
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-trifluoromethyl phenyl)-carboxylate (139f)



Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (5.00 mL, 68.9 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), 4-(trifluoromethyl) phenol (1.77 g, 10.9 mmol) and pyridine (0.65 mL, 7.99 mmol) was added and the reaction refluxed for 36 h. Water (50.0 mL) was added and the product was extracted with Et_2O (3 x 50.0 mL). The organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **139f** (2.28 g) as a brown oil. This was purified by column chromatography (9:1 petrol/ EtOAc) to furnish the title compound **139f** (1.52 g, 3.63 mmol, 50%) as an orange solid. R_f (9:1 petrol/ EtOAc) 0.48; m.p. 99 – 100 ^oC; ν_{max}/cm^{-1} 2934 (CH), 2110 (CN), 1756 (C=O); δ_H (400 MHz, $CDCl_3$) 7.64 (2H, d, *J* 8.5, Ar-<u>H</u>), 7.58 – 7.44 (2H, m, Ar-<u>H</u>), 7.35 (3H, m, Ar-<u>H</u>), 7.29 – 7.15 (3H, m, Ar-

H), 7.09 (2H, d, *J* 8.5, Ar-H), 5.08 (1H, s, ArC-CH-CCN), 4.50 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.91 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.31 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN); δ_C (100 MHz, $CDCl_3$) 165.2 (C=O), 152.7, 142.9, 142.3, 137.4, 136.8, 128.8 (6 x ArC), 128.1, 127.9, 127.2, 127.1, 127.0, 126.9, 126.6, 126.0, 125.0, 124.3, 123.7, 121.6 (12 x ArC-H), 119.0 (CN), 51.9 (ArC-CH-CCN), 47.6 (CH-C-CN), 43.1 (ArC-CH-CH_2), 38.1 (CH-CH_2-CCN); δ_F (376 MHz, $CDCl_3$) -62.4 (CF_3); *m/z* (ES^+) 442.1 $[M+Na]^+$, found 442.1025 $[M+Na]^+$ ($C_{25}H_{16}F_3NNaO_2$ requires 442.1031); Found C: 71.3, H: 3.8, N: 3.3, $C_{25}H_{16}F_3NO_2$ requires C: 71.6, H: 3.9, N: 3.3.

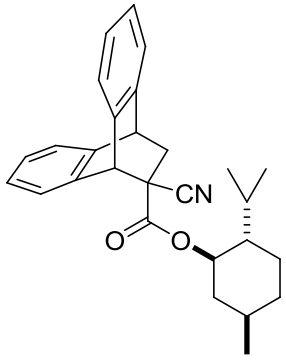
Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(2,4,6-chlorophenyl)-carboxylate (140a)



Carboxylic acid **49** (2.00g, 7.26 mmol) and thionyl chloride (5.00 mL, 68.9 mmol) were combined in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, the resultant acid chloride was combined with 2,4,6-trichlorophenol (2.15 g, 10.9 mmol) and pyridine (0.65 mL, 7.99 mmol) in chloroform (20.0 mL) and heated to reflux for 4 days. The reaction was quenched with water (20.0 mL) and the product was extracted with Et_2O (3 x 30.0 mL). The combined organic layers were washed with 2M aq. HCl (50 mL) and sat. aq.

$NaHCO_3$ (50.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **140a** (2.79 g) as orange oil. This was re-crystallised (hexane) to give the title compound **140a** (0.95 g, 0.94 mmol, 13%) as a pale yellow solid. R_f (4:1 petrol/ EtOAc) 0.47; m.p. 166-167 ^oC; v_{max}/cm^{-1} 2895 (CH), 2127 (CN), 1772 (CO); δ_H (400 MHz, $CDCl_3$) 7.57 – 7.51 (1H, m, Ar-H), 7.41 – 7.35 (2H, m, Ar-H), 7.33 – 7.30 (1H, m, Ar-H), 7.28 – 7.22 (2H, m, Ar-H), 7.20 – 7.08 (2H, m, Ar-H), 5.10 (1H, s, ArC-CH-CCN), 4.49 (1H, t, *J* 2.5, ArC-CH-CH_2), 2.86 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.49 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN); δ_C (100 MHz, $CDCl_3$) 163.9 (C=O), 142.6, 142.4, 142.3, 141.9, 138.1, 136.5, 132.8, 129.3 (8 x ArC), 128.8, 128.7, 127.8, 127.7, 126.9, 126.5, 126.4, 125.9, 123.9, 123.6 (10 x ArC-H), 118.7 (CN), 51.2 (ArC-CH-CCN), 47.5 (CH-C-CN), 43.1 (ArC-CH-CH_2), 39.4 (CH-CH_2-CCN); *m/z* (ES^+) 476.0 $[M+Na]^+$, found 475.9984 ($C_{24}H_{14}Cl_3NNaO_2$ requires 475.9988); found C: 63.2, H: 3.1, N: 3.1, $C_{24}H_{14}Cl_3NO_2$ requires C: 63.4, H: 3.1, N: 3.1.

Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-((-)-methyl)-carboxylate (140b)

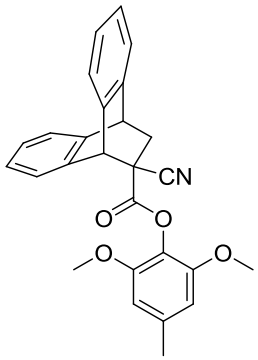


Carboxylic acid **49** (2.00 g, 7.26 mmol) was combined with thionyl chloride (5.00 mL, 68.9 mmol) in chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, chloroform (20.0 mL), (-)-menthol (1.70 g, 10.9

mmol) and pyridine (0.65 mL, 7.99 mmol) was added and the reaction refluxed for 36 h. Water (50.0 mL) was added and the product was extracted with Et_2O (3 x 50.0 mL). The organic phase was washed with 2M aq. HCl (100 mL) and sat. aq. $NaHCO_3$ (100 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product **140b** (2.92 g) as an orange oil. This was purified by column chromatography (9:1 petrol/ EtOAc) to yield title compound **140b** (1.13 g, 2.76 mmol, 38%) as a pale yellow oil (a mixture of two inseparable diastereoisomers in a 1:1 ratio, labelled as A and B). R_f (9:1 petrol/ EtOAc) 0.36; v_{max}/cm^{-1} 2954, 2195 (CN), 2868 (CH), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 7.55 – 7.43 (2H, m, Ar-H), 7.37 – 7.26 (4H, m, Ar-H), 7.24 – 7.13 (8H, m, Ar-H), 7.13 – 7.05 (2H, m, Ar-H), 4.87 (1H, s, A or B ArC-CH-CCN), 4.82 (1H, s, A or B ArC-CH-CCN), 4.59 (2H, qd, *J* 11.0, 4.5, A and B O-CH-CH_2), 4.43 – 4.39 (2H, m, A and B ArC-CH-CH_2), 2.80 (2H, dt, *J* 13.0, 2.5, A and B CH-$CH_{2ax/eq}$-CCN), 2.20 (2H, td, *J* 13.0, 2.5, A and B CH-$CH_{2ax/eq}$-CCN), 2.09 – 1.98 (2H, m, A and B CH_2-CH-CH_3), 1.87 – 1.81 (2H, m, A or B OCH-CH-CH_2), 1.80 – 1.73 (1H, m, A or B OCH-CH-CH_2), 1.73 – 1.61 (4H, m, A or B OCH-CH-CH_2 and A or B OCH-CH_2-CH), 1.57 – 1.47 (2H, m, A or B OCH-CH_2-CH), 1.47 – 1.32 (2H, m, A and B CH-CH-$(CH_3)_2$), 1.16 – 1.04 (1H, m, A or B O-CH-CH), 1.04 – 0.98 (4H, m, A and B CH_3-CH-CH_2-CH_2), 0.98 – 0.82 (12H, m, A and B CH-CH-$(CH_3)_2$), 0.76 (3H, d, *J* 7.0, A or B CH_2-CH-CH_3), 0.65 (3H, d, *J* 7.0, A or B CH_2-CH-CH_3); δ_C (100 MHz, $CDCl_3$) 166.5, 166.2 (A and B C=O), 143.1, 142.9, 142.5, 142.5, 138.4, 138.1, 137.0, 137.0 (A and B ArC), 127.6, 127.5, 127.4, 126.6, 126.6, 126.2, 126.2, 125.8, 125.7, 125.4, 125.3, 123.8, 123.7, 123.6, 123.6 (A and B Ar-CH), 120.1, 119.9 (A and B CN), 77.8, 77.6 (A and B O-CH-CH_2), 51.6, 51.6 (A and B ArC-CH-CCN), 48.0, 47.2 (A and B CH-C-CN), 47.0, 46.7 (A and B OCH-CH-CH_2), 43.2 (A and B ArC-CH-CH_2), 40.8, 39.9 (CH_2-CH_2-CH-CH_3), 38.2, 37.9 (A

and B CH-<u>C</u>H_2-CCN), 34.1, 34.0 (A and B OCH-CH-<u>C</u>H_2-CH_2), 31.4, 31.4 (A and B CH-<u>C</u>H$(CH_3)_2$), 26.0, 25.7 (A and B CH_2-<u>C</u>H-CH_3), 23.0, 22.9 (A and B OCH-<u>C</u>H_2-CH), 22.0, 21.9, 21.0, 20.9 (A and B CH(<u>C</u>$H_3)_2$), 15.9, 15.9 (A and B CH_2-CH-<u>C</u>H_3); *m/z* (ES^+) 436.2 $[M+Na]^+$, found: 436.2247 $[M+Na]^+$ ($C_{28}H_{31}NNaO_2$ requires 436.2252).

Ethyl 9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(4-methyl-2,6-dimethoxy-phenyl)carboxylate (140c)



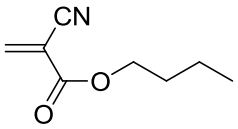
Carboxylic acid **49** (2.00 g, 7.26 mmol) and thionyl chloride (5.00 mL, 68.9 mmol) were combined in Chloroform (20.0 mL) and heated to reflux for 6 h. Excess thionyl chloride was removed *in vacuo*, 4-methyl-2,6-dimethoxy phenol (1.83 g, 10.9 mmol), pyridine (0.65 mL, 7.99 mmol) and chloroform (20.0 mL) were added and the reaction heated to reflux for 4 days. Water (20.0 mL) was added and the product extracted with Et_2O (3 x 30 mL). The combined organic layers were washed with 2M aq. HCl (50.0 mL) and $NaHCO_3$ (50.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **140c** (2.58 g) as an orange solid. This was purified by flash column chromatography (petrol/ EtOAc 1:1) to furnish the title compound **140c** (0.96 g, 2.25 mmol, 31%) as an off-white solid. R_f (1:1 petrol/ EtOAc) 0.56; m.p. 170 – 171 ^oC; v_{max}/cm^{-1} 2340 (CN), 1770 (C=O); δ_H (400 MHz, $CDCl_3$) 7.56 – 7.49 (1H, m, Ar-<u>H</u>), 7.42 (1H, d, *J* 7.0, Ar-<u>H</u>), 7.37 – 7.32 (1H, m, Ar-<u>H</u>), 7.28 (1H, d, *J*

7.0, Ar-H), 7.25 – 7.19 (2H, m, Ar-H), 7.17 – 7.08 (2H, m, Ar-H), 6.37 (2H, s, 2x (OCH_3)C-CH-C(CH_3)), 5.15 (1H, s, ArC-CH-CCN), 4.44 (1H, t, *J* 2.5, ArC-CH-CH_2), 3.75 (6H, s, 2x ArC-OCH_3), 2.86 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.35 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.30 (3H, s, ArC-CH_3); δ_C (100 MHz, $CDCl_3$) 165.1 (C=O), 151.6 (ArC-OCH_3), 142.9, 142.7 (2x ArC), 138.6 (ArC-CH_3), 137.1, 137.0 (2x ArC), 129.6, 127.5, 127.4, 126.6, 126.4, 126.0, 125.9, 123.7, 123.4, 121.0 (10x ArC-H), 119.6 (CCN), 105.6 (CH_3C-CH-$COCH_3$), 56.3, 56.0 (2x ArC-OCH_3), 51.3 (ArC-CH-CCN), 47.4 (CN), 43.3 (ArC-CH-CH_2), 38.7 (CH-CH_2-CCN), 22.1 (ArC-CH_3); *m/z* (ES^+) 448.2 $[M+Na]^+$, 426.0 $[M+H]^+$, found: 448.1523 $[M+Na]^+$ ($C_{27}H_{23}NNaO_4$ requires 448.1525); C: 75.9, H: 5.5, N: 3.3, $C_{27}H_{23}NO_4$ requires C: 76.2, H: 5.5, N: 3.3.

5.3.3 Cyanoacrylate monomers

5.3.3.1 Heating method

***n*-butyl 2-cyanoacrylate (141a)**



Butyl ester **138a** (15.0 g, 45.0 mmol) was heated with a hot air pistol under vacuum distillation conditions. At a vapour temperature of 100 ^oC to 130 ^oC product was distilled into a cooled collection flask to give the crude cyanoacrylate **141a** (2.53 g) as a colourless liquid. The crude mixture was purified by vacuum fractional distillation to yield the title compound **141a** (1.60 g, 10.4 mmol, 23%) as a colourless liquid. b.p. 105-107 ^oC (8 mbar), Lit.[223] b.p. 128-130 ^oC (2.66 mbar); δ_H (400 MHz, $CDCl_3$) 7.05 (1H, s, C=CH_2), 6.65 (1H, s, C=CH_2), 4.28 (1H, t, *J* 6.5,

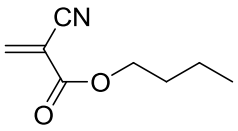
$OC\underline{H}_2$-CH_2), 1.75 – 1.63 (1H, m, OCH_2-$C\underline{H}_2$), 1.44 (1H, dq, *J* 14.5, 7.5, OCH_2-CH_2-$C\underline{H}_2$), 0.96 (2H, t, *J* 7.5, CH_2-$C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 160.5 ($\underline{C}$=O), 143.1 (C=$\underline{C}H_2$), 136.4 ($\underline{C}$-CN), 114.3 ($\underline{C}$N), 66.6 ($O\underline{C}H_2$-CH_2), 30.1 (OCH_2-$\underline{C}H_2$), 18.7 (OCH_2-CH_2-$\underline{C}H_2$), 13.5 (CH_2-$\underline{C}H_3$).

5.3.3.2 Maleic anhydride method

General procedure for retro-Diels-Alder reaction using maleic anhydride 47:

Esters **138-140** (1 eq., 16.3 mmol), maleic anhydride **47** (3 eq., 48.9 mmol), hydroquinone (0.5 eq., 8.15 mmol) and phosphorus pentoxide (0.5 eq., 8.15 mmol) were combined in xylene (0.30 M) and heated to reflux for 48-72 h. The reaction was removed from the heat and allowed to cool, benzene was added to precipitate out the solid anthracene – maleic anhydride adduct **48a** which was filtered off. The crude cyanoacrylates **141-143** were purified by vacuum fractional distillation.

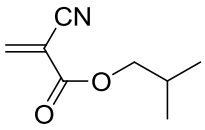
***n*-Butyl 2-cyanoacrylate (141a)**



The anthracene ester **138a** was reacted for 48 h, the crude mixture was purified by vacuum fractional distillation to furnish the title compound **141a** (1.25 g, 1.63 mmol, 10%) as a colourless liquid. b.p. 103-106 ^oC (8 mbar), Lit.[223] b.p. 128-130 ^oC (2.66 mbar); δ_H (400 MHz, $CDCl_3$) 7.06 (1H, d, *J* 2.0, C=$C\underline{H}_2$), 6.65 (1H, d, *J* 2.0 C=$C\underline{H}_2$), 4.28 (2H, t, *J* 6.5, $OC\underline{H}_2$-CH_2), 1.80 – 1.64 (2H, m, OCH_2-$C\underline{H}_2$), 1.45 (2H, dq, *J* 14.5, 7.5, OCH_2-CH_2-$C\underline{H}_2$), 0.96 (3H, t, *J* 7.5, CH_2-$C\underline{H}_3$); δ_C (100 MHz, $CDCl_3$)

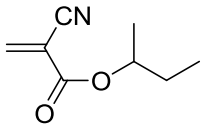
160.9 (C=O), 143.1 (C=CH_2), 136.1 (C-CN), 114.8 (CN), 66.61 (OCH_2-CH_2), 29.9 (OCH_2-CH_2), 19.0 (OCH_2-CH_2-CH_2), 13.7 (CH_2-CH_3).

***iso*-Butyl 2-cyanoacrylate (141b)**



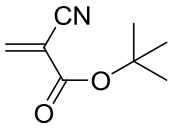
The anthracene ester **138b** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **141b** (1.54 g, 9.45 mmol, 58 %) as a colourless liquid. b.p. 110 – 112 ^{o}C (8 mbar); δ_H (400 MHz, $CDCl_3$) 7.07 (1H, d, *J* 2.0, CH_2=C), 6.65 (1H, d, *J* 2.0, CH_2=C), 4.07 (2H, d, *J* 6.5, OCH_2CH), 2.05 (1H, dt, *J* 13.5, 6.5, $OCH_2CH(CH_3)_2$), 0.99 (6H, d, *J* 6.5, $CH(CH_3)_2$); δ_C (100 MHz, $CDCl_3$) 164.2 (C=O), 143.2 (CH_2=C), 116.7 (CN), 114.4 (CH_2=C), 72.7 (OCH_2CH), 27.6 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$).

***sec*-Butyl 2-cyanoacrylate (141c)**



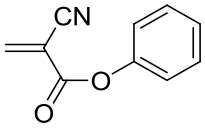
The anthracene ester **138c** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **141c** (1.88 g, 10.27 mmol, 63%) as a colourless liquid. b.p. 108-112 ^{o}C (8 mbar); δ_H (400 MHz, $CDCl_3$) 6.95 (1H, d, *J* 2.0, CH_2=C), 6.54 (1H, d, *J* 2.0, CH_2=C), 4.95 – 4.85 (1H, m, $OCH(CH_3)CH_2$), 1.69 – 1.49 (2H, m, $OCHCH_2CH_3$), 1.23 (3H, d, *J* 6.5, $OCHCH_3$), 0.86 (3H, t, *J* 7.5, CH_2CH_3); δ_C (100 MHz, $CDCl_3$) 163.4 (C=O), 142.0 (CH_2=C), 116.1 (CN), 113.6 (CH_2=C), 74.6 ($OCH(CH_3)CH_2$), 27.5 ($OCHCH_2$), 18.2 ($OCHCH_3$), 8.5 (CH_2CH_3).

***tert*-Butyl 2-cyanoacrylate (141d)**



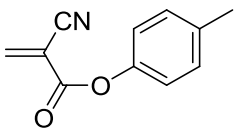
The anthracene ester **138d** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **141d** (1.10 g, 2.93 mmol, 18%) as a colourless liquid. b.p. (98 – 102 ^{o}C); δ_H (400 MHz, $CDCl_3$) 7.09 (1H, d, *J* 2.0, C$\underline{H}_2$=C), 6.95 (1H, d, *J* 2.0, C$\underline{H}_2$=C), 2.35 (9H, s, (C$\underline{H}_3$)$_3$); δ_C (100 MHz, $CDCl_3$) 163.1 ($\underline{C}$=O), 136.7 ($\underline{C}H_2$=C), 116.0 ($\underline{C}$N), 110.9 (CH_2=$\underline{C}$), 71.6 (O$\underline{C}$(CH$_3$)$_3$), 27.8 (C($\underline{C}$H$_3$)$_3$).

Phenyl 2-cyanoacrylate (142a)



The anthracene ester **139a** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **142a** (1.12 g, 7.17 mmol, 44%) as a colourless liquid. b.p. (130 – 134 ^{o}C); δ_H (400 MHz, $CDCl_3$) 7.52 (2H, t, *J* 7.5, CO-CH-C$\underline{H}$-CH), 7.40 – 7.29 (3H, m, CO-C$\underline{H}$-CH-C$\underline{H}$), 7.06 (1H, d, *J* 2.0, C$\underline{H}_2$=C), 6.74 (1H, d, *J* 2.0, C$\underline{H}_2$=C); δ_C (100 MHz, $CDCl_3$) 162.0 ($\underline{C}$=O), 149.5 (Ar$\underline{C}$-O), 144.9 (C=$\underline{C}H_2$), 130.1, 125.2, 121.8 (Ar$\underline{C}$-H), 115.8, 110.8 ($\underline{C}$N) and (CH_2=$\underline{C}$).

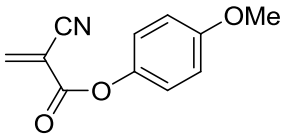
***p*-Tolyl 2-cyanoacrylate (142b)**



The anthracene ester **139b** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **142b** (1.20 g, 7.01 mmol, 43%) as a

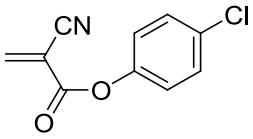
colourless liquid. b.p. (128 - 134 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.19 (2H, d, *J* 8.0, CH-C<u>H</u>-C(CH_3)), 7.04 (2H, d, *J* 8.0, CO-C<u>H</u>-CH), 7.01 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.65 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 2.32 (3H, s, C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 160.8 (<u>C</u>=O), 147.8 (Ar<u>C</u>-O), 144.6 (<u>C</u>H$_2$=C), 130.2, 120.7 (Ar<u>C</u>-H), 116.5, 114.2 (<u>C</u>N, CH$_2$=<u>C</u>).

***p*-Methoxyphenyl 2-cyanoacrylate (142c)**



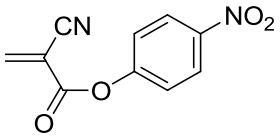
The anthracene ester **139c** was reacted for 72 h, the crude solution was distilled under vacuum to give the title compound **142c** (1.21 g, 8.64 mmol, 53%) as a colourless liquid. b.p. (124 - 128 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.29 (2H, d, *J* 7.5, CO-C<u>H</u>-CH), 7.18 (2H, d, *J* 7.5, C(OCH_3)-C<u>H</u>-CH), 7.01 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.68 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 3.78 (3H, s, OC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 161.3 (<u>C</u>=O), 156.4, 141.8 (Ar<u>C</u>-O), 138.9 (<u>C</u>H$_2$=C), 129.6, 122.4 (Ar<u>C</u>-H), 114.8, 111.9 (<u>C</u>N, CH$_2$=<u>C</u>), 55.6 (O<u>C</u>H$_3$).

***p*-Chlorophenyl 2-cyanoacrylate (142d)**



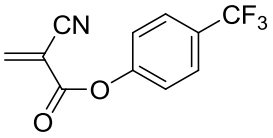
The anthracene ester **139d** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **142d** (1.25 g, 6.03 mmol, 37%) as a colourless liquid. b.p. (128 - 132 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.68 (2H, d, *J* 7.0, CH-C<u>H</u>-CCl), 7.60 (2H, d, J 7.0, CO-C<u>H</u>-CH), 7.02 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.68 (1H, d, *J* 2.0, C<u>H</u>$_2$=C); δ_C (100 MHz, $CDCl_3$) 163.4 (C=O), 148.4 (ArC-O), 145.6 (<u>C</u>H$_2$=C), 131.1 (Ar<u>C</u>-Cl), 128.0, 123.3 (Ar<u>C</u>-H), 115.8, 113.8 (<u>C</u>N, CH$_2$=<u>C</u>).

***p*-Nitrophenyl 2-cyanoacrylate (142e)**



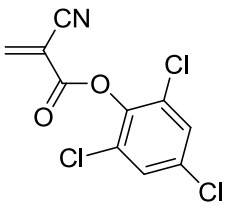
The anthracene ester **139e** was reacted for 72 h, the crude solution was distilled under vacuum to give the title compound **142e** (1.15 g, 6.03 mmol, 37%) as a pale yellow liquid. b.p. (120 - 122 ^{o}C); δ_H (400 MHz, $CDCl_3$); 8.27 (2H, d, *J* 7.5, CH-C<u>H</u>-CNO_2), 7.65 (2H, d, *J* 7.5, CH-C<u>H</u>-CO), 7.02 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.64 (1H, d, *J* 2.0, C<u>H</u>$_2$=C); δ_C (100 MHz, $CDCl_3$) 164.0 (<u>C</u>=O), 154.7 (Ar<u>C</u>-O), 145.7 (Ar<u>C</u>-NO_2), 136.8 (<u>C</u>H_2=C), 125.5, 122.1 (Ar<u>C</u>-H), 116.8, 112.3 (<u>C</u>N, CH_2=<u>C</u>).

***p*-(Trifluoromethyl)phenyl 2-cyanoacrylate (142f)**



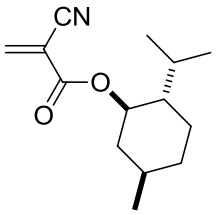
The anthracene ester **139f** was reacted for 72 h, the crude solution was distilled under vacuum to give the title compound **142f** (1.24 g, 7.66 mmol, 47%) as a colourless liquid. b.p. (118 - 124 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.75 (2H, d *J* 8.0, CH-C<u>H</u>-C(CF_3)), 7.31 (2H, d, *J* 8.0, CO-C<u>H</u>-CH), 7.02 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.71 (1H, d, *J* 2.0, C<u>H</u>$_2$=C); δ_C (100 MHz, $CDCl_3$) 165.0 (<u>C</u>=O), 145.4, 143.2 (Ar<u>C</u>-O, Ar<u>C</u>-CF_3), 136.5 (<u>C</u>H_2=C), 128.9, 121.7 (Ar<u>C</u>-H), 115.5, 113.8 (<u>C</u>N, CH_2=<u>C</u>).

2,4,6-Trichlorophenyl 2-cyanoacrylate (143a)



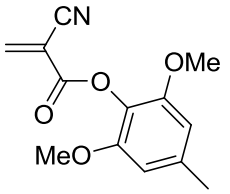
The anthracene ester **140a** was reacted for 48 h, the crude solution was distilled under vacuum to give the title compound **143a** (1.10 g, 9.29 mmol, 57%) as a colourless liquid. b.p. (130 - 134 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.52 (2H, s, C(Cl)-C<u>H</u>-C(Cl)), 7.07 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.75 (1H, d, *J* 2.0, C<u>H</u>$_2$=C); δ_C (100 MHz, $CDCl_3$) 164.0 (<u>C</u>=O), 142.5, 132.8, 130.3 (Ar<u>C</u>-O, Ar<u>C</u>-Cl), 129.8 (<u>C</u>H$_2$=C), 128.8 (Ar<u>C</u>-H), 116.7, 112.8 (<u>C</u>N, CH$_2$=<u>C</u>).

5-*iso*-Propyl-2-methylcyclohexyl 2-cyanoacrylate (143b)



The anthracene ester **140b** was reacted for 72 h, the crude solution was distilled under vacuum to give the title compound **143b** (1.12 g, 6.19 mmol, 38%) as a colourless liquid. b.p. (114 - 118 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.03 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 6.60 (1H, d, *J* 2.0, C<u>H</u>$_2$=C), 2.09 – 1.99 (1H, m, CH$_2$-C<u>H</u>-CH$_3$), 1.93 – 1.80 (1H, m, OCH-C<u>H</u>-CH$_2$), 1.75 – 1.69 (2H, m, OCH-C<u>H</u>$_2$-CH), 1.56 – 1.48 (2H, m, OCH-CH-C<u>H</u>$_2$), 1.17 – 1.05 (1H, m, O-CH-C<u>H</u>), 1.04 – 0.98 (2H, m, CH$_3$-CH-C<u>H</u>$_2$-CH$_2$), 0.93 (6H, dd, *J* 11.0, 4.5, CH-CH(C<u>H</u>$_3$)$_2$), 0.78 (3H, d, *J* 7.0, CH$_2$-CH-C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 165.2 (C=O), 142.9 (<u>C</u>H$_2$=C), 116.9, 111.8 (CN, CH$_2$=<u>C</u>), 77.6 (O-<u>C</u>H-CH$_2$), 46.9 (OCH-<u>C</u>H-CH$_2$), 40.4 (CH$_2$-<u>C</u>H$_2$-CH-CH$_3$), 34.2, (OCH-CH-<u>C</u>H$_2$-CH$_2$), 31.3 (CH-<u>C</u>H(CH$_3$)$_2$), 25.9 (CH$_2$-<u>C</u>H-CH$_3$), 22.9 (OCH-<u>C</u>H$_2$-CH), 21.6 (CH(<u>C</u>H$_3$)$_2$), 15.8 (CH$_2$-CH-<u>C</u>H$_3$).

2,6-Dimethoxy-4-methylphenyl 2-cyanoacrylate (143c)

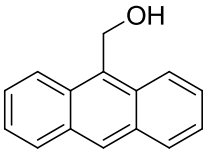


The anthracene ester **140c** was reacted for 72 h, the crude solution was distilled under vacuum to give the title compound **143c** (1.14 g, 5.71 mmol, 35%) as a colourless liquid. b.p. (130 - 134 ^{o}C); δ_H (400 MHz, $CDCl_3$); 7.04 (1H, d, *J* 2.0, C$\underline{H}_2$=C), 6.94 (2H, s, C$\underline{H}$-C(CH_3)), 3.79 (6H, s, OC$\underline{H}_3$), 2.32 (3H, s, C$\underline{H}_3$); δ_C (100 MHz, $CDCl_3$) 163.1 (<u>C</u>=O), 151.2, 139.0, 137.1 (Ar<u>C</u>-OCH_3, Ar<u>C</u>-CH_3, Ar<u>C</u>-O), 138.9 (<u>C</u>H_2=C), 116.6, 113.5 (<u>C</u>N, CH_2=<u>C</u>), 105.4 (Ar<u>C</u>-H), 56.2 (2x ArC-O<u>C</u>H_3), 22.0 (ArC-<u>C</u>H_3).

5.4 Experimental procedures for substrates synthesised in Chapter 4

5.4.1 9-substituted anthracenes 46c,d,e,j

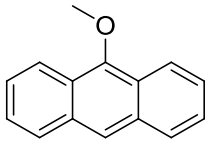
9-Hydroxymethylanthracene (46c)



9-Anthracenecarboxaldehyde **46f** (0.50 g, 2.42 mmol) and sodium borohydride (0.22 g, 5.82 mmol) were combined in THF at 0 ^{o}C, then refluxed o/n. The reaction was quenched with water (20.0 mL) and product was extracted with Et_2O (3 x 30.0 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (50.0 mL), dried ($MgSO_4$) and concentrated *in vacuo* to give crude product **46c** (0.49 g) as a yellow solid. This was re-crystallised (hexane) to yield the title compound **46c** (0.23 g, 1.11

mmol, 46%) as yellow needles. R_f (4:1 petrol/ EtOAc) 0.21; m.p. 162-164 ^oC; Lit[258] m.p. 162-163 ^oC; v_{max}/cm^{-1} 3434 b (OH), 2945 (CH); δ_H (400 MHz, $CDCl_3$) 8.42 (1H, s, CH-C-C<u>H</u>-C-CH), 8.36 (2H, d, *J* 8.5, C-C<u>H</u>-CH), 7.99 (2H, d, *J* 8.5, C-C<u>H</u>-CH), 7.56 – 7.50 (2H, m, CH-C<u>H</u>-CH-CH), 7.49 – 7.43 (2H, m, CH-CH-C<u>H</u>-CH), 5.60 (2H, s, C<u>H</u>$_2$OH), 1.84 (1H, s, CH$_2$O<u>H</u>); δ_C (100 MHz, $CDCl_3$) 131.0 (<u>C</u>-CH$_2$-OH), 131.6, 130.3 (<u>C</u>-CH-CH), 128.4 (CH-C-<u>C</u>H-C-CH), 129.2, 126.5, 125.1, 123.9 (<u>C</u>H-<u>C</u>H-<u>C</u>H-<u>C</u>H), 57.4 (<u>C</u>H$_2$OH); *m/z* (ES^+) 230.8 $[M+Na]^+$.

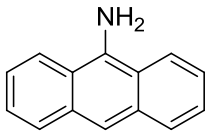
9-Methoxy anthracene (46d)



9-Bromoanthracene **46i** (1.00 g, 3.89 mmol), methanol (0.32 mL, 7.78 mmol), Cs_2CO_3 (1.90 g, 5.84 mmol), $Pd(OAc)_2$ (0.045g, 0.20 mmol) and X-Phos (0.10 g, 0.20 mmol) were combined in toluene (20.0 mL) and heated to 90 ^oC for 3 days. The reaction was removed from the heat, water (10 mL) was added and the product extracted with DCM (3 x 15 mL). The combined organic layers were washed with sat. aq. $NaHCO_3$ (30 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield the crude product **46d** (0.37 g) as a yellow solid. This was purified by flash column chromatography (9:1 petrol/ EtOAc) to give the title compound **46d** (0.12 g, 0.58 mmol, 15%) as a white solid. R_f (9:1 Petrol/EtOAc) 0.57; m.p. 90-92 ^oC; Lit[259] m.p. 92.3 – 93.3 ^oC; v_{max}/cm^{-1} 2845 (CH), 1620 (CO); δ_H (400 MHz, $CDCl_3$) 8.28 (2H, d, *J* 9.5, CH-C<u>H</u>-C-C(OMe)), 8.19 (1H, s, C-C<u>H</u>-C), 7.96 (2H, d, *J* 7.5, CH-C<u>H</u>-C-CH-C), 7.49 – 7.41 (4H, m, CH-C<u>H</u>-C<u>H</u>-CH), 4.12 (3H, s, OC<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 152.3 (<u>C</u>-OMe), 132.5, 131.7 (CH-<u>C</u>-CH-<u>C</u>-CH), 128.5, 128.2 (<u>C</u>H-C-CH-C-<u>C</u>H),

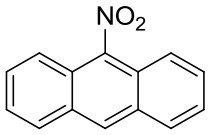
127.2, 126.3, 125.6, 125.4 (CH-CH-CH-CH), 124.5 (C-CH-C), 122.4, 122.3 (CH-C-COMe-C-CH), 122.4, 122.3 (CH-C-COMe), 63.2 ($O\underline{C}H_3$); *m/z* (ES^+) 209.1 $[M+H]^+$.

9-Aminoanthracene (46e)



9-Nitro anthracene **46j** (2.00 g, 8.96 mmol) was combined with glacial acetic acid (40.0 mL), stirred and heated to 80 ^oC for 30 minutes until all the solid had dissolved. $SnCl_2$ (8.5 g, 44.8 mmol) in conc. HCl (30.0 mL) were added *via* dropping funnel. The reaction was allowed to cool to r.t., filtered and washed with conc. HCl (3 x 5.00 mL). The resulting yellow solid was put into a flask and covered with 5% NaOH. This was left for 15 minutes with occasional manual stirring, filtered and washed with water until neutral (approx. 200 mL). The resulting yellow solid was stored in the dark and dried in a desiccator for 4 days to give crude product **46e** (0.67 g, 3.49 mmol, 39%) as a yellow solid. The product was used without further purification due to stability problems. R_f (9:1 petrol/ EtOAc) 0.36; m.p. 129 – 130 ^oC; Lit[260] m.p. 145 – 146 ^oC; ν_{max}/cm^{-1} 1632 (NH_2); δ_H (400 MHz, $CDCl_3$) 8.61 (1H, s, C-CH-C), 8.06 (2H, d, *J* 8.5, C-CH-CH), 7.93 (2H, d, *J* 8.5, C-CH-CH), 7.68 – 7.60 (2H, m, C-CH-CH-CH), 7.58 – 7.51 (2H, m, C-CH-CH-CH); δ_C (100 MHz, $CDCl_3$) 144.0 ($\underline{C}$-NH_2), 130.7 (CH-C-CH), 130.4 (C-CH-C), 128.4 (CH-C-CH), 128.2 (C-CH-C-CH-CH), 127.1 (C-CH-C-CH-CH), 126.2 (C-CH-CH-CH), 126.0 (C-CH-CH-CH), 125.2 (C-CH-CH-CH), 125.0 (C-CH-CH-CH), 122.6 (CH-C-CNH_2), 121.4 (CH-C-CNH_2), 121.3 ($C(NH_2)$-C-CH-CH), 121.1 ($C(NH_2)$-C-CH-CH); *m/z* (ES^+) 194.1 $[M+H]^+$, found: 194.0940 $[M+H]^+$ ($C_{14}H_{12}N$ requires 194.0970).

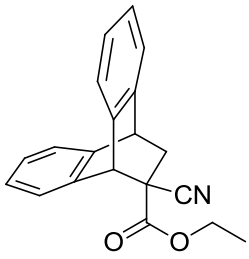
9-Nitro anthracene (46j)



Concentrated nitric acid (6.00 mL, 0.13 mol) was added drop-wise to a suspension of anthracene **46a** (15.0 g, 0.08 mol) and glacial acetic acid (60.0 mL), keeping the temperature below 30 ^{o}C. This was stirred vigorously for 1 h, until all of the solid had dissolved giving a clear orange solution. A mixture of concentrated HCl and glacial acetic acid (1:1, 100 mL) was added slowly, resulting in a yellow precipitate. This was filtered and washed with water until the washings were neutral (approx. 500 mL). The resulting yellow solid was treated with a warm solution (60-70 ^{o}C) of 10% NaOH (250 mL). This was filtered and washed with water until the washings were neutral (approx. 500 mL), the resulting solid was air-dried. This was re-crystallised in acetic acid to give the title compound **46j** (11.5 g, 0.08 mmol, 61%) as a yellow solid. R_f (9:1 petrol/ EtOAc) 0.32; m.p. 148 – 150 ^{o}C; Lit[261] m.p. 148-149 ^{o}C; v_{max}/cm^{-1} 3059 (CH), 1624 (NO_2); δ_H (400 MHz, $CDCl_3$) 8.52 (1H, s, C-C<u>H</u>-C), 8.00 (2H, d, *J* 8.5, NO_2C-C-C<u>H</u>-CH), 7.92 (2H, dd, *J* 9.0, 1.0, C-CH-C-C<u>H</u>-CH), 7.67 – 7.55 (2H, m, NO_2C-C-CH-C<u>H</u>-CH), 7.55 – 7.44 (2H, m, C-CH-C-CH-C<u>H</u>); δ_C (100 MHz, $CDCl_3$) 144.2 (<u>C</u>-NO_2), 130.7 (CH-<u>C</u>-CH-<u>C</u>-CH), 130.4 (C-<u>C</u>H-C), 128.9 (NO_2C-C-CH-<u>C</u>H-CH), 128.4 (C-CH-C-<u>C</u>H), 126.2 (C-CH-C-CH-<u>C</u>H), 122.6 (NO_2C-<u>C</u>-CH), 121.3 (NO_2C-C-<u>C</u>H-CH); *m/z* (ES$^+$) 224.1 $[M+H]^+$, 246.0 $[M+Na]^+$, found: 246.0525 $[M+Na]^+$ ($C_{14}H_9NNaO_2$ requires 246.0531).

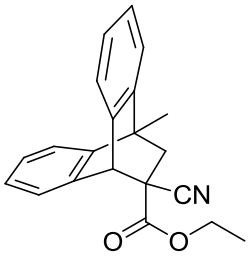
5.4.2 Substituted anthracene adducts 127a-m

Ethyl-9,10-dihydro-9,10-endo-ethanoanthracene-11-cyano-11-(ethyl)-carboxylate (127a)



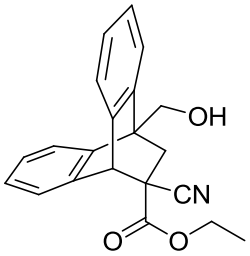
Anthracene **46a** (10.0 g, 60.0 mmol), ethyl cyanoacrylate **37** (10.0 g, 80.0 mmol) and MEHQ (0.40 g, 3.00 mmol) were combined in toluene (100 mL) and heated to reflux for 24 h. Once cool the reaction was concentrated *in vacuo* to give the crude product **127a** (16.5 g) as a pale yellow solid. This was purified by column chromatography (9:1 petrol/ EtOAc) to furnish the title compound **127a** (14.8 g, 48.6 mmol, 81%) as a white solid. R_f (9:1 petrol/ EtOAc) 0.41; m.p. 120-122 ^{o}C, lit[257] m.p. 118 ^{o}C; ν_{max}/cm^{-1} 2945 (C-H), 2120 (C-N), 1746 (C=O); δ_H (400 MHz, $CDCl_3$) 7.50 – 7.03 (8H, m, Ar-H), 4.87 (1H, s, ArC-CH-CCN), 4.39 (1H, t, *J* 2.5, ArC-CH-CH_2), 4.11 (2H, dq, *J* 11.0, 7.0, OCH_2-CH_3), 2.78 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 2.17 (1H, dd, *J* 13.0, 2.5, CH-CH_2-CCN), 1.23 (3H, t, *J* 7.0, OCH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 166.8 (C=O), 143.1, 142.4, 138.1, 137.2 (ArC), 127.6, 127.6, 126.7, 126.4, 125.9, 125.2, 123.9, 123.6 (ArC-H), 119.9 (CN), 63.2 (OCH_2-CH_3), 51.8 (ArC-CH-CCN), 47.4 (CCN), 43.2 (ArC-CH-CH_2), 38.0 (CH-CH_2-CCN), 14.1 (OCH_2-CH_3); *m/z* (ES^+) 326.1 $[M+Na]^+$, found: $[M+Na]^+$ 326.1151 ($C_{20}H_{17}NNaO_2$ requires 326.1157).

Ethyl-9-methyl, 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127b)



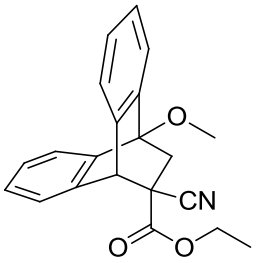
9-Methyl anthracene **46b** (0.05 g, 2.60 mmol), MEHQ (0.03 g, 0.26 mmol) and ethyl cyanoacrylate **37** (0.36 g, 2.86 mmol) were combined in toluene (5.00 mL) and heated to reflux for 8 h. The reaction was concentrated *in vacuo* to give crude product **127b** (1.07 g) as a yellow solid. This was purified by flash column chromatography (9:1 petrol/ EtOAc) to furnish the title compound **127b** (0.73 g, 2.29 mmol, 88%) as a white solid, both **127bT** and **127bK** products were observed in a 5:1 ratio in favour of **127bT**. R_f (9:1 petrol/ EtOAc) 0.21; m.p. 134-136 ^oC; ν_{max}/cm^{-1} 2964 (CH), 2215 (CN), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 7.49 – 7.45 ($1H_T$, m, Ar-H), 7.32 – 7.26 ($2H_T$, m, Ar-H), 7.25 – 7.10 ($5H_T$, m, Ar-H), 7.49 - 7.10 ($8H_K$, m, Ar-H), 4.84 ($1H_T$, s, ArC-CH-CCN), 4.19 - 4.10 ($2H_T$, m, OCH_2CH_3), 4.10 - 4.06 ($2H_K$, m, OCH_2CH_3), 3.84 ($1H_K$, t, *J* 13.0, ArC-CH-CCN), 2.61 ($1H_K$, dd, *J* 13.0, 3.0, $C(CH_3)$-CH_2-CCN), 2.60 ($1H_T$, d, *J* 13.0, $C(CH_3)CH_2$-CCN), 2.41 ($1H_K$, dd, *J* 13.0, 3.0, C(CH3)-CH_2-CCN), 2.03 ($3H_K$, s, C-CH_3), 2.01 ($1H_T$, d, *J* 13.0, $C(CH_3)CH_2$-CCN), 1.99 ($3H_T$, s, C-CH_3), 1.27 ($3H_T$, t, *J* 7.0, OCH_2CH_3), 1.14 ($3H_K$, t, *J* 7.0, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 166.8 (C=O), 145.2, 144.6, 138.5, 137.5 (4 x Ar-C), 127.5, 127.4, 126.4, 126.1, 125.6, 124.9, 121.2, 121.0 (8 x Ar-CH), 119.9 (CN), 63.2 (OCH_2-CH_3), 51.8 (ArC-CH-CCN), 48.4 (CCN), 44.3 ($C(CH_3)CH_2$-CCN), 42.0 (C-CH_3), 17.0 (C-CH_3), 14.1 (OCH_2-CH_3); *m/z* (ES^+) 339.9 $[M+Na]^+$, found 340.1308 ($C_{21}H_{19}NNaO_2$ requires 340.1313).

Ethyl 9-hydroxymethyl 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127c)



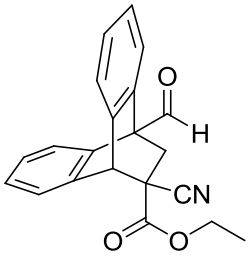
Anthracen-9-yl-methanol **46c** (0.50 g, 2.40 mmol), MEHQ (0.03 g, 0.24 mmol) and ethyl cyanoacrylate **37** (0.33 g, 2.64 mmol) were combined in toluene (5.00 mL) and heated to reflux for 2 days. The reaction was concentrated *in vacuo* to yield crude product **127c** (0.95 g) as a yellow solid. This was re-crystallised (hexane/ EtOAc) to give the title compound **127c** (0.38 g, 1.15 mmol, 48%) as a pale yellow solid. R_f (1:1 Petrol/ EtOAc) 0.49; m.p. 179 – 181 ^{o}C; v_{max}/cm^{-1} 3483 (OH), 2942 (C-H), 2361 (N-H), 1751 (C=O); δ_H (400 MHz, $CDCl_3$) 7.51 - 7.49 (1H, m, Ar-H), 7.44 - 7.39 (2H, m, Ar-H), 7.28 - 7.20 (4H, m, Ar-H), 7.14 - 7.10 (1H, m, Ar-H), 4.84 (1H, s, ArC-CH-CCN), 4.74 (2H, d, *J* 2.5, CH_2-OH), 4.16 (2H, m, O-CH_2-CH_3), 2.70 (1H, d, *J* 2.5, C(CH_2OH)CH_2-CCN), 2.10 (1H, d, *J* 2.5, C(CH_2OH)CH_2-CCN), 1.80 (1H, s, CH_2OH), 1.27 (3H, t, *J* 1.5, O-CH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 166.8 (C=O), 142.6, 142.1, 138.9, 137.9 (4 x ArC), 127.8, 127.5, 126.8, 126.3, 125.9, 125.2, 122.0, 121.8 (8 x ArCH), 119.8 (CN), 63.3 (CH_2-OH), 62.8 (O-CH_2-CH_3), 52.0 (ArC-CH-CCN , 47.1 (C-CN), 39.6 (C(CH_2OH)CH_2-CCN), 14.4 (O-CH_2-CH_3); *m/z* (ES^+) 356.1 $[M+Na]^+$, found 356.1259 $[M+Na]^+$ ($C_{21}H_{19}NNaO_3$ requires 356.1263).

Ethyl 9-methoxy10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127d)



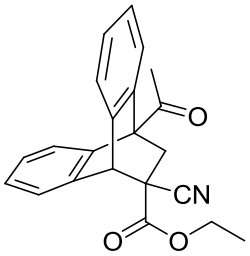
9-Methoxyanthracene **46d** (0.50 g, 2.40 mmol), ethyl cyanoacrylate **37** (0.33 g, 2.64 mmol) and MEHQ (0.03g, 0.24 mmol) were combined with toluene (5.00 mL) and heated to reflux for 48 h. The reaction was removed from the heat and concentrated *in vacuo* to give crude product **127d** (0.77 g) as an orange solid. This was purified by flash column chromatography (9:1 petrol/ EtOAc) to yield two adducts **127a**$_{maj}$ and **127d**$_{min}$ that couldn't be separated, in a 4:1 ratio (0.68 g, 2.04 mmol, 85%). R_f (14:1 petrol/ EtOAc) 0.31, m.p. 128-130 ^{o}C; v_{max}/cm^{-1} 2959 (CH), 2231 (CN), 1747 (C=O); δ_H (400 MHz, $CDCl_3$) 7.33 - 7.26 (3H$_{maj}$, m, Ar-H), 7.33 - 7.26 (3H$_{maj}$, m, Ar-H), 7.26 – 7.04 (4H$_{maj}$, m, Ar-H), 7.26 – 7.04 (4H$_{min}$, m, Ar-H), 4.86 (1H$_{maj}$, s, ArC-C<u>H</u>-CCN), 4.77 (1H$_{min}$, s, ArC-C<u>H</u>-CCN), 4.41 (1H$_{maj}$, t, *J* 2.5, ArC-C<u>H</u>-CH$_2$), 4.23 – 4.06 (2H$_{maj\ and\ min}$, m, OC<u>H$_2$</u>CH$_3$), 3.74 (3H$_{min}$, s, OC<u>H$_3$</u>), 2.97 (1H, d, *J* 12.0, CH-C<u>H$_2$</u>-CCN), 2.79 (1H$_{maj}$, dd, *J* 13.0, 2.5, CH-C<u>H$_2$</u>-CCN), 2.34 (1H, d, *J* 12.0, 1H$_{min}$, CH-C<u>H$_2$</u>-CCN), 2.18 (1H$_{maj}$, dd, *J* 13.0, 2.5, CH-C<u>H$_2$</u>-CCN), 1.27 (3H$_{min}$, t, *J* 7.0, OCH$_2$C<u>H$_3$</u>), 1.25 (3H$_{maj}$, t, *J* 7.0, OCH$_2$C<u>H$_3$</u>); δ_C (100 MHz, $CDCl_3$) 166.8, 166.4 (<u>C</u>=O), 143.3, 143.0, 142.7, 142.4, 138.0, 137.2, 136.8, 135.9 (Ar<u>C</u>), 127.7, 127.6, 127.5, 127.4, 127.3, 126.6, 126.4, 125.8, 125.6, 125.1, 124.7, 123.9, 123.6, 121.0, 120.7, 119.9 (Ar<u>C</u>-H), 116.0, 114.8 (<u>C</u>N), 63.5, 63.2 (O<u>C</u>H$_2$-CH$_3$), 53.6 (O<u>C</u>H$_3$), 51.8, 50.7 (ArC-<u>C</u>H-CCN), 47.5, 47.4 (<u>C</u>CN), 43.2 (ArC-<u>C</u>H-CH$_2$), 38.0 (CH-<u>C</u>H$_2$-CCN), 14.1 (OCH$_2$<u>C</u>H$_3$); *m/z* (ES$^+$) 356.1 [M+Na]$^+_{min,}$ 326.1 [M+Na]$^+_{maj}$.

Ethyl 9-carboxaldehyde 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127f)



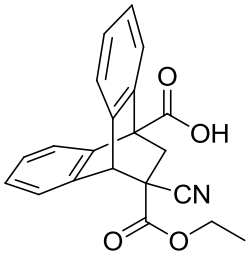
9-Anthracene carboxaldehyde **46f** (0.50 g, 2.42 mmol), MEHQ (0.03 g, 0.24 mmol) and ethyl cyanoacrylate **37** (0.33 g, 2.67 mmol) were combined in toluene (5.00 mL) and heated to reflux for 2 days. The reaction was concentrated *in vacuo* to give crude product **127f** (1.22 g) as a yellow solid. This was purified by column chromatography (9:1 petrol/ EtOAc) to furnish the title compound **127f** (0.33 g, 0.99 mmol, 41%) as a yellow solid. R_f (9:1 petrol/ EtOAc) 0.29; m.p. 143-145 ^{o}C; v_{max}/cm^{-1} 2983 (CH), 2240 (CN), 1747 (C=O), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 10.85 (1H, s, C<u>H</u>O), 7.57 (1H, dd, *J* 6.5, 2.0, Ar-<u>H</u>), 7.36 – 7.27 (4H, m, Ar-<u>H</u>), 7.27 – 7.14 (3H, m, Ar-<u>H</u>), 4.89 (1H, s, ArC-C<u>H</u>-CCN), 4.24 – 4.04 (2H, m, OC<u>H</u>$_2$-CH$_3$), 2.94 (1H, d, *J* 13.5, C(CHO)-C<u>H</u>$_2$-CCN), 2.36 (1H, d, *J* 13.5, C(CHO)-C<u>H</u>$_2$-CCN), 1.25 (3H, t, *J* 7.0, OCH$_2$-C<u>H</u>$_3$); δ_C (100 MHz, $CDCl_3$) 201.0 (<u>C</u>HO), 166.2 (<u>C</u>=O), 140.5, 139.9, 137.8, 136.9 (4 x Ar<u>C</u>), 127.7, 127.7, 127.5, 127.2, 126.5, 125.8, 121.8, 121.5 (8 x ArC<u>H</u>), 119.2 (<u>C</u>N), 63.5 (O<u>C</u>H$_2$-CH$_3$), 51.9 (ArC-<u>C</u>H-CCN), 47.4 (CH-<u>C</u>-CN), 37.7 (C(CHO)-<u>C</u>H$_2$-CCN), 14.0 (OCH$_2$-<u>C</u>H$_3$); *m/z* (ES$^+$) 353.9 $[M+Na]^+$, 354.1106 $[M+Na]^+$ found $C_{21}H_{17}NNaO_3$ requires 354.1106.

Ethyl 9-acteyl -10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127g)



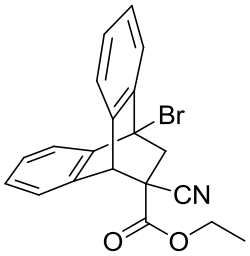
9-Actylanthracene **46g** (0.50 g, 2.27 mmol) was combined with ethyl cyanoacrylate **37** (0.31 g, 2.5 mmol) and MEHQ (0.02 g, 0.23 mmol) in toluene (5.00 mL) and heated to reflux for 2 days. The reaction was removed from the heat and concentrated *in vacuo* to give the crude product **127g** (0.73 g) as a yellow oil. This was purified by flash column chromatography (4:1 petrol/ EtOAc) followed by re-crystallisation (hexane) to furnish the title compound **127g** (0.08 g, 0.23 mmol, 10%) as a white solid. R_f (4:1 petrol/ EtOAc) 0.27; m.p. 112 - 115 ^{o}C; v_{max}/cm^{-1} 2246 (CN), 1752, 1701 (C=O); δ_H (400 MHz, $CDCl_3$) 7.58 – 7.52 (1H, m, Ar-H), 7.33 – 7.16 (7 H, m, Ar-H), 4.87 (1H, s, ArC-CH-CCN), 4.19 – 4.09 (2H, m, OCH_2CH_3), 3.00 (1H, d, *J* 13.0, $C(COCH_3)$-CH_2-CCN), 2.68 (3H, s, $COCH_3$), 2.40 (1H, d, *J* 13.0, $C(COCH_3)$-CH_2-CCN), 1.26 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 206.8 ($C{=}OCH_3$), 166.3 ($C{=}O$), 140.8, 140.1, 137.6, 136.7 (ArC), 127.8, 127.7, 127.3, 127.0, 126.3, 125.5, 122.9, 122.5 (ArCH), 119.3 (CN), 63.4 (OCH_2CH_3), 60.2 (ArC-$C(COCH_3)$-CH_2), 52.1 (ArC-CH-CCN), 48.1 (C-CN), 39.7 ($C(COCH_3)$-CH_2-CCN), 30.9 ($COCH_3$), 14.0 (OCH_2CH_3); *m/z* (ES^+) 368.1 $[M+Na]^+$, found 368.1259 $[M+Na]^+$ ($C_{22}H_{19}NNaO_3$ requires 368.1263).

Ethyl 9-carboxylic acid 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127h)



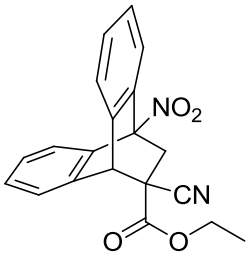
Anthracene-9-carboxylic acid **46h** (0.50 g, 2.25 mmol), ethyl cyanoacrylate **37** (0.31 g, 2.47 mmol) and MEHQ (0.03 g, 0.23 mmol) were combined in toluene (5 mL) and heated to reflux for 3 days. The reaction was concentrated *in vacuo* to give crude product **127h** (0.37 g) as a yellow solid. This was purified by flash column chromatography to yield the title compound **127h** (0.08 g, 0.23 mmol, 10%) as a yellow solid. R_f (4:1 petrol/ EtOAc) 0.42; m.p. 187-188 ^oC; v_{max}/cm^{-1} 2983 b (OH), 2245 (CN), 1749 and 1706 (C=O); δ_H (400 MHz, $CDCl_3$) 7.60 – 7.55 (3H, m, Ar-H), 7.36 – 7.30 (2H, m, Ar-H), 7.30 – 7.25 (2H, m, Ar-H), 7.24 – 7.18 (1H, m, Ar-H), 4.91 (1H, s, ArC-CH-CCN), 4.25 – 4.08 (2H, m, OCH_2CH_3), 3.14 (1H, d, *J* 13.5, $C(CO_2H)$-CH_2-CCN), 2.55 (1H, d, *J* 13.5, $C(CO_2H)$-CH_2-CCN), 1.28 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 175.9 (CO_2H), 166.3 (C=O), 140.3, 139.6, 137.1, 136.2 (Ar-C), 127.9, 127.9, 127.5, 127.2, 126.1, 125.4, 123.0, 122.6 (Ar-CH), 119.2 (CN), 63.5 (OCH_2CH_3), 55.0 (ArC-C-CO_2H), 52.0 (ArC-CH-CCN), 47.6 (CCN), 39.8 ($C(CO_2H)$-CH_2-CCN), 14.1 (OCH_2CH_3); *m/z* (ES^+) 370.1 $[M+Na]^+$, found 370.1050 $[M+Na]^+$ ($C_{21}H_{17}NNaO_4$ requires 370.1055).

Ethyl-9-bromo 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127i)



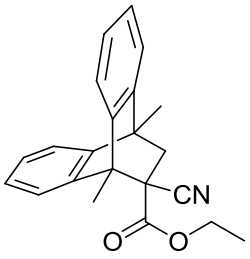
9-Bromoanthracene **46i** (0.50g, 1.94 mmol), MEHQ (0.02 g, 0.19 mmol) and ethyl cyanoacrylate **37** (0.27 g, 2.14 mmol) were combined in toluene (5.00 mL) and heated to reflux for 2 days. The reaction was concentrated *in vacuo* to yield the crude product **127i** (1.17 g) as brown oil. This was purified by flash column chromatography (9:1 petrol/ EtOAc) to give the title compound **127i** (0.19 g, 0.51 mmol, 26%) as a white solid. R_f (9:1 petrol/ EtOAc) 0.20; m.p. 142-145 ^{o}C; ν_{max}/cm^{-1} 2985 (CH), 2110 (CN), 1747 (C=O); δ_H (400 MHz, $CDCl_3$) 7.78 – 7.71 (2H, m, Ar-H), 7.50 – 7.45 (1H, m, Ar-H), 7.32 – 7.26 (3H, m, Ar-H), 7.22 – 7.17 (2H, m, Ar-H), 4.88 (1H, s, ArC-CH-CCN), 4.19 – 4.12 (2H, m, OCH_2-CH_3), 3.28 (1H, d, *J* 13.0, CBr-CH_2-CCN), 2.70 (1H, d, *J* 13.0, CBr-CH_2-CCN), 1.26 (3H, t, *J* 7.1, OCH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 165.9 (C=O), 142.0, 141.4, 136.3, 135.4 (4 x ArC), 128.0, 128.0, 127.8, 127.5, 125.3, 124.6, 124.6, 124.4 (8 x Ar-CH), 118.8 (CN), 63.6 (OCH_2-CH_3), 51.4 (ArC-CH-CCN), 49.0 (CCN), 48.5 (CBr-CH_2-CCN), 42.9 (CBr), 14.1 (OCH_2-CH_3); *m/z* (ES^+) 404.0 $[M+Na]^+$, found 404.0257 ($C_{20}H_{16}BrNNaO_2$ requires 404.0262).

Ethyl 9-nitro 10-hydro-9,10-endoanthracene-11-cyano-11-carboxylate (127j)



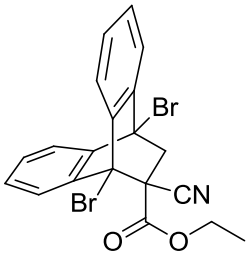
9-Nitro anthracene **46j** (0.50 g, 2.24 mmol), MEHQ (0.03 g, 0.22 mmol) and ethyl cyanoacrylate **37** (0.31 g, 2.46 mmol) were combined in toluene (5.00 mL) and heated to reflux for 3 days. The reaction was concentrated *in vacuo* to give crude product **127j** (0.96 g) as a yellow solid. This was purified by column chromatography (6:1 petrol/ EtOAc) to yield the title compound **127j** (0.07 g, 0.20 mmol, 9%) as a white solid. R_f (6:1 petrol/ EtOAc) 0.31; m.p. 192-194 ^{o}C; ν_{max}/cm^{-1} 2347 (CN), 1748 (C=O), 1544 (C-NO_2); δ_H (400 MHz, $CDCl_3$) 7.58 (1H, d, *J* 6.0, Ar-H), 7.40 – 7.32 (2H, m, Ar-H), 7.32 – 7.23 (5H, m, Ar-H), 4.93 (1H, s, ArC-CH-CCN), 4.31 – 4.00 (2H, m, OCH_2-CH_3), 3.40 (1H, d, *J* 13.0, $C(NO_2)$-CH_2-CCN), 2.79 (1H, d, *J* 13.0, $C(NO_2)$-CH_2-CCN), 1.27 (3H, t, *J* 7.0, OCH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 165.4 (C=O), 137.8, 137.2, 135.4, 134.6 (4 x ArC), 128.5, 128.4, 128.4, 128.2, 126.1, 125.2, 121.1, 120.7 (8 x Ar-CH), 118.3 (CN), 91.8 (C-NO_2), 63.9 (OCH_2CH_3), 51.6 (ArC-CH-CCN), 47.6 (CH-C-CN), 40.6 ($C(NO_2)$-CH_2-CCN), 14.0 (OCH_2CH_3); *m/z* (ES^+) 371.1 $[M+Na]^+$, 371.1013 $[M+Na]^+$ ($C_{20}H_{16}N_2NaO_4$ requires 371.1008).

Ethyl 9,10-dimethyl -9,10-endoanthracene-11-cyano-11-carboxylate (127k)



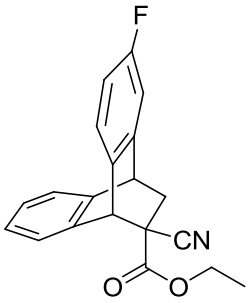
9,10-Dimethylanthracene **46k** (0.40 g, 1.94 mmol) was combined with ethyl cyanoacrylate **37** (0.27 g, 2.13 mmol) and MEHQ (0.02 g, 0.19 mmol) in toluene (4.00 mL) and heated to reflux for 8 h. The reaction was removed from the heat and concentrated *in vacuo* to give the crude product **127k** (0.62 g) as an orange solid. This was purified by flash column chromatography to yield the title compound **127k** as a pale yellow solid (0.56 g, 1.69 mmol, 87%). R_f 9:1 petrol/ EtOAc 0.20; m.p. 127-128 ^{o}C; v_{max}/cm^{-1} 2974 (CH), 2256 (CN), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 7.49 – 7.42 (1H, m, Ar-H), 7.38 – 7.29 (2H, m, Ar-H), 7.27 – 7.14 (5H, m, Ar-H), 4.17 – 4.01 (2H, m, OCH_2CH_3), 2.42 (1H, d, *J* 13.0, $C(CH_3)CH_2C(CN)$), 2.21 (1H, d, *J* 13.0, $C(CH_3)CH_2CCN$), 2.15 (3H, s, $C(CH_3)$), 1.99 (3H, s, $C(CH_3)$), 1.17 (3 H, t, *J* 7.0, OCH_2CH_3); δ_C (100 MHz, $CDCl_3$) 167.5 (C=O), 145.3, 145.1, 141.6, 139.9 (ArC), 127.1, 126.8, 126.3, 125.9, 122.8, 122.8, 120.9, 120.5 (8 x ArCH), 119.8 (CN), 62.8 (OCH_2CH_3), 53.5 ($C(CH_3)CCN$), 48.9 ($C(CH_3)$), 48.1 ($C(CH_3)CH_2CCN$), 41.2 ($C(CH_3)$), 17.5, 14.9 (2 x $C(CH_3)$), 14.0 (OCH_2CH_3); *m/z* (ES+) 354.1 $[M+Na]^+$, found 354.1465 $[M+Na]^+$ ($C_{22}H_{21}NNaO_2$ requires 354.1470).

Ethyl 9,10-dibromo-9,10-endoanthracene-11-cyano-11-carboxylate (127l)



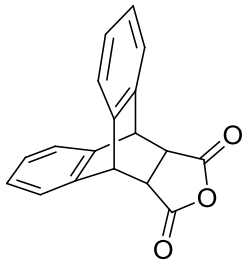
9,10-Dibromoanthracene **46l** (0.50 g, 1.49 mmol) was combined with ethyl cyanoacrylate **37** (0.21 g, 1.64 mmol) and MEHQ (0.02g, 0.15 mmol) in toluene (5.00 mL) and heated to reflux. After 4 days no further reaction was observed, the reaction was removed from the heat and concentrated *in vacuo* to yield crude product **127l** (0.96 g) as a yellow solid. This was purified by flash column chromatography (4:1 petrol/ EtOAc) to give the title compound **127l** (0.11 g, 0.24 mmol, 16%) as a yellow solid. R_f (4:1 petrol/ EtOAc) 0.45; m.p. 149 - 151 ^{o}C; v_{max}/cm^{-1} 2176 (CN), 1737 (C=O), 763 (C-Br); δ_H (400 MHz, $CDCl_3$) 7.93 – 7.87 (1H, m, Ar-C<u>H</u>), 7.83 – 7.70 (3H, m, Ar-C<u>H</u>), 7.40 – 7.36 (2H, m, Ar-C<u>H</u>), 7.36 – 7.28 (2H, m, Ar-C<u>H</u>), 4.17 (2H, qq, *J* 10.5, 7.0, OC<u>H</u>$_2$CH$_3$), 3.05 (2H, s, BrC-C<u>H</u>$_2$-CCN), 1.22 (3H, t, *J* 7.0, OCH$_2$CH$_3$); δ_C (100 MHz, $CDCl_3$) 165.5 (<u>C</u>=O), 140.3, 139.8, 137.3, 135.5 (Ar<u>C</u>), 128.9, 128.5, 128.3, 127.8, 126.5, 126.0, 124.4, 123.7 (Ar<u>C</u>H), 117.9 (<u>C</u>N), 63.7 (O<u>C</u>H$_2$CH$_3$), 62.4 (<u>C</u>CN), 58.1 (<u>C</u>Br-CCN), 53.0 (<u>C</u>Br-CH$_2$), 52.7 (BrC-<u>C</u>H$_2$-CCN), 13.9 (OCH$_2$<u>C</u>H$_3$); *m/z* (ES+) 481.9 $[M+Na]^+$, found 481.9362 $[M+Na]^+$ ($C_{20}H_{15}Br_2NNaO_2$ requires 481.9367).

2-Fluoro ethyl 9,10-dihydro-9,10-endoanthracene-11-cyano-11-carboxylate (127m)



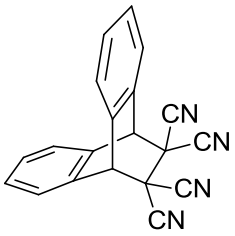
2-Fluoroanthracene **46m** (0.10 g, 0.51 mmol), MEHQ (0.01g, 0.05 mmol) and ethyl cyanoacrylate (0.07 g, 0.56 mmol) were combined in toluene (1.00 mL) and heated to reflux for 2 days. The reaction was concentrated *in vacuo* to yield crude product **127m** (0.20 g) as orange oil. This was purified by flash column chromatography (4:1 petrol/ EtOAc) to give the title compound **127m** (0.11 g, 0.35 mmol, 68%) as a colourless oil (an inseparable mixture of four compounds in a 1:2:2:2 ratio (*exo* and *endo* product for each regioisomer)). R_f (4:1 petrol/ EtOAc) 0.39; ν_{max}/cm^{-1} 2985 (CH), 2242 (CN), 1745 (C=O); δ_H (400 MHz, $CDCl_3$) 7.51 – 7.41 (1H, m, Ar-H), 7.35 – 7.01 (5H, m, Ar-H), 6.96 – 6.73 (1H, m, Ar-H), 4.87 – 4.84 (1H, m, ArC-CH-CCN), 4.44 – 4.38 (1H, m, ArC-CH-CH_2), 4.23 – 4.08 (2H, m, OCH_2-CH_3), 2.84 – 2.75 (1H, m, CH-CH_2-CCN), 2.24 – 2.15 (1H, m, CH-CH_2-CCN), 1.31 – 1.23 (3H, m, OCH_2-CH_3); δ_C (100 MHz, $CDCl_3$) 163.2 (C=O), 160.8 (C-F), 144.6, 141.6, 137.0, 132.9 (4 x ArC), 127.7, 126.9, 126.6, 125.8, 125.0, 124.0, 123.7 (7 x Ar-CH), 119.6 (CN), 63.3 (OCH_2-CH_3), 51.1 (ArC-CH-CCN), 43.3 (ArC-CH-CH_2), 37.7 (CH-CH_2-CCN), 14.1 (OCH_2-CH_3); δ_F (376 MHz, $CDCl_3$) -114.5, -114.8, -116.1, -116.4 (ArC-F); *m/z* (ES^+) 344.1 $[M+Na]^+$, found: 344.1059 $[M+Na]^+$ ($C_{20}H_{16}FNNaO_2$ requires 344.1063).

9,10-Dihydro-9,10-ethanoanthracene-11,12-dicarboxylic acid anhydride (48a)



Anthracene **46a** (0.50 g, 2.81 mmol) and maleic anhydride **47** (1.10g, 8.43 mmol) were combined in xylene (10.0 mL) and heated to reflux for 24 h. The reaction was removed from the heat, benzene added to precipitate out the product **48a**, the solution was filtered to give the title compound **48a** (0.61 g, 2.19 mmol, 78%) as an off-white solid. R_f (14:1 petrol/ EtOAc) 0.47; m.p. 266-267 ^{o}C; lit[262] m.p. 256 - 257 ^{o}C; ν_{max}/cm^{-1} 2972 (C-H), 1781 (C=O); δ_H (400 MHz, $CDCl_3$) 7.43 – 7.29 (4H, m, Ar-H), 7.23 – 7.16 (4H, m, Ar-H), (2H, t, *J* 1.5, ArC-CH-CH), 3.52 (2H, t, *J* 1.5, CH-CH-CO); δ_C (100 MHz, $CDCl_3$) 170.5 (C=O), 140.6, 138.1 (Ar-C), 127.8, 127.2, 125.2, 124.4 (ArC-H), 48.0 (ArC-CH), 45.4 (CH-CO); *m/z* (ES$^+$) 299.1 [M+Na]$^+$, found: 299.0679 [M+Na]$^+$ ($C_{18}H_{12}NaO_3$ requires 299.0684).

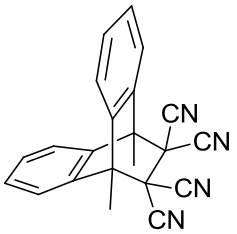
9,10-Dihydro-11,11,12,12-tetracyano-9,10-ethanoanthracene (160a)



Anthracene **46a** (25.0 mg, 0.14 mmol) and 1,1,2,2-tetracyanoethylene **159** (54.0 mg, 0.42 mmol) were combined in xylene (0.60 mL) and stirred at r.t. for 4 h. The solution was filtered to give the title compound **160a** (30.0 mg, 0.10 mmol, 70%) as a pale yellow solid. R_f (14:1 petrol/EtOAc) 0.53; m.p. 198-200 ^{o}C; ν_{max}/cm^{-1} 2952

(CH), 2231 (CN); δ_H (400 MHz, $CDCl_3$) 7.63 - 7.55 (4H, m, Ar-H), 7.51 – 7.43 (4H, m, Ar-H), 5.08 (2H, s, CH-CCN); δ_C (100 MHz, $CDCl_3$) 134.2, 131.9 (ArC), 130.0, 126.8 (ArC-H), 110.7 (CN), 53.1 (CH-CCN), 45.2 (CCN); *m/z* (ES^+) 329.1 $[M+Na]^+$, found: 329.0798 $[M+Na]^+$ ($C_{20}H_{10}N_4Na$ requires 329.0803).

9,10-Dimethyl-11,11,12,12-tetracyano-9,10-ethanoanthracene (160k)



9,10-Dimethylanthracene **46k** (20.0 mg, 0.06 mmol) and 1,1,2,2-tetracyanoethylene **159** (23.0 mg, 0.18 mmol) were combined in xylene (0.30 mL) and stirred at r.t. for 4 h. The solution was filtered to give the title compound **160k** (15.0 mg, 0.05 mmol, 75%) as a pale yellow solid. R_f (14:1 petrol/ EtOAc) 0.56; m.p. 207-208 ^oC v_{max}/cm^{-1} 2979 (CH), 2260 (CN); δ_H (400 MHz, $CDCl_3$) 7.61 – 7.53 (4H, m, Ar-H), 7.52 – 7.44 (4H, mm Ar-H), 2.45 (6H, s, 2 x CH_3); δ_C (100 MHz, $CDCl_3$) 136.9, 135.8 (ArC), 129.1, 124.6 (ArC-H), 110.8 (CN), 53.4 (C-CN), 50.6 (ArC-C-CH_3), 15.6 (CH_3); *m/z* (ES^+) 357.1 $[M+Na]^+$, found: 357.1111 $[M+Na]^+$ ($C_{22}H_{14}N_4Na$ requires 357.1116).

5.4.3 ^{1}H NMR monitoring experiments

General method for Diels-Alder reaction between substituted anthracene and ethyl cyanoacrylate

Anthracene **46a-m** (25.0 mg, 1.0 eq.) and ethyl cyanoacrylate **37** (1.1 eq.) were combined in d_8-toluene (0.25 M) with anisole (0.5 eq. ^{1}H NMR standard). The reaction was heated in a young's tap NMR Tube for 7 h at 70 ^{o}C. For anthracenes that are insoluble in toluene at r.t., the anthracene was pre-warmed in toluene 70 ^{o}C until fully dissolved before ethyl cyanoacrylate **37** was added.

General method for retro-Diels-Alder reaction of substituted anthracene adduct with maleic anhydride

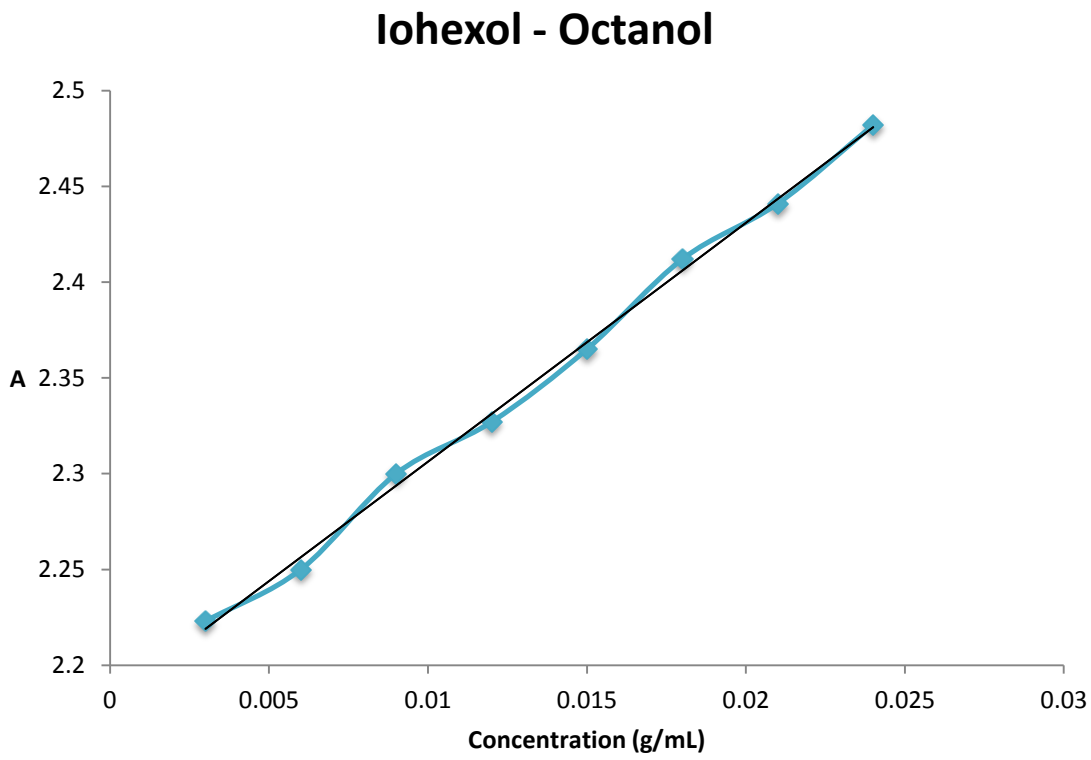
Anthracene adduct **127a-m** (25.0 mg, 1.0 eq.), maleic anhydride **47** (3.0 eq.), hydroquinone (0.5 eq.) and phosphrous pentoxide (0.5 eq.) were combined in xylene (0.25 M) with 1-methyl naphthalene (0.5 eq. ^{1}H NMR standard). The reaction was refluxed for 8 h and then concentrated *in vacuo* to remove the xylene.

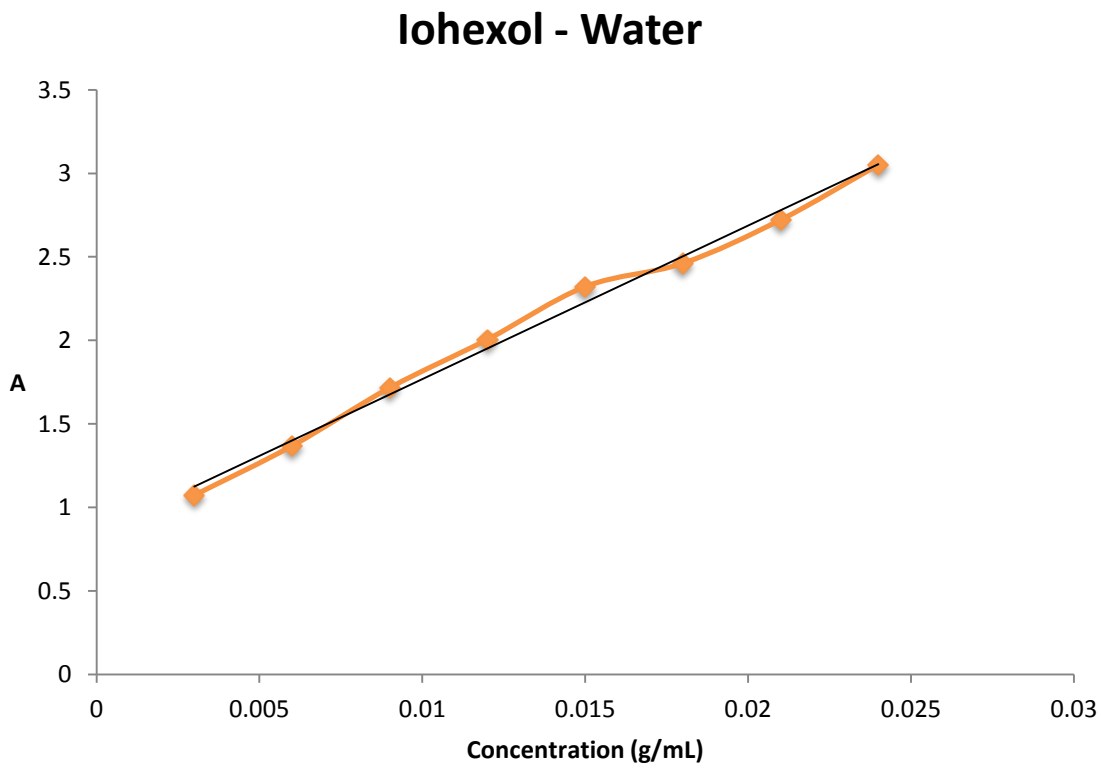
General method for retro-Diels-Alder reaction of substituted anthracene adduct with 1,1,2,2-tetracyanoethylene

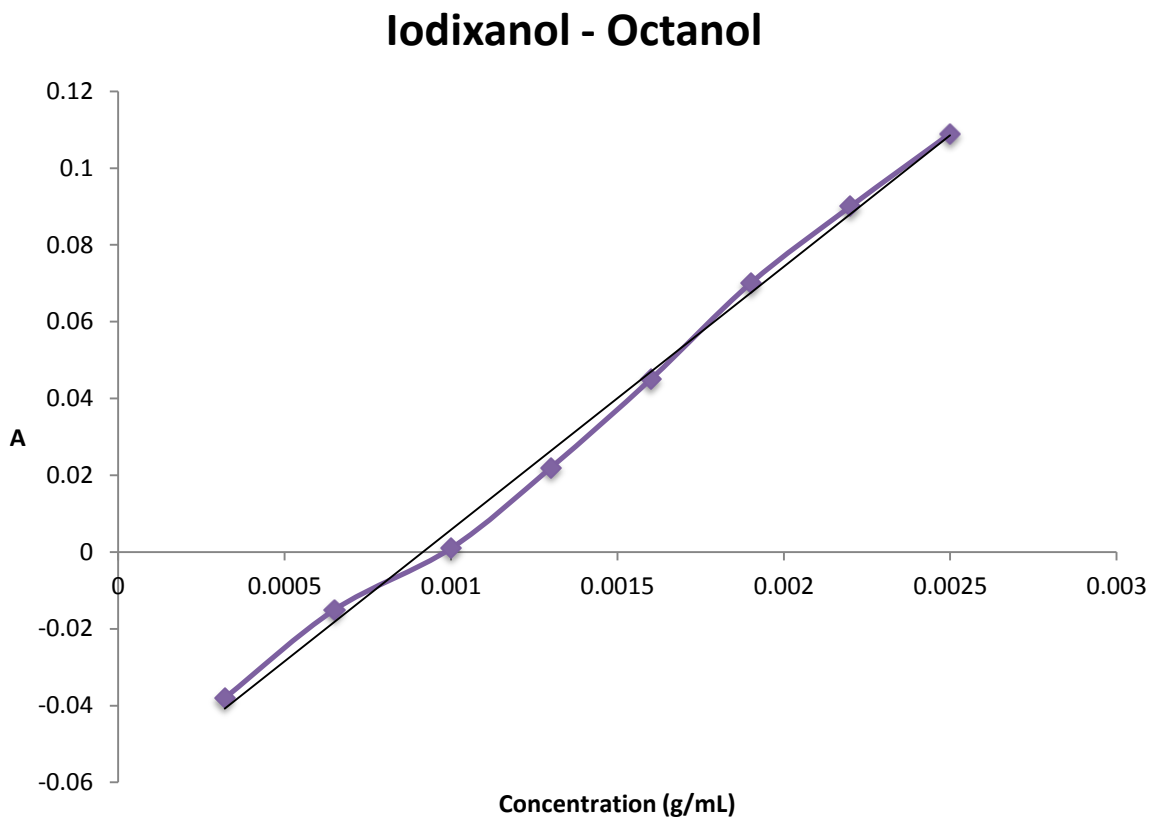
Anthracene adduct **127a,k** (25.0 mg) 1,1,2,2-tetracyanoethylene **159** (3.0 eq.), hydroquinone (0.5 eq.) and phosphrous pentoxide (0.5 eq.) were combined in xylene (0.25 M) with 1-methyl naphthalene (0.5 eq. ^{1}H NMR standard). The reaction was refluxed for 8 h and then concentrated *in vacuo* to remove the xylene.

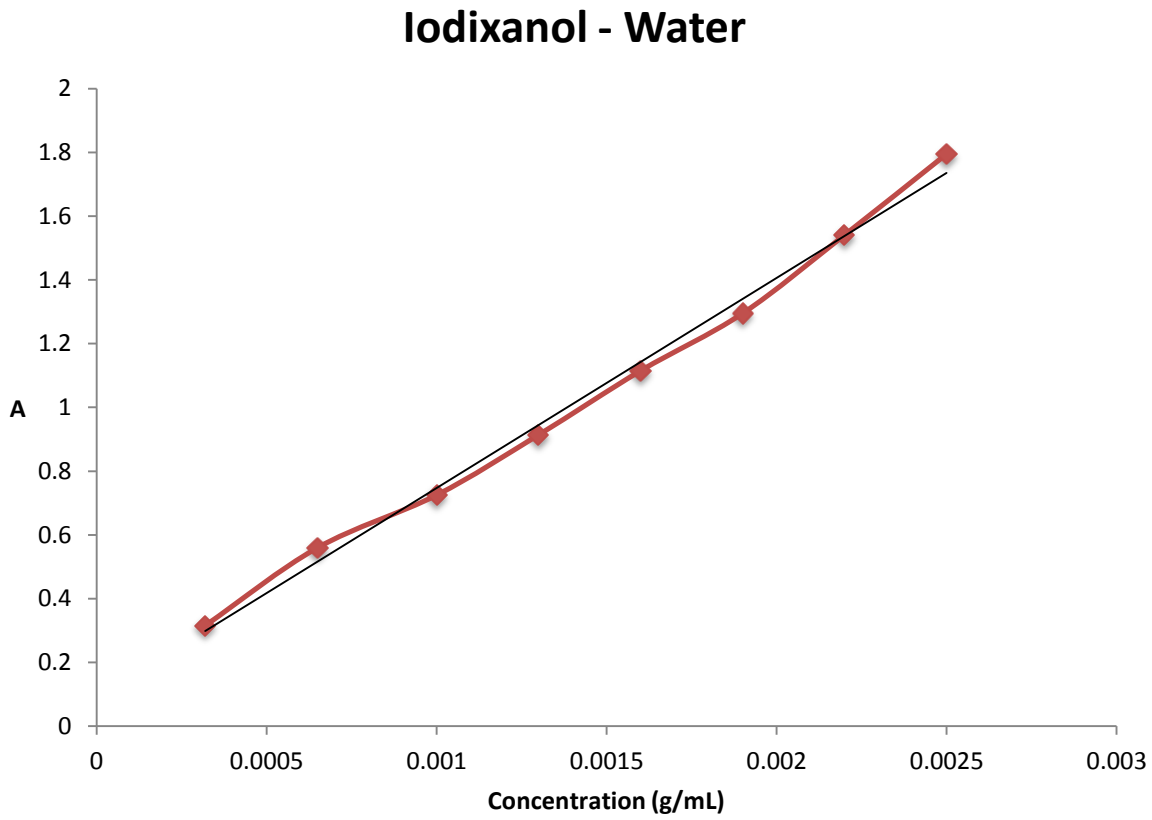
Appendix

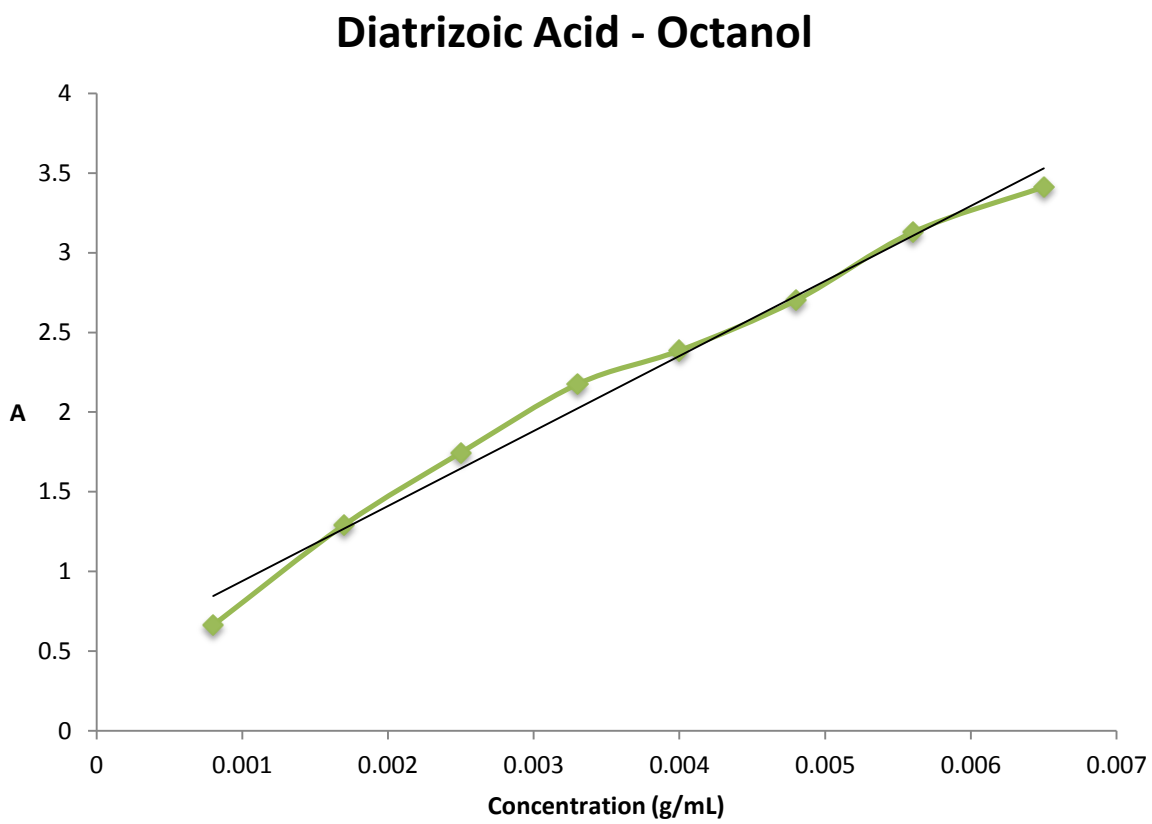
A.1 Partition Coefficient P_{ow}

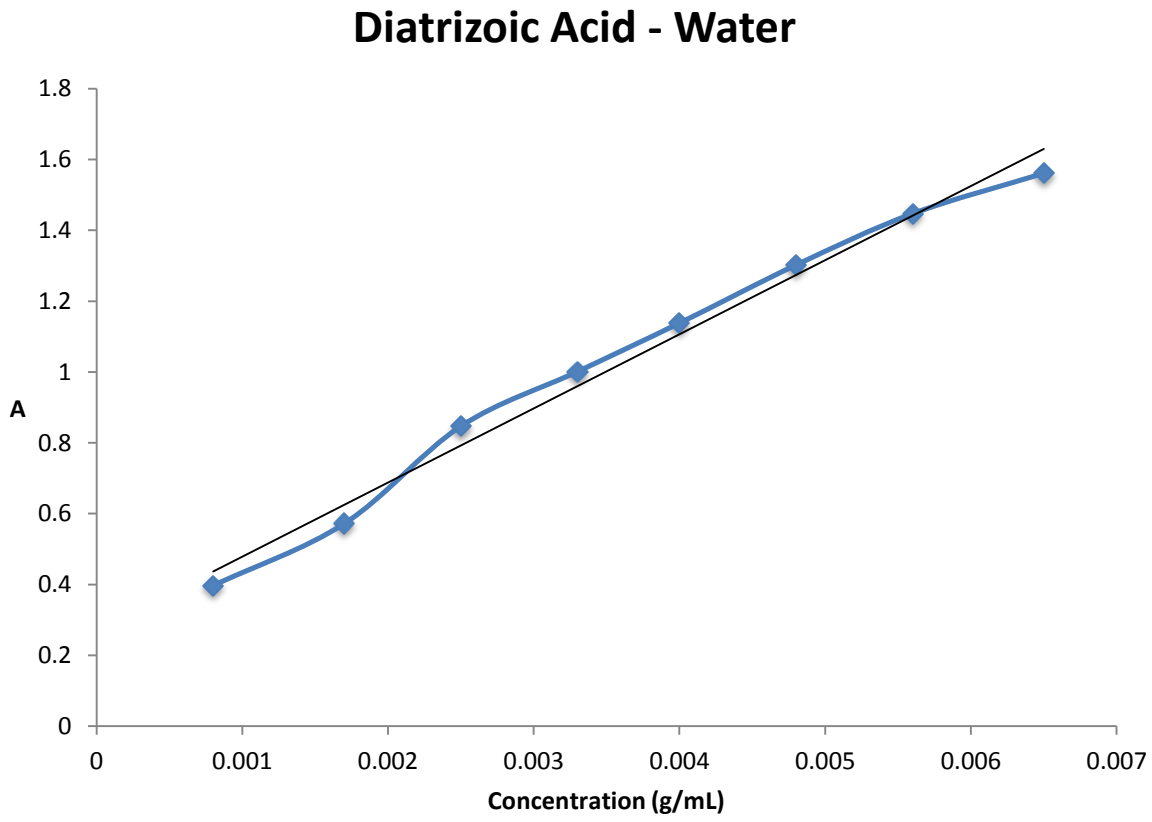





Iodixanol - Octanol
0.12
0.1
0.08
0.06
0.04
0.02
0
-0.02
-0.04
-0.06
A
0
0.0005
0.001
0.0015
0.002
0.0025
0.003
Concentration (g/mL)

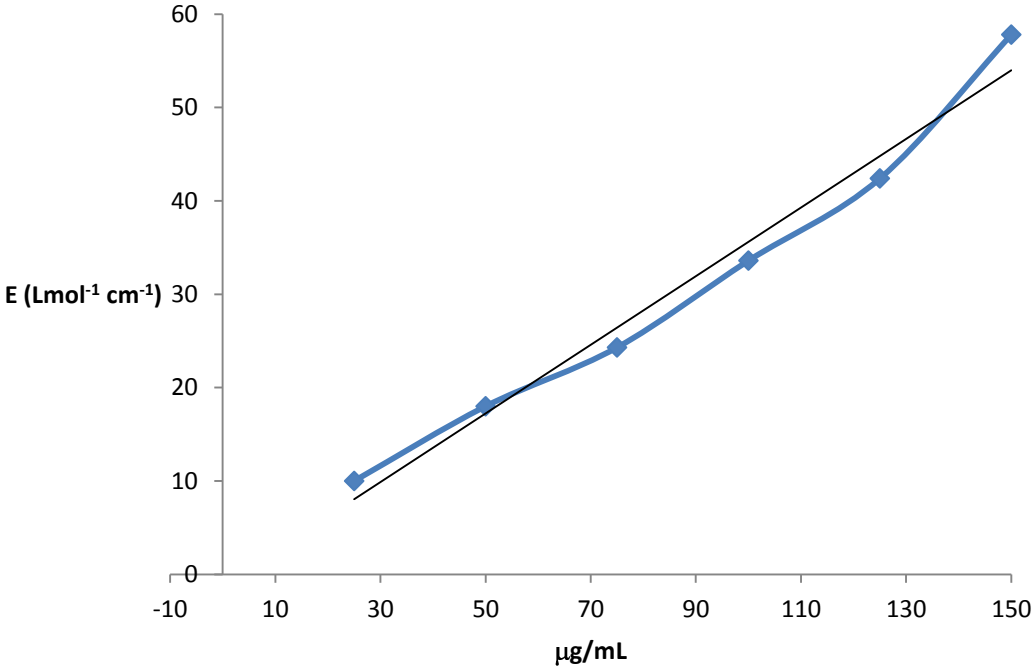

Iodixanol - Water
2
1.8
1.6
1.4
1.2
1
0.8
0.6
0.4
0.2
0
A
0
0.0005
0.001
0.0015
0.002
0.0025
0.003
Concentration (g/mL)


Diatrizoic Acid - Octanol
A
Concentration (g/mL)
0
0.5
1
1.5
2
2.5
3
3.5
4
0
0.001
0.002
0.003
0.004
0.005
0.006
0.007


Diatrizoic Acid - Water
A
Concentration (g/mL)
0
0.2
0.4
0.6
0.8
1
1.2
1.4
1.6
1.8
0
0.001
0.002
0.003
0.004
0.005
0.006
0.007

A.2 Formaldehyde Assay

Standards prepared at 25, 50, 75, 100, 125, 150 µg/mL levels of formaldehyde. The standards were prepared using pure para formaldehyde, decomposed in a sealed tube under heating (70-75 ^{o}C) in distilled water. Reaction with pentane-2,4-dione and ammonium acetate produced the highly coloured intermediate 3,5-diacetyl-1,4-dihydrolutidine, maximum absorption 412 nm.



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