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Metal Coordination and Cis-Trans Isomerisation of Benzene Dihydrodiols

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Metal Coordination and *Cis-Trans* Isomerisation of Benzene Dihydrodiols

By

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A Thesis submitted to the Dublin Institute of Technology
for the Degree of MPhil

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and

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Dedicated to Noel Swan

'Change is the law of life. And those who look only to the past or present are certain to miss the future'

John F. Kennedy

Abstract

In this thesis, a viable route for conversion of arene *cis*-dihydrodiols to their *trans* isomers was investigated. The *cis*-dihydrodiols can be produced by large scale fermentation but their *trans* analogues are not accessible using this approach. The *trans* dihydrodiols are potentially important chiral building blocks in synthetic chemistry particularly because they have the advantage that they are more stable than the *cis*-isomers. The principal aim of this work was to carry out parallel studies to inform the development of the synthetic pathway under study by; (a) synthesis of organometallic and organic intermediates and products and, (b) investigation of the intermediates in the synthetic pathway under examination using kinetic and equilibrium studies.

In the four step route being examined, the tricarbonyliron complex of an arene *cis*-dihydrodiol is formed and is reacted with acid to give a carbocation intermediate. This cation complex is then trapped stereoselectively by a nucleophile to afford the *trans* product. Decomplexation to remove the tricarbonyliron moiety is the final step. The isomerisation was carried out on *cis*-5,6-dimethoxycyclohexa-1,3-diene affording the *trans*-product in an overall yield of 31% for the four steps. In this case, the corresponding diol was too unstable to use as a starting material and thus the hydroxy substituents were converted to their methyl ethers. A trifluoromethyl and a bromo substituted dihydrodiol were each coordinated to tricarbonyliron by reaction with diironnonacarbonyl in yields ranging from 69 to 90%.

The synthetic intermediate examined in most detail was the cation complex, (η^5-6-methoxycyclohexadien-1-yl)tricarbonyliron, which was formed from the corresponding (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron complex. Rate constants for ionisation of this dimethoxy complex to form the coordinated methoxycyclohexadienyl cation were measured. The nucleophilic reaction of the cation complex with water to form (η^4-*trans*-5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron and conversion of this *trans* complex back to the cation were also studied, allowing a pH-profile (log *k* versus pH) to be constructed. An equilibrium constant, pK_R, = 2.80 for the coordinated methoxycyclohexadienyl cation [R^+] was determined

kinetically from measurements of the rate constants for hydrolysis of the cationic species and for the ionisation of the corresponding coordinated *trans*-5-hydroxy-6-methoxy substituted complex [ROH].

A comparison of the rate constants measured in this work for ionisation of the *endo*- and *exo*- (*i.e. cis* and *trans*) tricarbonyliron complexes serves as a useful model for comparison to the *endo* and *exo* isomers of other tricarbonyliron complexes. It was reported by Johnson and co-workers that the coordinated *exo* complexes formed faster than the *endo* complexes but that they do not differ significantly in stability. Therefore, it can be concluded that the *exo* products have a lower kinetic barrier to reaction.

The equilibrium constant determined for formation of the coordinated *trans*-5-hydroxy-6-methoxycyclohexadiene complex from its corresponding cation can be compared with other coordinated and uncoordinated hydroxy and methoxy substituted cyclohexadienes previously examined. It was found that the tricarbonyliron moiety displays a rate retarding effect on the coordinated cation species and that these cations are less reactive than the uncomplexed species. Also, it was evident that the β-methoxy substituent has a destabilising effect ($\Delta pK_R = 1.7$) on the cation complex. This effect is also observed when rate constants for formation of the cations were compared as the complex with the β-methoxy substituent reacts approximately 64 times more slowly than a complex lacking a β-methoxy substituent. The difference between the hydroxyl and methoxy substituents was found not to have a significant impact on reactivity.

It can be concluded that ionisation of the coordinated *endo* (i.e. *cis*-) diol to form the corresponding cation is the difficult step in the route to convert arene *cis*-dihydrodiols to their *trans* isomers. The final decomplexation step also requires some optimisation of the synthetic conditions.

Declaration

I certify that this thesis which I now submit for the award of an MPhil is entirely my own work and has not been taken from the work of others save and to the extent that such work has been cited and acknowledged within the text of my own work.

This thesis was prepared according to the Regulations for Postgraduate Study by Research of the Dublin Institute of Technology and has not been submitted in whole or in part for an award of any other Institute or University.

The work reported on in this thesis conforms to the principles and requirements of the Institute's guidelines for ethics in research.

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Signature_____ **Date**_____

Candidate

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Abbreviations and Symbols

A	Absorbance
Ac	Acetyl
Ac_2O	acetic anhydride
Apt	Apparent
Bda	Benzylideneacetone
B	buffer base
BH	buffer acid
Br s	broad singlet
Bu	Butyl
Bz	Benzoyl
°C	degree(s) celsius
cm^{-1}	Wavenumbers
^{13}C NMR	carbon 13 nuclear magnetic resonance
COSY	correlation spectroscopy
Δ	chemical shift
D	doublet
Dd	doublet of doublets
Ddd	doublet of doublet of doublets
DCM	dichloromethane
DME	1,2-dimethoxyethane
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
E	molar extinction coefficient / molar absorbtivity
Et	ethyl
EtO	ethoxy
equiv.	equivalents
FTIR	Fourier transform infrared spectroscopy
G	gram(s)

hr(s)	hour(s)
HMPA	hexamethylphosphoramide
^{1}H NMR	proton nuclear magnetic resonance
Hz	hertz
IR	infrared
J	coupling constant
k	rate constant
K_R	equilibrium constant
λ	wavelength
l	litre(s)
lit.	literature value
log	logarithm
M	moles / litre
m	multiplet
MHz	megahertz
m.p.	melting point
Me	methyl
MeO	methoxy
µl	microlitre(s)
ml	millilitre(s)
mmol	millimole(s)
NADPH	nicotinamide adenine dinucleotide phosphate
NIH	National Institutes of Health (Nucleophilic Intramolecular Hydride shift)
PAH(s)	polycyclic aromatic hydrocarbon(s)
Ph	phenyl
ppm	parts per million
R	alkyl substituent or buffer ratio
R_f	retention factor
RNA	ribonucleic acid
s	second(s) or singlet

t	triplet
TBDMS	*tert*-butyldimethylsilyloxy
TBDMSOTf	*tert*-butyldimethylsilyl trifluoromethanesulfonate
Temp	temperature
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	tetramethylsilane
UV	ultraviolet
Vis	visible
X	excess acidity function

CHAPTER 1

INTRODUCTION

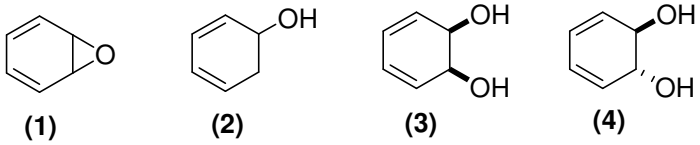
1 INTRODUCTION

Oxidative products of aromatic hydrocarbons and the study of organometallic compounds are two significant areas of interest in organic chemistry. This is because the oxidative products derived from aromatic compounds have considerable potential as starting materials for the synthesis of industrially useful target molecules and the use of organometallic compounds in organic synthesis often provides access to molecules that are not readily available otherwise. In the work described in this thesis, aspects of both fields are studied as the compounds under examination are iron complexes of oxidative metabolites of aromatic hydrocarbons. This chapter provides background information on this area and a summary of the relevant previous work.

The work carried out for this project was part of a larger study with the objective of developing efficient methods for conversion of arene *cis*-dihydrodiols to a variety of industrially important products, including phenols, catechols and arene *trans*-dihydrodiols. This thesis describes an investigation of a synthetic route for the conversion of arene *cis*-dihydrodiols to the corresponding *trans* analogues by means of complexation to iron tricarbonyl.

1.1 Oxidative Metabolites of Aromatic Hydrocarbons

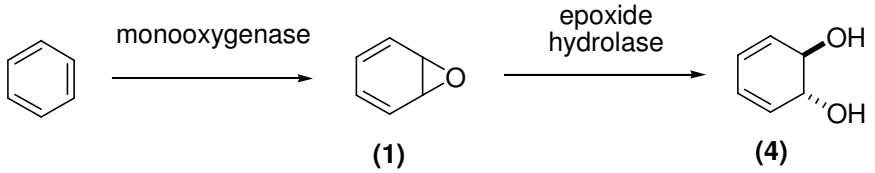
Oxidative metabolites are formed by the biocatalytic action of mono- and di-oxygenase enzymes upon aromatic and dihydroaromatic molecules. The metabolites produced are arene oxides **(1)**, arene hydrates **(2)**, arene *cis*-dihydrodiols **(3)** and arene *trans*-dihydrodiols **(4)**. Chart 1.1 shows the metabolites that are obtained when benzene is the aromatic substrate.



(1) (2) (3) (4)

Chart 1.1 Oxidative metabolites of benzene.

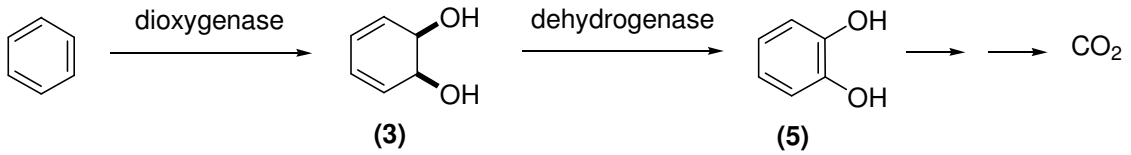
In eukaryotes (plants, animals and fungi) the metabolism of aromatic compounds involves the action of monooxygenase and epoxide hydrolase enzymes to yield an arene oxide intermediate **(1)** which is converted to the *trans*-dihydrodiol **(4)** by enzymatic hydrolysis, as shown in Scheme 1.1.[1] Monooxygenases are a class of enzymes that insert one atom of an oxygen molecule into the substrate while the other oxygen atom is reduced to water. Epoxide hydrolase enzymes are capable of epoxide ring cleavage by catalysing the addition of a water molecule in a hydrolysis reaction to yield a 1,2-diol.[1,2]



Scheme 1.1 Oxidative metabolism of aromatic hydrocarbons in eukaryotes.

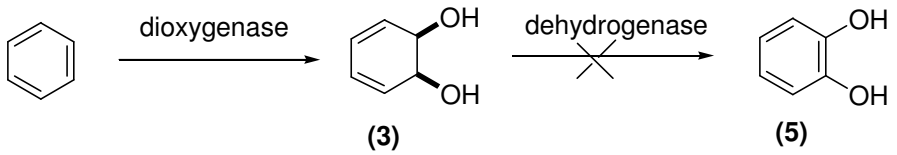
The oxidative metabolism process shown in Scheme 1.1 is the main means by which aromatic hydrocarbons can be degraded by mammals. This process occurs in the liver and involves formation of polar derivatives that can be excreted from the body readily due to their enhanced water solubility.[3] However, if *trans*-dihydrodiols derived from polycyclic aromatic hydrocarbons are further converted to their corresponding epoxy dihydrodiols these are then potentially carcinogenic compounds.[4] This will be discussed in more detail in Section 1.1.1.

In prokaryotes (for example, bacteria), metabolism of aromatic compounds involves the action of dioxygenase and *cis*-diol dehydrogenase enzymes which initially form the *cis*-dihydrodiol **(3)** referred to in the experimental sections as *cis*-cyclohexa-3,5-diene-1,2-diol.[1] Enzymatic dehydrogenation then takes place to produce the corresponding catechol **(5)**. This can be degraded further to form carbon dioxide, as shown in Scheme 1.2. Dioxygenases are multicomponent enzymes that incorporate both atoms of an oxygen molecule into the substrate and, in this case, are members of a family of aromatic ring-hydroxylating dioxygenase enzymes.[5] Dehydrogenase enzymes catalyse the removal of two hydrogen atoms on neighbouring carbons causing formation of a double bond, thus resulting in dehydrogenation.



Scheme 1.2 Oxidative metabolism of aromatic hydrocarbons in bacteria.

When bacteria lack the diol dehydrogenase enzyme, the corresponding catechol **(5)** cannot be formed, and the *cis*-dihydrodiol is therefore isolated, as shown in Scheme 1.3. An example of such a bacterium is a mutant strain (UV4) of *Pseudomonas putida*. The *Pseudomonas* species are gram-negative bacteria, typically found in the soil and water.[6] The recombinant UV4 strain of *Pseudomonas putida* has had a mutation incorporated. This mutation is a modification in the base sequence of the bacterial DNA resulting in an alteration in the protein encoded by the gene.[6] This causes the normal metabolic pathway of the microorganism to be interrupted.



Scheme 1.3 Formation of benzene *cis*-dihydrodiol product from the action of a mutant strain (UV4) of *Pseudomonas putida* on benzene.

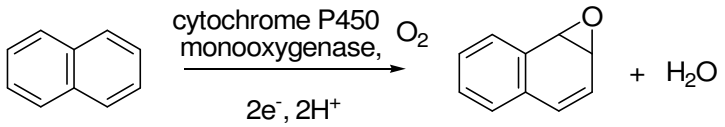
The formation of the three classes of metabolites, arene oxides, arene hydrates and the arene *cis*- and *trans*-dihydrodiols, and their respective roles in the metabolism of aromatic compounds will now be discussed in more detail.

1.1.1 Arene Oxides

Arene oxides are epoxide derivatives of aromatic molecules in which an oxygen atom has been added to a double bond of a ring; hence the ring becomes oxidised. An example of an arene oxide is benzene oxide **(1)** previously shown in Chart 1.1. In mammals, the enzymes that detoxify aromatic hydrocarbons by converting them to arene

oxides are found primarily in the liver and are classified as cytochrome P450 enzymes.[7] A cytochrome is defined by Nester *et al.* as a protein that carries an electron.[8] In the electron transport chain, the cytochrome contains a heme prosthetic group holding an iron atom at the centre which is capable of undergoing oxidation and reduction reactions. Cytochrome P450 was first discovered in 1962 by Omura and Sato and subsequently named due to the fact that the reduced form of its carbon monoxide complex shows an absorption band at 450 nm.[9]

The transformation of aromatic compounds to arene oxides has been extensively studied. A NADPH (nicotinamide adenine dinucleotide phosphate) supported reduction of one oxygen atom from an oxygen molecule to water accompanied by incorporation of the other oxygen atom into the substrate has been shown to occur in the mechanism. Scheme 1.4 shows the example of the formation of the epoxide of naphthalene, 1,2-naphthalene oxide **(7)**, from treatment of naphthalene **(6)** with the cytochrome P450 monooxygenase enzyme. In principle, three other isomers of naphthalene oxide could form, however, only the 1,2-addition product **(7)** is isolated as the epoxidation tends to occur at the bonds of highest electron density.[10] This will result in the aromaticity of one benzene ring still remaining intact.

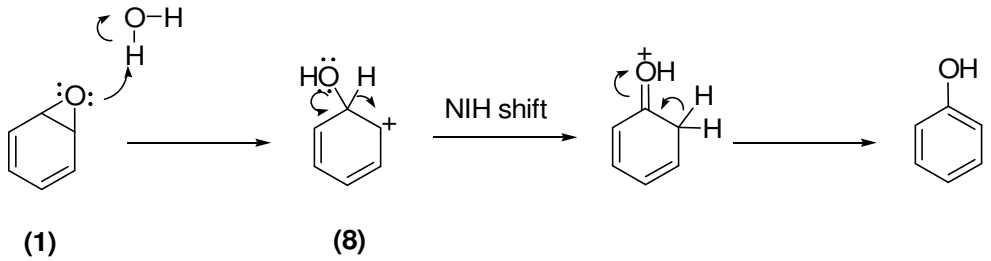


(6) **(7)**

Scheme 1.4 Formation of 1,2-naphthalene oxide from the reaction of naphthalene with cytochrome P450 monooxygenase enzymes.

Arene oxides are believed to be the initial metabolites in this oxidative metabolism process in eukaryotes. However, there are a variety of further enzymatic and non-enzymatic reactions the arene oxides undergo before they are in a form that can readily be excreted.

One possibility is the conversion of the arene oxides to phenolic products by aromatisation.[11] This involves the ring opening of the epoxide by protonation to form a carbocation **(8)** followed by a NIH shift[12] that yields the phenol metabolite as shown in Scheme 1.5. NIH stands for the "National Institutes of Health", the centre in which this rearrangement was discovered. The NIH shift is also known as a 1,2-hydride shift. It involves the migration of the hydrogen attached to the oxygen-bearing carbon atom of the carbocation intermediate **(8)** to an adjacent position on the ring forming a protonated ketone. Finally, removal of the proton from this species forms a phenol.

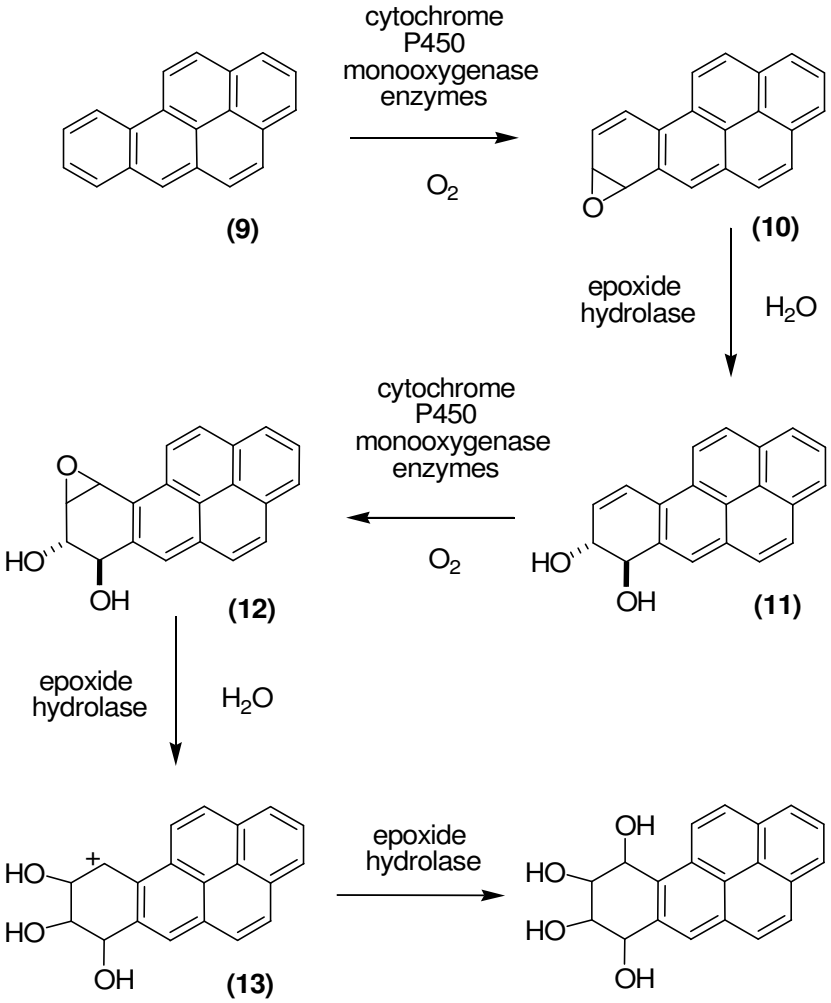


Scheme 1.5 Rearrangement of benzene oxide (1) to yield a phenol product incorporating a NIH shift.

Another metabolic pathway the arene oxides can undergo that was already mentioned is the formation of *trans*-dihydrodiols (Section 1.1, Page 2). When *trans*-dihydrodiols undergo further oxidation to give diol epoxides, nucleophilic attack on the epoxide carbon to form addition products can then take place. This reaction can be harmful as it can cause the onset of toxic and carcinogenic processes within a mammalian cell.[2] When polycyclic aromatic hydrocarbons are oxidised to the highly reactive diol epoxide species, they can combine covalently with the purine and pyrimidine bases of DNA and this can result in cancer causing mutations.

Benzo[a]pyrene **(9)**, a representative polycyclic aromatic hydrocarbon, is produced by the incomplete combustion of fossil fuels and is a component of tobacco smoke, car exhaust and chimney soot.[13] Many arene oxides can be formed from benzo[a]pyrene and the two that are the most harmful when further metabolised are benzo[a]pyrene-4,5-oxide and benzo[a]pyrene-7,8-oxide **(10)**. Benzo[a]pyrene-7,8-oxide

(10), shown in Scheme 1.6**,** is formed when benzo[a]pyrene is acted on by cytochrome P450 enzymes to form an arene oxide on the terminal benzo-ring. This epoxide then undergoes enzymatic hydrolysis by epoxide hydrolase to form a *trans*-diol **(11)**.[13] The *trans*-diol **(11)** then undergoes secondary epoxidation to form the bay region diol epoxide, benzo[a]pyrene-7,8-diol-9,10-oxide **(12)**. Bay-region diol epoxides are not easily detoxified by reaction with epoxide hydrolase enzymes. They can bind covalently to cellular DNA, thus damaging genetic material. This is the cause of the carcinogenic behaviour of certain hydrocarbons; hence the diol epoxides can be described as 'ultimate carcinogens'.



Scheme 1.6 Products formed from the action of cytochrome P450 monooxygenase enzymes on benzo[a]pyrene.

The bay region theory is one hypothesis used to explain and predict the carcinogenicity of benzo[a]pyrene and other members of this class of compounds. However, it should be noted that this explanation does not consider the stereochemical and metabolic factors that also contribute to the carcinogenicity of diol epoxides.[14] The simplest example of a 'bay region' epoxide is 1,2,3,4-tetrahydrophenanthrene-3,4-epoxide shown in Chart 1.2. When a diol epoxide has a 'bay region', it possesses relatively high stability and this contributes to its lack of reactivity to forming the unstable carbocation intermediate **(13)** which goes on to form a second diol as shown. The bay region diol epoxide derivatives act as electrophiles and trap various target biomolecules.[15] They can readily react with nucleophilic sites of DNA,[16] RNA and protein[3] as shown for the example of cytidine, a DNA base, in Scheme 1.7. The resulting DNA derivatives cannot be properly transcribed on replication leading to mutations which can cause cancer formation.[16]

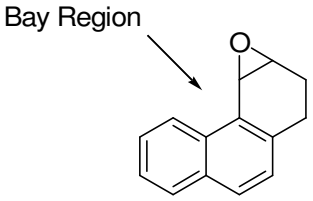
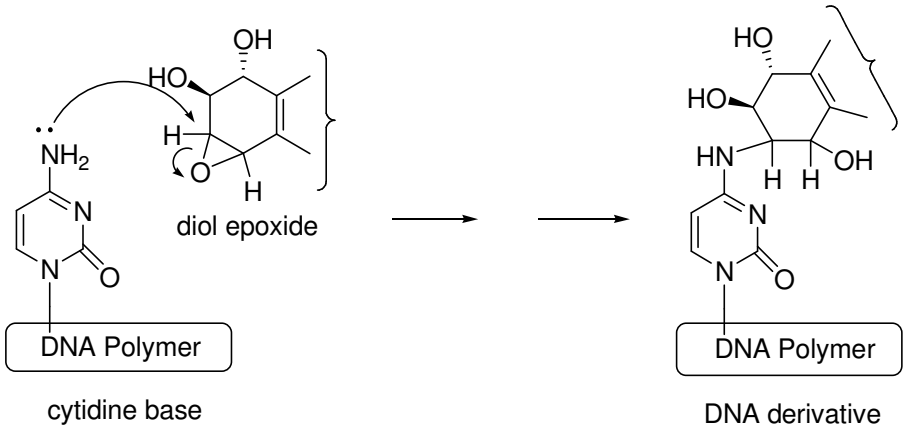


Chart 1.2 The bay region in 1,2,3,4-tetrahydrophenanthrene-3,4-epoxide.



Scheme 1.7 Interaction of a reactive diol epoxide with a nucleotide base of cellular DNA.

The rate of conversion of the arene diol epoxide to the corresponding carbocation intermediate **(13)** depends on the stability of this carbocation. The more stable the carbocation is, the less potential the diol epoxide has to be a carcinogen. If the carbocation is particularly unstable, epoxide ring opening to form the carbocation will be slow. Therefore, the diol epoxide will be more likely to undergo nucleophilic attack which can be cancer causing if this reaction occurs with DNA bases.

1.1.2 Arene *cis*- and *trans*-Dihydrodiols

In mammalian metabolism, aromatic hydrocarbons are dearomatised to yield arene oxides, which are then hydrolysed to form *trans*-dihydrodiols, as previously shown in Scheme 1.1. The alternative oxidative dearomatisation of aromatic hydrocarbons occurs in bacteria and yields the arene *cis*-dihydrodiols.

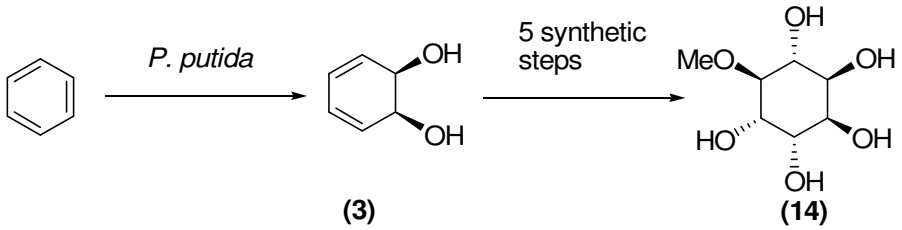
Unlike the arene *trans*-dihydrodiols, which have been relatively inaccessible up until now, the arene *cis*-dihydrodiols can be produced in large quantities by biotransformations using the mutant bacterium, *Pseudomonas putida* (UV4). The isolation of a *cis*-dihydrodiol from the action of *Pseudomonas putida* on benzene as a substrate was first reported by Gibson *et al.* in 1968[17] and this has proved to be a significant development in the accessibility of this class of metabolites. Improved biotransformations using the UV4 mutant strain of *Pseudomonas putida* have led to commercial quantities of a range of arene *cis*-dihydrodiols being prepared.

Large scale biotransformations capable of producing multi-kilogram quantities of the arene *cis*-dihydrodiols have been developed by Boyd in Queen's University Belfast[1] and by Hudlicky,[18] formerly at the University of Florida and presently at Brock University, Ontario. In a typical industrial biotransformation, the mutant strain of *Pseudomonas putida* (UV4) is grown on culture medium and an aromatic hydrocarbon substrate is introduced. This is then incubated for several days as the *cis*-dihydrodiol accumulates. When the biotransformation is complete, the mixture is centrifuged and the cells and high molecular weight debris are removed. The *cis*-dihydrodiol can then be isolated by evaporation of

water and extraction with ethyl acetate resulting in a relatively pure product. This can be further purified by recrystallisation from ethyl acetate.

The arene *cis*-dihydrodiols have found wide application in industry and laboratory synthesis as discussed by Sheldrake.[19] These diols have the potential to be used as chiral precursors in the synthesis of natural products and pharmaceuticals.[20] Much work in this area has been carried out by Ley, Hudlicky, and Carless and their approaches have resulted in the preparation of pinitols, conduritols and other cyclitols.

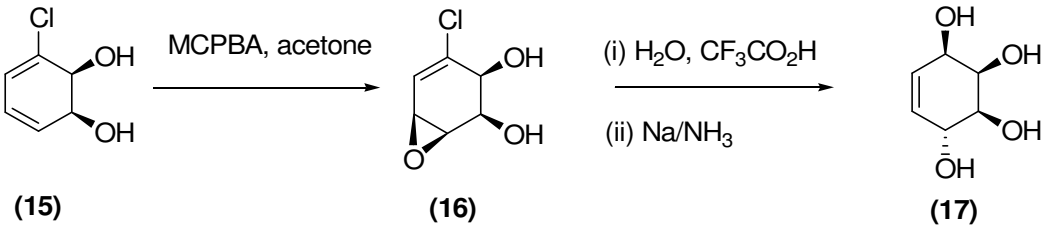
The naturally occurring cyclitol, (+)-pinitol **(14),** has been shown to possess a diverse range of biological activities and was first synthesised by Ley *et al.* in a six-step synthesis from benzene[21] as summarised in Scheme 1.8. The first step was the synthesis of *cis*-cyclohexa-3,5-diene-1,2-diol **(3)** by microbial oxidation with *Pseudomonas putida* (UV4). This synthetic strategy was subsequently adapted to produce both stereoisomers, (+)- and (-)-pinitol, in 1989.[22] Pinitol can act as a feeding stimulant for the larvae of the yellow butterfly (*Eurema hecabe mandarim)* and has also demonstrated significant hypoglycemic and antidiabetic properties in mice.[21,23] There has been a rapid growth in the use of arene *cis*-dihydrodiols as chiral precursors for multistep target synthesis since the initial work carried out by Ley *et al*.



Scheme 1.8 Summary of the synthesis of the biologically active (+)-pinitol by a six-step chemoenzymatic pathway from benzene.

Conduritols are a subclass of the cyclitol family which are widespread and have the potential to be used as glycosidase inhibitors. One of the earliest papers to report work in this area was written by Carless and Oak.[24] Since then, a wide range of syntheses for conduritols have been established using arene *cis*-dihydrodiols as precursors. The first

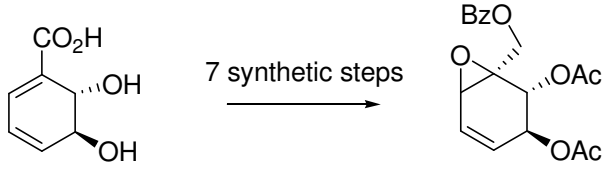
concise route to (-)-conduritol **(17)** based on the initial microbial oxidation of chlorobenzene was reported by Carless in 1991.[25] The chlorine atom introduced chirality into the system allowing the optically pure chlorodiol **(15)** to be formed. This was a four-step synthesis involving the formation of the vinylic epoxide **(16)** followed by the epoxide ring opening to give chloroconduritol which subsequently was converted to the (+)-conduritol C **(17).**



(15) **(16)** **(17)**

Scheme 1.9 Summary of the synthesis of (-)-conduritol C (17) by a four-step pathway from chlorobenzene.

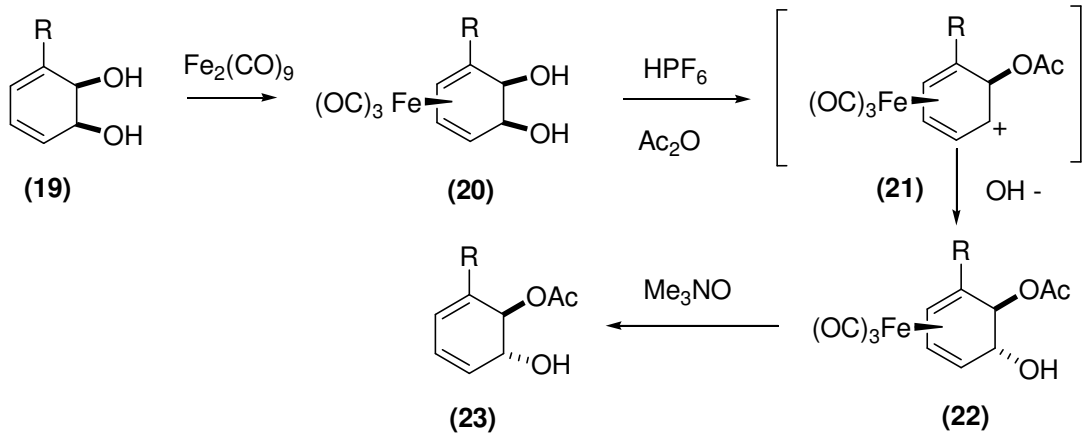
The *trans*-dihydrodiols are more stable than their corresponding *cis*-dihydrodiols[11] and therefore have the potential to be more useful as chiral building blocks. A drawback is that they are difficult to synthesise chemically in enantiopure form due to the lack of chiral precursors.[26] They can provide access to new structures of interest including inositols and conduritols. An example demonstrating the use of *trans*-diols as precursors in synthetic chemistry was reported by Franke *et al.* for the preparation of biologically active cyclohexene epoxides, such as ent-senepoxide **(18)** as shown in Scheme 1.10.[27]



(**18**)

Scheme 1.10 Summary of the synthesis of ent-senepoxide (18) by a seven-step pathway from a substituted *trans*-diol.

In 2007, conversion of arene *cis*-dihydrodiols to the corresponding *trans*-dihydrodiols *via* a seven-step synthetic route was reported.[28] Another promising approach for this conversion was suggested in a review by Boyd and Sharma[11] based on original research by Stephenson *et al*.[29] The strategy proposed introduces formation of tricarbonyliron complex intermediates. Following on from the suggested route reported by Boyd and Sharma, the synthetic strategy being examined in this work involves the formation of iron tricarbonyl complexes as intermediates and the transformations involved are summarised in Scheme 1.11. In this proposed synthetic route, an arene *cis*-dihydrodiol **(19)** is coordinated to a tricarbonyliron fragment and is then reacted with hexafluorophosphoric acid in the presence of acetic anhydride to form a cyclohexadienyl cation intermediate **(21)**. This cation traps a nucleophile *anti* to the metal yielding an arene *trans*-dihydrodiol tricarbonyliron complex **(22)**. A subsequent decomplexation with trimethylamine-*N*-oxide affords the arene *trans*-dihydrodiol **(23)**.



Scheme 1.11 Proposed synthetic route for conversion of arene *cis*-dihydrodiols to their *trans*-isomers (adapted from Boyd and Sharma).[11]

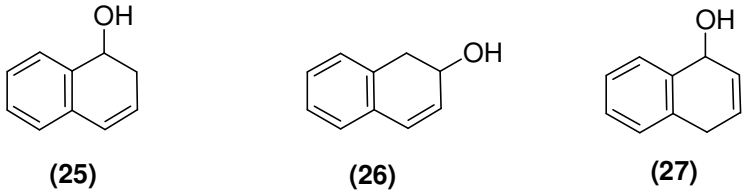
The aim of this study was to examine the feasibility of and optimise this proposed route for conversion of arene *cis*-dihydrodiols to their *trans*-isomers.

1.1.3 Arene Hydrates

Arene hydrates are a family of compounds in which the elements of water are added to the double bond of an aromatic molecule. An example of an arene hydrate is benzene hydrate **(2)**, shown in Chart 1.1. Unlike arene oxides and arene dihydrodiols, the hydrates are not usually produced by the metabolism of aromatic compounds but are formed from the metabolism of dihydroaromatic substances in bacteria.

The first example of an arene hydrate, 1-hydroxy-1,2-dihydronaphthalene, was prepared by Bamberger *et al*. in 1895.[30] The synthetic pathway Bamberger used involved dehydrohalogenation. A number of alternative routes have been developed since then, including one involving reduction of the corresponding arene oxide.[31]

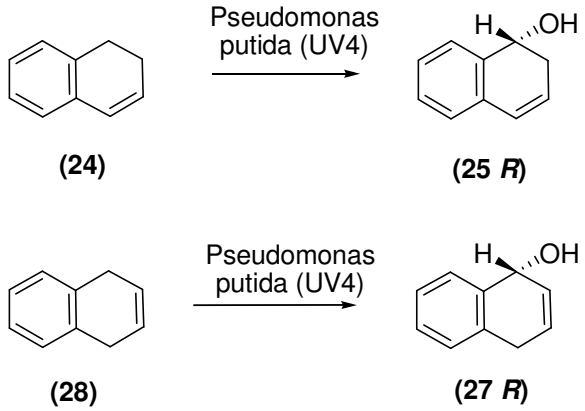
In 1955, Boyland and Solomon reported evidence that an arene hydrate was implicated as an initial metabolite of naphthalene in mammalian urine.[32] They found that an acid-labile metabolite was formed and naphthalene was only detected after acidification of the urine. The instability of these compounds precluded the isolation of these metabolites and therefore, it was not until 1989 that the first optically pure forms were isolated. Boyd and co-workers isolated (+)-(*R*)-1-hydroxy-1,2-dihydronaphthalene **(25 *R*)** as a metabolite formed from 1,2-dihydronaphthalene **(24)** using a mutant strain (UV4) of *Pseudomonas putida*.[33] Synthetic routes to three isomeric hydrates of naphthalene, 1-hydroxy-1,2-dihydronaphthalene, 2-hydroxy-1,2-dihydronaphthalene, and 1-hydroxy-1,4-dihydronaphthalene have been developed. These isomers are referred to as α, β, and γ respectively **(25, 26, 27)** as shown in Chart 1.3.



(25) **(26)** **(27)**

Chart 1.3 Three isomeric hydrates of napthalene, α (25), β (26)and γ (27).

In 1990, Boyd *et al.* isolated the *R* configuration of **(27 *R*)** in predominantly chiral form as an intermediate from the metabolism of 1,4-dihydronaphthalene **(28)** by the UV4 mutant strain of *Pseudomonas putida*.[34] The configurations of **(25 *R*),** and **(27 *R*)** are shown in Scheme 1.12.



Scheme 1.12 Formation of two of the arene hydrate derivatives of naphthalene using a mutant strain (UV4) of *Pseudomonas putida*.

1.2 Organometallic Chemistry

Since the 1950s, there has been a rapid development in organometallic chemistry which has been attributed to the accidental discovery of ferrocene by Kealy and Pauson.[35] Ferrocene, as shown in Chart 1.4, is a sandwich type compound consisting of two planar cyclopentadienyl rings around a metal ion, and unexpectedly, it was found to be very stable. The metal itself is rarely used in synthetic reactions but when coordinated to the ligand it was found to be useful, due to the stable carbon-iron π bond.[36]

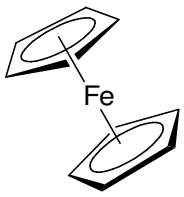
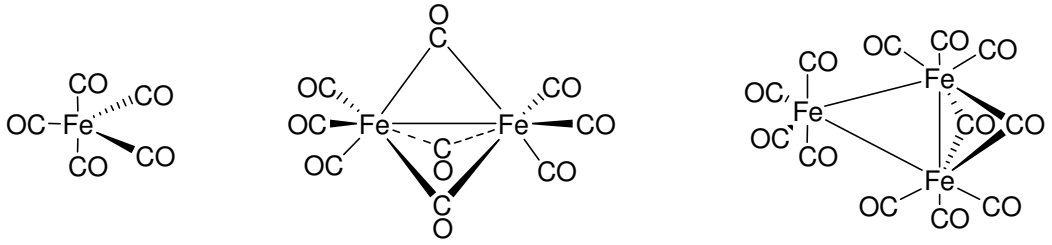


Chart 1.4 Structure of ferrocene, $Fe(C_5H_5)_2$.

A number of metal complexes were already known when ferrocene was discovered as the first ethylene complex of platinum, $K[Pt(C_2H_4)Cl_3]$, was prepared by Zeiss in 1827.[37] However, it was only in the latter half of the twentieth century that chemists began to have a greater understanding of these complexes due to development of X-ray crystallography and NMR spectroscopy for characterisation and structure determination. Pearson reports that this greater insight was also due to Orgel, Pauling and Zeiss who introduced the concept of π-backbonding in a model proposed for bonding in metal carbonyls.[38]

Many transition metals including chromium, magnesium, palladium and rhodium have been used in synthetic chemistry to produce a variety of complexes but this review is limited to organoiron compounds as the research undertaken involved formation of iron tricarbonyl complexes.

The most common type of organoiron complexes are the iron carbonyls. Pentacarbonyliron, $Fe(CO)_5$, was discovered in 1891 independently by Mond[39] and Berthelot.[40] It is one of the three stable carbonyl derivatives of iron; nonacarbonyldiiron $Fe_2(CO)_9$ and dodecacarbonyltriiron, $Fe_3(CO)_{12}$[38] are the others and they are all shown in Chart 1.5. Pentacarbonyliron **(29)** is a musty smelling yellow liquid obtained by a direct reaction between finely divided iron and carbon monoxide. Nonacarbonyldiiron **(30)** exists as shiny gold platlets and is prepared by photolysis of $Fe(CO)_5$ in acetic acid using a medium pressure mercury lamp. This was the iron carbonyl used in the present study and it contains a metal-metal bond and bridging carbonyl ligands. Dodecacarbonyltriiron **(31)** is prepared in a variety of ways, one of which is by thermal decomposition of nonacarbonyldiiron, and it exists as a dark green solid.[38]



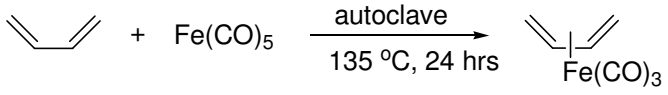
(29) (30) (31)

Chart 1.5 Structures of pentacarbonyliron (29), nonacarbonyldiiron (30) and dodecacarbonyltriiron (31).

Tricarbonyliron complexes of conjugated dienes represent very important intermediates for organic synthesis. Many reactions which are impossible to achieve by conventional methods can be carried out *via* these ironcarbonyl complexes. Thus, these compounds have found a wide range of applications in synthetic organic chemistry as starting materials for the stereoselective synthesis of natural products[41] and the tricarbonyliron moiety can be used either as a protecting group, activating group or sterochemical controller.

1.2.1 Initial Synthesis of Tricarbonyliron Complexes

Reihlen and co-workers described the first synthesis of a tricarbonyliron complex in 1930 when they isolated (η^4-buta-1,3-diene)tricarbonyliron **(33)** by heating an excess of buta-1,3-diene **(32)** with pentacarbonyliron as shown in Scheme 1.13.[42]

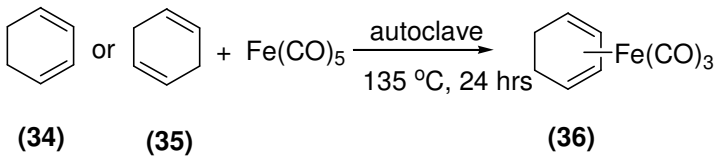


(32) (33)

Scheme 1.13 Synthesis of (η^4-buta-1,3-diene)tricarbonyliron (33) from buta-1,3-diene (32) using pentacarbonyliron.

Since then, a broad range of tricarbonyliron-butadiene complexes have been synthesised based on the procedure developed by Reihlen. In 1958, Hallam and Pauson extended this study to cyclic dienes when they prepared (η^4-cyclohexa-1,3-

diene)tricarbonyliron **(36)** in a similar manner to that for the butadiene complexes by direct reaction of cyclohexa-1,3-diene **(34)** with pentacarbonyliron[43] as shown in Scheme 1.14.



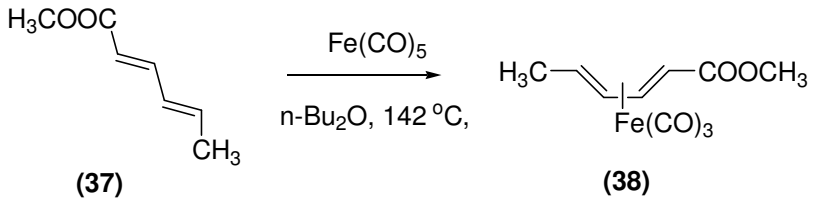
Scheme 1.14 Synthesis of the cyclic diene (η^4-cyclohexa-1,3-diene)tricarbonyliron (36) from either structural isomer of cyclohexadiene.

When Hallam and Pauson further investigated this reaction, they found that the coordination of the metal fragment to the diene had significantly altered its reactivity. These newly formed diene complexes resisted hydrogenation and Diels-Alder type reactions, which are typical reactions of carbon-carbon double bonds. The resistance to these reactions led to the conclusion that when the tricarbonyliron moiety is coordinated to the organic ligand, it has a stabilising effect and thus acts as a protecting group.[44]

The scope of this complexation was later improved in 1961 when Arnet and Pettit discovered that treatment of a non-conjugated diene with pentacarbonyliron unexpectedly resulted in a tricarbonyliron derivative.[45] For example, cyclohexa-1,4-diene **(35)** was found to react with pentacarbonyliron giving concomitant isomerisation of the diene to give the conjugated isomer **(36)** as shown in Scheme 1.14. A variety of substituted cyclohexa-1,4-dienes are available by a Birch reduction of the corresponding benzene derivatives.[46] Therefore, it became possible to synthesise a broad range of (η^4-cyclohexa-1,3-diene)tricarbonyliron complexes.

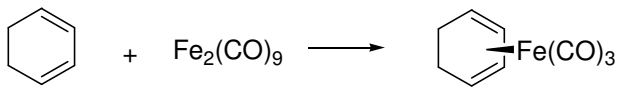
Since the investigation of the reactivity of butadiene tricarbonyliron by Hallam and Pauson, many workers extended the field to the complexation of other dienes and various experimental methods have been developed. The most common method used was developed by Cais and Maoz and involved the direct reaction of dienes with pentacarbonyliron by refluxing in di-n-butyl ether.[47] An example of a diene tricarbonyliron complex obtained by Cais and Maoz is the methyl sorbate complex **(38)** shown in Scheme

1.15 which was synthesised from methyl sorbate **(37)** using pentacarbonyliron giving a yield of 43%.[48]



Scheme 1.15 Synthesis of methyl sorbate complex (38) from methyl sorbate (37) using pentacarbonyliron.

The classical procedure for the coordination of dienes to a tricarbonyliron moiety involves the direct reaction with pentacarbonyliron, nonacarbonyldiiron or dodecacarbonyltriiron using either thermal or photochemical conditions. Nonacarbonyldiiron has the advantage of being employed under milder reaction conditions than the simpler mononuclear carbonyliron complex $Fe(CO)_5$, however this reagent is limited to the reaction with 1,3-dienes only.[44] For example, $Fe_2(CO)_9$ reacts with cyclohexa-1,3-diene **(34)** to form a (η^4)-cyclohexa-1,3-diene tricarbonyliron complex **(36)**, as shown in Scheme 1.16, but will not react with the 1,4-diene **(35)**.



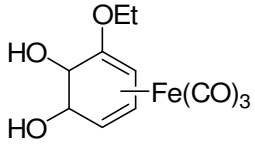
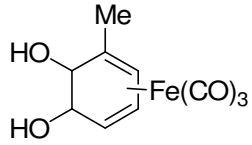
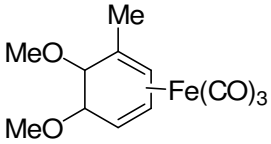
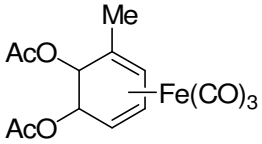
Scheme 1.16 Formation of (η^4)-cyclohexa-1,3-diene tricarbonyliron (36) using nonacarbonyldiiron.

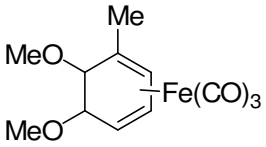
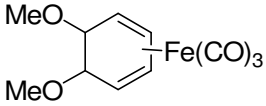
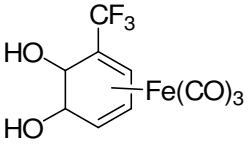
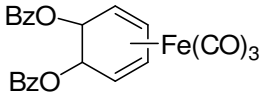
The yields obtained for the complexation reactions mentioned so far are usually quite moderate (30-50%) and, in order to achieve high yields, a large excess of the ironcarbonyl reagent is required. This can result in the formation of pyrophoric iron, which is hazardous on work up.[44] Also, some of the dienes can be sensitive to heat or UV light and therefore conventional thermal or photolytical methods would be destructive to them. However, complexation can be achieved under milder reaction conditions and with greater

selectivity by using a transfer reagent. Some of these transfer reagents will be discussed in Section 1.2.2.

Despite complications involved in using an excess of the ironcarbonyl reagent, numerous complexes have been formed by coordination of the $Fe(CO)_3$ fragment to the 1,3-dienes by direct complexation using nonacarbonyldiiron. Various reaction conditions have been used for the synthesis of substituted and unsubstituted diene complexes depending on the desired product and a summary of these is provided in Table 1.1.

Table 1.1 Summary of methods used by various research groups for the tricarbonyliron coordination of cyclohexadiene compounds.

Complex	**Equiv. of $Fe_2(CO)_9$**	**Solvent**	**Temp./ Time**	**Work up**	**% Yield**
	No details supplied.	THF	Room Temp.	No details supplied.	69[49]
	3.1	THF	Room Temp. / 18 hrs.	Standard work-up followed by chromatography (DCM) on silica.	35[50]
	1.7	Ether	Reflux / 18 hrs.	Filtration through Kieselguhr followed by removal of solvent. Purified by chromatography petroleum then ether: petroleum ether, 5:95 on silica.	55[50]
	4	Toluene	Sonoloy -sed for 22 hrs.	Filtration through Kieselguhr followed by removal of solvent. Purified by chromatography (petroleum ether, then ethyl acetate).	96[50]

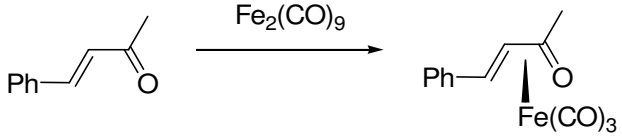
	No details supplied.	Ether	34 ºC / 16 hrs.	No details supplied.	53[51]
	No details supplied.	Ether	Reflux	Purified by chromatography.	40[52]
	3	Diethyl ether	Reflux / 5 hrs	Filtered through celite, washed with ether followed by removal of solvent. Purified by chromatography EtOAc : hexane, 1:1 (R_f 0.4) on silica. Recrystalisation from 10% EtOAc in hexane.	68[53]
	2	THF	Reflux / 2 hrs	Filtered through a silica gel column, washed with ether followed by removal of solvent. Purified by chromatography EtOAc : hexane, 1:15 (R_f 0.4) on silica.	58[54]

1.2.2 Tricarbonyliron Complexation Using Tricarbonyliron Transfer Reagents

Tricarbonyliron transfer reagents offer a useful alternative for preparing tricarbonyliron complexes of dienes. These unstable tricarbonyliron complexes involve a relatively weak coordination between the ligand and the metal which allows the transfer of the metal to the diene to form a more stable tricarbonyliron complex. [41,49]

1.2.2.1 (η^4-1-Oxabuta-1,3-diene)tricarbonyliron Complexes

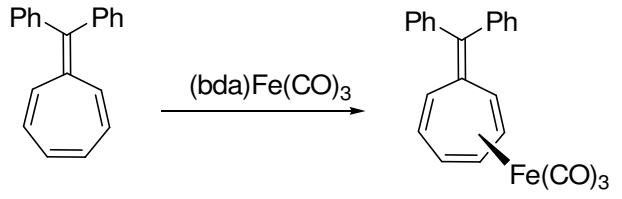
In 1964, Weiss first reported the preparation of π-cinnamaldehyde tricarbonyliron from the class of (η^4-1-oxabuta-1,3-diene)tricarbonyliron complexes[55] which were introduced by Lewis as transfer reagents in 1972.[56] (η^4-Benzylideneacetone)tricarbonyliron, (bda)$Fe(CO)_3$ **(40)**, was found to a very efficient transfer reagent[41] that acts as a convenient source for the tricarbonyliron moiety in the synthesis of diene tricarbonyliron complexes. This transfer reagent reacts under mild conditions and has been shown to be useful for sensitive dienes or where iron carbonyls are unsatisfactory.[57] (bda)$Fe(CO)_3$ is synthesised from benzylideneacetone **(39)** using nonacarbonyldiiron in a thermal reaction as shown in Scheme 1.17.



(39) **(40)**

Scheme 1.17 Synthesis of (bda)$Fe(CO)_3$ (40).

An example demonstrating how it has been utilised to good effect is the synthesis of (8,8-diphenylheptafulvene)tricarbonyliron **(42)**. In this reaction, the heptafulvene **(41)** is reacted with a slight excess of (bda)$Fe(CO)_3$ in toluene as shown in Scheme 1.18 and a 70% yield is obtained. Prior to the development of the (bda)$Fe(CO)_3$ reagent, the complexation of this compound was not possible as the free diene is sensitive to both heat and UV light and therefore $Fe(CO)_5$ and $Fe_3(CO)_{12}$ could not be used as reagents and reaction with $Fe_2(CO)_9$ yielded an unstable hexacarbonyldiiron complex.[56]

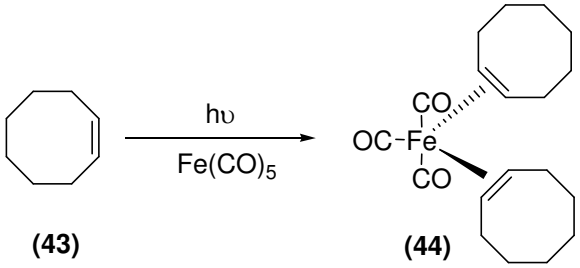


(41) **(42)**

Scheme 1.18 Synthesis of (η^4-8,8-diphenylheptafulvene)tricarbonyliron (42) utilising the tricarbonyliron transfer reagent (bda)$Fe(CO)_3$.

1.2.2.2 Bis(η^2-cis-cyclooctene)tricarbonyliron (Grevels' Reagent)

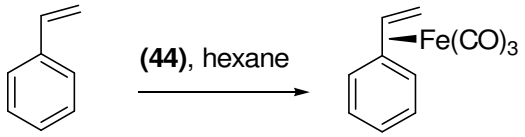
Another tricarbonyliron transfer reagent commonly used, *bis*(η^2-*cis*-cyclooctene)tricarbonyliron, was synthesised by Grevels in 1984.[58] This transfer reagent, known as Grevels' reagent **(44)**, was isolated by the photolysis of pentacarbonyliron in the presence of an excess of *cis*-cyclooctene **(43)** as shown in Scheme 1.19.



Scheme 1.19 Synthesis of Grevels' reagent (44) by direct reaction of pentacarbonyliron with cyclooctene (43).

The mild reaction conditions that can be used with Grevels' reagent led Fleckner *et al.* to examine the versatility of the complex as a source of the $Fe(CO)_3$ moiety. Grevels' reagent was found to be useful in a broad range of reactions forming complexes with cyclic dienes, heterodienes, vinyl and substituted aromatic compounds.[58] This reagent has two main advantages when compared to the (bda)$Fe(CO)_3$ transfer reagent. Firstly, Grevels' reagent can react at temperatures below 0 °C and secondly it is capable of complexing to 1,4-dienes by the concomitant isomerisation to the 1,3-diene in contrast to (bda)$Fe(CO)_3$ which is unreactive toward non-conjugated dienes.[49]

An example in which Grevels' reagent has been applied to complex formation with vinyl-substituted aromatic compounds is seen for the preparation of (η^4-styrene)$Fe(CO)_3$. In this case, styrene **(45)** was reacted below 0 °C with Grevels' reagent resulting in a 90% yield of the desired complex **(46)** as shown in Scheme 1.20.[49]

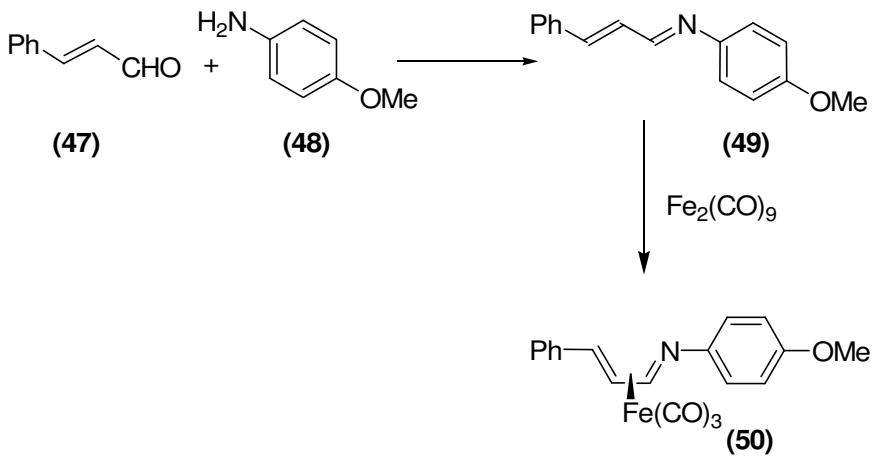


(45) **(46)**

Scheme 1.20 Synthesis of (η^4-styrene)tricarbonyliron (46) utilising Grevels' transfer reagent.

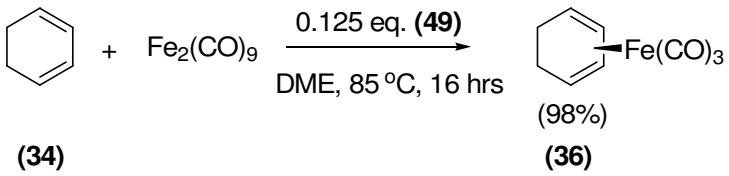
1.2.2.3 (η^4-1-Azabuta-1,3-diene)tricarbonyliron Complexes

Further developments in the field of tricarbonyliron-diene chemistry have involved optimisation of conditions and extension of the range of suitable starting materials for the complexation step when it is performed with tricarbonyliron transfer reagents.[59] Otsuka[60] and Lewis[61] first reported tricarbonyliron complexes of 1-azabuta-1,3-dienes four decades ago and found them to have only a few applications. More recently, these complexes have proved to be a very useful class of tricarbonyliron transfer reagents. Investigations by Knölker *et al.* found that the (η^4-1-azabuta-1,3-diene) tricarbonyliron complexes were an excellent choice being the most efficient, highly stable and selective tricarbonyliron transfer reagents.[41,49,59] The azabutadienes have been synthesised using various procedures. The most convenient approach is outlined in Scheme 1.21 for the example of (η^4-1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene)tricarbonyliron, the most efficient of the series of transfer reagents prepared by Knölker.[41,62] An imine condensation of *trans*-cinnamaldehyde **(47)** with *p*-anisidine **(48)** provides 1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene **(49)**. Reaction of this diene with nonacarbonyldiiron affords the transfer reagent **(50)**.



Scheme 1.21 Synthesis of the tricarbonyliron transfer reagent, (η^4-1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene)tricarbonyliron (50).

Knölker achieved the complexation of 1,3-cyclohexadiene to iron tricarbonyl to produce the irontricarbonyl(η^4-1,3-diene)complex **(36)** in 98% yield by generating the 1-azabuta-1,3-diene complex **(50)** *in situ*. The complexation was achieved by reaction with diironnonacarbonyl and a catalytic amount of the transfer reagent **(49)** as shown in Scheme 1.22.[62]



Scheme 1.22 One step synthesis of (η^4-cyclohexa-1,3-diene)tricarbonyliron (36) using the tricarbonyliron transfer reagent 1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene) (50).

Prior to the application of the 1-azabuta-1,3-diene family of catalysts to the synthesis of complex **(36)**, the reaction was performed by direct complexation of cyclohexadiene with pentacarbonyliron, nonacarbonyldiiron or dodecarbonyltriiron resulting in low yields varying from 21 to 77%.[41] Since then, use of a range of (η^4-1-azabuta-1,3-diene) tricarbonyliron complexes in the one step procedure shown in Scheme 1.22 has resulted in an increase in product yields to between 70 and 90%. The

azabutadiene-tricarbonyliron complexes offer several advantages as tricarbonyliron transfer reagents over (bda)$Fe(CO)_3$ and Grevels' reagent which were previously mentioned in Sections 1.2.2.1 and 1.2.2.2 respectively. A major advantage is that the coordination of cyclohexa-1,3-diene can be performed in a one step procedure[59] as shown in Scheme 1.22. For the preparation of the azadiene iron complex, a sub-stoichiometric quantity of the free ligand may be used[59] and therefore an excess of iron carbonyl is not required. Also, the free ligand can then be recovered after use by recrystallisation in a 95% yield.[49] One limiting factor in relation to the azabutadiene-tricarbonyliron complexes is that they do not undergo complexation reactions with non-conjugated dienes.

It has also been established that (η^4-1-azabuta-1,3-diene)tricarbonyliron complexes can be used in the preparation of enantiopure tricarbonyliron complexes. Knölker *et al*. described the first asymmetric catalytic complexation of prochiral dienes using chiral camphor derivatives of the 1-azabutadienes as catalysts.[63] The enantiopure compounds formed have been used as building blocks in the steroselective synthesis of spirocyclic compounds.[49,64]

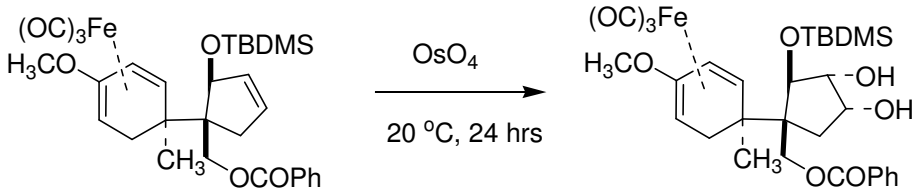
1.2.3 Synthetic Applications of Tricarbonyliron Complexes

The tricarbonyliron complexes are a useful class of organometallic compounds and have found many applications in organic synthesis because of the useful properties displayed by the tricarbonyliron group. As already noted, they can be used as protecting groups, activating groups and stereochemical controllers and an outline of these applications is provided in the following sections.

1.2.3.1 The Tricarbonyliron Fragment as a Protecting Group

As discussed in Section 1.2.1 on page 16, in 1958, Hallam and Pauson first observed that when transition metals complex with organic compounds, they confer upon the organic compound properties which differ from those observed before complexation. Therefore, the coordination of the tricarbonyliron fragment reduces the reactivity of the diene forming stable η^4 complexes and thus can act as a useful protecting group.[65]

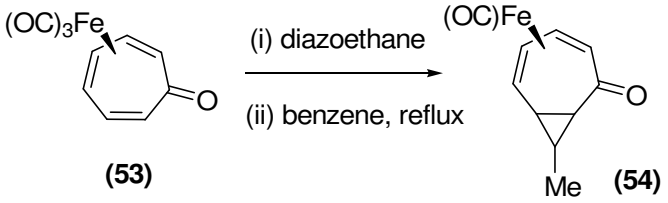
An example demonstrated by Pearson and Chen adds to the growing number of studies involving the use of a coordinated tricarbonyliron fragment as a protecting group during a multistep synthesis. In this case, the $Fe(CO)_3$ moiety is used to control the position at which an osmylation reaction occurs as shown in Scheme 1.23 during a multistep reaction to form 3,14-dihydroxytrichothecenes.[66] Osmylation is therefore selectively performed on the uncomplexed double bond.



(51) **(52)**

Scheme 1.23 The tricarbonyliron moiety ($Fe(CO)_3$) acting as a protecting group allowing selective osmylation to occur.

Another example in which the tricarbonyliron fragment is utilised to block unwanted carbon-carbon bond forming reactions has been demonstrated by Franck-Neumann and Martina. The cyclopropanation of the tropone-$Fe(CO)_3$ complex **(53)** with diazoethane was selectively performed affording complex **(54)**. This transformation can be seen in Scheme 1.24.[67]



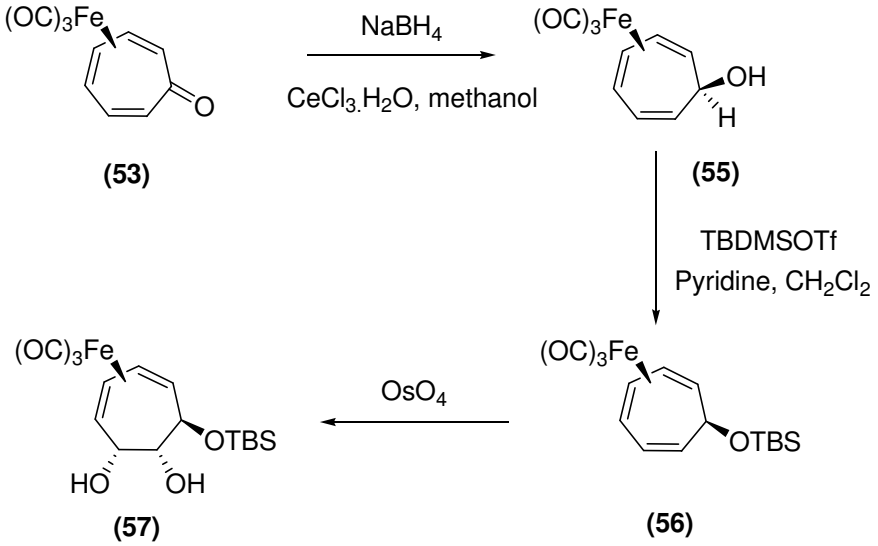
(53) **(54)**

Scheme 1.24 Cyclopropanation of the tropone-$Fe(CO)_3$ complex (54).

1.2.3.2 Stereochemical Control Using the Tricarbonyliron Group

The bulky iron tricarbonyl fragment of the tricarbonyliron complex allows for sterochemical control of reactions.[65] Pearson and Srinivasan demonstrated the utility of the

tricarbonyliron diene complexes in controlling stereochemistry and blocking unwanted reactions in the intermediate steps towards the synthesis of hepitol derivatives.[68] This stereo-controlled synthesis is of great value to synthetic chemists because of their potential to be used as glycosidase inhibitors.[69] The tropone-tricarbonyliron complex **(53)** is reduced with sodium borohydride to produce a single diastereomer **(55)**. The stereodirecting effect of the tricarbonyliron forces the addition of the hydride to the organic ligand on the face opposite the iron.[68,59] Protection of the alcohol using TBDMSOTf (*tert*-butyldimethylsilyl trifluoromethanesulfonate) followed by osmylation of the unprotected double bond afforded the triol derivative **(57)** as shown in Scheme 1.25.

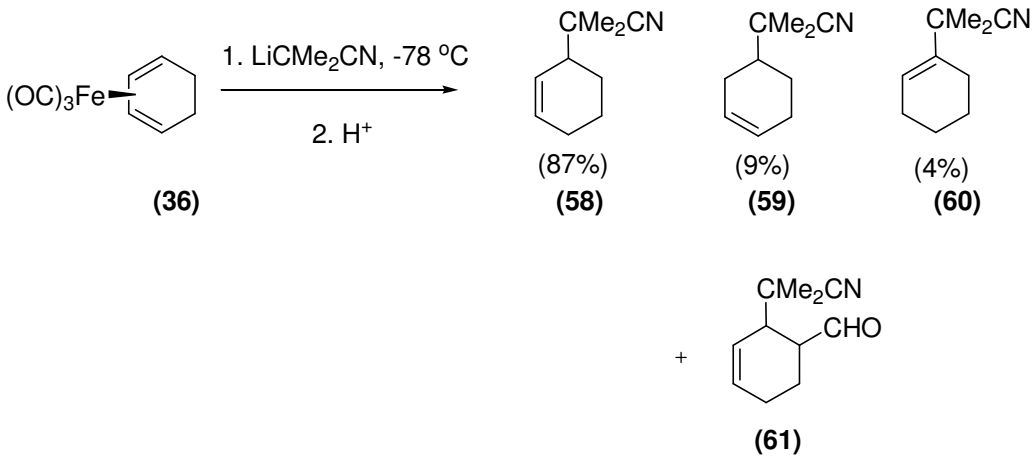


Scheme 1.25 Example of stereochemical control using the tricarbonyliron group.

1.2.3.3 The Tricarbonyliron Moiety as an Activating Group

Another application of the tricarbonyliron moiety is as an activating group as it facilitates nucleophilic addition reactions which do not proceed in the uncomplexed compounds. This addition is possible due to the strong electron withdrawing effect of the iron fragment.[70] Unsaturated organic compounds (alkenes, alkynes and arenes) are unreactive toward nucleophiles because they are electron rich. However, their reactivity changes when these unsaturated molecules coordinate to electron deficient metals. The

coordination decreases the electron density of these unsaturated molecules, which become reactive toward nucleophilic attack. For example, nucleophilic addition of 2-lithio-2-methylpropionitrile ($LiCMe_2CN$) to (η^4-cyclohexa-1,3-diene)tricarbonyliron **(36)** occurs. When this is followed by decomplexation, the four products shown in Scheme 1.26, **(58)**, **(59)**, **(60)** and **(61)**, are obtained, although **(61)** is only isolated when the reaction mixture is allowed to warm to room temperature before treatment with acid.[71,38]



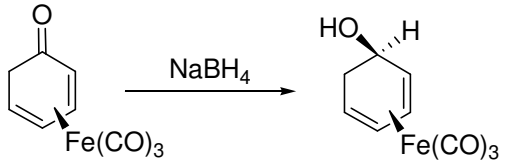
Scheme 1.26 Nucleophilic addition of 2-lithio-2-methylpropionitrile to (η^4-cyclohexa-1,3-diene)tricarbonyliron (36).

The tricarbonyliron complexes are uncharged and only undergo direct reactions with a limited number of nucleophiles.[72] However, converting these complexes to the corresponding cations allows reaction with a virtually unlimited range of nucleophiles and this will be discussed in Section 1.2.4 on page 28.

1.2.3.4 Stabilising Ability of the Tricarbonyliron Unit

Cyclohexadienone, a tautomer of phenol, is stabilised by coordination to the tricarbonyliron fragment.[46] An uncomplexed cyclohexadienone would undergo tautomerisation to the phenol but, when coordinated to the tricarbonyliron fragment, the cyclohexadienone-tricarbonyliron complex remains in the keto form and can be used in subsequent reactions. It has been found to react with a limited number of nucleophiles, one of which is shown in Scheme 1.27.[38] When **(62)** is treated with a solution of sodium

borohydride, an *endo* hydroxy complex **(63)** is formed by addition of the hydride nucleophile *anti* to the metal.

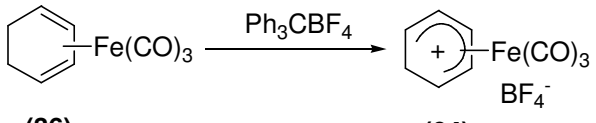


(62) **(63)**

Scheme 1.27 The complexed keto tautomer of phenol, cyclohexadienone-tricarbonyliron (62), utilised for synthesis.

1.2.4 Cyclohexadienyl-tricarbonyliron Complexes

A significant synthetic breakthrough in the chemistry of tricarbonyliron complexes occurred in 1960 when Fischer and Fischer reported hydride abstraction from a neutral complex using triphenylmethyl tetrafluoroborate.[73] The neutral complex (η^4-cyclohexa-1,3-diene)tricarbonyliron **(36)** is transformed to its stable salt, (η^5-cyclohexadieny)tricarbonyliron tetrafluoroborate **(64)**, as shown in Scheme 1.28. The irontricarbonyl group has the ability to activate the allylic C-H bonds, which enables this hydride abstraction.



(36) **(64)**

Scheme 1.28 Fischer and Fischer synthesis of (η^5-cyclohexadienyl)tricarbonyliron tetrafluoroborate (64).

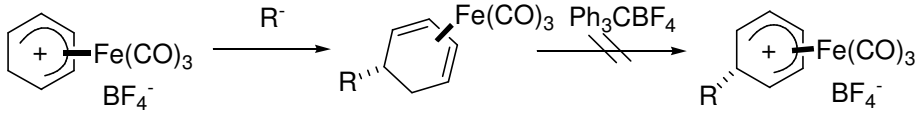
It is reported that the cyclohexadienyl complexes formed are not completely planar. The iron is bonded simultaneously to five sp^2 carbon atoms that are all planar[74] but non-equivalence of the sixth carbon in the cyclohexadienyl ring can occur as it is sp^3 hybridised and can occupy a position above **(65a)** or below the plane **(65b)**, as illustrated in Chart 1.6.[75] It was confirmed by Carvalho and co-workers using geometry optimisation and a comparison with crystal structures of similar complexes that, for the (η^5-

cyclohexadienyl)tricarbonyliron tetrafluoroborate complex, the more stable configuration is as shown in **(65a)**.[76] This is favoured due to the repulsive interaction with the metal in structure **(65b)**.

(65a) **(65b)**

Chart 1.6 The sp^3 carbon in the (η^5-cyclohexadienyl)tricarbonyliron tetrafluoroborate complex occupying a position above (65a) and below (65b) the plane of the five sp^2 carbon atoms.

The reactions of the dienyl complexes are characterised by high regioselectivity as attack occurs at the dienyl terminus and by complete stereoselectivity *anti* to the metal. There is one restriction to the hydride abstraction reaction in cyclohexadienyl complexes **(64)**. When a substituent is at the carbon-5 position, *anti* to the metal, the abstraction does not proceed.[38] Therefore further reactions are not possible as shown in Scheme 1.29.

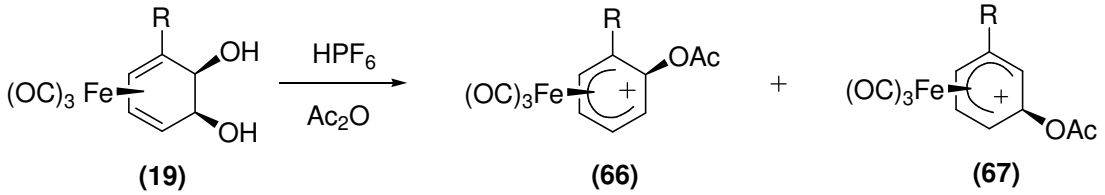


(64)

Scheme 1.29 Pathway showing limitation of the hydride abstraction process for cyclohexadienyl complexes with substituents at carbon 5.

Regioselectivity has also been examined for cation formation from the mono-substituted cyclohexadiene-1,2-diol tricarbonyliron complexes. Stephenson *et al.* reported that, for the formation of these cyclohexadienyl complexes, electron withdrawing substituents greatly influence the regioselectivity.[29] For example, diene complexes bearing a methoxy **(19a)** and chloro **(19b)** substituent formed one structural isomer, **(66a)** and

(66b) in favour of the **(67a)** and **(67b)** complexes in a ratio of 2:1 and 7:2 respectively as shown in Scheme 1.30. In comparison, the use of a trifluoromethyl substituent provided complete regiocontrol forming the complex **(66c)** exclusively.



(19) **(66)** **(67)**

(a) R = OMe
(b) R = Cl
(c) R = CF_3

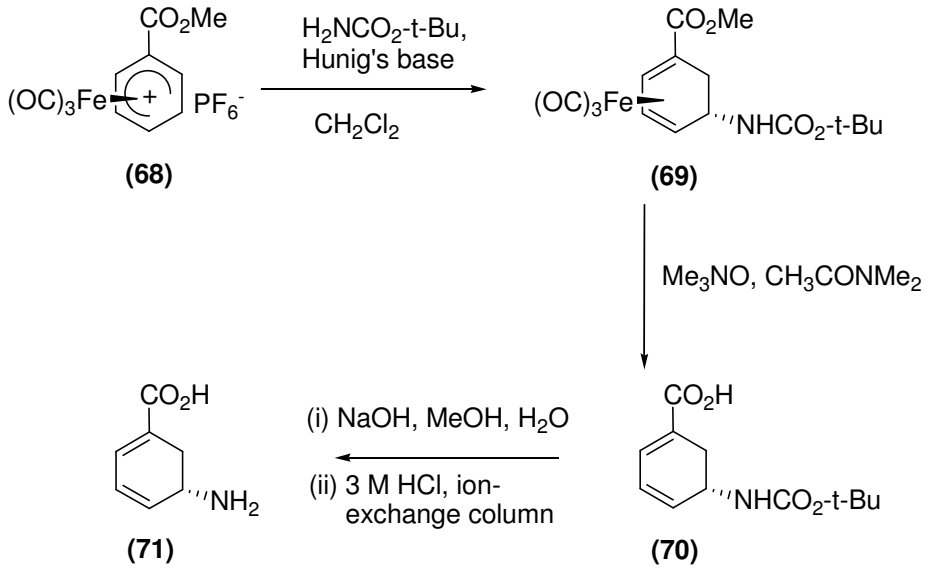
Scheme 1.30 Substituent effect on the formation of the (η^5-cyclohexadienyl)tricarbonyliron complexes.

1.2.5 Synthetic Applications of Cyclohexadienyl-tricarbonyliron Complexes

The reactivity of these dienyl complexes has attracted a great deal of interest in organometallic chemistry, due to their strong electrophilic nature and their ability to undergo nucleophilic attack with a virtually unlimited range of nucleophiles.[77] The stereo- and regio-control involved is an essential consideration when planning the design and synthesis of useful products. In principle, dienyl complexes can undergo nucleophilic reactions resulting in attack *syn* or *anti* to the metal.[78] However, chemical evidence indicates that, with few exceptions, the addition of hydroxide to tricarbonyliron complexes gives the *exo* substituted complex. Many research groups have reported evidence to support different pathways for nucleophilic attack on tricarbonyliron cyclohexadienyl complexes. This reaction may result in addition to the metal or to the carbonyl group.[79] Alternatively, the nucleophile may attack directly on the ring, although it has not been established conclusively whether this reaction proceeds *via* direct attack or *via* initial attack on the metal or carbonyl group.[80]

Birch *et al.* illustrated the use of the cyclohexadienyl-tricarbonyliron complex **(68)** to prepare (-)-gabaculine **(71)**, a naturally occurring amino acid. It is potentially useful

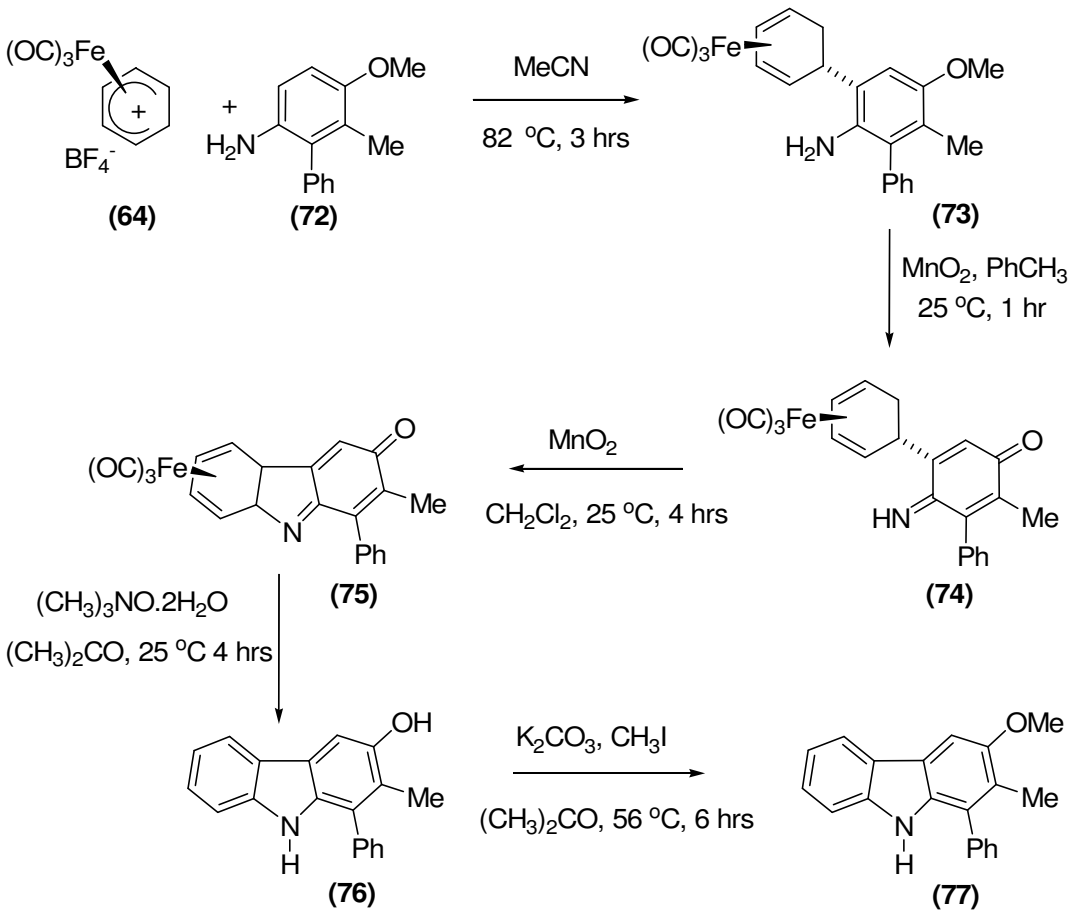
in the treatment of Parkinsonism, schizophrenia and epilepsy.[81] When the brain levels of gamma-aminobutyric acid (GABA) are low, these diseases can develop. However, gabaculine can allow a build up of GABA brain levels. The synthesis of (-)-gabaculine is initiated when **(68)** is trapped by the heteroatom nucleophile *tert*-butyl carbamate *anti* to the metal to yield the neutral complex **(69)**. Decomplexation is achieved by dissolving **(69)** in dimethylacetamide and reacting with trimethylamine-N-oxide to afford the gabaculine protected compound **(70)**. This is followed by hydroxide ion promoted ester hydrolysis of **(70)** to provide the (-)-gabaculine **(71)** product.



Scheme 1.31 Synthesis of the amino acid, (-)-gabaculine (71), by Birch *et al.* utilising a cyclohexadienyl-tricarbonyliron complex.

Many carbazole alkaloids have been isolated from natural sources. They are of interest due to their useful biological activities. They demonstrate potent neuronal cell protection and have been shown to exhibit free radical scavenging activity. Knölker *et al.* completed the enantioselective total synthesis of the first carbazole alkaloid of marine origin, hyellazole, in 1999.[82] This is a five step synthesis and the synthetic route is shown in Scheme 1.32. Nucleophilic trapping of the cyclohexadienyl complex **(64)** provided enantiopure arylamine **(73)** which then underwent a highly chemoselective oxidation to afford the quinine imine **(74)**. Cyclisation of the tricarbonyliron complex to form **(75)**

followed by decomplexation using trimethylamine-*N*-oxide afforded the 3-hydroxy-2-methyl-1-phenyl-9H-carbazole **(76).** Selective *O*-methylation with iodomethane and potassium carbonate in acetone provided hyellazole **(77)**.



Scheme 1.32 Enantioselective synthesis of hyellazole (77) by Knölker *et al.* utilising a cyclohexadienyl-tricarbonyliron complex.[82]

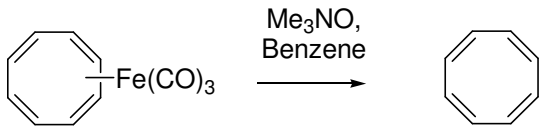
In addition, in 2007, a lab-scale synthesis of oseltamivir (Tamiflu®) *via* a tricarbonyliron coordinated cation was reported.[83]

1.2.6 Decomplexation of Tricarbonyliron Complexes

As discussed in Section 1.2.3, the use of tricarbonyliron complexes has been investigated since the 1900s. However, in order for the tricarbonyliron moiety to be of use synthetically, it is important that it can be introduced and removed easily and in high yields.

This decomplexation of tricarbonyliron complexes is usually achieved using oxidising reagents including ferric chloride, ceric ammonium nitrate and trimethylamine-*N*-oxide (Me_3NO).[84] Trimethylamine-*N*-oxide was first used to disengage an organic ligand from an iron carbonyl complex in 1963 by Shvo and Hazum.[85] This is by far the most widely used decomplexing agent and it is chosen in preference to others due to its mild reaction conditions. Also, it does not generate acidic conditions and therefore is suitable for use with acid sensitive functional groups.

An example of a decomplexation is shown in Scheme 1.33 and it involves reacting the (cycloocta-1,3,5,7-tetraene)tricarbonyliron complex **(78)** with a large excess of Me_3NO in refluxing benzene giving a 95% yield.



(78)

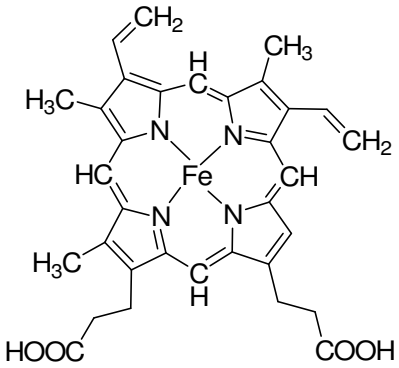
Scheme 1.33 Decomplexation of a tricarbonyliron complex using trimethylamine-*N*-oxide.

1.2.7 Medicinal Applications of Tricarbonyliron Complexes

Other compounds synthesised recently which are similar in structure to the arene *cis*-dihydrodiol complexes of interest in the current study have been examined as potential carbon monoxide releasing molecules.

Carbon monoxide (CO) is constantly generated in mammals during the degradation of heme by heme oxygenase enzymes.[86,87] Hemoglobin is a globular protein containing iron that transports oxygen around the body. It is a heme dependent protein and is also required as a substrate for the production of carbon monoxide. Heme oxygenase enzymes catalyse the conversion of heme to ferrous iron, carbon monoxide and biliverdin within the body.[88] The structure of heme **(79)** is shown in Chart 1.7. The endogenously

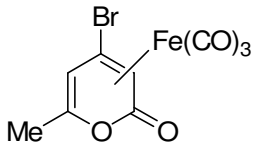
produced carbon monoxide has a versatile role in important physiological processes in the body. Carbon monoxide controls proliferation of vascular smooth muscle cells and suppresses the rejection of transplanted hearts.[89] It is known to dilate blood vessels and has been recently shown to possess anti-inflammatory properties.



(79)

Chart 1.7 Structure of Heme (79).

A reduced level of production of carbon monoxide can be harmful leading to growth retardation, renal dysfunction and vascular damage.[90] Until recently, the use of carbon monoxide gas was the only approach available to remedy this. However, due to the noxious effects of carbon monoxide, great care is necessary to control the dose and therefore this strategy is not ideal.[91] The development of carbon monoxide releasing molecules has thus become a drug discovery and development target. These compounds are designed to provide a safe and controlled method for administering carbon monoxide to a specific part of the body.[88] Transition metal carbonyls possess the ability to liberate carbon monoxide under appropriate conditions and function as carbon monoxide releasing molecules (CO-RMs) in biological systems.[86] The first direct evidence that metal carbonyls have the ability to function as CO-RMs was reported by Motterlini *et al*. in 2002.[92] An example of a CO-RM developed by Fairlamb and co-workers is the iron carbonyl complex bearing a substituted 2-pyrone ligand **(80)**, which contains iron and a η^4-coordinated diene ligand[87] as shown in Chart 1.8. This compound is a tricarbonyliron moiety coordinated to a diene ligand that is part of a six atom ring.



(80)

Chart 1.8 An example of a (η^4-2-pyrone)$Fe(CO)_3$.

The medicinal application of these CO-RMs is progressing quickly. Therefore, in the near future, it is probable that there will be a new range of CO-RMs for the treatment of many physiological and pathophysiological processes. This should result in more interest in the use of bioorganometallic chemistry and also the application of iron tricarbonyl compounds.

1.2.8 The Role of Iron in Dioxygenase Enzymes

Boyd and Bugg[93] recently reviewed the available information on the structure and mechanism of a range of arene dihydroxylating enzymes. As discussed in Section 1.1.2, page 8, these dioxygenase enzymes are used to produce the *cis*-dihydroxylated products of a range of aromatic compounds by means of biotransformations. Iron is central to the structure of the active site of the enzymes and Boyd and Bugg report that it has been shown that there is a Rieske iron-sulfur cluster [2Fe2S] and a mononuclear iron(II) centre present.[93] The enzymes act by supplying two electrons to dioxygen to produce a species that is a very strong oxidising agent in which the activated dioxygen is linked to the mononuclear iron centre. In the case of the naphthalene dioxygenase enzyme (NDO), it has been shown that one mononuclear iron(II) centre and one Rieske cluster are oxidised during the catalytic cycle.[94]

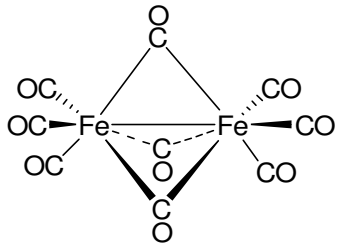
Boyd and Bugg[93] remark that several mechanisms have been proposed for the action of the *cis*-hydroxylating dioxygenase enzymes but that there is little agreement over which is the most likely to occur. It is interesting to note that iron plays a central role in the active site of the enzymes responsible for the stereoselective hydroxylation of aromatic substrates and that coordination to iron is also crucial to the synthetic strategy applied in

this work to achieve conversion from arene *cis*-dihydrodiols to their *trans*- isomers as can be seen in Scheme 1.11 (page 11) and Scheme 1.30 (page 30).

1.2.9 The Transition Metal in Organometallic Complexes

1.2.9.1 The Eighteen Electron Rule

The 18 electron rule for organometallic compounds is comparable to the octet rule for organic compounds. In general, if a metal has an electron count of 18 in its valence shell, the complex should be stable. However, many organometallic compounds that do not obey this rule can be stable.[95,96] The 18 electrons in the valence shell are comprised of the two *s* orbital electrons, six *p* orbital electrons and ten *d* orbital electrons. Several methods exist for counting the total number of valence electrons and an example for nonacarbonyldiiron is shown in Chart 1.8.



(30)

3 (CO)	6 electrons
3 (μ-CO)	3 electrons
Fe	8 electrons
Fe-Fe	1 electron
	18 electrons

Chart 1.8 18-electron count for nonacarbonyldiiron (30).

Iron atoms have eight valence electrons based on their position in the periodic table. The metal-metal bond is assumed to contribute one electron to each metal atom. The carbonyl ligands are each considered to donate two electrons from a lone pair to an empty *d* orbital. The bridging carbonyls, denoted μ-CO, donate one electron to each iron atom. That provides a total valence shell electron count of eighteen for the iron in the nonacarbonyldiiron complex.

1.2.9.2 Back Bonding

When a transition metal is bonded to a ligand, the bonds arise from a combination of forward and back donation of electrons. A sigma bond (σ) is formed when a ligand (such as the carbonyl ligand) donates a pair of electrons to a vacant *d* orbital of the metal. Electrons can then be accepted back from a filled metal orbital and usually occupy an *anti*-bonding orbital (denoted π*) of the ligand (CO) to form a π bond. This reverse metal to ligand electron transfer is termed 'back bonding'.[97] To use carbonyl ligands as an example, this back donation of electrons strengthens the metal-carbon bond but weakens the carbon-oxygen bond. An example of the formation of π bonds formed by back bonding from a metal to a carbonyl ligand is shown in Chart 1.9. The shaded orbitals are full and the unshaded orbitals are empty.

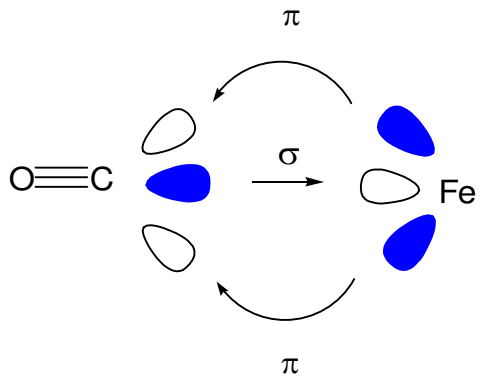
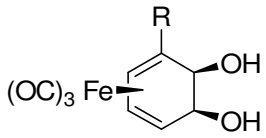


Chart 1.9 Formation of sigma and pi bonds between a carbonyliron moiety and a carbonyl ligand.

1.2.9.3 The Electron Environment in Cyclohexadiene Complexes

For the (η^4-cyclohexa-1,3-diene)tricarbonyliron complexes and the coordinated arene *cis*-diol derivatives **(19)** shown in Chart 1.10, forward coordination arises when the lone pair electrons situated on the carbon atom of the carbonyl ligand are donated to the vacant metal orbital to form a sigma bond. The back donation of electrons occurs from the filled orbital in the metal to the ligand's lowest unoccupied molecular orbital (LUMO). The result of this back bonding is an increase in the strength of the metal-carbon bond and a decrease of electron density of the iron.[98] This will also result in a decrease in the strength of the carbon-oxygen bond. The bonding between the metal and the π bonds of the other

ligand coordinated to it, cyclohexadiene, results in a weak coordination. The bonding consists of a transfer of electron density from the highest occupied molecular orbital (HOMO) of the diene to the empty *d* orbital of the metal atom.[99] This is accompanied by back bonding from the filled metal *d* orbital to the LUMO of the diene.[100]



(19)

Chart 1.10 Derivatives of the cyclohexa-3,5-diene-1,2-diol tricarbonyliron complexes (19).

In common with the (cyclohexadiene)tricarbonyliron complexes, the bonding of the cyclohexadienyl tricarbonyliron cation involves forward coordination which arises from the interaction of the bonding orbitals of the dienyl ligand with the vacant iron orbitals and back bonding which arises due to back donation of electrons from the filled metal *d* orbitals to the vacant molecular orbitals of the dienyl ligand.[98]

1.3 Stability of Coordinated Cyclohexadienyl Cations

The stability of coordinated cyclohexadienyl cations can be determined by measurement of K_R, the equilibrium constant for the conversion of the coordinated cyclohexadienyl carbocation (R^+), to the coordinated arene hydrate (ROH), based on the reaction represented in Scheme 1.34.

$$R^+ + H_2O \underset{k_H}{\overset{k_{H2O}}{\rightleftharpoons}} ROH + H^+$$

Scheme 1.34 Formation of a coordinated arene hydrate (ROH) from a coordinated cyclohexadienyl cation (R^+).

In Scheme 1.34, k_H is the rate constant for the acid catalysed ionisation of the coordinated arene hydrate to form the corresponding coordinated cyclohexadienyl cation. The rate constant, k_{H2O}, refers to the rate of the reverse attack of water on the coordinated cyclohexadienyl cation. The equilibrium constant, K_R, can conveniently be expressed in terms of its negative logarithm defined as pK_R (pK_R = -log K_R).

In principle, there are two methods by which the constant K_R can be determined, which are:

1 By a direct measurement of the equilibrium concentrations of the arene hydrate tricarbonyliron complex combined with the cyclohexadienyl tricarbonyliron carbocation.
2 By kinetic measurements of the forward and reverse rates for ionisation of the arene hydrate tricarbonyliron complex and hydrolysis of the cyclohexadienyl tricarbonyliron carbocation complex respectively, under the same conditions.

1.3.1 Direct Equilibrium Measurements

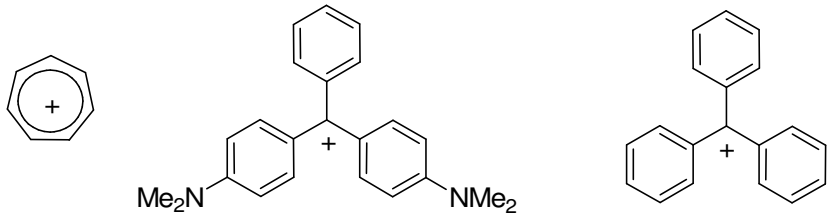
The relationship between the concentrations of reactants and products for direct equilibrium measurements of the equilibrium constant K_R, from Scheme 1.34, is given by Equation 1.1.

$$K_R = \frac{[ROH]\,[H^+]}{[R^+]} \qquad (1.1)$$

UV-Vis spectroscopy is commonly used to carry out direct determinations of K_R. This is achieved by determining the relative concentrations of the neutral complex and the carbocation being studied at equilibrium at particular acid concentrations. An appreciable change in spectrum is required between the fully ionised and fully neutral species and both species must be sufficiently stable to be directly observable. Examples of cations that are stable enough to allow equilibrium measurements in dilute acid solutions

are the tropylium cation **(81)** and di-(*p*-dimethylaminophenyl)-phenylmethyl cation **(82)** and they are shown in Chart 1.11.[101,102]

For cations such as the triphenylmethyl cation **(83)** the measurements were carried out in more concentrated acid solutions.[103,104] As a result of medium effects, the K_R value had to be extrapolated to water using the acidity function method. By use of reference reactions, a plot of log K_R versus the acidity function, X_0, can be obtained and the value of K_R is determined in the absence of acid by extrapolating to pure water for which $X_0 = 0$ is determined.[105,106]



(81) **(82)** **(83)**

Chart 1.11 Tropylium (81), di-(*p*-dimethylaminophenyl)-phenylmethyl (82) and triphenylmethyl (83) cations.

In practice, concentrated aqueous-strong acid mixtures lead to massive medium effects which affect protonation equilibria. Much work has been carried out on measuring the medium effect on protonation equilibria in hydrochloric acid, sulphuric acid and perchloric acid. This medium effect may be expressed by the relationship shown in equation 1.2, where K is the equilibrium constant at various acid concentrations, K_{H2O} is the equilibrium constant in water, and m* is the slope of the relationship.

$$\log \frac{K}{K_{H2O}} = m^* X_0 \qquad (1.2)$$

The acidity function parameter X_0 is defined by Cox and Yates as $\log(K / K_{H2O})$, where K and K_{H2O} refer to equilibrium constants for a reference acid-base reaction.[113]

1.3.2 Kinetic Measurements

An alternative to employing equilibrium measurements to determine K_R is the use of kinetic measurements. In this approach, the equilibrium constant is obtained by combining the forward and reverse reaction rates, k_H and k_{H2O} respectively, as is shown in Equation 1.3.

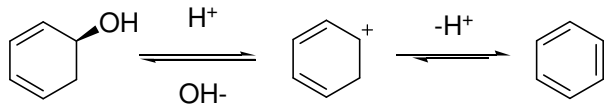
$$K_R = \frac{k_{H2O}}{k_H} \qquad (1.3)$$

For uncoordinated carbocations, k_{H2O} can be difficult to measure as, in the case of very reactive carbocations, reaction of the carbocation with water occurs very rapidly and the reactive species are difficult to isolate as reactants.

In an example related to the carbocations examined in this study, the stabilising ability of the tricarbonyliron moiety allowed the rate constant, k_{H2O}, to be measured directly from reaction of cyclohexadienyl tricarbonyliron cations to yield the corresponding arene hydrate complex. The rate constant, k_H, for carbocation formation from alcohols has been determined by various methods. For the coordinated cyclohexadienyl cations being examined in this work k_H can be measured by first allowing the coordinated cation to react fully to form the complementary hydrate complex and subsequently quenching this hydrate into a solution of sufficiently lower pH that will allow the formation of the cation to be observed.

1.3.3 Relevant Complexes Studied Previously

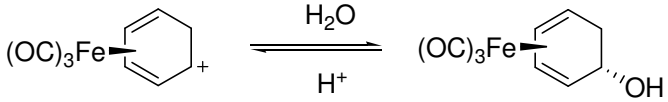
The pK_a and the pK_R for the uncoordinated benzenonium ion **(84)** have been determined[107] and these equilibria are shown in Scheme 1.35. it was calculated that, in one molar acid, less than one molecule per mole of benzene exists in the protonated cyclohexadienyl cation **(84)** form and, in aqueous solution, it is deprotonated at a rate close to the limiting rate of relaxation of the solvent.



(2) **(84)**

Scheme 1.35 Equilibrium reaction for the uncoordinated benzenonium ion (84).

The pK_R for the tricarbonyliron cyclohexadienyl cation **(64)** has previously been determined in this laboratory and this equilibrium reaction is shown in Scheme 1.36.[108] Studies of the equilibrium between the coordinated cyclohexadienyl cation and the corresponding *exo* hydrate **(85)** allowed a rate constant, k_H, for ionisation of this *exo*-isomer of 7.2×10^3 $M^{-1}s^{-1}$ to be estimated.[108]



(64) **(85)**

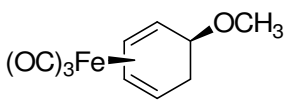
Scheme 1.36 Nucleophilic attack of hydroxide on (cyclohexadienyl)tricarbonyliron.

A striking contrast to this result is observed for the tricarbonyliron cyclohexadienyl cation **(64)** as it is readily isolated as its tetrafluoroborate (BF^-_4) and hexafluorophosphate (PF^-_6) salts, is stable at mildly acidic pH and can be recrystallised from water.[46] Furthermore, in the presence of bases, deprotonation doesn't take place. Instead, nucleophilic substitution occurs to form the corresponding *exo* arene hydrate **(85)** as shown in Scheme 1.36. Thus, this is evidence to support the fact that the stability of cyclohexadienyl cations and their analogues is greatly increased upon coordination to tricarbonyliron.

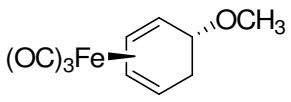
In the coordinated arene hydrate **(85)** the OH group has an *exo* configuration with respect to the iron tricarbonyliron group.The *endo* isomer of this complex has been prepared by Birch *et al.* by sodium borohydride reduction of the tricarbonyliron coordinated keto complex **(62)** as shown in Scheme 1.27 (page 28).[46] The two isomers are distinguished by their NMR spectra.The rate constant for the acid catalysed conversion of the *endo* substituted coordinated complex **(63)** to the corresponding cyclohexadienyl cation

complex **(64)** was measured[109] and was found to be 2.0 x 10^{-3} $M^{-1}s^{-1}$, which is 10^7 times smaller than the rate constant for the corresponding *exo* hydrate **(85)**.[108] This indicates that the *endo* isomer is less reactive than its *exo* analogue. A possible explanation for the low reactivity of the *endo* isomer would be that a favourable interaction between the tricarbonyliron moiety and the *endo* hydroxyl oxygen has a stabilising effect.[108]

However, similar studies by Johnson *et al*. demonstrated that, in mildly acidic methanol the corresponding methoxycyclohexadiene tricarbonyliron complexes are slowly interconverted between the *endo* **(86)** and *exo* **(87)** isomers (Chart 1.12) with an equilibrium ratio of [*endo*] / [*exo*] of approximately 2 being reached.[110] When the (η^5-cyclohexadienyl)tricarbonyliron cation **(64)** was refluxed in methanol they found that the *exo*-complex formed initially, however, after 1.5 hours some of the *endo*-isomer was observed. This implies that the *endo* **(86)** and *exo* **(87)** isomers do not differ significantly in stability but do have different kinetic stabilities. If it is assumed that a similar ratio of [*endo*] / [*exo*] of 2 occurred for the isomers **(85)** and **(63)**, it can be concluded that the *endo* and *exo* isomers do not differ significantly in stability. They therefore have similar thermodynamic but different kinetic stabilities and a larger kinetic barrier to reaction for the *endo* isomer would therefore be implied. This larger kinetic barrier could be a result of the difference in how the species are formed, for example, the *endo* isomer may be formed *via* initial attack of water or methanol on the metal centre.[46] It could also be because coordination by the tricarbonyliron group severely inhibits attack from the *endo* direction.



(86)



(87)

Chart 1.12 Structures of the *endo* (86) and *exo* (87) isomers of methoxycyclohexadiene tricarbonyliron complexes

It can be concluded that the coordinated *exo* and *endo* complexes have similar stabilities. However, the *exo* products have a lower kinetic barrier to reaction and therefore

are kinetically favoured while the *endo* products have a larger kinetic barrier to reaction. This means that attack of the nucleophile is preferred on the opposite face to the tricarbonyliron moiety. Therefore, the *exo* isomer will form more easily as it does not experience any steric or electronic hindrance from the tricarbonyliron but, if left to react long enough, eventually the *endo* isomer will form.

1.4 Organometallic Coordination of Oxidative Metabolites of Aromatic Hydrocarbons - Aims of this Study

The work undertaken for this project was part of a larger study with the objective of developing efficient methods for conversion of arene *cis*-dihydrodiols to a variety of industrially important products, including phenols, catechols and arene *trans*-dihydrodiols. The principal goal of this project was to investigate a viable route for conversion of arene *cis*-dihydrodiols to their *trans*-isomers.

As was discussed in Section 1.1, arene *cis*-dihydrodiols can be produced in significant quantities from biotransformations using mutant and recombinant strains of bacteria[1] and have found many uses as chiral precursors for the formation of enantiopure products of synthetic and industrial importance. The *trans*-analogues are potentially important chiral synthons, particularly as they are more stable than their *cis*-isomers. They can be used to synthesise new structures of interest including inositols and conduritols. The *trans*-isomers are not yet accessible on a commercial scale but a number of enzymatic and chemoenzymatic pathways that could be used to synthesise substituted arene *trans*-dihydrodiols have been described in a review by Boyd and Sharma.[10] Although a number of pathways are available, they are multistep in character and generally of limited synthetic scope and low yield.

One of the most promising and direct chemical routes was outlined in Scheme 1.11 and it involves coordination of arene *cis*-dihydrodiols with a tricarbonyliron moiety. This is the synthetic route being examined in this project. As the synthesis involves the formation of tricarbonyliron complexes as intermediates, it was decided to study the

reactivity of the tricarbonyliron complexes formed to allow the synthetic route to be optimised. Thus the aims of this research are;

- To carry out the metal coordination route proposed for conversion of arene *cis*-dihydrodiols to their *trans* isomers on a number of substrates.
- To investigate each step of the synthetic pathway using kinetic and equilibrium studies to provide the information required to optimise the route and in so doing add to the existing knowledge of the relatively unexplored organometal complexes involved.

CHAPTER 2

RESULTS

2 RESULTS

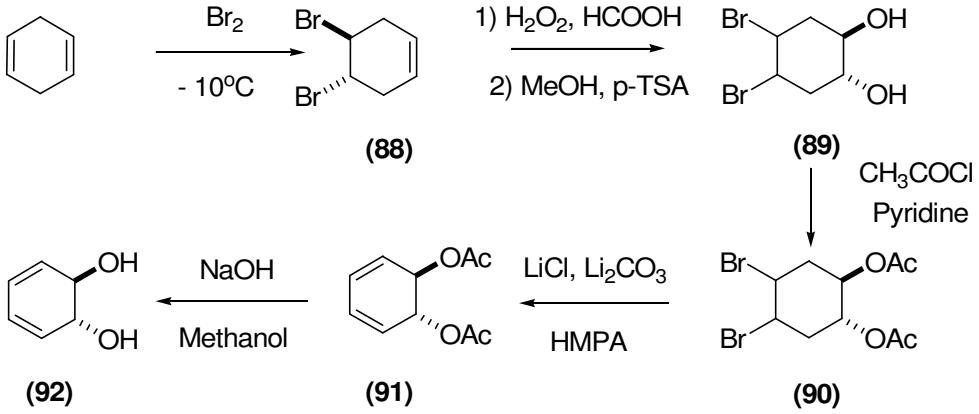
The results are presented in two sections which entail (a) synthesis of relevant organic and organometallic compounds and (b) investigation of the intermediates in the synthetic pathway being developed using kinetic and equilibrium studies.

2.1 Synthesis of Organic and Organometallic Substrates

This section will outline the syntheses performed in this study and give information on the organic and organometallic compounds produced. Tables of results summarise the reaction conditions and yields obtained. The synthesis and characterisation of these compounds will be examined in more detail in the discussion.

2.1.1 *trans*-Cyclohexa-3,5-diene-1,2-diol

trans-Cyclohexa-3,5-diene-1,2-diol **(92)** was synthesised in five steps from 1,4-cyclohexadiene **(87)** as shown in Scheme 2.1.[111] The aim was to build up a stock for further synthesis as it is then converted to the corresponding *trans* dimethyl ether and coordinated to tricarbonyliron to allow the stability of this complex to be examined. Each compound formed was characterised by ^{1}H NMR spectroscopy and all spectra corresponded with previous characterisation. The final product, *trans*-cyclohexa-3,5-diene-1,2-diol **(92)**, an orange oil, was synthesised in an overall yield of 15% (see Table 4.1, page 107).



Scheme 2.1

2.1.2 *cis*- and *trans*-5,6-Dimethoxycyclohexa-1,3-diene

cis- and *trans*-Cyclohexa-3,5-diene-1,2-diol were converted to their dimethyl ethers which are shown in Chart 2.1. The benzene *cis*-dihydrodiol used was available from Queen's University Belfast where it was produced in bulk by fermentation in a bioreactor. The complexation of the irontricarbonyl moiety directly to the unprotected diols has been reported to give a product which was unstable for purification by flash chromatography.[54] The methoxy group is less reactive than the hydroxyl group and thus these ethers are stable enough to undergo complexation and purification. Furthermore, protection of the diol is important because the corresponding cation of the coordinated *trans*-diol is a very unstable complex (see Scheme 3.2, page 77).[52] The methylation reactions resulted in low yields, ranging between 20 to 30% for the *cis*-5,6-dimethoxycyclohexa-1,3-diene **(93)** and between 35 to 42% for the *trans*-5,6-dimethoxycyclohexa-1,3-diene **(94)**. This is due to a large proportion of a side product, anisole, being formed. A summary of the reaction conditions and yields for the synthesis of the dimethoxy complexes **(93)** and **(94)** are shown in Table 2.1.

(93) **(94)**

Chart 2.1

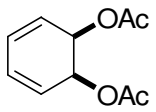
Table 2.1 Reaction conditions and yields for the formation of *cis*-5,6-dimethoxycyclohexa-1,3-diene **(93)** and *trans*-5,6-dimethoxycyclohexa-1,3-diene **(94)** by methylation of the corresonding diols.

Compound	Scale (grams)	Reaction Conditions	Solvent	R_f	% Yield
(93)	8.48	(i) 3.0 equiv., NaH, 30 mins, 0 °C (ii) 4.0 equiv., CH_3I, 2 hrs, room temp. (iii) flash chromatography (cyclohexane: ethyl acetate, 95: 5)	THF (anhydrous)	0.4[a]	20
(94)[b]	0.50	(i) 3.0 equiv. NaH, 15 mins, 0 °C (ii) 4.0 equiv. CH_3I, 3 hrs, room temp. (iii) flash chromatography, (cyclohexane: ethyl acetate, 95: 5)	THF (anhydrous)	0.6[a]	42

[a] The solvent system used to monitor the reaction by TLC was cyclohexane: ethyl acetate, 1: 1. [b] The *trans*-compound was never synthesised with satisfactory purity following the procedure by Platt *et al.*[111]

2.1.3 *cis*- and *trans*- 5,6-Diacetoxycyclohexa-1,3-diene

Additional synthesis involved converting benzene *cis*-dihydrodiol to the corresponding *cis*-5,6-diacetoxycyclohexa-1,3-diene **(95)** shown in Chart 2.2. This modification should again give a less reactive and more stable carbocation than the corresponding diol. This synthetic procedure was attempted in the hope of achieving a better yield than the methylation step. This was accomplished and a yield of 65% was obtained for the *cis*-diacetate product. The reaction conditions and yield are summarised in Table 2.2. Characterisation of the *cis*-diacetate included a ^{1}H NMR spectrum which will be examined in Section 3.4 (page 94) and Section 4.3.4.1 (page 117). *trans*-5,6-Diacetoxycyclohexa-1,3-diene **(91)** had already been synthesised in the fourth step in the synthesis of *trans*-cyclohexa-3,5-diene-1,2-diol **(92)** as described in Section 4.3.1, page 107.



(95)

Chart 2.2

Table 2.2 Reaction conditions and yield for the formation of *cis*-5,6-diacetoxycyclohexa-1,3-diene **(95)** from the corresponding diol.

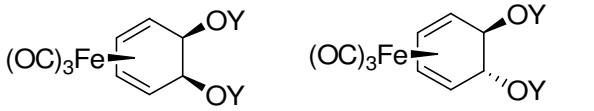
Compound	Scale (grams)	Reaction Conditions	Solvent	R_f	% Yield
(95)	0.51	(i) 4.0 equiv., acetyl chloride, 4 hrs, room temp. (ii) extraction, flash chromatography (75: 25 cyclohexane: ethyl acetate)	CH_2Cl_2, pyridine (anhydrous)	0.4[a]	65

[a] The solvent system used for flash chromatography was cyclohexane: ethyl acetate, 75: 25.

2.1.4 *cis* and *trans* Isomers of (5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron and (5,6-Diacetoxycyclohexa-1,3-diene)tricarbonyliron

The next step was to coordinate the tricarbonyliron moiety to the arene *cis*- and *trans*- protected diols from Sections 2.1.2 and 2.1.3 forming the *cis*- and *trans*-dihydrodiol derivatives shown in Chart 2.3. This reaction was initially attempted on the *cis*-dimethoxy complex **(93)** using 1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene (1 equiv.), 5,6-dimethoxy-1,3-cyclohexadiene (8 equiv.) and diironnonacarbonyl (3 equiv.) and THF as the solvent. However, coordination was not achieved and it was decided to carry out this reaction by direct complexation, without any catalyst, which meant that a large excess of the diironnonacarbonyl was used. Based on literature reports, the reaction was performed using ether and THF as solvents which gave 58% and 80% yields respectively for (*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** as shown in Table 2.3. The THF was used as it gave a better yield. The complexation of *trans*-5,6-dimethoxycyclohexa-1,3-diene

(94) to give **(98)** gave lower yields, ranging between 3 and 8% and although the desired complex was produced, the ^{1}H NMR spectrum confirmed that it was not of high purity. As noted in Table 2.3, complexation of the *trans* compounds to form products **(98)** and **(100)** that were sufficiently pure was not achieved. Thus, it was not possible to use these *trans* complexes in equilibrium studies.



(97) Y = Me
(99) Y = Ac

(98) Y = Me
(100) Y = Ac

Chart 2.3

The coordination of tricarbonyliron to the diacetate compounds **(95)** and **(96)** was performed under similar reaction conditions. These reaction conditions and the yields obtained are summarised in Table 2.3. For the *cis*- isomer, the reaction was left to reflux for 13 hours but starting material was still evident at that stage. The reaction was worked up and purified by flash chromatography to give a poor yield of 13% of **(99)**. Characterisation of complexes **(97)** and **(99)** are reported in the experimental details (pages 120 and 118)

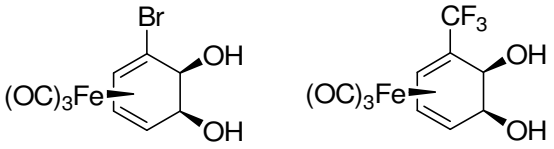
Table 2.3 Reaction conditions and yields for the formation of tricarbonyliron complexes.

Compound	Scale (grams)	Equivalents of $Fe_2(CO)_9$	Reaction time (hours)	R_f	% Yield
(97)[b]	0.30	2.3	4	0.3[c]	58
(97)	0.20	2.0	2	0.3[c]	82
(98)[e]	0.15	2.8	6	0.2[d]	5
(99)	0.53	2.5	13	0.2[d]	13
(100)[e]	0.33	3.0	5	0.4[d]	17

[a] The solvent used in all reactions was THF unless otherwise stated. [b] The solvent used in this reaction was diethyl ether. [c] The solvent system used to monitor the reaction by TLC was pentane: ethyl acetate, 85: 15. [d] The solvent system used to monitor the reaction by TLC was pentane: ethyl acetate, 8: 2. [e] These *trans*-complexes were never synthesised with satisfactory purity.

2.1.5 Tricarbonyliron Complexes of Substituted Benzene *cis*-Dihydrodiols

Two substituted benzene-*cis*-dihydrodiols were coordinated to tricarbonyliron by direct complexation using the same reaction conditions as described for (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron and (η^4-*cis*-5,6-diacetoxycyclohexa-1,3-diene)tricarbonyliron in the previous section. The structures of the tricarbonyliron complexes of the 3-bromo- **(101)** and 3-trifluoromethyl- **(102)** substituted benzenedihydrodiols which were prepared are shown in Chart 2.4. These reactions gave percentage yields of 90% and 69% for complexes **(101)** and **(102)** respectively as shown in Table 2.4. In this case, the hydroxyl functional groups of the dihydrodiols did not need to be protected initially, as these compounds are relatively more stable than the corresponding unsubstituted diol. Characterisation will be discussed in Section 3.4.1, page 97.



(101) **(102)**

Chart 2.4

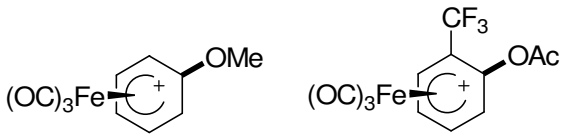
Table 2.4 Reaction conditions and yields for the preparation of (η^4-*cis*-3-bromocyclohexa-3,5-diene-1,2-diol)tricarbonyliron **(101)** and [η^4-*cis*-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102).**

Compound	Scale (grams)	Equivalents of $Fe_2(CO)_9$	Reaction time (hours)	R_f	% Yield
(101)	0.33	3.0	3	0.4[a]	90
(102)	0.30	2.9	2	0.3[a]	69

[a] The solvent system used to monitor the reaction by TLC and for flash chromatography was cyclohexane: ethyl acetate, 1: 1.

2.1.6 Tricarbonyliron Substituted Cyclohexadienyl Cation Complexes

The (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** and [η^4-*cis*-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102)** complexes were treated with TFA and HPF_6 respectively to form their corresponding substituted cyclohexadienyl cations, the structures of which are shown in Chart 2.5. These reactions gave percentage yields of 90% and 48% for complexes **(103)** and **(104)** respectively as shown in Table 2.5. Characterisation of these cations will be examined in the discussion on page 99.



(103) **(104)**

Chart 2.5

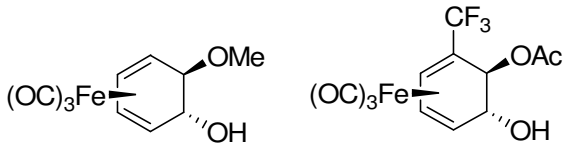
Table 2.5 Reaction conditions for the formation of the tricarbonyliron cyclohexadienyl complexes, (η^5-6-methoxycyclohexa-2,4-dien-1-yl)tricarbonyliron hexafluorophosphate **(103)** and [η^5-2-acetoxy-3-(trifluoromethyl)cyclohexadien-1-yl]tricarbonyliron hexafluorophosphate **(104).**

Compound	Scale (grams)	Equivalents of acid	Reaction conditions	R_f	% Yield
(103)	0.38	3.0 equiv. of TFA	(i) 1 hr, 0 ºC (ii) – 78 ºC	0.2[a]	90
(104)	0.21	2.6 equiv. of HPF_6 in acetic anhydride	(i) 3 hrs, 0 ºC	0.4[a]	48

[a] The solvent system used to monitor the reaction by TLC was cyclohexane: ethyl acetate, 1: 1.

2.1.7 *trans*-6-Methoxycyclohexa-2,4-diene-1-ol and *trans*-2-Acetoxy-3-(trifluoromethyl)cyclohexa-3,5-diene-1-ol Tricarbonyliron Complexes.

Formation of these compounds required the dissolution of the complexed carbocation salts **(103)** or **(104)**, in acetonitrile and subsequent addition to an aqueous solution of sodium hydrogen carbonate. The corresponding *trans*- products, **(105)** and **(106)**, shown in Chart 2.6 are formed. They result when hydroxide ion attacks the complexed carbocation *anti* to the methoxy or acetoxy substituent. The reaction conditions and yields are summarised in Table 2.6.



(105) **(106)**

Chart 2.6

Table 2.6 Reaction conditions and yields for the formation of (η^4-*trans*-6-methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron **(105)** and (η^4-*trans*-2-acetoxy-3-trifluoromethyl-cyclohexa-3,5-diene-1-ol)tricarbonyliron **(106)**.

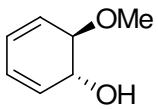
Compound	Scale (grams)	Equivalents of base ($NaHCO_3$)	Reaction conditions	R_f	% Yield
(105)	0.84	4.0	1 hr, 0 ºC	0.3[a]	51
(106)	0.12	4.0	1 hr, 0 ºC	0.2[a]	92

[a] The solvent system used to monitor the reaction by TLC was cyclohexane: ethyl acetate, 1: 1.

2.1.8 Decomplexation of the Tricarbonyliron Complexes.

The final step in the route to form *trans*-diols from their *cis* analogues involved a decomplexation reaction using mildly basic reaction conditions. The removal of the tricarbonyliron fragment leaves the diene compound as a free ligand, and this transformation requires completely anhydrous conditions.[85] This reaction was found to be

difficult to achieve and was only successful in this work for (*trans*-6-methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron **(105)** which was decomplexed to form η^4-*trans*-6-methoxycyclohexa-2,4-diene-1-ol **(107)**, shown in Chart 2.7. The reaction conditions and yield are summarised in Table 2.7.



(107)

Chart 2.7

Table 2.7 A summary of reaction conditions and yield for the formation of *trans*-6-methoxycyclohexa-2,4-diene-1-ol **(107)**.

Compound	Scale (grams)	Equivalents of Me_3NO	Solvent	Reaction conditions	R_f	% Yield
(107)	0.16	12	CH_3CN	5 hrs, room temp., 7 hrs reflux	0.5[a]	79

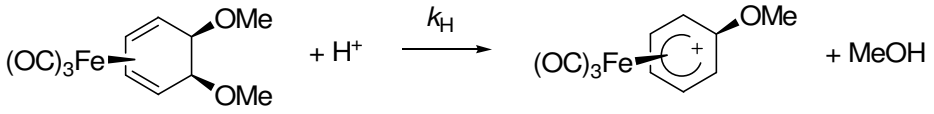
[a] The solvent system used to monitor the reaction by TLC was cyclohexane: ethyl acetate, 1: 1.

2.2 Kinetic and Equilibrium Measurements on Organometallic Substrates

In this section of the chapter, measurements of rate constants for cation formation from (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** are described. Measurements which lead to the evaluation of pK_R for the (methoxycyclohexadienyl)tricarbonyliron cation **(103)** are also presented. In addition, a pH profile is constructed for the hydrolysis of the (methoxycyclohexadienyl)tricarbonyliron cation **(103)**.

2.2.1 Ionisation of (η^4-*cis*-5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron

Initial studies of the ionisation of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** to form the corresponding cyclohexadienyl complex **(103)**, as shown in Scheme 2.2, allowed a rate constant to be measured for this reaction. This was determined spectrophotometrically in aqueous perchloric acid solutions at 25 ºC, by measuring the change in UV absorption.



(97) **(103)**

Scheme 2.2

A solution of the dimethoxy complex **(97)** was prepared by dissolving it in acetonitrile to a concentration of 3.0 x 10^{-3} M. The cation **(103)** was generated by injecting 20 µl of this substrate solution into a cuvette containing 2 cm^3 of 4.0 M $HClO_4$. Repetitive scans collected at regular time intervals were used to follow the progress of the reaction of the iron complex in the acid and to determine the wavelength of choice for kinetic studies. This reaction exhibits a repetitive scan with a decrease in absorption occurring in the range 200 to 230 nm as shown in Figure 2.1.

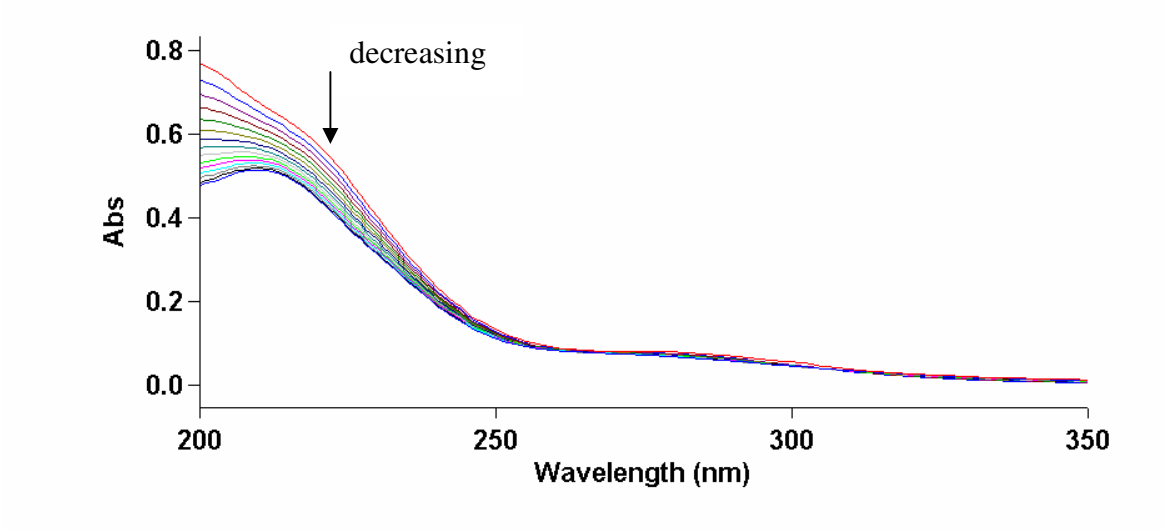


Figure 2.1 Repetitive scan for the ionisation of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron (97) in 4.0 M perchloric acid (cycle time 42 seconds) at 25 °C and a substrate concentration of 3.0 x 10^{-5} M.

The rate constant was determined by measuring the decrease in absorbance with time at 211 nm in a range of aqueous acid solutions. This wavelength was chosen because it was the wavelength at which the greatest change in absorbance was observed between the reactant and product in their UV spectra. The measured first and second rate constants (k_{obs} and k_2) are shown in Table 2.8. A representative kinetic plot obtained in 3.0 M $HClO_4$ at 211 nm is displayed in Figure 2.2.

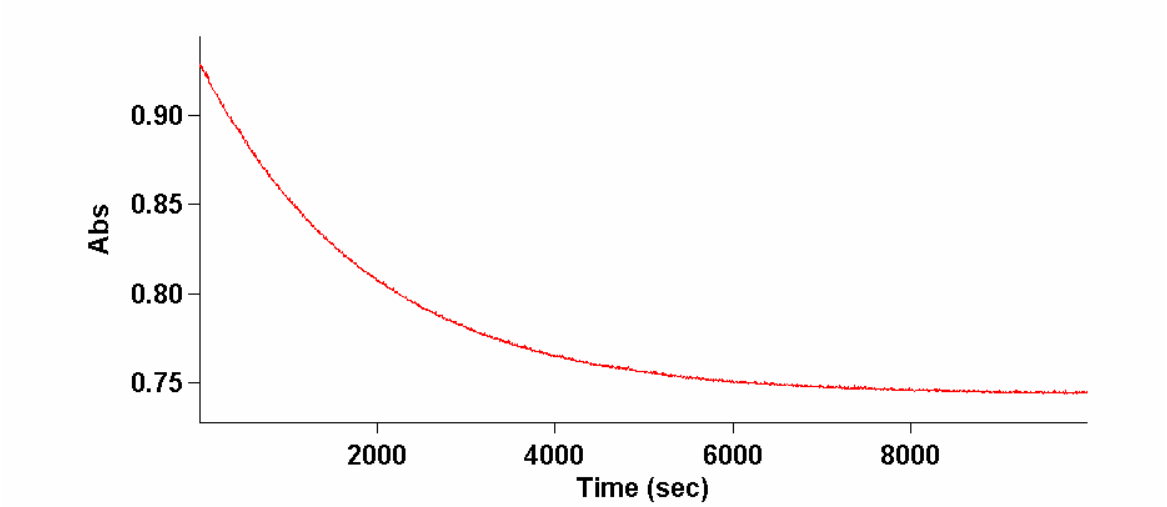


Figure 2.2 **Kinetic measurement at 211 nm for the ionisation of (η^4-*cis*-5,6-dimethoxy-cyclohexa-1,3-diene)tricarbonyliron (97) in 3.0 M perchloric acid at 25 °C and a substrate concentration of 3.0 x 10^{-5} M.**

Table 2.8 First and second order rate constants for the ionisation of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in aqueous acid solutions at 25 °C.[a]

$[HClO_4]$ (M)	$10^{-4}\ k_{obs}$ (s^{-1})	$10^{-4}\ k_{obs}/[H^+]$ ($M^{-1}s^{-1}$)	$\log(k_{obs}/[H^+])$	X_0
4.2	32.5	7.74	- 3.11	1.160
3.6	12.2	3.39	- 3.47	0.930
3.0	5.31	1.77	- 3.75	0.750
2.4	2.30	95.8	- 4.02	0.560
1.8	0.702	38.9	- 4.41	0.430
1.2	0.303	25.0	- 4.60	0.310
0.9	0.201	22.2	- 4.65	0.250

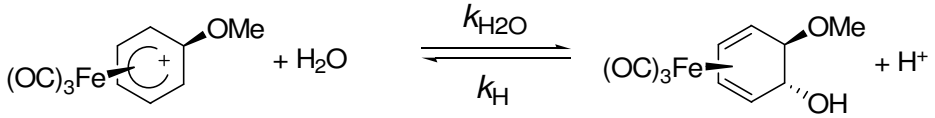
[a] Measurements were carried out at 211 nm and a substrate concentration of 3.0 x 10^{-5} M.

In the strongly acidic solutions used for the kinetic measurements, we are no longer dealing with ideal aqueous solutions.[96] Since the ionisation reactions were carried

out in concentrated perchloric acid solutions, values of $k_{obs}/[H^+]$ were not constant but increased with acid concentration. It was therefore necessary to extrapolate the measured rate constants to dilute acid solution. This was done using the acidity parameter, X_0 which was discussed on page 40.[112,113] Values of $\log(k_{obs}/[H^+])$ were plotted against X_0 to obtain a linear correlation as shown in Figure 3.1 (page 79). By extrapolating to $X_0 = 0$, the log of the second order rate constant in dilute acid solutions was found to be $\log k_2 = -5.097$ which corresponds to $k_2 = 8.0 \times 10^{-6}\ M^{-1}\ s^{-1}$.

To ensure that the carbocation of interest in this UV study had been formed, ^1H NMR spectra of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in a 1:1 mixture of deuterated methanol and concentrated deuterium chloride (~12 M DCl) were obtained. In the acidic solution, a rapid reaction to yield the (6-methoxycyclohexadienyl)tricarbonyliron carbocation **(103)** occurred. The NMR spectra of the reactant and the product are compared in Section 2.2.4, page 70.

2.2.2 pK_R for (η^4-*trans*-5-Hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron



(103) **(105)**

Scheme 2.3

Evaluation of the equilibrium constant, K_R, for the hydrolysis reaction of the coordinated cation **(103)** to (η^4-t*rans*-5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron **(105)** shown in Scheme 2.3 was undertaken. The equilibrium constant can be defined by Equation 2.1 on the following page.

$$K_R = [ROH][H^+]/[R^+] \qquad (2.1)$$

The equilibrium constant, K_R, may also be expressed in terms of the rate constants for the reaction of the carbocation **(103)** with water to form the *trans*-complex **(105)** and the reverse reaction of this complex with acid to reform the methoxycyclohexadienyl tricarbonyliron cation **(103)** as shown in Equation 2.2. In contrast, to the reaction of the *cis*-dimethoxy complex **(97)** described in Section 2.2.1, equilibrium between the cation **(103)** and the *trans*-hydroxyl-methoxy complex **(105)** is rapidly established.

$$K_R = k_{H2O} / k_H \qquad (2.2)$$

2.2.2.1 Hydrolysis of (6-Methoxycyclohexadienyl)tricarbonyliron

When the (6-methoxycyclohexadienyl)tricarbonyliron cation **(103)** was reacted with water in weakly basic buffer solutions a change in the UV spectrum was observed which could be used to monitor the reaction. UV-Vis spectra for the (6-methoxycyclohexadienyl)tricarbonyliron cation **(103)** in buffer solutions and in water are shown in Figure 2.3.

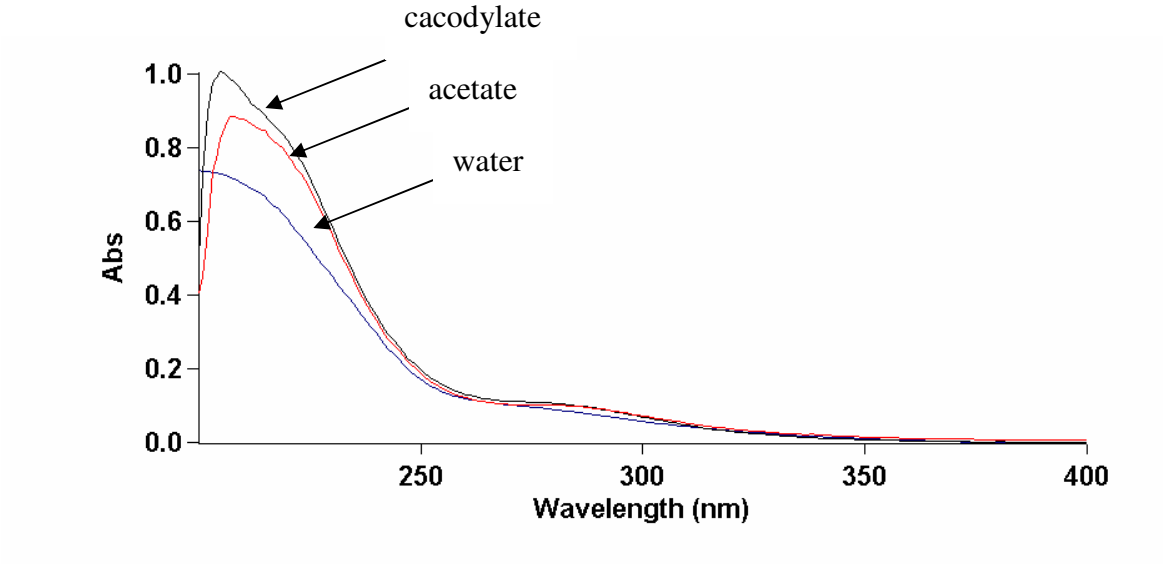


Figure 2.3 Overlay of UV spectra for 6-methoxy-cyclohexadien-1-yl tricarbonyliron cation (103) in buffer solutions at 25 °C and a substrate concentration of 1.8 x 10^{-4} M. The black, red and blue traces represent the cation in cacodylate buffer (pH 5.8), acetate buffer (pH 5) and water respectively.

As the reaction was too fast to measure by injecting the substrate solution into a UV cuvette, its rate was determined using a spectrophotometer with a rapid mixing accessory. A solution of the cation was prepared by dissolving the neutral dimethoxy compound **(97)** in 0.5 cm^3 of acetonitrile and adding to 1.5 cm^3 of 6.0 M $HClO_4$ to give a substrate concentration of 2.8 x 10^{-2} M. After formation of the cation was complete, this solution was diluted with water to an overall substrate concentration of 1.8 x 10^{-4} M and an acid concentration of 0.03 M. One syringe of the fast mixing accessory was filled with this cation solution. The second syringe contained a buffer solution with an excess of buffer base to neutralise the acid present with the cation. After mixing, an increase in absorbance at 230 nm was monitored. An example of a kinetic measurement recorded in 0.04 M sodium cacodylate at 230 nm and 25 °C is shown in Figure 2.4. The measured rate constants at varying buffer concentrations are given in Table 2.9.

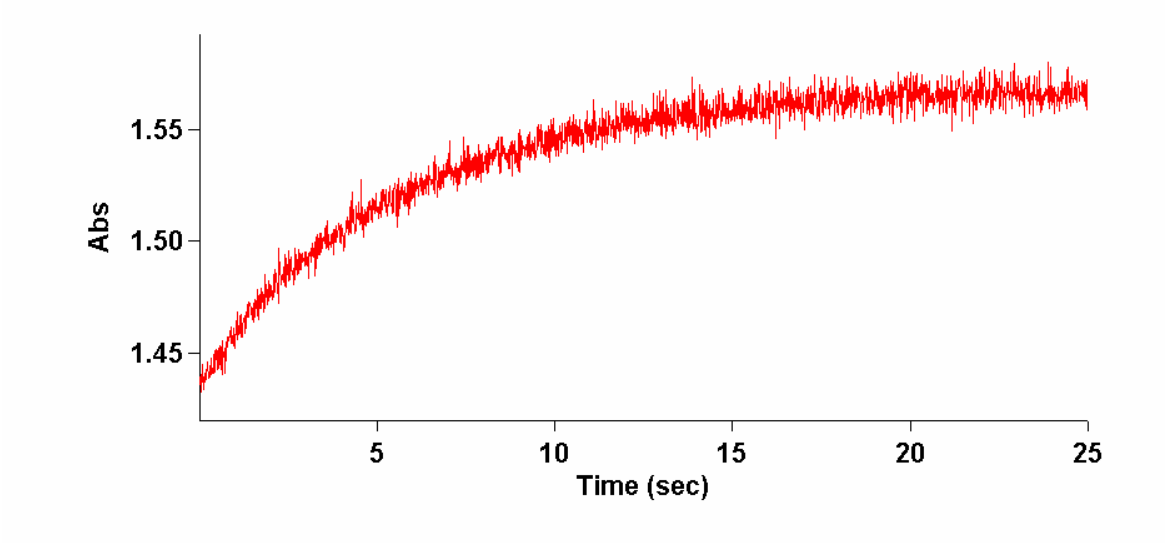


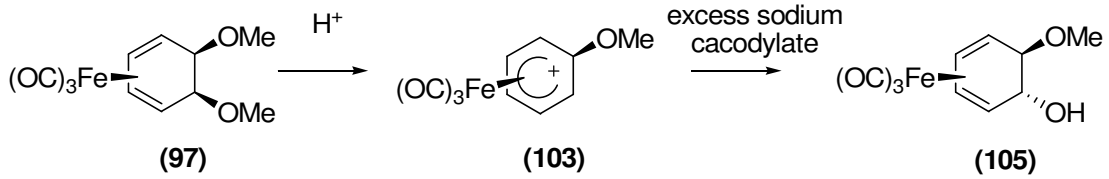
Figure 2.4 **Kinetic measurement at 230 nm using a fast mixing apparatus for the hydrolysis of (6-methoxycyclohexadienyl)tricarbonyliron cation (103) in aqueous cacodylate buffer (pH 5.32) at 25 °C and a substrate concentration of 1.8 x 10^{-4} M.**

Table 2.9 First order rate constants for the hydrolysis of (6-methoxycyclohexadienyl)tricarbonyliron **(103)** in aqueous buffer solutions at 25ºC.[a]

[Buffer in syringe] (M)	[buffer base]/[buffer acid]	R[b]	pH	k_{obs} (s^{-1})
0.06 [c]	[0.015]/[0.015]	1	5.80	0.20
0.04 [c]	[0.005]/[0.015]	0.33	5.32	0.20
0.06 [d]	[0.015]/[0.015]	1	4.30	0.21
0.04 [d]	[0.005]/[0.015]	0.33	3.82	0.21

[a] All measurements were carried out at 230 nm and a substrate concentration of 1.8 x 10^{-4} M. [b] R = [buffer base]/[buffer acid], [c] cacodylate buffer, [d] acetate buffer.

2.2.2.2 Rate Constant for Ionisation of (trans-5-Hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron



(97) **(103)** **(105)**

Scheme 2.4

The reverse of the hydrolysis reaction of **(103)** was also studied and rate constants were measured. Representative UV spectra of a solution of the *trans*-5-hydroxy-6-methoxy complex **(105)** and of the coordinated cation **(103)** formed when the solution of this substrate is acidified using 0.018 M $HClO_4$ are shown in Figure 2.5.

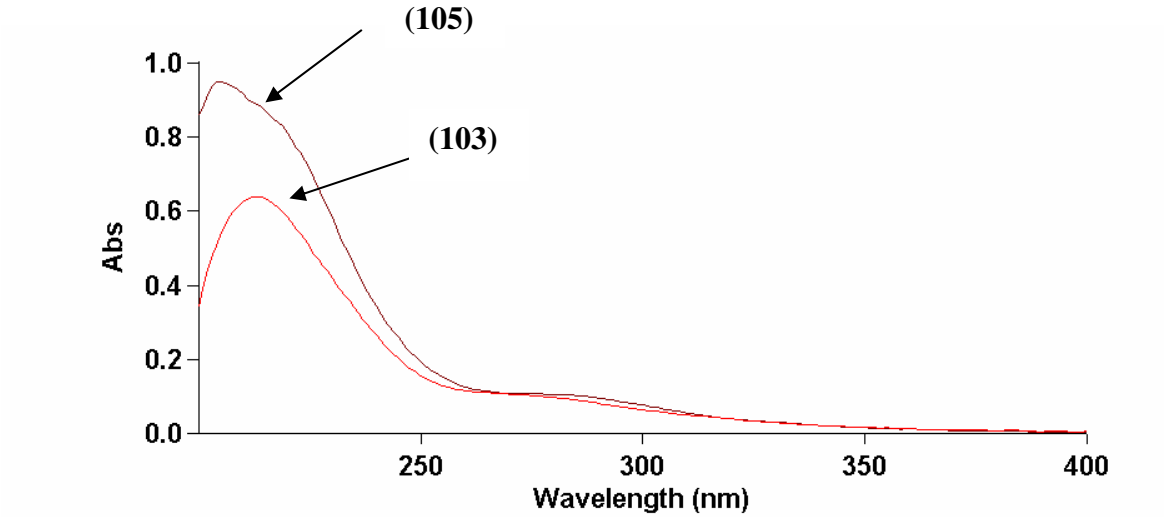


Figure 2.5 UV spectra for the *trans*-5-hydroxy-6-methoxy complex (105, dark red trace) generated as shown in Scheme 2.4 and for the (6-methoxycyclohexadienyl)tricarbonyliron cation (103, bright red trace) formed when this solution is acidified using 0.018 M $HClO_4$. The spectra were recorded at 25 °C and a final substrate concentration of 9.0 x 10^{-5} M.

The reactant, (*trans*-5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron **(105)**, was formed in two stages as shown in Scheme 2.4. (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** was dissolved in acetonitrile and ionised in 6.0 M $HClO_4$ to form (6-methoxycyclohexadienyl)tricarbonyliron cation **(103)** as described on page 60. This cation solution was then diluted with water to an acid concentration of 0.03 M, and mixed with an equal volume of 0.04 M sodium cacodylate to hydrolyse the cation to form (5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron **(105)** at a concentration of 9.0 x 10^{-5} M. After mixing, the solution contained 0.015 M $HClO_4$ and 0.02 M sodium cacodylate and therefore, the resulting solution of buffer was composed of 0.005 M sodium cacodylate and 0.015 M cacodylic acid. This solution was then mixed with a range of acid solutions to determine the rate constant for the ionisation of the hydrated cation **(105)** to reform the corresponding cation **(103)**. A kinetic trace from mixing a solution in cacodylate buffer with 0.018 M $HClO_4$ to give a final acid concentration of 6.5 x 10^{-3} M is presented in Figure 2.6. The observed rate constants for the ionisation are presented in Table 2.10.

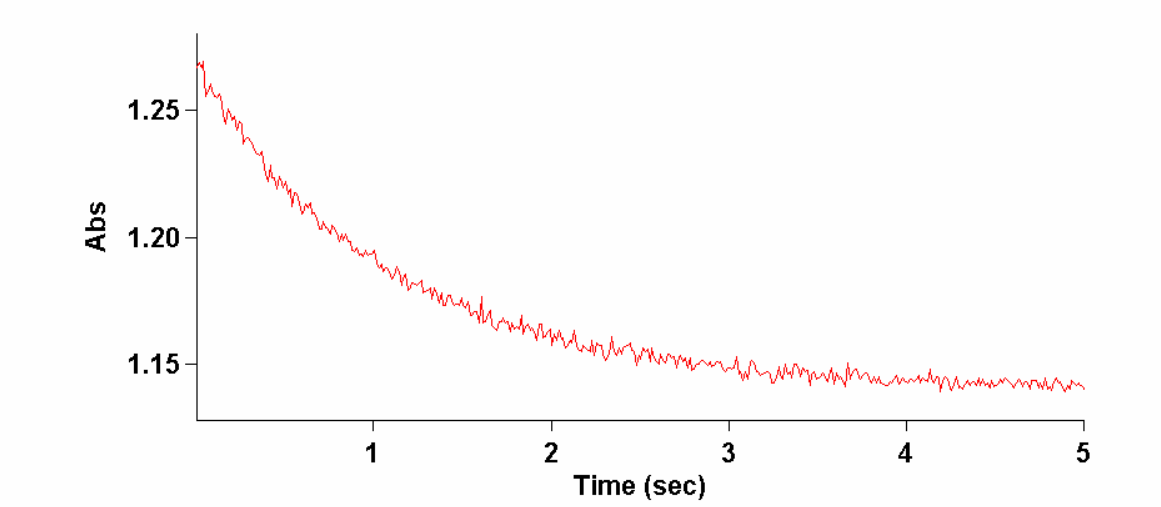


Figure 2.6 Kinetic measurements at 230 nm for the ionisation of (5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron (105) at an acid concentration of 6.5 x 10^{-3} M $HClO_4$ at 25 ºC and a substrate concentration of 9.0 x 10^{-5} M.

Table 2.10 First order rate constants for the ionisation of (*trans*-5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron **(105)** in perchloric acid solutions at 25 ºC.[a]

10^2 $[H^+]$ (M)	pH	k_{obs} (s^{-1})	$k_{obs}/[H^+]$ (M^{-1} s^{-1})	Log($k_{obs}/[H^+]$)
0.35	2.46	0.56	160.0	2.20
0.65	2.19	0.92	141.5	2.15
0.95	2.02	1.26	132.6	2.12
1.25	1.90	1.54	123.2	2.09
1.55	1.81	2.11	136.1	2.13
4.20	1.73	2.32	55.2	1.74
5.40	1.61	3.38	62.6	1.80
6.00	1.56	3.57	59.5	1.77

[a] All measurements were carried out at 230 nm using a fast mixing apparatus and at a substrate concentration of 9.0 x 10^{-5} M. The concentrations of acids shown in the table are those obtained after mixing the substrate solution with perchloric acid solutions varying in concentration from 0.012 M $HClO_4$ to 0.06 M $HClO_4$. They are corrected for the presence of 0.005 M sodium cacodylate in the substrate solution.

The first order rate constants measured are shown plotted against acid concentration in Figure 2.7. These rate constants correspond to the sum of rate constants for forward and reverse reactions for the hydrolysis reaction as shown in Equation 2.3 and Scheme 2.3 (page 59). In principle, the two rate constants may be obtained from the slope and the intercept of the straight line plot in Figure 2.7 as summarised in Equation 2.4 based on Equation 2.3.

$$k_{obs} = k_H[H^+] + k_{H2O} \qquad (2.3)$$

$$k_{obs} = 129.4 \pm 4.7\ M^{-1}s^{-1}\ [H^+] + 0.066 \pm 0.08\ s^{-1} \qquad (2.4)$$

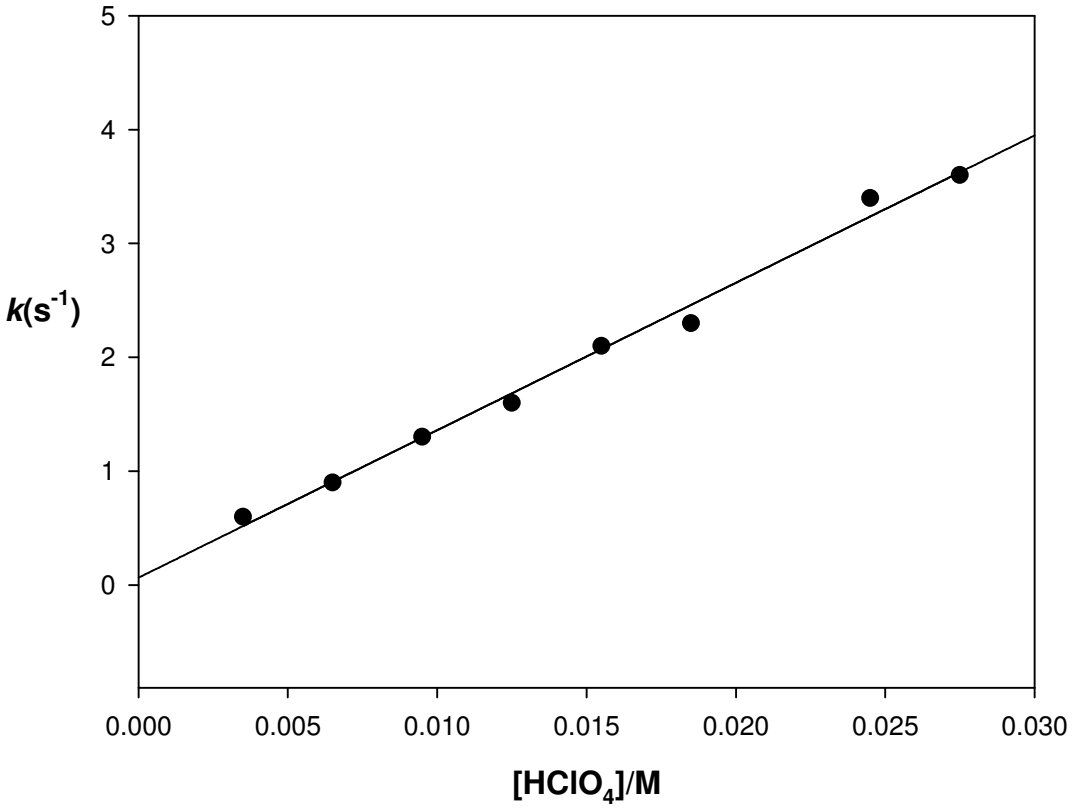


Figure 2.7 Plot of first order rate constant against acid concentration for the ionisation of (5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron (105) in perchloric acid solutions at 25 °C.

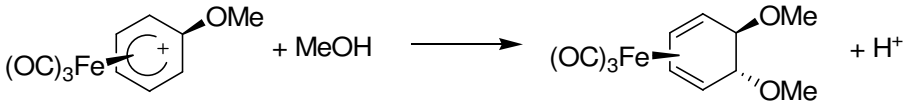
However, in practice the intercept from the plot in Figure 2.7 is too small to determine precisely and a more accurate value of the rate constant, $k_{H2O,}$ was taken from the direct measurement of the reaction of the methoxy cation in more basic buffer solutions. This gave a value of 0.205 ± 0.006 s^{-1} from Table 2.9, page 62. Combination of this rate constant with k_H, from Equation 2.4 gives the equilibrium constant K_R as k_{H2O} / k_H. Thus, K_R = 0.205 s^{-1} / 129.4 M^{-1} s^{-1} = 1.58 x 10 $^{-3}$ M^{-1}. This corresponds to a value of pK_R = -logK_R = 2.80.

2.2.2.3 pH Profile

The rate constants for the hydrolysis of the (6-methoxycyclohexadienyl)tricarbonyliron cation **(103)** and the acid-catalysed reverse reaction can be combined to construct a pH profile for the reaction. These rate constants are shown plotted as log k_{obs} *versus* pH in Figure 3.2 (page 81). The structure of the pH profile reflects the change from forward to reverse reaction on changing the acidity of the reaction medium. In the pH range 0 to 3, the measured rate constants correspond to the ionisation of the coordinated methoxy-substituted arene hydrate **(105)** to the coordinated cation. At pH 3, there is an inflection point in the pH profile and the measured rate constants represent the sum of the forward and reverse rate constants for this reaction. Above pH 3, the dominant rate constant is that for the hydrolysis reaction of the coordinated cyclohexadienyl cation.

The kinetic expression for the reaction is given in Equation 2.3 and the line drawn through the points is based on this expression with values of k_{H2O} = 0.205 s^{-1} from Table 2.9 and k_H = 129.4 M^{-1} s^{-1} from Figure 3.2.

2.2.3 Methanolysis of (6-Methoxycyclohexadienyl)tricarbonyliron



(103) **(107)**

Scheme 2.5

An attempt was made to estimate an equilibrium constant pK_R, for the methanolysis reaction shown in Scheme 2.5 by taking spectrophotometric measurements in a range of perchloric acid solutions in methanol containing 5% water. The change in UV spectrum associated with the equilibrium was small but measurable. The (*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron complex **(97)** was dissolved in 0.5 cm^3 acetonitrile to give a 0.1 M solution. This solution was added to 1.5 cm^3 of 6.0 M $HClO_4$ and diluted to 3 cm^3 with water to form the (6-methoxycyclohexadienyl)tricarbonyliron

cation **(103)**. This substrate solution had an overall concentration of 1.8 x 10^{-2} M. For each measurement, 20 μl of this solution was injected into a cuvette containing acid in methanol of known concentration. This allowed the equilibrium between the carbocation complex **(103)** and the *trans*-dimethyl ether complex **(107)** to be studied. Table 2.11 lists absorbance measurements made at 210 nm at different acid concentrations.

Table 2.11 Absorbance measurements for methanolysis of (6-methoxycyclohexadienyl)tricarbonyliron cation **(103)** in 5% aqueous perchloric acid solutions at 25 °C.[a]

$[H^+]$ (M)	pH	Absorbance
0.062	1.21	0.62
0.093	1.03	0.59
0.123	0.91	0.57
0.176	0.75	0.56
0.234	0.63	0.56
0.410	0.39	0.48
0.580	0.23	0.45

[a] All measurements were carried out at 210 nm and a substrate concentration of 1.8 x 10^{-2} M in 95 vol % methanol-water mixtures.

A spectrophotometric titration curve in which absorbance is plotted against pH is shown in Figure 2.8. The best fit line to the data points was obtained using Equation 2.5 below, which also allowed the pK_R value to be estimated.

$$A = \{K_R A_B + A_{BH}^+[H^+]\} / \{K_R + [H^+]\} \quad (2.5)$$

In this equation, A is the measured absorbance at the acid concentration indicated and A_B and A_{BH+} are limiting absorbances for the the dimethoxy substrate **(107)** and its ionised form **(103)** respectively. Equation 2.5 is derived from rearrangement of the normal expression for spectrophotometric evaluation of K_R shown in Equation 2.6.

$$K_R = (A_{BH+} - A)\,[H^+] / (A - A_B) \qquad (2.6)$$

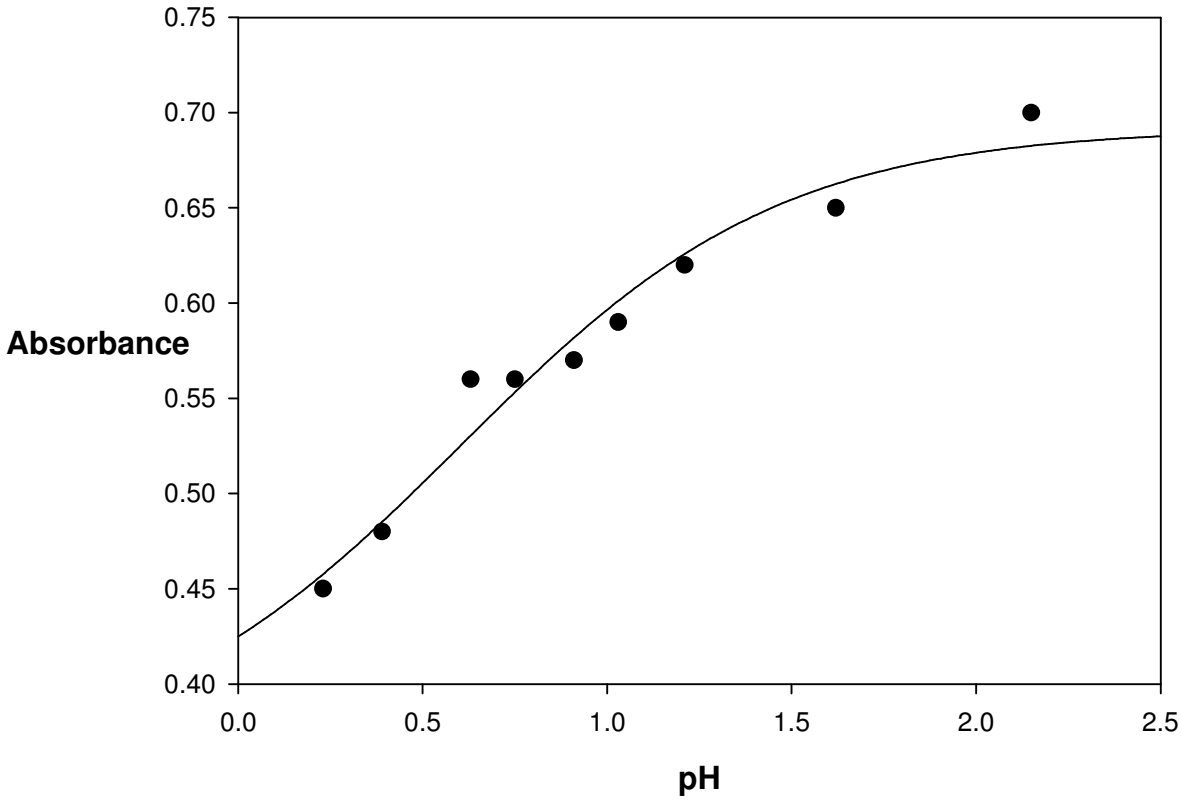


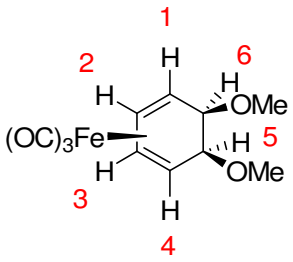
Figure 2.8 **Plot of absorbance against pH for the methanolysis of the cation (103) to form the *trans*-5,6-dimethoxycyclohexa-1,3-diene complex (107) in methanol at 25 °C.**

Based on the best fit of Equation 2.5 to Figure 2.8, values of $A_B = 0.4$ and $A_{BH+} = 0.7$, $pK_R = 0.56$ in methanol containing 5 % water were obtained. One surprising aspect of this result is that the difference from $pK_R = 2.80$ in water (see page 65) is only 2.14 log units. This is significantly less than the corresponding difference between the pK_R values for the tricarbonyliron cyclohexadienyl cation ($\Delta pK_R = 3.80$). Partly for this reason, the measurements were checked by NMR spectroscopy.

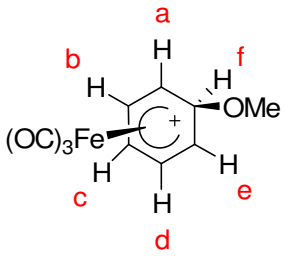
2.2.4 ^{1}H NMR Study on (6-Methoxycyclohexadienyl)tricarbonyliron

A study was undertaken on the formation of the 6-methoxycyclohexadienyl cation **(103)** from (*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** under acidic conditions using ^{1}H NMR spectroscopy. This was to ensure that the changes inferred from monitoring the UV-Vis spectra of the coordinated dimethoxy complex **(97)** in acid were supported by structural characterisation using NMR spectroscopy. A ^{1}H NMR spectrum of the neutral complex, (η^4-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)**, was recorded in deuterated methanol and is shown in Figure 2.9. A spectrum of the fully formed cation **(103)**, shown in Figure 2.10, was obtained by dissolving the complex in 50% deuterated methanol and 50% 12.5 M deuterium chloride (DCl). The acidic solution was deep yellow in colour compared with the pale yellow of the neutral solution.

A study was then performed to estimate the acid concentration at which the cation and dimethoxy complex were in equilibrium. This was initiated by adding 15 µl portions of DCl to the NMR sample tube that contained the neutral complex dissolved in deuterated methanol. The solution was shaken vigorously to ensure mixing and a spectrum was taken after each addition of DCl. As the volume of DCl added increased, as expected, an increase in the intensity of the signals representing the cation and a decrease in the intensity of the signals representing the neutral complex were observed. Using this method, the acid concentration required for the sample to contain equal concentration of each component was found to be approximately 1.5 M DCl. Figure 2.11 shows a ^{1}H NMR spectrum of the mixture at this acid concentration. The structures of complexes **(97)** and **(103)** and the numbering system used to identify the protons in each compound are shown in Chart 2.8. Table 2.12 summarises the spectroscopic data from the ^{1}H NMR spectra in Figures 2.9, 2.10 and 2.11. The entire spectra can be seen in Appendix A. It is noteworthy that changes in UV absorbance in Figure 2.8 indicate half ionisation of the dimethoxycyclohexadiene complex at approximately 0.3 M HCl which is in disagreement with the NMR measurements. This suggests that changes in absorbance may be an artifact or have a different explanation.



(97)



(103)

Chart 2.8

Table 2.12 ^{1}H NMR spectral data for (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in deuterated methanol, in deuterated methanol and 105 µl of DCl and in 50:50 deuterated methanol: DCl. [a]

Complex	δH / ppm[b]	Solvent Solution
(97)	3.09 (H-1, H-4), 3.27 (2 x OCH_3), 3.34 (H-5, H-6), 5.29 (H-2, H-3)	0.75 cm^3 of deuterated methanol
(103)	3.40 (OCH_3), 3.90 (H-f), 4.18 (H-a, H-e), 5.90 (H-b, H-d), 7.12 (H-c)	50% deuterated methanol and 50% 12.5 M DCl
(97)/(103)	3.1 (H-1, H-4), 3.26 (2 x OCH_3), 3.38 (H-5, H-6), 5.32 (H-2, H-3), 3.41 (OCH_3), 3.90 (H-f), 4.17 (H-a, H-e,) 5.94 (H-b, H-d), 7.14 (H-c)	Mixture of 0.75 cm^3 of deuterated methanol and 0.105 cm^3 of 12.5 M DCl (1.5 M [D^+] effectively)

[a] Spectra were recorded at an operating frequency of 400 MHz. [b] Numbering and lettering of H atoms refers to the structures shown in Chart 2.8.

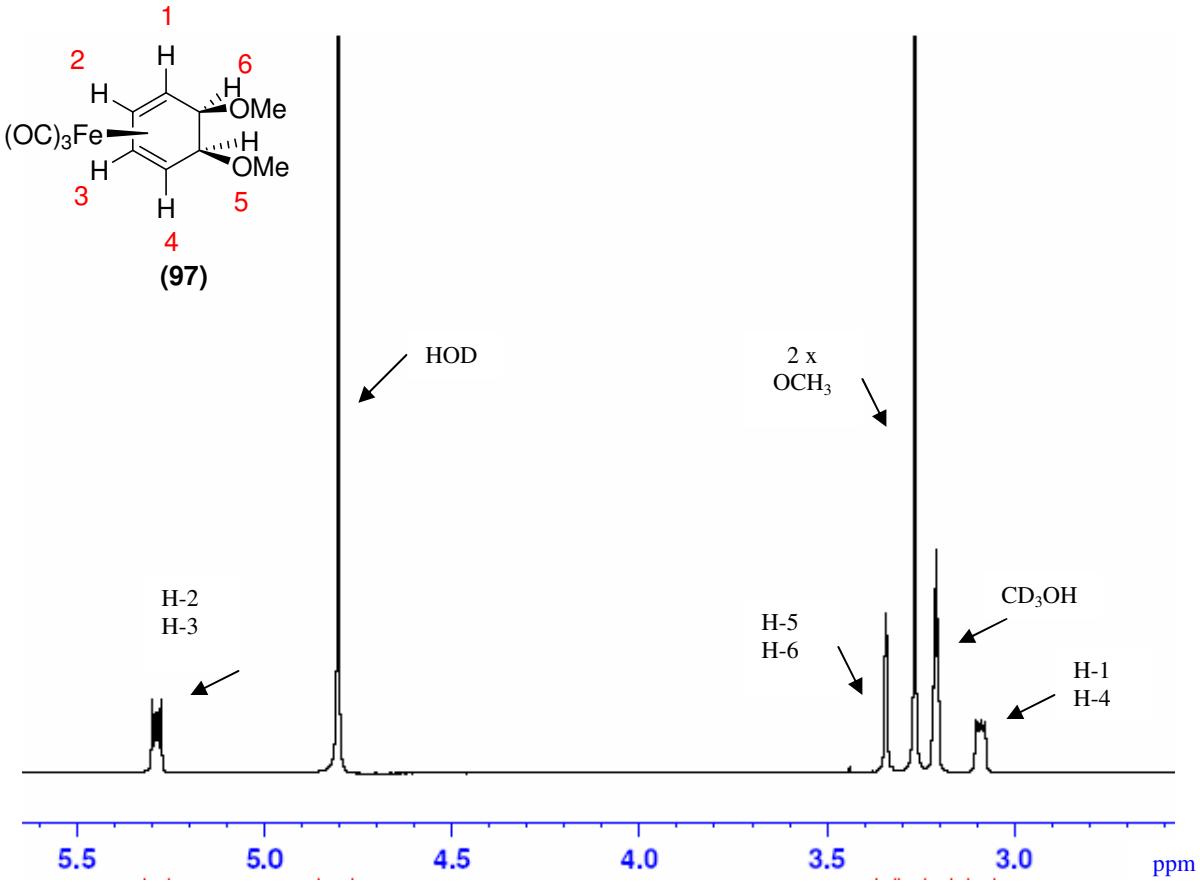


Figure 2.9 ^{1}H NMR spectrum of (η^{4}-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron (97) in deuterated methanol.

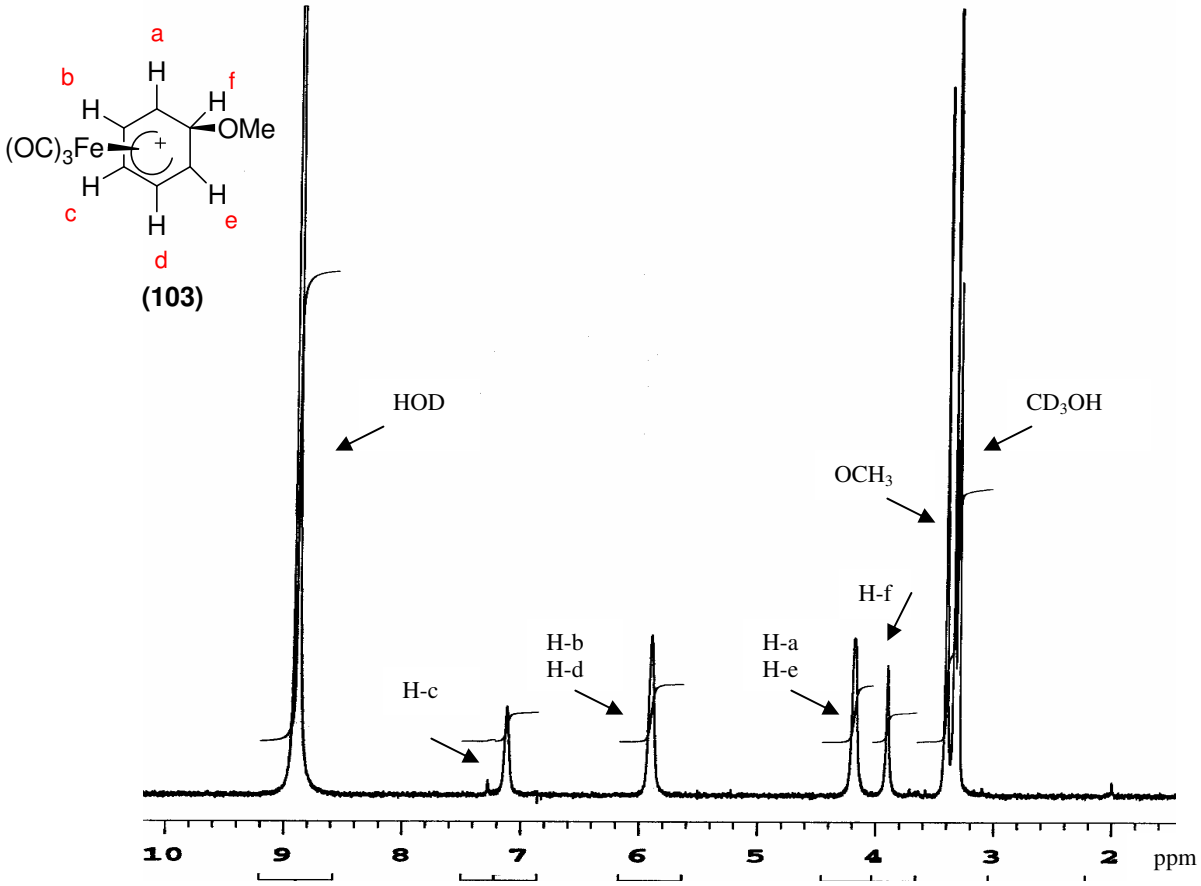


Figure 2.10 **^{1}H NMR spectrum of the (η^5-6-methoxycyclohexa-2,4-dien-1-yl)tricarbonyliron Hexafluorophosphate (103) in 50 % deuterated methanol and 50 % 12.5 M deuterium chloride.**

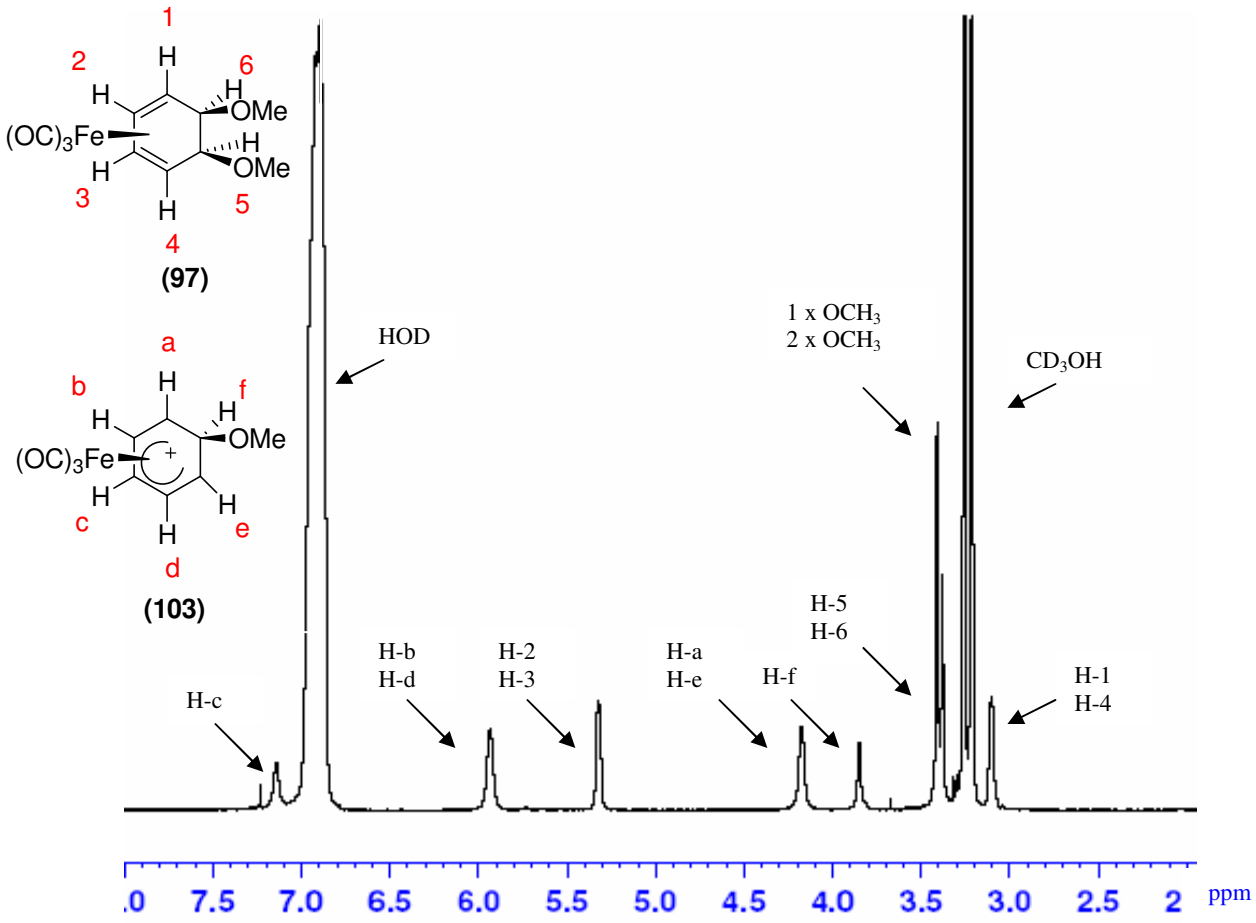


Figure 2.11 **^{1}H NMR spectrum of a mixture of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron (97) and the (η^5-6-methoxycyclohexa-2,4-dien-1-yl)tricarbonyliron Hexafluorophosphate (103) in deuterated methanol to which deuterium chloride has been added. (The effective acid concentration is 1.5 M DCl).**

CHAPTER 3

DISCUSSION

3 DISCUSSION

The principal aim of the work undertaken in this study was to develop a viable route for conversion of arene *cis*-dihydrodiols to their *trans*-isomers by means of their irontricarbonyl complexes. An initial part of this work was the study and optimisation of the coordination of tricarbonyliron to the *cis*-5,6-dimethoxycyclohexa-1,3-diene **(93)**. The method developed was then applied to some benzene *cis*-dihydrodiols of interest. Once the complexation to the tricarbonyliron had been successfully achieved, the conversion of *cis*-5,6-dimethoxycyclohexa-1,3-diene (**93**) and two benzene *cis*-dihydrodiols to their corresponding *trans*-isomers using the tricarbonyliron route proposed by Boyd and Sharma[11] (see Scheme 1.11, page 11) was attempted. The synthesis of the *trans* analogue of *cis*-5,6-dimethoxycyclohexa-1,3-diene (**93**) was successfully completed but only one of the two *cis*-dihydrodiols used was brought through all of the steps involved in the conversion and difficulties were encountered during the final decomplexation step.

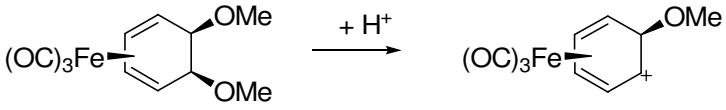
The reactivity of the tricarbonyliron complex of *cis*-5,6-dimethoxycyclohexa-1,3-diene synthesised was examined. The stability of the coordinated carbocation intermediate formed from the dimethoxy complex was examined and kinetic and equilibrium measurements were performed. These results could be compared with those reported for a number of uncoordinated benzene *cis*-dihydrodiols previously studied.[114]

3.1 Kinetic and Equilibrium Measurements on Organometallic Substrates

In this section, measurements of rate constants for cation formation from ((η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in water and methanol will be discussed. Also, a pH profile constructed for the hydrolysis of the (methoxycyclohexadienyl)tricarbonyliron cation **(103)** which led to the evaluation of pK_R, will be described.

3.1.1 Initial Studies

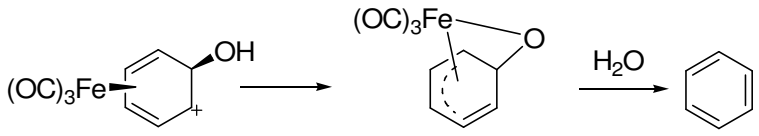
The methoxycyclohexadienyl cation **(103)** was produced by ionising (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** as shown in Scheme 3.1. The dimethoxy complex **(97)** had been previously prepared by Stephenson *et al.* [52,115] but rate constants for ionisation of this complex **(97)** to form the cation **(103)** had not been determined.



(97) **(103)**

Scheme 3.1

The dimethoxy complex **(97)** was used in preference to its parent dihydrodiol complex **(92)** for two reasons. The first is that it has been reported that, upon coordination of the tricarbonyliron moiety to the arene *cis*-dihydrodiol **(3)**, the complex formed is unstable to purification by flash chromatography.[54] Secondly, the α-hydroxy coordinated carbocation **(63)** has been reported to be unstable and, in methanol or moist acetone it can spontaneously form benzene.[116] The decomposition of **(63)** has been proposed to occur *via* the intermediate **(108)** as shown in Scheme 3.2.[116] Therefore, protection of the hydroxy group was required.[52,116]



(63) **(108)**

Scheme 3.2

It had been reported by Stephenson *et al.* that TFA was used to remove one of the methoxy substituents of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** to form the 6-*endo*-methoxy dienyl cation **(103)**.[52] This implies that addition of a strong acid would be required to generate the cation **(103)**. On examining **(97)** in aqueous

acid, this became apparent and, therefore, the dimethoxy compound was reacted in 4.5 M $HClO_4$. The formation of the cation was confirmed by the fact that the UV spectrum observed was similar to that of the coordinated cyclohexadienyl cation **(64)** previously studied.[108] The formation of the 6-methoxy dienyl cation **(103)** was also later confirmed by ^1H NMR spectroscopy (Table 2.12, page 71 and Section 4.3.5.3, page 121).

The ionisation of **(97)** was accompanied by a small absorbance change at 211 nm which could be used for kinetic measurements. Since the reaction was very slow the measurements were carried out in concentrated perchloric acid solutions and values for the second order rate contants were extrapolated to water using the *X*-acidity function, X_0.[112] Figure 3.1 shows a plot of the logarithms of second order rate constants against X_0 for acid concentrations in the range from 0.9 to 4.2 M. Extrapolation to $X_0 = 0$ yields a rate constant in aqueous solution of 8.0×10^{-6} $M^{-1}s^{-1}$.

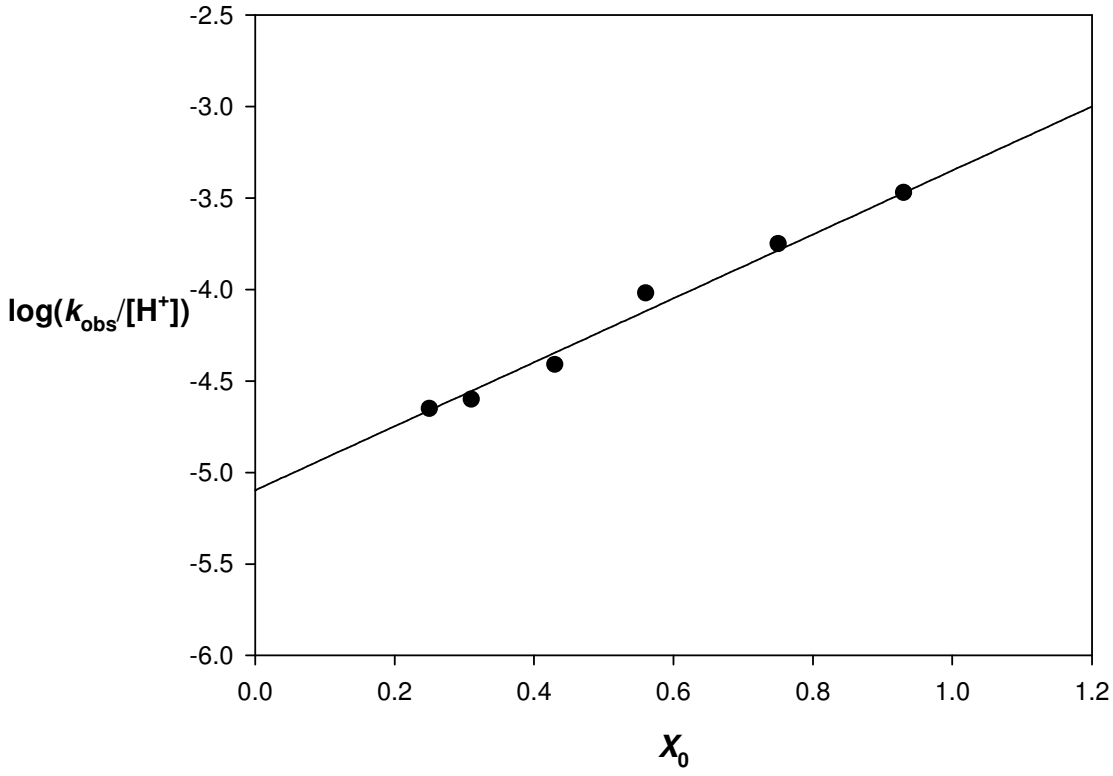
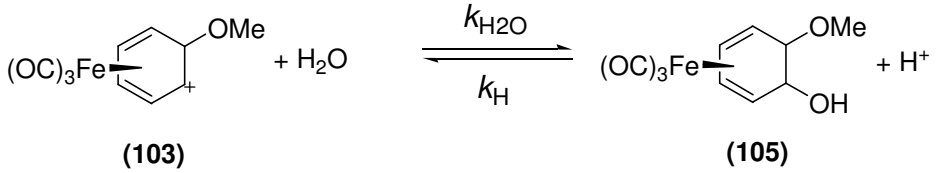


Figure 3.1 Plot of the logarithms of second order rate constants against X_0 for the ionisation of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron (97) in perchloric acid solutions at 25 °C.

3.1.2 Kinetic Determination of pK_R in Aqueous Solutions

To investigate the reaction of the 6-methoxycyclohexadienyl cation **(103)** with water, a solution of (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in acetonitrile was added to 4.5 M $HClO_4$ and allowed to react for 10 minutes until complete conversion to the cation had occurred. It was then necessary to dilute this solution to a lower acid concentration to facilitate quenching to a sufficiently high pH for attack by water to occur. After dilution by a factor of 150, the resulting solution was reacted with sodium acetate (pH 5.32) and sodium cacodylate (pH 5.8) buffers using a rapid mixing apparatus, as a means of making kinetic measurements. These measurements showed that the rate of reaction was independent of the buffer

concentration above pH 3.5. It was concluded that the reaction with water to give a hydroxymethoxy cyclohexadiene complex as shown in Scheme 3.3 had occured and that the measured rate constant was k_{H2O}.



(103) **(105)**

Scheme 3.3

The reverse reaction from the 5-hydroxy-6-methoxy complex **(105)** to the cation **(103)** was then studied by generating **(105)** from the cation and subsequently reacting it in acidic solutions. Again, the cation was prepared by adding a solution of the 5,6-dimethoxy tricarbonyliron complex **(97)** to strong acid diluting this solution and then quenching it with buffer base to a higher pH to form the complex **(105)** (see Scheme 2.4, page 63). The ionisation of the hydroxy coordinated complex **(105)** to the cation could again be monitored by UV (at 230 nm) and was found to be a rapid reaction in comparison to ionisation of the *cis*-dimethoxy complex **(97)** which occured at a much slower rate. In fact, it was again necessary to use the fast mixing apparatus to monitor the reaction. The reaction was found to be acid catalysed and a rate constant, k_H = 129.4 $M^{-1}s^{-1}$, was measured. This compares with k_H = 8.0 x 10^{-6} $M^{-1}s^{-1}$ for the *cis*-dimethoxy compound **(97)**, a difference of more than 10^7 fold.

A pH profile for the ionisation of the hydroxy-methoxy tricarbonyliron complex **(105)** and the reverse hydrolysis of the cation **(103)** is shown in Figure 3.2. The results on which it is based are presented in Section 2.2.2 (page 59). The completion of a pH profile allowed representation of the changes from forward to reverse reaction as the acidity of the reaction medium was varied.[117] As indicated, rate constants above pH 3 were measured by quenching the cation in acetate and cacodylate buffers. Rate constants below pH 3 were measured for the reverse process by quenching substrate that had been hydrolysed in dilute cacodylate buffers into excess acid. The line through the points is based on a best fit to the expression $k_{obs} = k_{H2O} + k_H[H^+]$. The values of k_{H2O} and k_H may

be combined to give an equilibrium constant for the process, K_R = [**(105)**][H^+]/[**(103)**] = k_{H2O}/k_H = 0.205 s^{-1} / 129.4 $M^{-1}s^{-1}$ = 1.58 x 10^{-3} M^{-1}, and this corresponds to pK_R = 2.80.

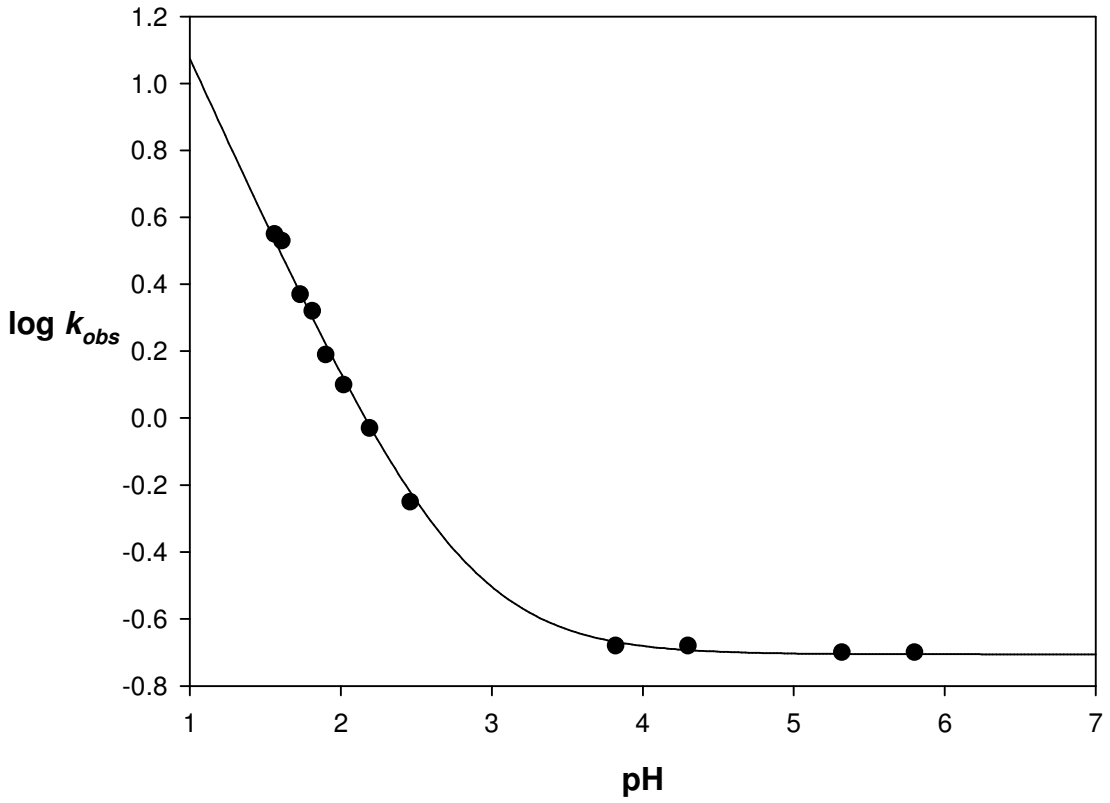


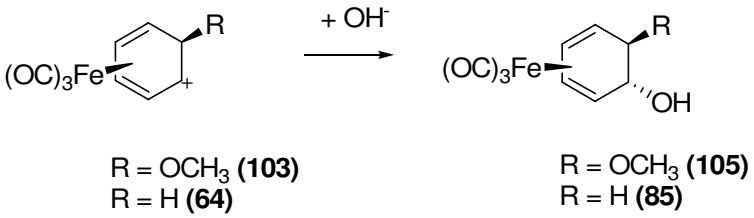
Figure 3.2 pH profile (log k_{obs} *versus* pH) for the hydrolysis of the methoxy-substituted cyclohexadienyl tricarbonyliron cation (103) to the coordinated substituted hydrate (105).

This analysis does not explain the very large difference in rate constants for the acid catalysed ionisation of the hydroxy-methoxy complex **(105)** and the dimethoxy complex **(97)**. The ratio of their rate constants is 129.4 / 8.0 x 10^{-6} = 1.6 x 10^7. This difference cannot be due to a difference in reactivity of hydroxy and methoxy leaving groups because they normally differ in reactivity by less than a factor of 2.[118] However, a reasonable conclusion is that it arises from the difference in stereochemistry of the leaving groups. The methoxy groups in the *cis*-dimethoxy cyclohexadiene complex are known to have an *endo* configuration and it is also known that quenching the cation

(103) should yield a *trans*-hydroxy-methoxy hydrolysis product with an *exo*-configuration for the hydroxyl groups. Evidence that the addition of a hydroxyl group occurs on the face opposite the tricarbonyliron fragment to form the *exo*-product as shown in Scheme 3.4 (R = OCH_3) has been previously reported in the literature.[46,119]

The relative reactivities of the coordinated *endo* and *exo* isomers showed a similar trend similar for both the coordinated hydroxyl-methoxy and coordinated hydroxyl cyclohexadiene complexes. In analogy with the 10^7 fold difference in reactivity between the *endo* **(97)** and *exo* **(105)** isomers of the dimethoxy and hydroxy methoxycyclohexadiene, the *endo*-hydroxycyclohexadiene was found to be 10^6 times less reactive than its *exo*-isomer.[108] This is because, in the acid catalysed reaction, the *trans* hydroxy or methoxy group reacts readily but the same groups in the *endo* configuration are much less reactive.

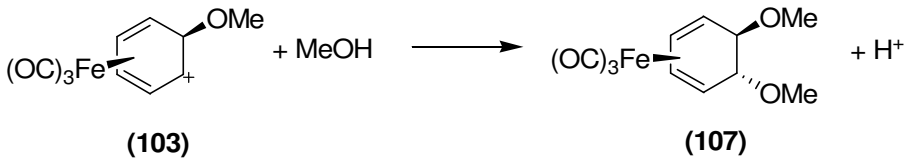
Evidence for the rapid formation of the *exo*-isomer is also obtained from spectroscopic data.[46] NMR spectroscopy can be used to identify stereochemistry by comparing coupling constants and chemical shifts. Birch *et al*. have shown that the *exo*-isomer forms on addition of a hydroxide anion to the cyclohexadienyl coordinated complex **(64)** as shown in Scheme 3.4 (R = H).[46] This observation was supported by Atton and Kane-Maguire who isolated only the *exo* isomer from nucleophilic attack by hydroxide on the same cyclohexadienyl complex **(64)**.[119] The ^{1}H NMR spectrum recorded when the methoxy substituted cation **(103)** was reacted in aqueous sodium hydrogen carbonate in the synthetic step described in 4.3.5.4 (page 122) shows a signal at 3.97 ppm for the proton adjacent to the *exo* hydroxyl group (H-1). This signal is shifted further downfield by almost 0.5 ppm from the signal for the proton adjacent to the *endo* methoxy group which occurs at 3.39 ppm (H-6). This difference in chemical shift is slightly greater than that which would be predicted from the difference between the effects of an adjacent hydroxyl compared to a methoxy group. This indicates that the chemical shifts of these protons also differ due to the face of the tricarbonyliron-complexed cyclohexadiene ring they are attached to.



Scheme 3.4

3.1.3 Attempted Measurement of pK_R in Methanol

The reaction of (η^5-6-methoxycyclohexadienyl)tricarbonyliron **(103)** in methanol was also monitored. It was hoped that this would allow the equilibrium constant, pK_R, for the interconversion, shown in Scheme 3.5, between the methoxy substituted cation **(103)** and its *trans*-dimethoxy substituted analogue **(107)** to be determined.



Scheme 3.5

Analysis of spectrophotometric measurements for the 6-methoxycyclohexadienyl complex **(103)** in methanolic solutions containing 5% aqueous perchloric acid provided a pK_R value of 0.56. This pK_R was estimated from a spectrophotometric titration curve in which the absorbance is plotted against pH as shown in Figure 2.8 (page 69). This can be compared with the pK_R value for the reaction in water which was 2.80. The difference in pK_R between water and methanol is ΔpK_R = 2.24. This difference may be compared with the difference in the pK_R values for the reaction of the cyclohexadienyl tricarbonyliron **(64)** in water and in methanol, ΔpK_R = 3.80, which is considerably larger (refer to Section 3.2.1, page 86). This implies that the pK_R value obtained for the methanolysis reaction is smaller than expected and, for this reason, NMR studies were undertaken to check the accuracy of this measurement.

3.1.4 ^{1}H NMR Spectroscopic Studies

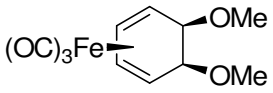
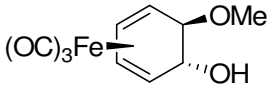
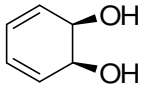
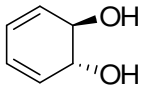
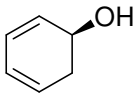
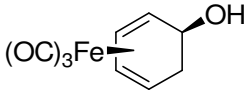
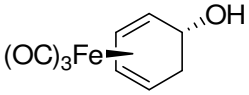
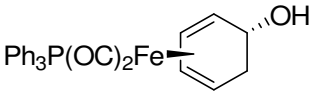
A ^{1}H NMR study was performed on (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** in deuterated methanol in the absence and presence of DCl in D_2O. This allowed two pieces of information to be determined. Firstly, it could be confirmed that the cation was formed when the neutral complex was dissolved in concentrated acid. UV spectra provide no structural information about the compounds that are being examined but the NMR spectra confirmed that ionisation of the dimethoxy complex **(97)** did give the 6-methoxycyclohexadienyl complex **(103)**.

Secondly, it was possible to determine the concentration of the acid required to reach equilibrium between the cation **(103)** and the *trans*-dimethoxy complex **(107)**. This was found to be 1.5 M D^+, which was when the concentration of the dimethoxy complex and cation were equal (at which concentration $[H^+] = K_R$). This is considerably higher than $[H^+]$ = 0.27 M which was indicated by the UV spectrophotometric measurement discussed in the previous section and suggests that those measurements may not have given a reliable value of K_R. Also, the value of K_R implied from the NMR measurements is more consistent with that expected from the difference in pK_R values in water and methanol found for the cyclohexadienyl cation complex.[108]

3.2 Comparisons of Kinetic and Equilibrium Data

Extensive studies of uncomplexed and complexed hydroxycyclohexadienyl compounds provide a reference data set with which reactivities of the methoxy cation **(103)** can be compared. Such a comparison allows the effect of coordination to the tricarbonyliron moiety on the reactivity of the cyclohexadienyl ring to be explored. It also allows us to determine the effect of the methoxy substituent, which is important for understanding the influence that this substituent has on the reactivity and stability of the corresponding cation. Table 3.1 lists the acid catalysed rate constants, k_H, for formation of the carbocations from their corresponding benzene hydrates or dihydrodiols as well as k_{H2O} for the reverse attack of water on the cations. It also shows the equilibrium constants pK_R for hydrolysis of the cations (where $K_R = k_{H2O} / k_H$).

Table 3.1 Rate constants and pK_R values for coordinated and uncoordinated hydroxyl and methoxy substituted cyclohexadienes cations.

Diene Complex	k_H ($M^{-1}s^{-1}$)	k_{H2O} (s^{-1})	pK_R
 **(97)**	8.0×10^{-6}	-	-
 **(105)**	129.4	0.205	2.8
 **(3)**	0.11[a]	-	-
 **(4)**	5.0×10^{-6} [a]	-	-
 **(2)**	180 [b]	2.3×10^{4}	-2.4
 **(63)**	2.0×10^{-3} [c]	4.0×10^{-8}	4.5
 **(85)**	8.3×10^{3} [d]	0.177	4.7
 **(87)**	3.6×10^{3} [d]	4.53×10^{-7}	9.9

[a] A. McCormack *et al.*[107], [b] A. J. Birch *et al.*[46], [c] S. Pelet *et al.*[109], [d] M. Galvin.[108]

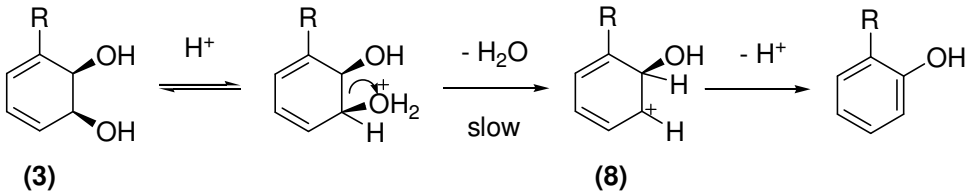
3.2.1 Equilibrium Constants

The equilibrium constant, pK_R, for formation of the hydroxy-methoxy substituted coordinated complex **(105)** from the corresponding cation **(103)** determined in the present work was 2.8. This can be compared to the previously determined pK_R values for the coordinated benzene hydrate **(63)**[108], its triphenylphosphine substituted analogue **(87)** and the uncoordinated benzene hydrate **(2)**[107] which were 4.7, 9.9 and -2.4 respectively. The difference in pK_R values (ΔpK_R) between the tricarbonyliron coordinated **(63)** and the uncoordinated benzene hydrate **(2)** is 7.1. The positive value for this difference shows that coordination of the tricarbonyliron group has a stabilising effect on the coordinated cation when it is compared to the uncoordinated cyclohexadienyl moiety. When the coordinated hydroxy-methoxy substituted complex **(105)** is compared to the coordinated benzene hydrate **(63),** the difference in stability (ΔpK_R = 1.7) indicates that the β-methoxy group has a destabilising effect on the complex. It is also interesting to note that the dicarbonyltriphenylphosphineiron coordinated cation is more stable than complexes **(103)** and **(63).** This is to be expected as the triphenylphosphine ligand is electron donating and stabilises the formal carbocation centre on the cyclohexadienyl cation.

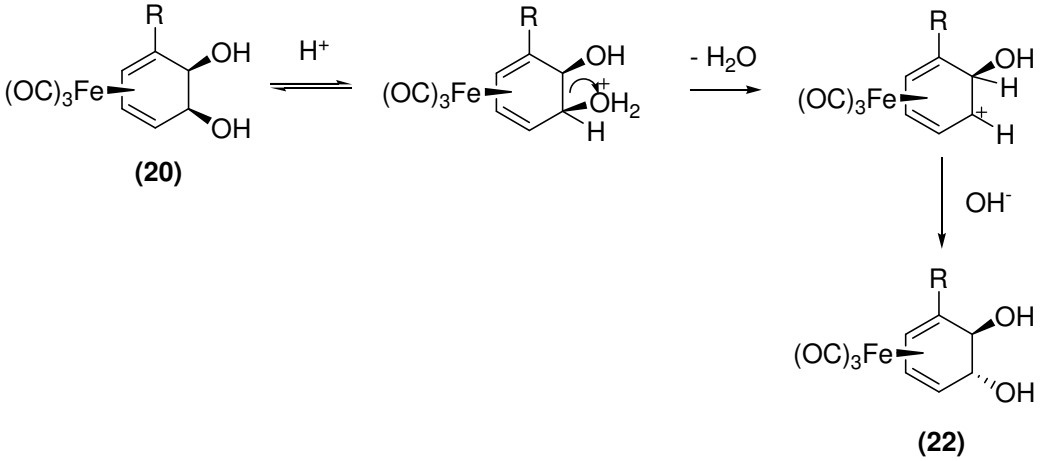
3.2.2 Comparisons of Acid Catalysed Rate Constants

When comparing rate constants between coordinated and uncoordinated substrates, it is helpful to recognise differences in the mechanisms between their reactions. The protonation of benzene hydrate results in the formation of the corresponding cation intermediate which deprotonates rapidly to form benzene.[120] Acid catalysed ionisation of the *cis*-dihydrodiol **(3)** gives the corresponding cation intermediate and subsequent deprotonation gives phenol.[114] The mechanism for the dehydration reaction involves the generation of a carbocation intermediate **(8)** in the rate determining step. This can be followed by direct formation of the aromatic product by deprotonation as shown in Scheme 3.6. Alternatively, the carbocation can undergo a hydride shift (NIH shift) (see Scheme 1.5, page 5) followed by deprotonation to form a cyclohexadienone, which tautomerises to the phenolic product. It is proposed that the deprotonation will be a fast step because the cation intermediate thus forms a phenol

product that is stabilised by aromatisation.[121] In contrast, when the arene dihydrodiol is coordinated to a tricarbonyliron moiety the corresponding tricarbonyliron cyclohexadienyl cation that forms undergoes nucleophilic attack instead of deprotonation as shown in Scheme 3.7.[29] Despite this difference, rate constants for carbocation formation can be measured and compared for both coordinated and uncoordinated substrates.



Scheme 3.6



Scheme 3.7

Initially, it is of interest to compare the rates constants measured for the 5,6-dimethoxycyclohexadiene tricarbonyliron complex **(97)** with the uncoordinated *cis*-benzene dihydrodiol **(3)**. The rate constant for ionisation of the coordinated *cis*-dimethoxy complex **(97)** was found to be 8.0 x 10^{-6} M^{-1} s^{-1} which is 10^4 times slower than that for *cis*-benzene dihydrodiol **(3)**. Assuming that the change from methoxy to hydroxy groups has only a small effect, this shows that the tricarbonyliron moiety has a large rate retarding effect on the acid catalysed reaction.

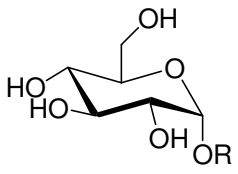
The effect of the β-methoxy group can be seen when the coordinated *exo*-hydrate **(85)** and coordinated *trans*-hydroxyl-methoxy cyclohexadiene **(105)** are compared. These structures differ by the presence of an extra methoxy group at a carbon β to the reacting carbon atom in the cyclohexadiene complex **(105)**. The rate difference between the coordinated hydroxyl-methoxy complex **(105)** and the coordinated hydrate **(85)** is similar to the corresponding difference in equilibrium constants, K_R. The complex **(105)** was found to have an acid catalysed rate constant 64 times slower than complex **(85)** compared with a ratio of their K_R values of 79.

These differences may be compared with the rate reducing effect of the methoxy group when the *endo*-dimethoxycyclohexadiene **(97)** and *endo*-cyclohexadiene hydrate **(63)** tricarbonyliron complexes are examined. As can be seen in Table 3.1, the acid catalysed rate constant for **(97)** is 250 times smaller than **(63)**. This is more evidence to show the rate reducing effect of the β-methoxy group and this also implies that the hydroxyl and methoxy substituents result in a difference in reactivity of a factor of 4 which is relatively small. However, the difference may also arise because the methoxy group is a slightly poorer leaving group than the hydroxyl group as the comparison involves a change in leaving group as well as substituent groups.

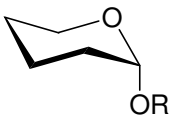
A further comparison in Table 3.1 indicates that benzene hydrate **(2)** reacts 1600 times faster than *cis*-benzene dihydrodiol **(3)**.[121] The β-hydroxyl group should have a similar rate-retarding effect to a β-methoxy group because both are controlled by the the unfavourable effect the electronegative oxygen has on the stability of the carbocation intermediate. If this is correct, the larger rate retarding effect for the uncoordinated cation that forms from **(3)** is consistent with a greater localisation of positive charge at the cation centre in this case.

There are many examples in the literature of the rate retarding effect of β-hydroxyl substituents upon carbocation reactions and therefore a decrease in rate was certainly an expected observation. One extreme example of hydroxyl substituent effects is in the acid catalysed hydrolysis of methyl α-D-glucoside **(109)** which was examined by

Dean *et al.*[122] This was compared to the reaction of the tetrahydropyranyl acetal **(110)** and it was found that the reaction is over 10^7 times slower in the presence of the hydroxyl groups. These structures are shown in Chart 3.1.



(109)



(110)

Chart 3.1

3.2.3 Comparisons of Rate Constants for Hydrolysis

The rate constant, k_{H2O}, listed for conversion of the cyclohexadienyl cation to the hydrate **(2)** in Table 3.1 has been estimated from data for pK_R and k_H for the formation of this ion by More O'Ferrall *et al.*[107] The rate constant is 2.3×10^4 s^{-1}, which is 10^5 times faster than for the coordinated methoxycyclohexadienyl **(103)** and cyclohexadienyl **(64)** tricarbonyliron cations to form **(105)** and **(85)** respectively. Surprisingly, this is much greater than the corresponding difference in rate constants, k_H, for acid catalysed formation of coordinated and uncoordinated cations from **(85)** and **(2)** which is only 46. The coordination of the tricarbonyliron thus seems to affect the rate of hydrolysis more than the rate of ionisation. Interestingly, for the dicarbonyltriphenylphosphineiron coordinated complex **(87)** the opposite is seen and it was found to have an effect on the rate of hydrolysis and not the acid catalysed rate.

It is noteworthy that, (η^5-methoxycyclohexadienyl)tricarbonyliron **(103)** and the cyclohexadienyl tricarbonyliron cation **(64)** react at almost the same rate to form the corresponding hydrate complexes (k_{H2O} = 0.177 s^{-1} and 0.205 s^{-1} respectively). The relatively small difference between **(103)** and **(64)** confirms that the *endo* methoxy group must not a have a large impact on the reactivity of the coordinated cations. This contrasts with the case of carbocation formation where the rate difference of 64 times is close to

the difference in K_R of 79. The acid catalysed rate constants would be expected to follow the opposite pattern as the more stable carbocation forms more rapidly.

3.2.3.1 Comparisons of Stereochemistry

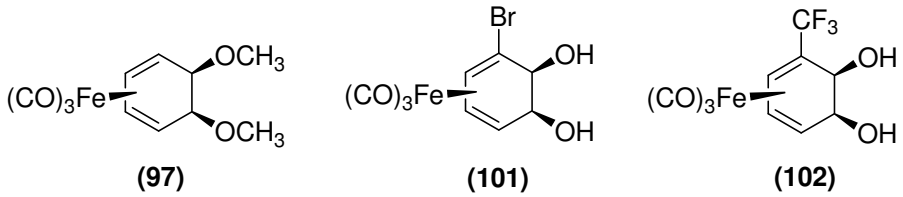
In this work, the (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** and the (η^4-*trans*-5-hydroxy-*cis*-6-methoxycyclohexa-1,3-diene)tricarbonyliron **(105)** complexes (see Table 3.1) were studied and rate constants for their acid catalysed reactions were measured. The *endo*-complex **(97)** has two methoxy substituents and the *exo*-complex **(105)** has a methoxy and a hydroxyl substituent but, as already suggested, this is not likely to have a large effect on their relative reactivities. The rate constant, $k_{H,}$ for the ionisation of *endo*-isomer **(97)** was 8.0 x 10^{-6} $M^{-1}s^{-1}$and that for the ionisation of complex **(105)**, was found to be 129.4 M^{-1} s^{-1}. This implies that ionisation of the *endo*-isomer is 2 x 10^7 times slower than for the *exo*-isomer. As similar observations have been made for the complexed *endo* and *exo* benzene hydrate,[108,109] such a difference is not unexpected. Studies by Johnson[110] showed, by equilibration in a methanol solution, that there is only a small difference in thermodynamic stability of the isomers, so the difference must arise from a difference in activation energies or kinetic barriers.

Interestingly, a similar difference in kinetic barrier exists for the uncoordinated *cis* and *trans* benzenedihydrodiols. In this case, again there is only a very small difference in stabilities of the diol reactants[123] yet the ratio of rates of the acid catalysed rate constants k_{cis} / k_{trans} = 2.2 x 10^4. On the other hand, in striking contrast to the metal coordinated substrate, it is the *cis*-diol rather than the *trans*-diol which is the more reactive. The explanation for the effect of stereochemistry or reactivity must be quite different in the two cases, therefore, for the uncoordinated diols the difference is believed to be due to more favourable hyperconjugation with the carbocation centre by an axial β-C-H than by the β-C-OH bond in the transition state for reaction of the *cis*-diol. It is clear that this cannot play any part in the reactions of the coordinated dimethoxy and hydroxyl-methoxy cyclohexadiene. In these cases, it seems most likely that the reverse attack of water on the coordinated carbocation occurs on the opposite side of the cation from the tricarbonyliron coordination in a bimolecular nucleophilic

substitution S_N2-like displacement. As there is little or no difference in equilibrium constants for *endo* and *exo* reactions, this difference must represent a difference in energies of the transition state which applies also to the reverse process of acid catalysed formation of the coordinated cations. As explained below, this has implications for the synthetic conversion of *cis*-benzenedihydrodiols to their *trans*-isomers.

3.3 Implications for *Cis-Trans* Conversion of Benzene Dihydrodiols

The principal aim of this thesis was to explore the conditions for conversion of *cis*-diol complexes to their *trans* analogues. This was achieved by attempting the synthetic pathway proposed while also studying the rates and equilibria for reaction of the intermediates in the pathway. The latter studies allowed implications for the metal coordination route to be considered. The synthetic pathway was then attempted on a number of substrates including the dimethoxy complex **(97)**, (6-bromocyclohexa-3,5-diene-1,2-diol)tricarbonyliron **(101)** and [6-(trifluoromethyl)-cyclohexa-3,5-diene-1,2-diol]tricarbonyliron as **(102)** shown in Chart 3.2.



(97) **(101)** **(102)**

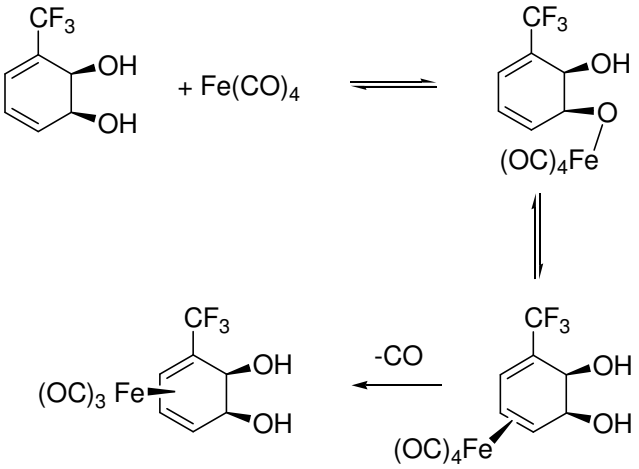
Chart 3.2

3.3.1 Step 1 - Coordination

Initially, as mentioned in Section 2.1.2, page 48, the *cis*-dihydrodiol **(3)** was converted to 5,6-dimethoxycyclohexa-1,3-diene **(93)** and was then reacted with $Fe_2(CO)_9$ to give the (η^4-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron complex **(97)**. Our conclusion from the equilibrium studies of *endo* and *exo* isomers of methoxy cyclohexadienyl complexes by Johnson *et al.*[110] is that there is little difference in stability between the *exo* and *endo* complexes examined in this work. It therefore seems clear that the *endo* complex does not experience any strong stabilisation from interaction between

the iron atom and hydroxyl groups as has been postulated in the literature in the past. It has also been confirmed that the reaction of the *cis*-diol with pentacarbonyliron ($Fe(CO)_5$) or nonacarbonylirondiiron ($Fe_2(CO)_9$) yields an *endo* complex in preference to the *exo* complex.

A mechanism proposed by Pearson for the reaction of the diironnonacarbonyl with a diene ligand involved the hydroxyl or methoxy substituents acting as a stereodirector for the reaction as illustrated in Scheme 3.8.[53] In this case, the reactive $Fe(CO)_4$ complex is generated by cleavage of $Fe_2(CO)_9$ which adds to the hydroxyl group or the methoxy group first and then gets transferred to the olefinic group on the diene.



Scheme 3.8

3.3.2 Step 2 - Cation Formation

In the kinetic studies on the *endo*-dimethoxy complex **(97)**, it was necessary to use a strong acid to initiate the ionisation reaction. The results from this work therefore suggest that formation of the methoxycyclohexadienyl cation complex **(103)** from the tricarbonyliron coordinated *cis*-dimethoxycyclohexadiene **(97)** will be the most difficult step in the synthetic route to a *trans*-product. The synthetic conditions reported in the literature involve reaction with hexafluorophosphoric acid (HPF_6) in acetic anhydride solvent for the ionisation of the diol complexes[53,29] or reaction with trifluoroacetic acid

(TFA) for ionisation of the methoxy substituted complexes.[52] Overall, the complex was difficult to protonate but, once the cation was formed, it was stable enough to allow nucleophilic addition to occur. Therefore, this route for the conversion of a derivative of a *cis*-dihydrodiol to the *trans*-isomer using a coordinated complex **(97)** looks promising.

3.3.3 Step 3 - Nucleophilic Attack

This brings us to the next step in the isomerisation route, which is the nucleophilic attack of hydroxide ion on the complexed cation. It is clear from the kinetic measurements that the cation is easily quenched in an aqueous solvent at mild pH which rapidly leads to reaction at the *exo* position forming the coordinated *trans* product.[52] In this work, it was shown that the rate constants, k_{H2O}, for the reaction of the cations with a nucleophile were much faster than for the cation formation. This suggests that it should be an easy step to perform synthetically.

Synthetically, this step worked well as the reaction time was relatively fast and purification by chromatography gave a pure product. The evidence obtained with respect to the reaction of (η^5-methoxycyclohexadienyl)tricarbonyliron **(103)** with water supports the proposal that at pH >3 the reactions proceeds by *anti* addition to the formal carbocation centre providing the *exo* substituted complex. Addition of a nucleophile to other sites in the complex such as the metal or carbonyl ligands were not observed.

3.3.4 Step 4 - Decomplexation

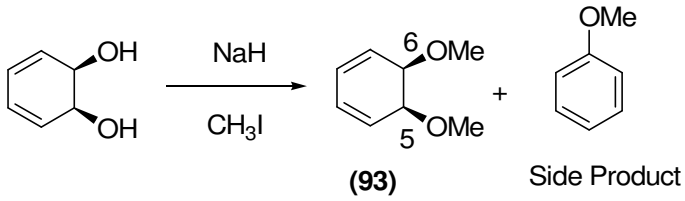
Another important aspect of the synthesis was to optimise the decomplexation of the coordinated complex. This decomplexation step is difficult to achieve and can be destructive to certain functional groups of the organic ligand. It was reported in the literature by Shvo and Hazam that decomplexation can be achieved using Me_3NO and that, due to the mild basic conditions involved, it proved successful for many organic ligands.[85] The rate constant for ionisation of the 5-hydroxy-6-methoxy coordinated complex **(105)** was much faster than for the *endo*-complex **(97)**. Therefore, the reformation of the corresponding cation could occur easily and this implies that mild

basic reaction conditions would be necessary to remove the metal fragment without destroying the organic ligand. In order to achieve the decomplexation, conditions must be completely anhydrous. This step was attempted on the coordinated trifluoromethyl substituted diol **(102)** and the 5-hydroxy-6-methoxy complex **(105)** but was only successful for **(105)** for which it gave a 79% yield. The difficulty with the trifluoromethyl substituted diol may have been due to the small scale it was necessary to use and this result would need to be confirmed.

3.4 Summary of the Synthesis of Organic and Organometallic Substrates

Tricarbonyliron complex intermediates were required for the synthetic pathway to produce arene *trans*-dihydrodiols from their readily available *cis*-analogues proposed by Boyd *et al.*[11] and discussed in Section 1.4 (page 44). The *cis*-benzenedihydrodiol used was available from Queen's University Belfast where it was produced in bulk by fermentation in a bioreactor. However, a recent paper by Suemune *et al.* reported that, when the *cis*-diol was reacted with $Fe_2(CO)_9$, a complex formed that was not stable to purification by chromatography.[54] Therefore they then converted the diol to the corresponding dibenzoate ester, which was sufficiently stable to be complexed.

In this work, *cis*-benzenedihydrodiol was converted to its dimethyl ether **(93)** as shown in Scheme 3.9 and was found to be stable enough to undergo complexation to irontricarbonyl including purification by flash chromatography. Due to a large proportion of a side product, anisole, being formed, the initial methylation reaction resulted in low yields, ranging between 20 and 30%. Characterisation of the product **(93)** included a ^{1}H NMR spectrum which showed the disappearance of the broad OH signal of the starting material and the presence of a newly formed singlet for the methoxy protons at 3.42 ppm. The four olefinic protons were represented by a multiplet at 6.03 ppm. The analysis of the side product by ^{1}H NMR spectroscopy showed that it was anisole due to the occurrence of aromatic signals in the 7 ppm region.



Scheme 3.9

The *cis*-benzenedihydrodiol **(92)** was also transformed into its diacetate ester **(95)** which gave a higher yield (65%) than the previous methylation step described. Characterisation included a ^{1}H NMR spectrum where the disappearance of the broad OH signal at 3.3 ppm and the presence of a newly formed signal for the acetate protons at 2.08 ppm was observed. The IR spectrum was also helpful in characterising the newly formed product. The main absorption of interest was a strong stretch at 1737 cm^{-1} indicating the presence of a carbonyl functional group and a stretch at 1243 cm^{-1} for the carbon oxygen bond of the ester.

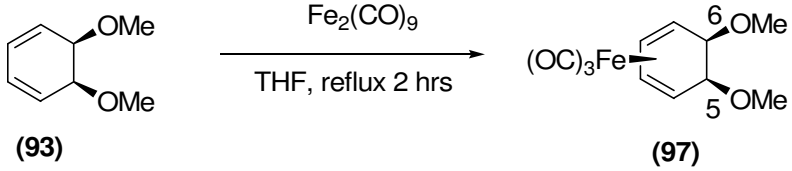
3.4.1 Tricarbonyliron Complexes

The next step was to coordinate tricarbonyliron to the *cis*-dimethoxy compound **(93)** prepared. This reaction was initially attempted using a simple one step procedure with 1-(4-methoxyphenyl)-4-phenyl-1-azabuta-1,3-diene as an iron tricarbonyl transfer catalyst along with diironnonacarbonyl and THF. This one pot procedure in which the tricarbonyliron is introduced to the cyclohexadiene in the presence of the catalyst to form the required irontricarbonyl(η^4-1,3-diene)complex had been identified as the preferred method and was reported by Knolker *et al.* to give high yields (84%) for other substrates.[65] This method had also been used by other researchers in this group to coordinate the unsubstituted 1,3-cyclohexadiene.[108]

The catalyst used was selected because it could be prepared in 100% yield as reported by Knölker.[41] Use of the transfer reagent has the advantage that the product can be prepared under less hazardous conditions, as an excess of diironnonacarbonyl is not required. However, the coordination did not take place when these conditions were used for the compounds of interest in this work. It was performed many times under varying

reaction conditions and on different scales but, in each case, the reaction was unsuccessful**.** The desired product was never isolated using this approach.

Having come to a conclusion that this method of tricarbonyliron complexation was not going to work for this substrate, an alternative method was examined. Literature research was performed and, as can be seen in Table 1.1 (page 18), many compounds similar to the *cis*-dimethoxy substrate **(93)** have been complexed to the tricarbonyliron but the information provided on the experimental procedure was often limited. By attempting the various methods described by a number of research groups, a successful approach was finally found. The procedure used is shown in Scheme 3.10 and was a direct complexation (no transfer reagent was used) and was similar to the coordination procedure developed by Suemune *et al*.[54] As there was no catalyst used, a significant excess of diironnonacarbonyl (2 equivalents) was used. This is a drawback as pyrophoric iron can form which is hazardous on workup. In addition, significant amounts of iron pentacarbonyl form as a side product and this compound must be isolated from the crude product and decomposed by treatment with bromine water or bleach.[38,124] Thus, this method required considerable care during work up but, on the scale used in this work, the reaction proved to be very successful. A protocol has now been written for carrying out this reaction safely (See Appendix B).



(93) **(97)**

Scheme 3.10

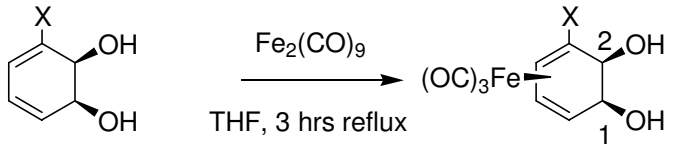
As previously mentioned (page 50), the reaction was performed using THF as this solvent gave an 80% yield of (*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)**. It has been reported by other workers that this reaction was affected significantly by the solvent used. In a study by Suemune *et al.,* it was reported that THF gave the best results in the reaction forming [5,6-bis(benzyloxy)cyclohexa-1,3-

dienyl]tricarbonyliron.[54] This is backed up by a report by Cotton and Troup which stated that diironnonacarbonyl reacted more quickly and more extensively in THF as solvent.[125]

The ^{1}H NMR chemical shifts of the substituents at C-5 and C-6 can often provide a good guide to their stereochemistry.[72,126] The ^{1}H NMR spectrum for this complex **(97)** shows one single signal representing the chemically equivalent methoxy groups in the *endo* position. The 'inner' protons, H-2 and H-3, are virtually unchanged by the coordination and were observed at 5.23 ppm. However, the 'outer' protons, H-1 and H-4, were shifted upfield to 3.14 ppm. IR spectroscopy also provided evidence for the coordination of the $Fe(CO)_3$ moiety to the substituted cyclohexadiene with absorption bands observed in the infrared at 2062, 2000 and 1973 cm^{-1} for the iron carbonyl groups.

This reaction was also carried out on the diacetate **(95)** to produce (η^4-*cis*-5,6-diacetoxy-1,3-cyclohexadiene)tricarbonyliron **(99)**. However, the complexation resulted in a poor yield of 13%. Characterisation of **(99)** by NMR and IR spectroscopy and elemental analysis showed that a pure product was isolated. The coordination of the metal fragment had no effect on the NMR signal for the protons in the acetate groups as it was still found at 2.07 ppm. The effect of the tricarbonyliron was obvious however from the upfield shift of the H-1 and H-4 protons from 5.90 to 3.03 ppm. If this reaction could be optimised, it would be very useful for future work as the corresponding cation formed from these products is an important intermediate in the synthetic route from the *cis*-diols to their *trans* analogues.

3-bromo-cyclohexa-3,5-diene-1,2-diol and 3-trifluoromethyl-cyclohexa-3,5-diene-1,2-diol were again coordinated by direct complexation as shown in Scheme 3.10. The bromine and trifluoromethyl group are electron-withdrawing and are therefore used to provide efficient regiocontrol both in the formation of the cationic complexes and in their reactions with nucleophiles.[53] The reactions were carried out with diironnonacarbonyl in THF and the desired complexes were isolated as yellow solids in 69% and 90% yields for **(101)** and **(102)** respectively.



(101) X = Br
(102) X = CF_3

Scheme 3.11

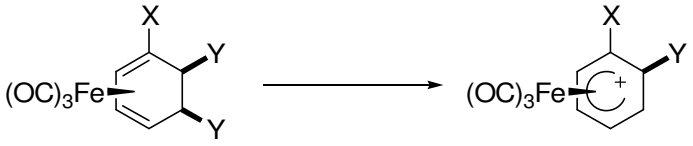
Both complexes were clearly identifiable by IR spectroscopy, elemental analysis, and ^{1}H NMR. A COSY NMR was used to assist in the signal assignment. As can be seen in Table 3.2**,** on coordination to the tricarbonyliron, an upfield shift was observed for all of the protons with the exception of the two hydroxyl groups. The presence of the electron withdrawing group at an adjacent carbon to 4-H causes some deshielding and therefore this signal is observed furthest downfield. A D_2O shake was performed on **(101)** to determine which signals in the ^{1}H NMR spectra represented the two hydroxyl protons and they were found to occur at 3.00 and 3.11 ppm.

Table 3.2 Summary of the ^{1}H NMR spectral data for **(101)** and **(102)** tricarbonyliron complexes of substituted *cis*-diols.

Compound	δ_H (ppm)					
(101)	3.00 (1 H, d, 2-OH)	3.11 (2 H, m, 1-OH, 6-H)	3.87 (1 H, m, 1-H)	3.94 (1 H, dd, 2-H)	5.15 (1 H, ddd, 5-H)	5.67 (1 H, dd, 4-H)
(102)	2.69 (1 H, br d, 2-OH)	2.87 (1 H, br s, 1-OH)	3.27 (1 H, m, 6-H)	3.93 (2 H, br m, 1-H, 2-H)	5.25, (1 H, dd, 5-H)	5.65 (1 H, dd, 4-H)

3.4.2 Tricarbonyliron Substituted Cyclohexadienyl Complexes

Once the tricarbonyliron complexes had been successfully produced, the three remaining steps of the synthetic pathway proposed were attempted using (η^4-*cis*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)**, (η^4-3-bromocyclohexa-3,5-diene-1,2-diol)tricarbonyliron **(101)** and [η^4-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102)**, although they were only successfully carried out for the two complexes shown in Scheme 3.12. The next step involved conversion of the substituted cyclohexadiene complexes to their corresponding cations.



(97) X = H, Y = OMe
(102) X = CF_3, Y = OH

(103) = X = H, Y = OMe
(104) = X = CF_3, Y = OAc

Scheme 3.12

(η^4-*cis*-5,6-Dimethoxy-1,3-cyclohexadiene)tricarbonyliron **(97)** was reacted with 3 equivalents of TFA at 0 °C for 1 hour resulting in removal of the methoxy substituent. This is due to electrophilic attack at the methoxy group and subsequent loss of methanol converting the diene complex into a cation.[115] Ammonium hexafluorophosphate was added and a yellow precipitate of the corresponding salt formed in a 95% yield.

The cation **(104)** was formed from [η^4-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102)** by reaction with HPF_6 and acetic anhydride in DCM at 0 °C as reported by Pearson *et al*.[53] The desired complex was isolated as a yellow solid in a 48% yield. This compound has been reported to be water sensitive and very unstable as it can easily undergo nucleophilic attack. Although a satisfactory ^{1}H NMR spectrum was obtained immediately the cation salt was formed, a day later, decomposition of the cation complex salt was observed when another ^{1}H NMR (of the same sample which had been stored in the freezer) was run and aromatic signals were observed in the spectrum.

Spectral data for both of the cations synthesised were consistent with the structures **(103)** and **(104)** shown in Scheme 3.12. ^{1}H NMR spectroscopy indicated the formation of the methoxy substituted cation from **(97)** as the signal at 3.39 ppm integrates for 3 hydrogens representing only one methoxy group and formation of the cation **(104)** from **(102)** by the disappearance of the signals at 2.65 and 2.82 ppm representing the hydroxyl groups and a newly formed singlet at 2.26 ppm indicating the presence of the three protons from the acetate group as can be seen in Table 3.3. The IR spectrum also confirmed that the formation of the cation had occurred due to a shift in the absorption of the carbonyl groups from 2062, 2000 and 1973 to 2118, 2084 and 2062 cm^{-1} for **(103)** and from 2253, 2071 and 2010 to 2135 and 2085 cm^{-1}for **(104)**.

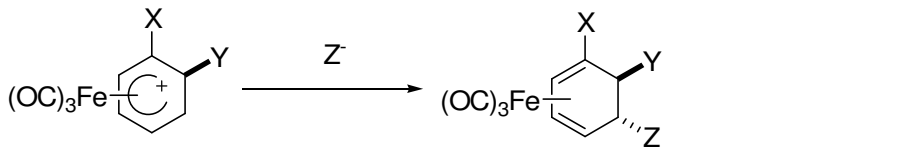
Table 3.3 Summary of the ^{1}H NMR data for the cations **(103)** and **(104)** formed from (η^4-*cis*-5,6-dimethoxy-1,3-cyclohexadiene)tricarbonyliron **(97)** and [η^4-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102)**.

Compound	δ_H (ppm)					
(103)	3.39 (3 H, s, OCH_3)	3.77 (1 H, m, H-6)	4.01 (2 H, m, H-1, H-5)	5.75 (2 H, m, H-2, H-4)	6.96 (1 H, m, H-3)	
(104)	2.26 (3 H, s, CH_3)	4.54 (1 H, d, 1-H)	5.27 (1 H, br s, 2-H)	6.03 (1 H, br m, 6-H)	6.61 (1 H, d, 4-H)	7.60 (1 H, t, 5-H)

3.4.3 Nucleophilic Attack to give the *trans*-Complexes

This step required dissolving the dienyl salt in acetonitrile at 0 °C. A sodium hydrogen carbonate solution was used as the source of the nucleophile and the products were purified by flash chromatography, resulting in pale yellow solids obtained in 58 % and 91% yields respectively for **(105)** and **(106)**. Nucleophiles can react with organometallic electrophiles by several pathways which depend on the nature of the nucleophile, solvent temperature *etc*. The iron centre directs the attack of the nucleophile

anti to the metal forming the *trans* product.[52] This reaction was a fast reaction as expected from the stability of the cation and the corresponding *trans* hydroxyl substituted compound was formed in 10 minutes.



(103) = X = H, Y = OMe
(104) = X = CF_3, Y = OAc

(105) = X = H, Y = OMe, Z = OH
(106) = X = CF_3, Y = OAc, Z = OH

Scheme 3.13

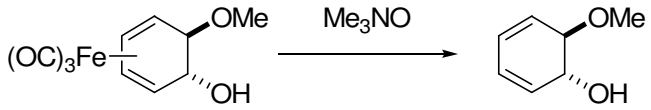
When the complex has a trifluoromethyl group in the 3 position resulting in an unsymmetrially substituted cyclohexadienyl tricarbonyliron, nucleophilic addition occurs extensively at the C-1 position. These products were characterised by ^{1}H NMR spectroscopy and the newly formed *trans*-complexes were clearly identified by the presence of a new signal representing the *trans*-hydroxyl groups at 3.20 and 3.19 ppm for **(105)** and **(106)** respectively as seen in Table 3.4.

Table 3.4 Summary of the ^{1}H NMR data for (η^4-6-methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron **(105)** and (η^4-2-acetoxy-3-(trifluoromethyl)cyclohexa-3,5-diene-1-ol)tricarbonyliron **(106)**.

Compound	δ_H (ppm)						
(105)	2.95 (2 H, m, H-2, H-5)	3.20 (1 H, s, OH)	3.39 (4 H, s, OCH_3, H-6)	3.97 (1 H, t, m, H-1)	5.40 (1 H, m, H-3 or H-4)	5.51 (1 H, m, H-3 or H-4)	
(106)	2.14 (3 H, s, CH_3)	3.15 (1 H, t, 6-H)	3.19 (1 H, d, 2-H)	3.95 (1 H, s, 1-H)	4.42 (1 H, s, OH)	5.48 (1 H, t, 5-H)	5.84 (1 H, d, 4-H)

3.4.4 Decomplexation of the Tricarbonyliron Complexes.

After the coordinated *cis* compound has gone through the required transformations to form the *trans* complex, demetallation is required to provide the free *trans* analogue. The final step in the route for the formation of the *trans*-diols from their *cis* counterparts involved a decomplexation reaction using mildly basic reaction conditions as shown in Scheme 3.14.



(106) **(107)**

Scheme 3.14

This decomplexation step was carried out under completely anhydrous conditions using a large excess of the trimethylamine-N-oxide, as most of the reagent will escape the reaction mixture as the volatile trimethylamine. The *trans*-product was isolated in a 79% yield. The structure was readily confirmed by ^{1}H NMR spectroscopy and all of the expected signals associated with the uncoordinated *trans* product were observed as shown in Table 3.5. The ^{13}C NMR and IR spectra clearly identified that the decomplexaton had been successful with the absence of the the signal for the C=O at 210 ppm and the absence of bands representing the carbonyl functional groups between 2000 and 1900 cm^{-1}.

Table 3.5 Summary of the ^{1}H NMR data for *trans*-6-methoxycyclohexa-2,4-diene-1-ol (**107**).

Compound	δ_H (ppm)				
(107)	2.55 (1 H, br s, OH)	3.42 (3 H, br s, OCH_3)	4.04 (1 H, m, H-6)	4.50 (1 H, m, H-1)	5.87-5.95 (4 H, m, 4 x CH)

3.5 Summary

An initial investigation to obtain mechanistic information allowed implications to be considered for the synthesis of the arene *trans*-dihydrodiols from their *cis*-counterparts.

The coordinated dimethoxy complex was examined as a model for various synthetic substrates that contained a β-methoxy or β-hydroxy group on the charge centre. The presence of a substituent was found to have a slight rate retarding effect on the formation of the cation. However, the difference between having a hydroxyl and methoxy substituent does not have a large impact. The coordinated methoxy cation intermediate formed from the acid catalysed ionisation of the dimethoxy complex was difficult to generate and required a strong acid. However, the *trans*-product was formed easily by nucleophilic attack of the hydroxide ion on the cation. This nucleophilic addition reaction formed only the *exo* product and no other reaction was observed. A rapid equilibrium between the methoxy cation and the *trans*-product was found to occur. The key to the synthetic procedure was finding an optimum method to coordinate the diene complex to the diironnonacarbonyl. A complication did occur in the synthesis of the cation as it was found to be unstable and decompose quickly. Therefore, it was necessary to carry out the next step immediately.

The main conclusion to be drawn is that the best strategy for improving the synthetic procedure is to continue to examine the reactants and intermediates not yet studied and optimise the route. Future work would include optimisation of conditions to isolate the cation complex and for the upscale of the coordination to the iron complex.

CHAPTER 4

EXPERIMENTAL DETAILS

4 EXPERIMENTAL DETAILS

4.1 General Materials and Instrumentation

All commercially available reagents were used as supplied unless otherwise stated. Anhydrous reagents were purchased in a Sure-Seal™ bottle from Aldrich Chemical Company and used as received. All glassware for moisture sensitive reactions was washed, oven dried for approximately 19 hours and cooled in a dessicator over potassium bromide. Glass syringes, needles, spatulas and stirring bars were treated similarly. All moisture sensitive reactions were performed in anhydrous conditions under an atmosphere of nitrogen or argon, using oven-dried glassware and anhydrous solvents.

Thin layer chromatography was carried out using aluminium-backed or plastic-backed Merck Kieselgel F_{254} plates. Plates were visualized by UV light using a Camag 254 nm lamp and developed if necessary using a potassium permanganate dip, [$KMnO_4$ (3 g), K_2CO_3 (20 g), 5% aqueous NaOH (5 cm^3) and water (300 cm^3)] with further heating. Flash chromatography was performed as described by Leonard *et al.*[127] using silica gel (Merck, Grade 9385, 230-300 Mesh, 60 Angstrom). Melting points were determined in capillary tubes using an Electrothermal 9100 Series Melting Point Apparatus. Microanalyses were carried out by the Microanalytical Unit, School of Chemistry and Chemical Biology, University College Dublin. IR spectra were recorded over the 4000-400 cm^{-1} operating range on a Perkin Elmer Paragon Series FT-IR 1000 instrument or a Perkin Elmer Spectrum GX FT-IR spectrometer. Certain semi-solid products were dissolved in chloroform and a drop of the solution was dispersed on sodium chloride plates and allowed to dry. Nuclear magnetic resonance spectra were recorded in deuterated chloroform with tetramethylsilane (TMS) as an internal reference unless otherwise stated. The instrument used was a Varian operating at 300 MHz, Bruker Avance II 400 or a Bruker Avance III 400 both operating at 400 MHz.

cis-Diols used in the synthesis were obtained from the Questor Centre in Queen's University Belfast from Prof. Derek Boyd where they are produced in bulk by fermentation in a bioreactor.

4.2 Nomenclature

The compounds synthesised for this thesis were generally named according to the IUPAC system. This involves giving priority to certain functional groups. For example, the alcohol functional group has higher priority over the other functional groups that occur (ethers and alkenes). Therefore, for example, compound **(102)** is named as [η^4-3-(trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron.

It is worth noting that nomenclature of these complexes in the literature is not consistent and this may lead to some initial confusion when consulting them for example structure **(102)** is also known as [η^4-1-(trifluoromethyl)cyclohexa-1,3-diene-5,6-diol]tricarbonyliron in a report by Pearson *et al*.[53]

In the case of compound **(105)**, two names have been used to refer to it in this thesis. In the experimental section, it is named using the IUPAC system as (η^4-6-methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron**.** However, in the results and in the discussion, complex **(105)** is referred to as (η^4-t*rans*-5-hydroxy-6-methoxycyclohexa-1,3-diene)tricarbonyliron as a consistency in numbering of the carbons in the ring allows for an easier comparison of this compound with the dimethoxy complex **(97)**, (η^4-*cis*-5,6 dimethoxycyclohexa-1,3-diene)tricarbonyliron and corresponding cation, **(103)** (η^5-6-methoxycyclohexa-2,5-dien-1-yl)tricarbonyliron. Appendix C provides a list of the complexes prepared in this work along with their structures and corresponding names.

4.3 Synthesis of Organic and Organometallic Substrates

4.3.1 Synthesis of *trans*-Cyclohexa-3,5-diene-1,2-diol

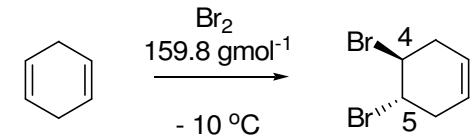
The title compound was synthesised in a five step synthesis according to the method of Platt and Oesch.[111] Table 4.1 shows a summary of the reaction conditions used and yields obtained for each step of this synthesis.

Table 4.1 Reaction conditions and yields for the five step synthesis of *trans*-cyclohexa-3,5-diene-1,2-diol **(92)**.

Compound	Scale (grams)	Reaction Conditions	Solvent	% Yield
(88)	17.00	4.66 hr, -8 to -2 °C	CH_2Cl_2	70
(89)	35.55	(i) 22 hr, room temp. (ii)1.75 hr, reflux	CH_2Cl_2	67
(90)	22.87	(i) 2 hr, room temp. (ii) extraction, recrystallisation form ethanol	Pyridine (anhydrous)	74
(91)	21.69	(i) 3.5 hr, reflux (ii) extraction, flash chromatography, R_f (0.6)[a]	HMPA (anhydrous)	91
(92)	7.96	(i) 1 hr, room temp. (ii) flash chromatography, R_f (0.2)[b]	Methanol	46

[a] The solvent system used was 1: 1 ethyl acetate: cyclohexane. [b] The solvent system used was 70: 30 ethyl acetate: cyclohexane.

4.3.1.1 trans-4,5-Dibromocyclohexene



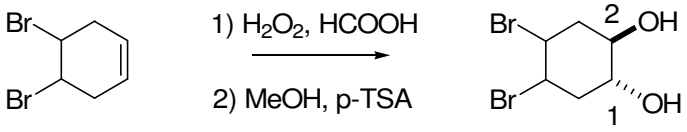
(88)

80.1 gmol^{-1} 240.0 gmol^{-1}

1,4-Cyclohexadiene (17.00 g, 0.212 mol) was dissolved in dichloromethane (80 cm^3) and cooled on an ice-salt bath (-10 °C). Bromine (34 g, 10.9 cm^3, 0.212 mol, 1 equiv.) was added dropwise using a pressure equalising funnel over a period of 4 hours. The rate of addition of bromine was adjusted so that the temperature of the reaction mixture was maintained between -2 and -8 °C. The reaction mixture was left stirring for 40 minutes at 0 °C and then filtered under vacuum. The solvent was evaporated from the filtrate under reduced pressure to afford **(88)** *trans*-4,5-dibromocyclohexadiene (35.56 g, 70%) as a light orange oil.

υ_{max} (nujol mull)/cm^{-1}:	3038 (sp^2 C-H stretch), 1660 (C=C stretch), 1420 (-CH_2- C-H bend) 981, 879 (-CH=CH-, C-H bend) 663 (C-Br stretch)
δ_H / ppm (400 MHz; $CDCl_3$):	2.62 (2 H, dm, J_{gem} = 16.8 Hz, 3-H, 6-H), 3.20 (2 H, dm, J_{gem} = 16.8 Hz, 3-H, 6-H), 4.52 (2 H, m, 4-H, 5-H), 5.67 (2 H, apt s, 1-H, 2-H)
δ_C / ppm (100 MHz; $CDCl_3$):	31.0 (2 x C-3, C-6), 48.4 (C-4, C-5), 122.0 (C-1, C-2)

4.3.1.2 trans-4,5-Dibromocyclohexane-1,2-diol



(88)
240.0 $gmol^{-1}$

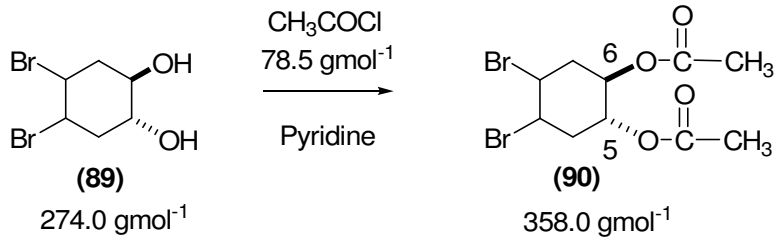
(89)
274.0 $gmol^{-1}$

trans-4,5-Dibromocyclohexene **(88)** (35.55 g, 0.148 mol) was dissolved in dichloromethane (25 cm^3) and was added dropwise at room temperature over a period of 3 hours to a stirred solution of 30% aqueous hydrogen peroxide (23 cm^3) and formic acid (90 cm^3, 98%). The reaction mixture was stirred overnight (19 hours approximately) and then the dichloromethane was removed by evaporation. Methanol (327 cm^3) and *p*-toluenesulphonic acid (0.33 g) were added and the mixture was heated under reflux for 1 hour and 45 minutes, at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of the product (R_f 0.3) and the absence of starting material. The reaction mixture was concentrated under reduced pressure to yield a white semi-solid. It was then recrystallised from dichloromethane (300 cm^3) to form **(89)** as a white crystalline solid, (23.68 g, 67%), m.p. 118.4-119.5 ºC (lit.,[111] 124 ºC).

υ_{max} (KBr disc)/cm^{-1}: 3398 (O-H stretch), 2912 (sp^3 C-H stretch), 1438, (-CH_2- C-H bend) 1179, 1059 (C-O stretches), 656 (C-Br stretch)

δ_H / ppm (400 MHz; $(CD_3)_2SO$): 2.25 (4 H, br s, 3-H, 6-H), 3.62 (2 H, br s, 1-H, 2-H), 4.54 (2 H, br s, 2 x OH), 5.10 (2 H, d, *J* = 3.2, H-4, H-5)

4.3.1.3 trans-5,6-Diacetoxy-1,2-dibromocyclohexane



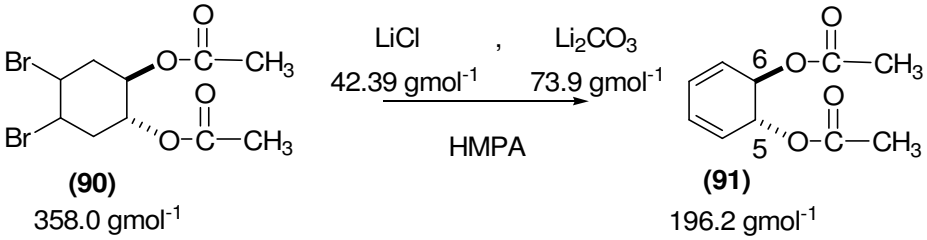
trans-4,5-Dibromocyclohexane-1,2-diol **(89)** (22.87 g, 0.083 mol) was dissolved in pyridine (27 cm^3, anhydrous) and acetyl chloride (26.2 cm^3, 0.334 mol, 4 equiv.) was added dropwise over a period of 30 minutes using a pressure equalising dropping funnel. The reaction mixture was kept under a nitrogen atmosphere using a bubbler system. The reaction mixture was stirred for 2 hours and dichloromethane (90 cm^3) was then added to dissolve the residue that formed. 0.2 M HCl (350 cm^3) was then added gradually to quench the reaction.

The organic and aqueous layers were separated and the aqueous layer was extracted with dichloromethane (2 x 75 cm^3). The combined organic layers were washed with water (2 x 150 cm^3) and sodium hydrogen carbonate (200 cm^3 of saturated aqueous solution) and dried over anhydrous sodium sulfate. This was then filtered using a Buchner funnel. The solvent was removed under vacuum to afford a dark yellow oil, which solidified in the freezer to give a dark yellow solid. The material was recrystallised twice from ethanol and dried to give **(90)** as a light yellow crystalline solid (21.26 g, 74%), m.p. 110.4-111.2 ºC (lit.,[111] 110 ºC).

υ_{max} (KBr disc)/cm^{-1}: 2959 (sp^3 C-H stretch), 1745 (C=O ester stretch), 1374 (CH_3 C-H bend), 1238, 1032 (C-O stretch), 690 (C-Br stretch)

δ_H / ppm (400 MHz; $CDCl_3$): 2.07 (6 H, s, 2 x CH_3), 2.39 (2 H, m, 1-H, 4-H), 2.61 (2 H, m, 1-H, 4-H), 4.49 (2 H, br m, H-1, H-2), 5.25 (2 H, br m, H-5, H-6)

4.3.1.4 trans-5,6-Diacetoxycyclohexa-1,3-diene



(90) 358.0 gmol^{-1} **(91)** 196.2 gmol^{-1}

trans-5,6-Diacetoxy-1,2-dibromocyclohexane **(90)** (21.69 g, 0.061 mol), lithium carbonate (10.29 g, 0.139 mol, 2.3 equiv.) and lithium chloride (7.19 g, 0.17 mol, 2.8 equiv.) were dissolved in HMPA (75 cm^3) and heated under reflux at 100 °C for 3.5 hours at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of the desired product (R_f 0.6) and the disappearance of the starting material. Ethyl acetate (50 cm^3) was added to dissolve the white solid which formed during the reaction. The reaction mixture was cooled in an ice bath and 2 M HCl (250 cm^3) was added slowly until effervescence stopped.

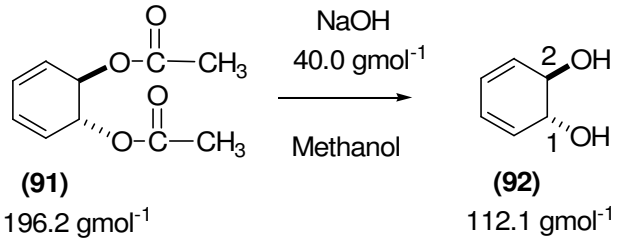
The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (2 x 75 cm^3). The combined organic layers were washed with water (2 x 100 cm^3) and sodium hydrogen carbonate (200 cm^3 of saturated aqueous solution) dried over anhydrous sodium sulfate and then filtered using a Buchner funnel. The solvent was removed under vacuum to afford a deep orange oil.[℘] The material was

[℘] The water bath for the rotary evaporator must be kept at a temperature of < 40 °C and the Flash chromatography must be carried out immediately as aromatisation of the diacetate to the phenyl acetate can be observed over time or if it is subjected to heat over a long period of time. This was also reported to occur in the synthesis of the diacetate by Platt and Oesch.[111]

purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1) to afford **(91)** the diacetate (10.86 g, 91%) as a yellow oil.

υ_{max} (thin film)/cm^{-1}:	2983, 2931 (sp^3 C-H stretch), 1736 (C=O ester stretch), 1446, 1374 (CH_3 C-H bend), 1240, 1047 (C-O stretch)
δ_H / ppm (300 MHz; $CDCl_3$)*	2.08 (6 H, br s, 2 x CH_3), 5.58 (2 H, d, 5-H, 6-H), 5.80 (2 H, m, 1-H, 4-H) 6.08 (2 H, m, 1-H, 2-H)
δ_C / ppm (75 MHz; $CDCl_3$):	21.1, 21.5 (2 x OCH_3), 71.1, 71.7, (C-5, C-6), 124.8, 125.1, (C-1, C-4), 125.9 (C-2, C-3), 170.5 (C=O)

4.3.1.5 trans-Cyclohexa-3,5-diene-1,2-diol



(91) 196.2 $gmol^{-1}$ **(92)** 112.1 $gmol^{-1}$

trans-5,6-Diacetoxycyclohexa-1,3-diene **(91)** (7.96 g, 0.041 mol) was dissolved in methanol (126 cm^3) and 50% aqueous NaOH (4.87 g made up to 10 cm^3 with water, 0.122 mol, 3 equiv.). The reaction mixture (red colour) was stirred for 1 hour at room temperature at which point TLC analysis (ethyl acetate: cyclohexane, 70: 30) indicated formation of the product (R_f 0.2) and the absence of starting material. The solvent was removed under vacuum to yield a dark brown solid, which was purified by

* Other signals that could not be assigned were also observed. Therefore, some unidentified impurities were present.

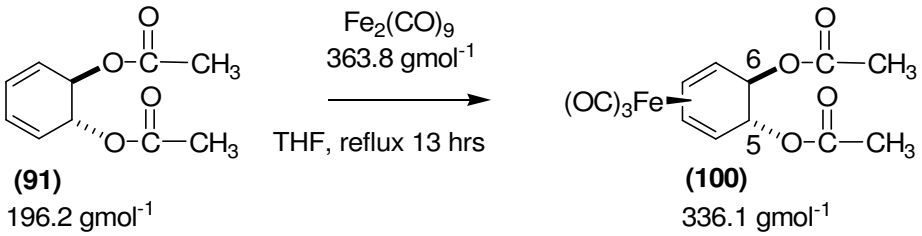
flash chromatography (ethyl acetate: cyclohexane, 70: 30) to afford the *trans*-diol product **(92)** (1.93 g, 42 %) as a deep orange oil.[℘]

δ_H / ppm (300 MHz; $CDCl_3$):[*] 4.01 (2 H, br s, 2 x OH), 4.49 (2 H, s, 1-H, 2-H), 5.86 (4 H, br s, 4 x CH)

4.3.2 Synthesis of (η^4-*trans*-5,6-diacetoxycyclohexa-1,3-diene)tricarbonyliron

4.3.2.1 (η^4-trans-5,6-Diacetoxycyclohexa-1,3-diene)tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of irontricarbonyl to a benzyl ester analogue.



(91) 196.2 $gmol^{-1}$ **(100)** 336.1 $gmol^{-1}$

trans-5,6-Diacetoxycyclohexa-1,3-diene **(91)** (0.33 g, 1.68 mmol) and diironnonacarbonyl (1.84 g, 5.05 mmol, 3 equiv.) were dissolved in THF (30 cm^3, anhydrous) forming a deep red solution. The reaction mixture was refluxed for 5 hours under argon (using a bubbler apparatus) at which point TLC analysis (pentane: ethyl acetate, 90: 10) indicated formation of the desired product (R_f 0.3). The reaction mixture was passed through a short silica column (diethyl ether) and then concentrated under reduced pressure. The residue was purified by flash chromatography (pentane: ethyl acetate, 85: 15) on silica gel to yield the irontricarbonyl complex **(100)** (0.11 g, 17% yield) as a yellow oil.[χ]

[℘] This product is not stable and is converted to an aromatic product. It should not be subjected to heat over a long period of time and the flash chromatography must be performed immediately.

[*] Other signals that could not be assigned were also observed. Therefore, some unidentified impurities were present.

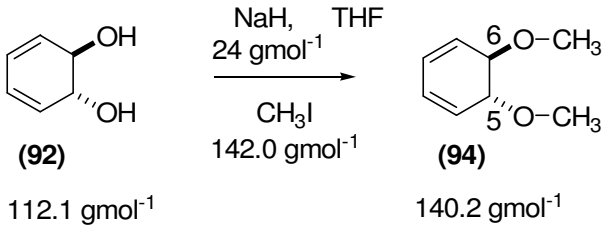
[χ] See appendices on protocol for safe handling of irontricarbonyl.

δ_H / ppm (400 MHz $CDCl_3$): 2.06 (6 H, br s, 2 x CH_3), 3.11 (2 H, m, 1-H, 4-H) 3.19 (1 H, d[**], *J* = 6.4 Hz, 5-H or 6-H) 4.68 (1 H, m, 5-H or 6-H), 5.32 (2 H, m, 2-H, 3-H)

δ_C / ppm (100 MHz; $CDCl_3$): 21.3 (2 x OCH_3), 59.8 (C-1, C-4), 63.4 (C-6), 69.9 (C-5) 83.3 (C-3) 85.5 (C-2)[***]

4.3.3 Synthesis of (η^4-*trans*-5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron

4.3.3.1 trans-5,6-Dimethoxycyclohexa-1,3-diene



trans-Cyclohexa-3,5-diene-1,2-diol **(92)** (0.50 g, 4.5 mmol) in THF (5 cm^3, anhydrous) was added dropwise from a pressure equalising funnel to a solution of 60% NaH in mineral oil (0.54 g, 13.4 mmol, 3 equiv.) and THF (10 cm^3, anhydrous) in a 2-neck 50 cm^3 round bottom flask cooled to 0 °C in an ice-bath. The reaction mixture was stirred for 15 minutes and then methyl iodide (2.53 g, 17.8 mmol, 4 equiv.) was added. The reaction mixture was then stirred for a further 3 hours at room temperature, at which point TLC analysis (ethyl acetate: cyclohexane, 1: 1) indicated formation of the product (R_f 0.6) and the absence of starting material. 100 cm^3 of water was added gradually to quench the reaction.

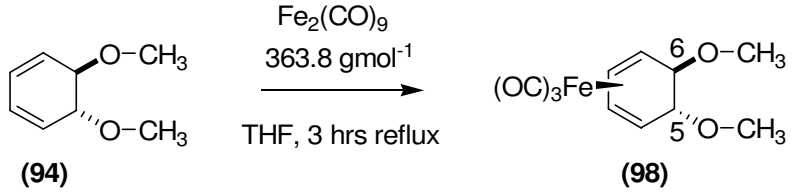
[**] Multiplet expected but could not be resolved on the spectrum obtained.
[***] C=O bond has not been resolved in this C^{13} spectrum.

Most of the THF was removed from the reaction mixture on a rotary evaporator until a partition between the aqueous and organic phase could be observed. The organic and aqueous layers were then separated and the aqueous layer was extracted with ethyl acetate (3 x 15 cm^3). The combined organic layers were washed with water (2 x 25 cm^3) and sodium hydrogen carbonate (15 cm^3 of saturated aqueous solution) and dried over anhydrous sodium sulfate. This was then filtered using a Buchner funnel. The solvent was evaporated under vacuum to yield the crude product as an orange oil. The residue was purified by flash chromatography (cyclohexane: ethyl acetate, 95: 5) to yield **(94)** as a yellow oil (0.26 g, 42%).

υ_{max} (thin film, $CDCl_3$)/cm^{-1}	2989, 2930 (sp^3 C-H stretch), 1469, 1376 (CH_3 C-H bend), 1102 (C-O stretch)
δ_H / ppm (400 MHz; $CDCl_3$):*	3.43 (6 H, m, 2 x OCH_3), 4.10 (2 H, apt d, 5-H, 6-H), 5.90 – 6.00 (4 H, m, 4 x CH)
δc / ppm (100 MHz; $CDCl_3$):	55.59, 55.93 (2 x OCH_3), 75.38, 76.01 (C-5, C-6), 124.00, 124.309, 125.79, 126.00 (4 x CH)

4.3.3.2 (η^4-trans-5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of irontricarbonyl to a benzyl ester analogue.



(94) 140.2 $gmol^{-1}$ **(98)** 280.1 $gmol^{-1}$

* Other signals that could not be assigned were also observed. Therefore, some unidentified impurities were present.

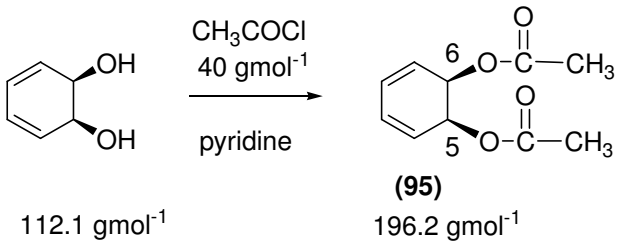
trans-5,6-Dimethoxycyclohexa-1,3-diene **(94)** (0.15 g, 1.07 mmo1) and diironnonacarbonyl (0.90 g, 3.0 mmol, 3 equiv.) were dissolved in THF (25 cm^3, anhydrous) forming a dark red/brown solution. The reaction mixture was refluxed for 6 hours under argon (using a bubbler apparatus) at which point TLC analysis (pentane: ethyl acetate, 90: 10) indicated formation of the product (R_f 0.2). The reaction mixture was passed through a short silica column (diethyl ether) and then concentrated under reduced pressure. The residue was purified by flash chromatography (pentane: ethyl acetate, 8: 2) on silica gel to yield the desired irontricarbonyl complex **(98)** as a yellow oil, (0.01 g, 5%).

υ_{max} (thin film, $CDCl_3$)/cm^{-1}:	2055, 1983 (C=O stretches), 1652 (C=C stretch), 1465, 1382 (CH_3 C-H bend), 1080 (C-O), 980, 727 (sp^2 C-H bend)
δ_H / ppm (400 MHz; $CDCl_3$)*	3.04 (1 H, m, 1-H or 4-H), 3.19 (3 H, s, OCH_3), 3.25 (1 H, m, 1-H or 4-H), 3.36 (3 H, s, OCH_3), 3.60 (1 H, apt t, J = 3.6, 5-H or 6-H), 4.72 (1 H, dd, $J_{5,6}$ = 4.8, $J_{5,4}$ =3.2 Hz, 5-H or 6-H), 5.21 (2 H, m, 2-H, 3-H)
δ_C / ppm (100 MHz; $CDCl_3$):	58.9 (OCH_3), 64.1 (C-5, C-6), 81.9 (C-1, C-4), 84.4 (C-2, C-3), 210.4 (C=O)

* Other signals that could not be assigned were also observed. Therefore, some unidentified impurities were present.

4.3.4 Synthesis of (η^4-*cis*-5,6-Diacetoxycyclohexa-1,3-diene)tricarbonyliron

4.3.4.1 cis-5,6-Diacetoxycyclohexa-1,3-diene



cis-Cyclohexa-3,5-diene-1,2-diol (0.51 g, 4.6 mmol) was dissolved in pyridine (0.6 cm^3, anhydrous) and acetyl chloride (1.43 g, 18 mmol, 4 equiv.) was added dropwise using a pressure equalising funnel. The reaction mixture was left stirring at room temperature for 4 hours under an atmosphere of nitrogen using a bubbler system, at which point TLC analysis (cyclohexane: ethyl acetate, 75: 25) indicated formation of the product (R_f 0.4). Dichloromethane (8 cm^3) was added to dissolve the off white precipitate that had formed and 1 M HCl (8 cm^3) was added gradually to quench the reaction.

A small-scale work up was performed in a test tube. Ethyl acetate (2 cm^3) and the reaction mixture were added to the test tube and they were mixed well. The organic and aqueous layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 2 cm^3). The combined organic layers were washed with water (2 cm^3) and dried over magnesium sulfate. The magnesium sulfate was removed by filtering through a pasteur pipette containing some cotton wool. The solvent was removed from the filtrate under vacuum and the residue was purified by flash chromatography (cyclohexane: ethyl acetate 75: 25) to afford **(95)** as a clear oil (0.58 g, 65%).

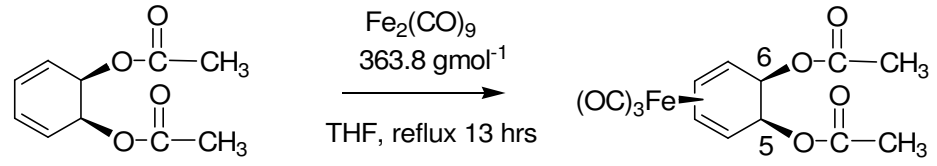
υ_{max} (thin film, $CDCl_3$)/cm^{-1}: 1737 (C=O, ester band), 1648 (C=C), 1412, 1371 (CH_3 C-H bend), 1243, 1063 (C-O stretch),

δ_H / ppm (400 MHz $CDCl_3$): 2.08 (6 H, s, 2 x CH_3), 5.55 (2 H, br s, 5-H, 6-H), 5.90 (2 H, m, 1-H, 4-H), 6.14 (2 H, m, 2-H, 3-H)

δ_C / ppm (100 MHz; $CDCl_3$): 21.3 (OCH_3), 67.36 (C-5, C-6), 125.7 (C-1, C-4), 126.7 (C-2, C-3), 170.8 (C=O)

4.3.4.2 (η^4-cis-5,6-Diacetoxycyclohexa-1,3-diene)tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of irontricarbonyl to a benzyl ester analogue.



(95) 196.2 $gmol^{-1}$ **(99)** 336.1 $gmol^{-1}$

cis-5,6-Diacetoxycyclohexa-1,3-diene **(95)** (0.53 g, 2.70 mmol) and diironnonacarbonyl (2.46 g, 6.75 mmol, 2.5 equiv.) were dissolved in THF (60 cm^3, anhydrous) forming a dark brown/red solution. The reaction mixture was refluxed for 13 hours under argon (using a bubbler apparatus) at which point TLC analysis (pentane: ethyl acetate, 90: 10) indicated formation of the desired product (R_f 0.2). The reaction mixture was passed through a short silica column (diethyl ether) and then the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (pentane: ethyl acetate, 85: 15) on silica gel to yield the irontricarbonyl complex **(99)** (0.12 g, 13% yield) as a yellow solid, m.p. 119.2 -120.4 ºC.

Analysis found: C, 46.0; H, 3.8; Fe, 16.25%

$C_{13}H_{12}FeO_7$ Requires: C, 46.5; H, 4.6; Fe, 16.6 %.

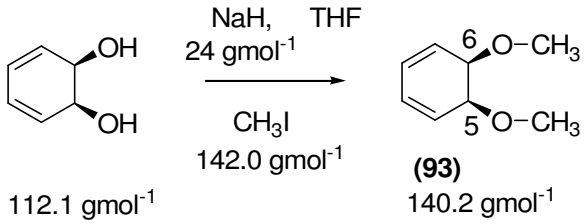
υ_{max} (thin film)/cm^{-1}: 2979 (sp^3 C-H stretch), 2058, 1993, 1969 (C=O stretches), 1794 (C=O ester band), 1622 (C=C), 1463, 1380 (sp^3 C-H bend), 1257, 1090 (C-O stretch), 907, 733 (sp^2 C-H bend)

δ_H / ppm (400 MHz $CDCl_3$): 2.07 (6 H, s, 2 x CH_3), 3.03 (2 H, m, 1-H, 4-H), 4.86 (2 H, s, 5-H, 6-H), 5.34 (2 H, dd, *J* = 5.2, 2.8 Hz, 2-H, 3-H)

δ_C / ppm (100 MHz; $CDCl_3$): 20.6 (2 x OCH_3), 61.9 (C-1, C-4), 70.0 (C-5, C-6), 83.6 (C-2, C-3), 169.9 (C=O)

4.3.5 Synthesis of *trans*-6-Methoxycyclohexa-3,5-diene-1-ol

4.3.5.1 cis-5,6-Dimethoxycyclohexa-1,3-diene



cis-Cyclohexa-3,5-diene-1,2-diol (8.48 g, 0.076 mol) in THF (20 cm^3, anhydrous) was added dropwise from a pressure equalising funnel to a solution of 60% sodium hydride in mineral oil (9.08 g, 0.227 mol, 3 equiv.) and THF (20 cm^3, anhydrous) in a 500 cm^3 2-neck round bottom flask cooled in an ice bath. The reaction mixture was stirred for 30 minutes at which stage methyl iodide (18.9 cm^3, 0.3 mol, 4 equiv) was added. The reaction mixture was stirred for a further 2 hours at room temperature, at which point TLC analysis (cyclohexane: ethyl acetate 1: 1) indicated formation of the product (R_f 0.4), some anisole side product (R_f 0.5) and the absence of starting material. 200 cm^3 of water was added gradually to quench the reaction.

The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 100 cm^3). The combined organic layers were washed with water (2 x 100 cm^3) and sodium hydrogen carbonate (50 cm^3 of saturated aqueous

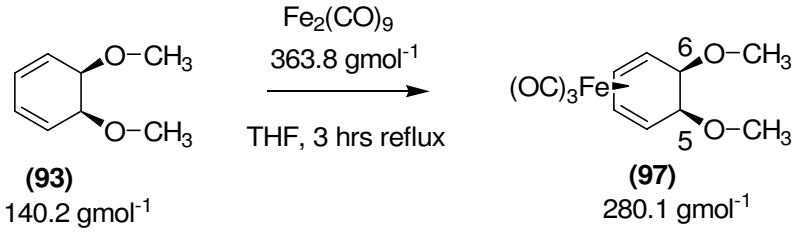
solution) and dried over anhydrous sodium sulfate. The solvent was removed from the filtrate under vacuum and the residue was purified by flash chromatography (cyclohexane: ethyl acetate 95: 5) to afford **(93)** as an orange oil (2.09 g, 20%).

δ_H / ppm (400 MHz; $CDCl_3$): 3.42 (6 H, s, 2 x OCH_3), 3.91 (2 H, br s, 5-H, 6-H), 6.00 (4 H, m, 4 x CH).

δc / ppm (100 MHz; $CDCl_3$): 56.8 (2 x OCH_3), 74.4 (C-5, C-6), 125.4, 127.3 (C-1, C-2, C-3, C-4).

4.3.5.2 (η^4-cis-5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of irontricarbonyl to a benzyl ester analogue.



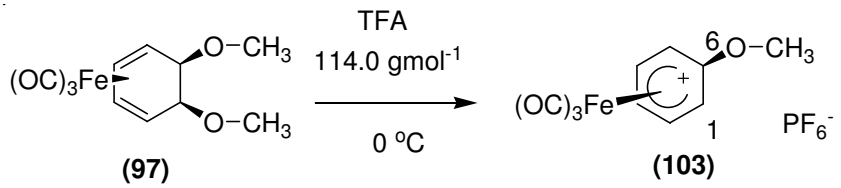
cis-5,6-Dimethoxycyclohexa-1,3-diene **(93)** (0.20 g, 1.43 mmol) and diironnonacarbonyl (1.04 g, 2.85 mmol) were dissolved in THF (25 cm^3, anhydrous) forming a dark brown/red solution. The reaction mixture was refluxed for 2 hours under argon (using a bubbler apparatus) at which point TLC analysis (pentane: ethyl acetate, 9:1) indicated formation of the product (R_f 0.2). The reaction mixture was passed through a short silica column (diethyl ether) and then concentrated under reduced pressure. The residue was purified by flash chromatography (pentane: ethyl acetate, 85: 15) on silica gel to yield the irontricarbonyl complex **(97)** (0.33 g, 82% yield) as a yellow sticky solid, m.p. 89.1-89.9 ºC.

Analysis found: C, 48.7; H, 4.3; Fe, 18.7%

$C_{11}H_{12}FeO_5$ Requires:	C, 47.2; H, 4.3; Fe, 19.9%
υ_{max} (nujol)/cm^{-1}:	2062, 2000, 1973 (C=O stretch), 1652 (C=C stretch), 1155 (C-O).
δ_H / ppm (400 MHz; $CDCl_3$):	3.14 (2 H, apt t, *J* = 4 Hz, 1-H, 4-H), 3.40 (8 H, br s, 2 x OCH_3, 5-H, 6-H) 5.23 (2 H, dd, *J* = 5.6, 2.8 Hz, 2-H, 3-H)
δc / ppm (100 MHz; $CDCl_3$):	58.1 (C-1, C-4), 63.9 (OCH_3, C-5, C-6), 83.5 (C-2, C-3), 210.7 (C=O).

4.3.5.3 (η^5-6-Methoxycyclohexa-2,4-dien-1-yl)tricarbonyliron Hexafluorophosphate

The title compound was synthesised according to the method of Stephenson *et al.*[50]



(97) 280.1 $gmol^{-1}$ **(103)** 394.0 $gmol^{-1}$

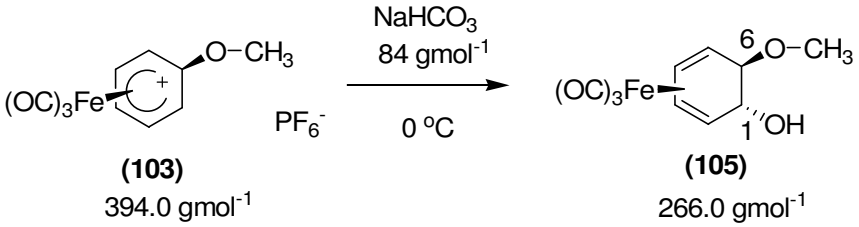
(η^4-*cis*-5,6-Dimethoxycyclohexa-1,3-diene)tricarbonyliron **(97)** (0.38 g, 1.4 mmol) and trifluoroacetic acid (TFA) (0.50 g, 4.3 mmol, 3 equiv.) were added to a 10 cm^3 round bottomed flask and left stirring under anhydrous conditions in an ice-bath at 0 °C for 1 hour. The reaction mixture was then cooled to -78 °C using a liquid nitrogen /ethyl acetate slush bath and ammonium hexafluorophosphate (0.27 g, 1.6 mmol, 1.2 equiv.) was added. The round bottomed flask was then immersed in a water bath at room temperature and the reaction mixture was allowed to return to room temperature. The precipitate formed was isolated by vacuum filtration and washed with deionised water (4 x 3 cm^3 portions). The residue was dried overnight to give the dienyl complex (1.25 g) as

a yellow crystalline solid. It was attempted to reprecipitate the product from a solution in acetonitrile by the addition of cold diethyl ether, however precipitation did not occur and the solvent was removed from the solution under reduced pressure to give **(103)** as a yellow oil[℘] (0.52 g, 95% yield).

υ_{max} (thin film)/cm^{-1}:	2118, 2084, 2062 (C=O stretches), 1638 (C=C stretch), 1413, 1335 (CH_3, C-H bend), 1200, 1111 (C-O, ether), 893, 838 (sp^2 C-H bend)
δ_H / ppm (400 MHz CD_3CN):	3.39 (3 H, s, OCH_3), 3.77 (1 H, m, 6-H), 4.01 (2 H, m, 1-H, 5-H), 5.75 (2 H, m, 2-H, 4-H), 6.96 (1 H, m, 3-H)
δ_C / ppm (100 MHz; CD_3CN):	56.1 (OCH_3), 66.9 (C-6), 69.9 (C-1, C-5), 87.53 (C-2, C-4), 99.7 (C-3)[***]

4.3.5.4 (η^4-trans-6-Methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron

The title compound was synthesised in a similar manner according to the method of Pearson *et al.*[53]



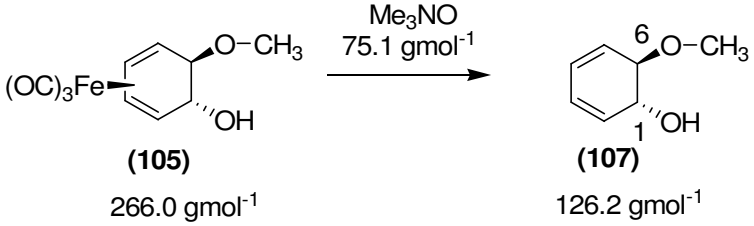
(η^5-6-Methoxycyclohexadien-1-yl)tricarbonyliron hexafluorophosphate **(103)** (0.84 g, 2.13 mmol) was dissolved in acetonitrile (10 cm^3, anhydrous) in a conical flask and was left on an ice bath to cool to 0 °C. Sodium hydrogen carbonate (0.72 g, 8.51

[℘] In future reprecipitation will not be performed.
[***] The C=O band was not intense enough to be seen on the spectrum.

mmol, 4 equiv) was dissolved in the minimum amount of deionised water and was also left on an ice bath to cool to 0 °C. The dienyl salt solution was then added dropwise to the buffer and allowed to return to room temperature. The reaction mixture was extracted with diethyl ether, and dried over magnesium sulfate. The solvent was removed from the filtrate under reduced pressure and the residue was purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1, R_f 0.3) to give **(105)** as a pale yellow solid, (0.29 g, 51% yield).

Analysis found:	C, 45.21 H, 3.8 %[℘]
$C_{11}H_{12}FeO_5$ Requires:	C, 43.8; H, 3.8; Fe, 21.0 %
δ_H / ppm (400 MHz $CDCl_3$):	2.95 (2 H, m, 2-H, 5-H), 3.20 (1 H, s, OH), 3.39 (4 H, s[with shoulder]), OCH_3, 6-H), 3.97 (1 H, br m, 1-H), 5.40 (1 H, m, 3-H or 4-H), 5.51 (1 H, m, 3-H or 4-H)
δ_C / ppm (100 MHz; $CDCl_3$):	55.9 (C-2, C-5), 58.4 (C-OH), 61.5 (OCH_3, C-1), 82.2 (C-6), 84.3, 84.9 (C-1, C-4), 210.4 (C=O)

4.3.5.5 trans-6-Methoxycyclohexa-2,4-diene-1-ol



(η^4-*trans*-6-Methoxycyclohexa-2,4-diene-1-ol)tricarbonyliron **(105)** (0.16 g, 0.61 mmol) was dissolved in dichloromethane (8 cm^3, anhydrous) and stirred under

[℘] The instrument to analyse the % Fe was not available to be used at the time and, due to the instability of these compounds, further tests were restricted.

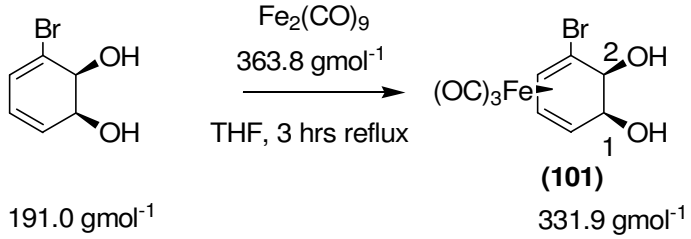
argon (using a bubbler apparatus) at room temperature. Trimethylamine-*N*-oxide (0.46 g, 6.05 mmol, 10 equiv.) was then weighed out under a stream of argon and transferred quickly to the reaction mixture. The brown solution was left stirring overnight at room temperature but TLC analysis showed that the reaction had not progressed. Further equivalents of trimethylamine-*N*-oxide (0.55 g, 7.26 mmol, 12 equiv.) were added to the reaction mixture and it was allowed to reflux for 8 hours at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of some product (R_f 0.3). The crude product was purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1) to yield **(107)** as a pale yellow oil, (0.06 g, 79%).

Analysis found:	C, 65.3; H, 8.1%
$C_{13}H_{12}Fe$ Requires:	C, 66.6; H, 8.0%
υ_{max} (thin film)/cm^{-1}:	3402 (O-H stretch), 2933, 2825 (sp^2 C-H stretches), 1648 (C=C), 1456 (-CH_2- bend), 1403, 1357 (CH_3 C-H bend), 1193, 1109 (C-O), 820, 692 (sp^2 C-H bend)
δ_H(400 MHz $CDCl_3$):	2.55 (1 H, br s, OH), 3.42 (3 H, br s, OCH_3), 4.04 (1 H, m, 6-H)*, 4.50 (1 H, m, 1-H), 5.87-5.95 (4 H, m, 4 x CH)
δ_C(100 MHz; $CDCl_3$):	55.4 (C-OH), 70.6 (OCH_3), 75.7 (C-6), 81.9 (C-1), 122.8, 123.8, 125.9, 129.2 (4 x CH)

* Doublet of doublets expected.

4.3.6 Synthesis of (η^4-*cis*-3-Bromocyclohexa-3,5-diene-1,2-diol)tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of tricarbonyliron to a benzyl ester analogue.



cis-3-Bromocyclohexa-3,5-diene-1,2-diol (0.33 g, 1.7 mmo1) and diironnonacarbonyl (1.88 g, 5.2 mmol) were dissolved in THF (40 cm^3, anhydrous) forming a dark red/brown solution. The reaction mixture was refluxed for 3 hours under argon (using a bubbler apparatus) at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of the product (R_f 0.4). The reaction mixture was passed through a short silica column (diethyl ether) and then concentrated under reduced pressure.[℘] The residue was purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1) on silica gel to yield the irontricarbonyl complex **(101)** as a yellow solid, (0.57 g, 90%); m.p. 99.4-100.1 ºC.

Analysis found:	C, 32.9; H, 2.1; Fe, 16.5%
$C_{13}H_{12}FeO_5$, Requires:	C, 32.6; H, 2.1; Fe, 16.8 %
υ_{max} (thin film, DCM)/cm^{-1}:	3351 (O-H stretch), 2890 (sp^3 C-H stretch), 2062, 1990 (C=O stretches), 1633 (C=C), 1218, 1065 (C-O), 974, 847, 739 (sp^2 C-H bend)
δ_H / ppm (400 MHz $CDCl_3$):	3.00 (1 H, d, $J_{2\text{-OH},2}$ = 4.4 Hz, 2-OH), 3.11 (2 H, m, 1-OH, 6-H (becomes 1 H after D_2O shake), 6-H), 3.87 (1 H, m, 1-H), 3.94 (1 H, dd, $J_{2,2\text{-OH}}$ = 4.4 Hz,

[℘] See appendix A on protocol for safe handling of irontricarbonyl.

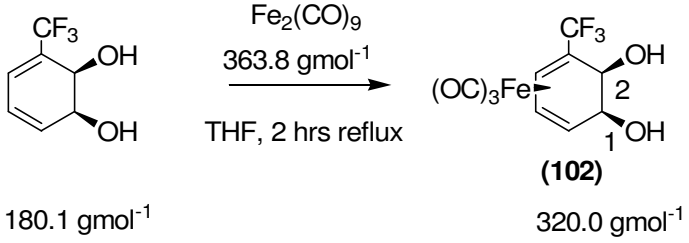
$J_{1,2}$ = 6.4 Hz, 2-H), 5.15 (1 H, ddd, $J_{5,6}$ = 6.8, $J_{5,4}$ = 4.0, $J_{5,1}$ = 0.8 Hz, 5-H), 5.67 (1 H, dd, $J_{4,5}$ = 4.4, $J_{4,6}$ = 1.2 Hz, 4-H)

δ_C / ppm (100 MHz; $CDCl_3$): 66.0, 68.2 (C-6, C-1), 73.3 (C-2), 79.2 (C-5), 81.0 (C-4), 87.3 (C-3)[℘]

4.3.7 Synthesis of [η⁴-*trans*-2-Acetoxy-3-(trifluoromethyl)cyclohexa-3,5-diene-1-ol]tricarbonyliron

4.3.7.1 [η⁴-cis-3-(Trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron

The compound was synthesised in a similar manner to that reported by Suemune *et al.*[54] for the coordination of tricarbonyliron to a benzyl ester analogue.



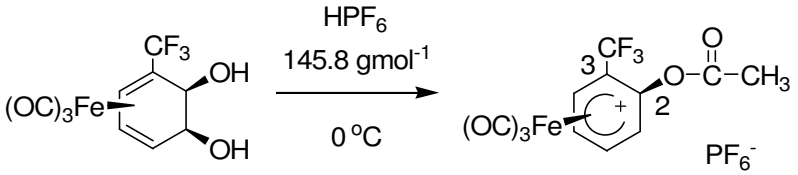
cis-3-(Trifluoromethyl)cyclohexa-3,5-diene-1,2-diol (0.30 g, 1.67 mmo1) and diironnonacarbonyl (1.74 g, 4.79 mmol) were dissolved in THF (30 cm^3, anhydrous) forming a dark red/brown solution. The reaction mixture was refluxed for 2 hours under argon (using a bubbler apparatus) at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of the product (R_f 0.3). The reaction mixture was passed through a short silica column (diethyl ether) and then concentrated under reduced pressure.[℘] The residue was purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1) on silica gel to yield the irontricarbonyl complex **(102)** as a yellow solid, (0.37 g, 69%); m.p. 110.5-111.7 ºC (lit.,[53] 114-115 ºC).

[℘] The C=O band was not intense enough to be seen on the spectrum.
[℘] See appendix A on protocol for safe handling of irontricarbonyl.

Analysis found:	C, 37.6; H, 2.2; Fe, 17.0%
$C_{13}H_{12}FeO_5$ Requires:	C, 37.5; H, 2.2; Fe, 17.5%
υ_{max} (nujol)/cm^{-1}:	3152 (O-H stretch), 2253, 2071, 2010 (C=O stretch), 1470, 1377 (CH_3 C-H bend), 1288, 1153 (C-O), 908, 732 (sp^2 C-H bend)
δ_H / ppm (400 MHz; $CDCl_3$):	2.69 (1 H, br d, $J_{2\text{-}OH,2}$ = 4.4 Hz, 2-OH), 2.87 (1 H, br s, 1-OH), 3.27 (1 H, m, 6-H),** 3.93 (2 H, br m, 1-H, 2-H), 5.25 (1 H, dd, $J_{5,4}$ = 4.8, $J_{5,6}$ = 6.4 Hz, 5-H) 5.65 (1 H, dd, $J_{4,5}$ = 4.8 $J_{4,6}$ = 1.6 Hz, 4-H)
δ_C / ppm (400 MHz; $CDCl_3$):	66.7 (C-6), 67.0, 67.5 (C-1, C-2), 70.8 (C-5), 81.9 (C-4), 84.2 (C-3), 127.8 (CF_3)*

4.3.7.2 [η^5-2-Acetoxy-3-(trifluoromethyl)cyclohexadien-1-yl]tricarbonyliron Hexafluorophosphate

The compound was synthesised in a similar manner to that reported by Pearson *et al.*[53]



(102) 320.0 $gmol^{-1}$ **(104)** 490.0 $gmol^{-1}$

** Doublet of doublets expected.
* The C=O band was not intense enough to be seen on the spectrum.

[η^4-*cis*-3-(Trifluoromethyl)cyclohexa-3,5-diene-1,2-diol]tricarbonyliron **(102)** (0.21 g, 0.64 mmol) was dissolved in dichloromethane (1.5 cm^3) and stirred under argon in a salt ice bath until a temperature of 0 °C was reached. Acetic anhydride (1.5 cm^3) and hexafluorophosphoric acid (0.4 cm^3, 2.6 mmol), were both added to the reaction mixture *via* syringe and a pale yellow solution formed. This was left stirring at 0 °C for 3 hours at which point TLC analysis (cyclohexane: ethyl acetate, 1: 1) indicated formation of the product (R_f 0.4). The product was isolated by adding the solution dropwise to diethyl ether (10 cm^3), decanting the solvent and rinsing the residue by decantation with diethyl ether (3 x 5 cm^3). The crude product was isolated as an oil which was then recrystallised from dry acetonitrile to give a yellow precipitate. The precipitate was collected by vacuum filtration to yield the desired complex salt **(104)** (0.15 g, 48%) as yellow crystals.[℘]

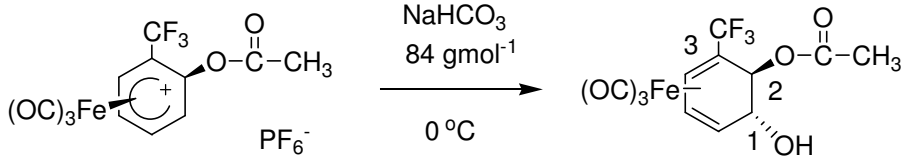
υ_{max} (nujol)/cm^{-1}:	2135, 2085 (C=O), 1763 (C=O), 1300 (*sp*^{3} C-H bend), 1155, 1073 (C-O)
δ_H / ppm (400 MHz; CD_3CN):	2.26 (3 H, s, CH_3), 4.54 (1 H, apt d, $J_{1,2}$ = 8 Hz, 1-H), 5.27 (1 H, br s (with shoulder), 2-H)[**], 6.03 (1 H, br m, 6-H), 6.61 (1 H, d, $J_{4,5}$ = 5.6 Hz, 4-H), 7.60 (1 H, t, $J_{5,6,4}$ = 5.6 Hz, 5-H)

[℘] This compound is extremely unstable and therefore was used for the next step straight away. As a result further analysis was not performed. This fast decomposition of the cation complex salt was shown by NMR a day later when aromatisation was observed (signals at 7-8 ppm).

[**] Doublet of doublets expected.

4.3.7.3 [η⁴-2-trans-Acetoxy-3-(trifluoromethyl)cyclohexa-3,5-diene-1-ol]tricarbonyliron

The compound was synthesised in a similar manner to that reported by Pearson *et al.*[53]



(104)
490.0 gmol^{-1}

(106)
362.0 gmol^{-1}

[η^5-2-Acetoxy-3-(trifluoromethyl)cyclohexadien-1-yl]tricarbonyliron hexafluorophosphate **(104)** (0.12 g, 0.25 mmol) was dissolved in acetonitrile (2 cm^3, anhydrous) in a conical flask and was cooled on a salt-ice bath to 0 °C. Sodium hydrogen carbonate (0.08 g, 0.98 mmol, 4 equiv.) was dissolved in the minimum amount of distilled water and was also cooled on an ice bath to 0 °C. The dienyl salt was then added dropwise to the buffer and the mixture was allowed gradually to return to room temperature. The reaction mixture was extracted with diethyl ether and dried over anhydrous magnesium sulfate. The solvent was evaporated from the filtrate under reduced pressure and the residue was purified by flash chromatography (cyclohexane: ethyl acetate, 1: 1, R_f 0.4) to give **(106)** as pale yellow crystals[℘] (81 mg, 91%), m.p. 104.6 – 105.9 °C (lit.,[53] 100-101°C).

υ_{max} (nujol)/cm^{-1}: 3351 (O-H stretch), 2072, 2013, 2004 (C=O), 1715 (C=O ester stretch), 1461, 1377 (CH_3 C-H bend), 1248, 1116 (C-O), 722, 674 (sp^2 C-H)

δ_H / ppm (400 MHz; $CDCl_3$): 2.14 (3 H, s, CH_3), 3.15 (1 H, m, 6-H), 3.19 (1 H, d, $J_{2,1}$ = 2.4 Hz, 2-H), 3.95 (1 H, br s, 1-H), 4.42 (1 H,

[℘] A minor amount of another compound (approximately 10%) was detected in the ^{1}H NMR spectrum.

br s, OH), 5.48 (1 H, t, J = 5.2 Hz, 5-H), 5.84 (1 H, d, $J_{4,5}$ = 4.4 Hz, 4-H)

4.4 Reagents Used for Kinetic and Equilibrium Measurements

4.4.1 Solvents

Water was doubly distilled and deionised and stored in brown glass bottles. HPLC grade water (Romil Super Purity Solvent) was also used. Methanol and Acetonitrile were HPLC grade and they were obtained Riedel-de Haën.

4.4.2 Acids and Buffers

Hydrochloric acid solutions were prepared by dilution of BDH Aristar grade concentrated HCl (~ 12 M) and standardised with sodium hydroxide solution using phenolphthalein as an indicator.

Perchloric acid solutions were prepared from BDH Analar grade concentrated acid (60% or 70%) and standardised with sodium hydroxide solution using phenolphthalein as an indicator.

Buffer solutions were prepared by partial neutralisation of the base with hydrochloric acid or by partial neutralisation of the acid with sodium hydroxide. Commercial reagents were used without further purification. All pK_a values for buffers were obtained from Perrin and Dempsey.[128]

Acetate buffers were prepared from sodium acetate trihydrate (Riedel de Haën, 99.5%) and hydrochloric acid.

Carbonate buffers were prepared from sodium carbonate (Fluka, 99.5%) and sodium hydrogen carbonate (Fluka, 99%).

Cacodylate buffers were prepared using either cacodylic acid (Aldrich, 98%) and sodium hydroxide or sodium cacodylate (Fluka, 98%) and hydrochloric acid.

4.5 Instrumentation for Kinetic and Equilibrium Measurements

4.5.1 UV Spectrophotometry

A Varian Cary 50 scan spectrophotometer was used which covered the range 190 - 800 nm with a Xenon lamp as the light source. This spectrophotometer was a single beam instrument and was equipped with an eighteen cell changer compartment. A Hitachi U-2010 double beam spectrophotometer was also used. This required placing a second quartz cuvette containing only the background acid, base, buffer or solvent solution in the cell holder and a background absorbance was automatically taken and subtracted throughout the kinetic run. Both instruments could be operated in either spectral or single wavelength monitoring modes. 1 cm wide quartz cuvettes fitted with Teflon caps were used and the temperature in the cell compartment was maintained at 25.0 ± 0.1 °C by circulating water from a thermostatted water bath (Julabo, ED5).

4.5.2 UV-Vis Spectrophotometry Using a Fast Mixing Apparatus

A fast mixing accessory must be used to monitor reactions of which the lifetime is measured in seconds. In this study, a RX 2000 rapid kinetics stopped-flow mixing accessory (Applied Photophysics) as shown in Chart 4.1 was used. This apparatus allows for the monitoring of reactions which are up to a thousand times faster than those which can be examined when manual mixing is performed.

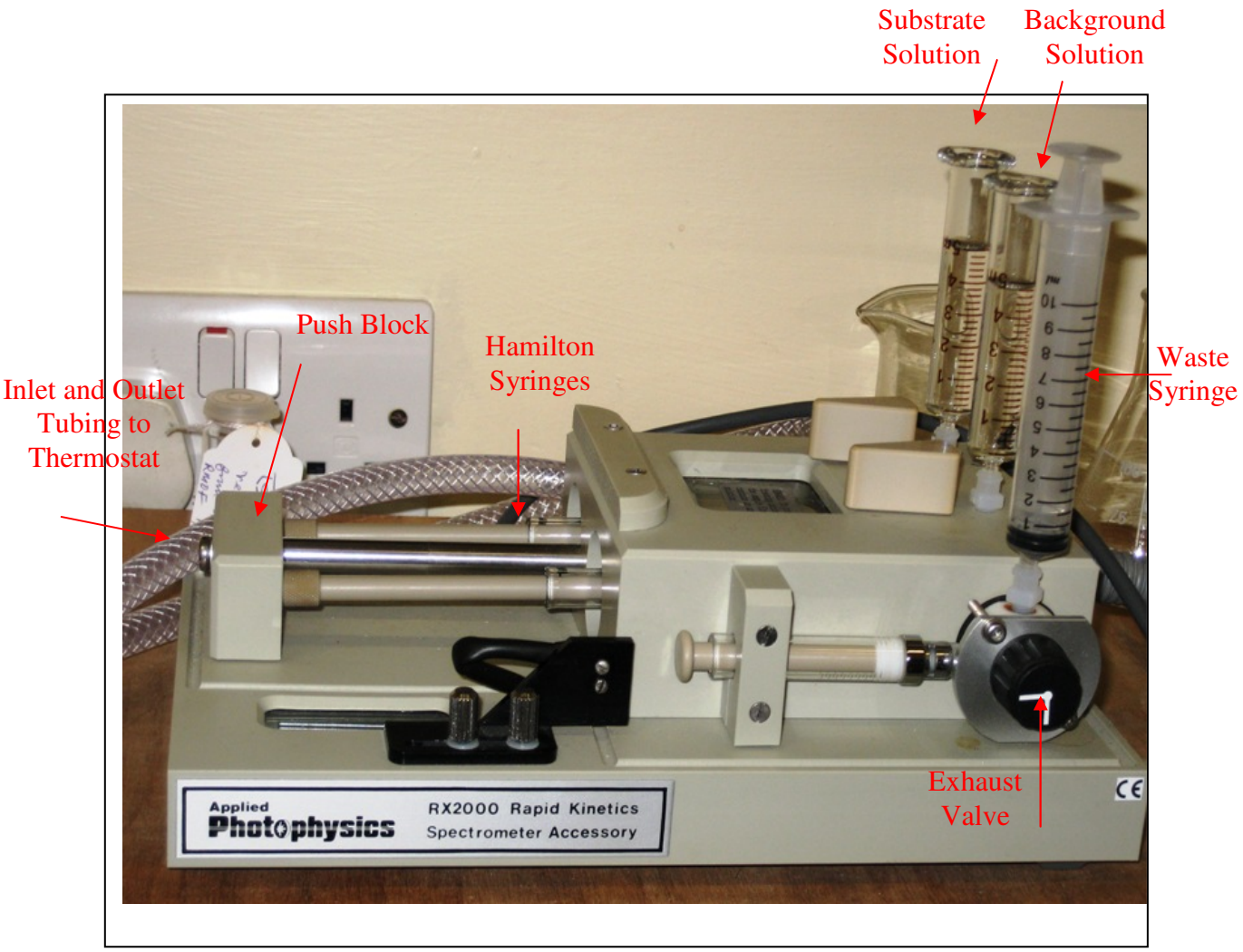


Chart 4.1 Picture of the RX 2000 Rapid Kinetics Stopped-Flow Mixing Accessory (Applied Photophysics).

A thermostatted water bath was connected to the RX 2000 accessory to maintain the temperature of the sample solution at 25.0 ± 0.1 °C. The reagent system contains two Hamilton syringes, which, along with an inlet tube from the water bath, are connected to a specialised cuvette *via* an umbilical tube. The specialised cell is constructed with standard dimensions of 10 x 10 mm in order to be readily connected to standard instrumentation with a cuvette compartment of equal size. The cell is a micro-cell fitted with four observation windows and is made of silica. It can be used with a pathlength of 2 or 10 mm. For experiments carried out in this study, a pathlength of 10 mm was used.

4.6 Kinetic and Equilibrium Measurements

All measurements were made at 25 °C in aqueous solution unless otherwise stated.

4.6.1 Equilibrium Measurements

The equilibrium constant, pK_R, obtained for the ionisation of (5-hydroxy-6-methoxy-cyclohexa-1,3-diene)tricarbonyliron and the hydrolysis of (6-methoxy-cyclohexadienyl)tricarbonyliron was determined from kinetic measurements for these reactions performed in aqueous solution (Section 2.2.2.1, page 60 and Section 2.2.2.2, page 63).

The pK_R value obtained for the for the interconversion between the methoxy substituted cation, (6-methoxycyclohexadienyl)tricarbonyliron, and its *trans*-dimethoxy substituted analogue, *trans*-5,6-dimethoxycyclohexa-1,3-diene)tricarbonyliron, was determined spectrophotometrically by the method of Albert and Serjeant.[129] Spectra were recorded for the fully ionised species and fully unionised species and also for the partially ionised species as described in Section 2.2.3 on page 67. The equilibrium constant for this methanolysis was calculated according to the method described in Section 4.6.2 which follows.

4.6.2 Calculation of Spectrophotometrically Determined Equilibrium Constants

Using an equilibrium method, determination of the equilibrium constant, pK_R, for formation of the coordinated *trans*-dimethoxy substituted cyclohexadiene examined in this study involved manipulating the data to provide a plot of absorbance versus pH using Sigmaplot software. The best fit line through the data points was required in order for the pK_R value to be obtained at the point of inflection. The equations governing the best fit lines were derived as shown below.

The equilibrium constant, K_R, for the reaction expressed in Scheme 4.1 is given in Equation 4.1 where [B] is the concentration of the coordinated *trans*-dimethoxy

substituted complex and $[BH^+]$ is the concentration of the coordinated methoxy-substituted cyclohexadienyl cation.

$$[BH^+] + H_2O \rightleftharpoons [B] + [H^+]$$

Scheme 4.1

$$K_R = [B]\,[H^+] / [BH^+] \qquad (4.1)$$

Chart 4.1 shows the hypothetical absorbances that would be observed when the coordinated cyclohexadienyl cation (A_{BH^+}) and the coordinated coordinated *trans*-dimethoxy cyclohexadiene (A_B) are in their fully formed states respectively. The absorbance, A, refers to any absorbance measured when an incomplete reaction has been observed from either the cation to the dimethoxy complex or from the dimethoxy complex to the cation.

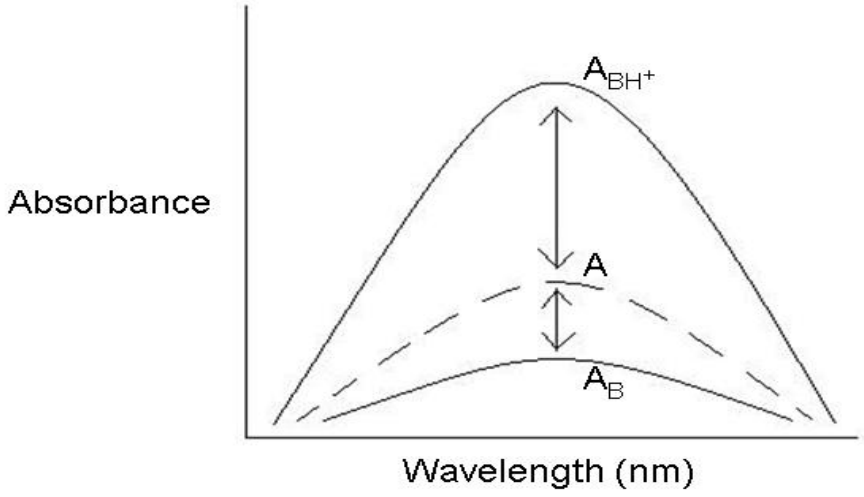


Chart 4.2 **A diagram of absorbance versus wavelength showing the hypothetical spectra of A_{BH+} (the coordinated cyclohexadienyl cation), A_B, (the coordinated dimethoxy complex) and A (the observed absorbance for an incomplete methanolysis of the cation to the dimethoxy complex or vice versa)**

Assuming the total concentration of $[BH^+]$ and [B] remains constant, the ratio of the observed absorbances is related to the concentrations as shown in Equation 4.2.

$$(A_{BH^+} - A) / (A - A_B) = [B] / [BH^+] \quad (4.2)$$

Substituting for $[B] / [BH^+]$ in Equation 4.1 using Equation 4.2 provides Equation 4.3 which, when rearranged to express the equation in terms of A, affords Equation 4.4.

$$K_R = [H^+] \{(A_{BH^+} - A) / (A - A_B)\} \quad (4.3)$$

$$A = \{K_R A_B + A_{BH^+}[H^+]\} / \{K_R + [H^+]\} \quad (4.4)$$

The absorbance, A, can be calculated for each pH value if $[H^+]$, A_B, K_R and A_{BH^+} are known. These constraints are iterated to provide a best fit of calculated to observed values of A, showing the calculated values as a continuous plot of A versus pH. Equation 4.4, the equation that governs the absorbance versus pH plots is shown in Section 2.2.3 on page 69, as Equation 2.5.

4.6.3 Kinetic Measurements

Kinetic measurements were made by accurately pipetting 2.0 cm^3 of aqueous acid or buffer solution into a 1 cm wide spectrophotometric cell that was allowed to reach a constant temperature of 25 °C in the cell compartment of the spectrometer over 10 minutes. The reaction was initiated by injecting substrate solution into the reaction solution using a Hamilton microlitre syringe. The concentration of the substrate solution was usually 10^{-3} - 10^{-5} M in spectroscopic grade methanol or acetonitrile, which gave a final concentration of 10^{-5} – 10^{-6} M in the UV cell.

4.6.4 Calculations for Kinetic Measurements

First Order Kinetics

First order rate constants, k_{obs}, determined by UV spectrophotometry were calculated in two ways:

1. By inputting absorbance versus time measurements into Sigmaplot v 8.0 software and then using the regression wizard to fit the first order plot to a regression equation. For a first order increase in absorbance with time, the data were fitted to an exponential rise to maximum as in Equation 4.5:

$$y = y_0 + a(1-e^{-bx}) \quad (4.5)$$

Where x = time, y = absorbance and b = k_{obs}. For a first order decrease in absorbance, the data were fitted to an exponential decay equation as in Equation 4.6:

$$y = y_0 + ae^{-bx} \quad (4.6)$$

Where x = time, y = absorbance and b = k_{obs}.

2. By using the UV-Vis spectrophotometer software, Cary Win UV Scanning Kinetics program v 3.0 or Cary Win UV Kinetics program v 3.0, and selecting the "analyse data" function to fit the first order plot to a regression equation. Results obtained with this software were compared to those obtained using Sigmaplot v 8.0 and they agreed.

Second order rate constants were obtained as $k_2 = k_{obs} / [H^+]$ or more often from a plot of k_{obs} versus $[H^+]$.

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Abbreviations:

Angew. Chem. Int. Ed.	Angewandte. Chemie International Edtion
Angew. Chem. Ed.Engl.	Angewandte. Chemie Edition England
Angew. Chem.	Angewandte. Chemie
Aust. J. Chem.	Australian Journal of Chemistry
Biochem. J.	Biochemical Journal
Bioorg. Med. Chem. Lett.	Bioorganic Medical Chemistry Letters
Chem. Comm.	Chemical Communications
Chem. Rev.	Chemical Reviews
Chem. Soc. Rev.	Chemical Society Reviews
Circ. Res.	Circulation Research
C.R. Hebd. Seances. Acad. Sci.	Comptus Rendus Hebdomadaires des Seances de l'Academie des Sciences
Current Opin. Biotechnol.	Current Opinion in Biotechnology
Drug. Metab. Rev.	Drug Metabolism Reviews
Eur. J. Inorg. Chem.	European Journal of Inorganic Chemistry
Inorg. Chem.	Inorganic Chemistry
J. Am. Chem. Soc.	Journal of the American Chemical Society
J. Biol. Chem.	Journal of Biological Chemistry
J. Chem. Soc.	Journal of the Chemical Society
J. Chem. Soc. A	Journal of the Chemical Society A
J. Chem. Soc. Chem. Comm.	Journal of the Chemical Society, Chemical Communications
J. Chem. Soc. Dalton. Trans.	Journal of the Chemical Society, Dalton Transactions
J. Liebig. Ann. Chem.	Justus Liebigs Annalen der Chemie
J. Molec. Cat. B: Enzymatic	Journal of Molecular Catalysis B: Enzymatic
J. Org. Chem.	Journal of Organic Chemistry
J. Organometallic Chem.	Jounal of Organometallic Chemistry
Nat. Prod. Rep.	Natural Product Reports
Org. Biomol. Chem.	Organic and Bimolecular Chemistry
Pure App. Chem.	Pure Applied Chemistry
Phil. Trans. R. Soc. Lond. A.	The Philosophical Transactions of the Royal Society
Seances Acad. Sci.	Seances Acadamic Science
Tetrahedron Asym.	Tetrahedron Asymmetry
Tetrahedron Lett.	Tetrahedron Letters

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