SYNTHESIS, STRUCTURE DETERMINATION AND MECHANISM IN THIOPHENE DERIVATIVES

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ABSTRACT

A series of O_2N_2 and O_3N_2 macrocycles incorporating thiophene have been prepared. Various carbon chain lengths exist between the donor atoms (nitrogen or oxygen) giving a range of macrocycles with ring sizes varying from 14 to 20 atoms. Semi-large scale synthesis (*circa* 50 g) was carried out on the production of α,ϖ-bis(3-oxythienyl)alkanes from the starting material methyl 3-hydroxythiophene-2-carboxylate. A series of *N*,*N*′-bis-(R,R′-benzyl)-alkane-diamine compounds was also synthesised on a semi-large scale. The aminomethylation of thiophene (the Mannich reaction) was used to facilitate the production of thiophene-based macrocycles from the mentioned starting material without resorting to elaborate purification techniques. Thiophene-based macrocycles (where R = NH_2) were appended to a polymeric support (a Merrifield based resin).

Competition ring formation has been found during some Mannich reactions, in some cases preventing effective synthesis of the intended macrocycles. Along with observations, some limitations to ring formation using the Mannich reaction are discussed.

The X-ray crystallographic data for a 15-membered thiophene-based macrocycle is presented together with discussion of its geometry. Intramolecular non-bonded contacts between nitrogen and phenyl-H explain the unexpected geometry of this compound. The calculation of the bonding cavity size of this 15-membered macrocycle along with metal-ion binding studies are discussed.

Acknowledgements

The author wishes to thank Dr. Joan C. Halfpenny for her supervision and patience throughout this work and to Dr. Patrick R. Huddleston for useful discussions and advice in aspects of this study.

I am very grateful to the EPSRC and Inspec Fine Chemicals (formerly Synthetic Chemicals), Four Ashes, Wolverhampton for funding, and to Laporte Fine Chemicals R&D, Seal Sands, Middlesbrough for a 3-month industrial placement in 1999.

Thanks are also due to Mr. M. L. Wood for NMR spectra; Dr. A. M. Franklin for the majority of mass spectra; and Mr. T. J. Spencer (The University of Nottingham) for elemental analysis.

Abbreviations

AAS	Atomic Absorption Spectroscopy
br.	broad
b.p.	boiling point
cadaverine	1,5-pentanediamine
d	doublet
dd	double doublet
DCM	dichloromethane
DMAB	dimethylamine borane complex
DMF	*N,N'*dimethyl formamide
DMSO	dimethyl sulphoxide
e^-	charge of the electron
EDTA	ethylenediaminetetraacetic acid
EtOAc	ethyl acetate
EtOH	ethanol
ethylenediamine	ethane-1,2-diamine
EXAFS	Extended X-ray Absorption Fine Stucture
eqv	equivalent
F.W.	formula weight
g.AcOH	glacial acetic acid
i	denotes in (used to described the lone-pair of electrons on nitrogen in aza-crown ethers)
IPA	isopropylalcohol
IR	(FTIR) Fourier Transform Infrared Spectroscopy (ν_{max}/cm^{-1})
J	coupling constant (NMR)
2,6-lutidine	2,6-dimethylpyridine
KOH	potassium hydroxide
m	multiplet
M	molecular weight or molarity
MS	mass spectroscopy (m/z)
m.p.	melting point
MeOH	methanol

NaHS	sodium hydrosulphide
NMR	Nuclear Magnetic Resonance Spectroscopy (∂_H & ∂_C)
o	denotes out (used to described the lone-pair of electrons on nitrogen in aza-crown ethers)
Pd-C	palladium supported on carbon
Ph	C_6H_4
Ph′	C_6H_5
py	pyridine
q	quartet or quintet
R_f	retardation factor
s	singlet
t	triplet
THF	tetrahydrofuran
tlc	thin-layer chromatography
UV	Ultra Violet Spectroscopy

Instrumentation

The following instruments were used to collect data contained in this thesis. Details of the X-ray crystallography instrument can be found in the Experimental section 2.8.

Melting points	Gallenkamp Melting Point Apparatus (Cat. No. MFB 595 010M)
FTIR	Perkin Elmer 1600 Series FTIR
NMR	JEOL EX 270 with delta upgrade.
MS	Finnigan LCQ quadrupole ion trap mass spectrometer (ITMS) (Finnigan MAT, San Jose, CA) equipped with an APci (Atmospheric Pressure chemical ionisation source).
AAS	Perkin Elmer Atomic Absorption Spectrometer 3110

CONTENTS

INTRODUCTION

1.1 - Macrocycles

Macrocyclic chemistry is concerned with large ring systems of greater than eight atoms and containing at least three donor atoms (usually nitrogen N, oxygen O and sulphur S) in a molecule.

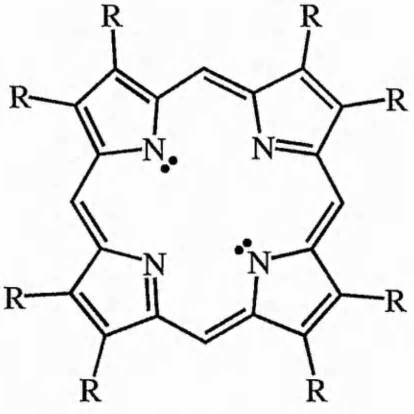
Such systems usually incorporate *normal* rings (containing 5 or 6 atoms) such as benzene, pyridine, pyrrole etc. to give some rigidity to the macrocycle. Moieties of the *normal* rings serve as good sources of starting material for the synthesis of macrocycles.

Macrocycles display high stability when complexed to particular metal ions as compared with their open-chained analogues. Such an effect is termed the 'macrocyclic effect[1,2].

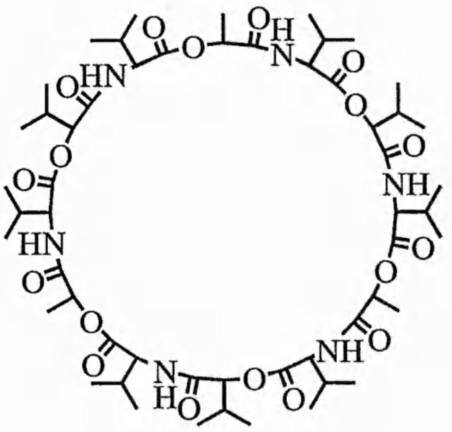
The synthetic macrocycles emerged in importance in the 1960's and much of the impetus came from the need to mimic biological systems.

1.2 - Natural Macrocycles

Natural macrocycles have importance in biological mechanisms[3]. The porphyrin systems **I**, for example contribute to the uptake (in blood) and the storage (in muscle) of dioxygen in mammalian species. The responsible proteins for these processes are haemoglobin and myoglobin respectively and both contain an iron complexed porphyrin unit. Other related porphyrin systems such as the magnesium complex in chlorophyll facilitate photosynthesis in green plants; the vitamin B_{12} coenzyme is a cobalt corrin (a reduced saturated type of porphyrin). Other natural macrocyclic systems are attributed to the mechanism of alkali metal ion transport into a cell across the cell membrane. As one example, the six-ester carbonyls of the antibiotic valinomycin **II** form a relatively stable complex to potassium. The enveloping of the macrocycle by the potassium ion when complexed allows for a hydrophilic interior and the *tert* butyl groups give a lypophilic exterior. This is necessary if the complex is to traverse the 'hydrocarbon slab' of the cell wall (~70 Å in length) and release the cation within the cell. One molecule of valinomycin can repeat this process at a rate of thousands of ions per second.



I



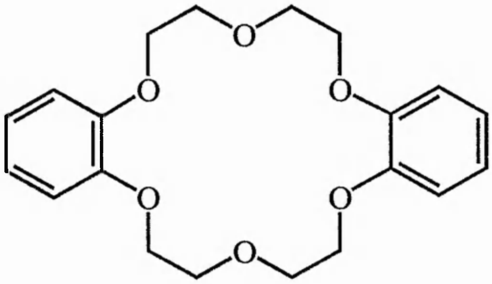
II

Such systems allowing for cation complexation, followed by transport across lipid bilayers or organic phases and release are known as ionophores.

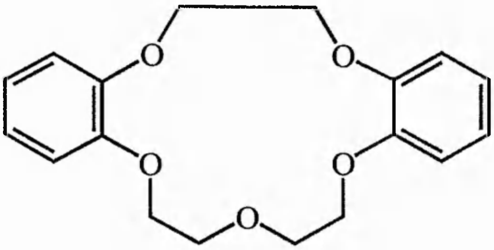
1.3 - Crown Ethers and Related Systems

Cyclic polyethers prepared from resorcinol[4] and from hydroquinone[5] were first isolated in the 1930's and 1940's. However, since the discovery of the crown ethers[6] by Pedersen in 1960, acknowledged by his share along with Lehn and Cram in the 1987 Nobel Prize for chemistry, there has been an enormous expansion in the field of macrocycles. The crowns are cyclic polyether molecules and were so named as they not only look like a monarch's crown in structure models but also 'crown' cations. The numbers arising in the name correspond to the number of atoms in the largest ring and the number of oxygen atoms respectively; dibenzo-18-crown-6 **III** and dibenzo-15-crown-5 **IV** are typical (page 3).

Pederson noted that some of the crowns enabled metal salts to dissolve in benzene. It is this property of the crowns – the ability to facilitate the dissolution of metal salts in non-polar solvents - which makes them of chemical value. The cyclic polyethers and their complexes with metal salts have been extensively reported[7-9]. For the alkali and alkaline earth metals, oxygen numbers of four, five and six in a dibenzo crown ether, where the ratio of carbon ring atoms to donor atoms is 2:1, selectively complex to lithium, sodium and potassium respectively.



III



IV

This indicates that each metal ion complexes preferentially to a polyether cavity of comparable size. Pedersen also noted that the anions of salts do affect their solubility with polyethers; that moreover it is the dehydrogenated dibenzo crowns, *i.e.* the corresponding cyclic hexyl derivatives, which are more effective complexing agents than their aromatic counterparts. This is believed to occur due to the lower basicity of the oxygen atoms in the cyclic hexyl derivatives[8]. A comprehensive report of the thermodynamic and kinetic studies of the crowns has been published[10].

Metals when complexed to crown ethers in organic solvents have given rise to a range of usually unpermitted reactions. Some examples are:

(1) The potassium permanganate salt of dicyclohexyl-18-crown-6 in benzene (often referred to as purple benzene) permits the oxidation of alkenes to the corresponding acid. Sam and Simmons[11] reported this finding in 1972 amongst the oxidising of alcohols and aldehydes to their acids. In all tabulated results, high yields were obtained. Potassium permanganate has no detectable solubility in benzene, and without the crown to aid solubility, no reaction is observed.

(2) Saponification of the hindered esters of 2,4,6-trimethylbenzoic acid has been accomplished[8] using potassium hydroxide complexed to dicyclohexyl-18-crown-6 in

benzene or toluene. This latter reaction is thought to occur due to the presence of free uncomplexed hydroxide ions, which are unsolvated in the apolar medium, thus rendering the nucleophile action stronger than in polar solvents where the ion is solvated.

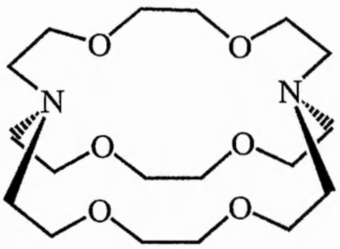
(3) Organic acetates obtained from the reaction of organic bromides using potassium acetate in the presence of 18-crown-6 in a heterogeneous system have been reported[12]. The crown in acetonitrile acts as a *phase transfer* catalyst, transporting small quantities of complexed potassium acetate from the solid phase to the liquid phase that contains the organic bromide. A 100% yield for the conversion of benzyl bromide to benzyl acetate was accomplished, while in the absence of the crown a conversion of only 5% was obtained.

The protonisable crown ethers[13] are modified crowns with pendant ionisable groups, like carboxylic or phenolic hydroxy groups for instance, attached. These systems eliminate the need to transport hard anions like chlorides, nitrates and sulphates during cationic complexation to crowns of this type in organic media. The ionised crown itself acts as the counter-ion for such a process. The attraction of these systems is that the crowns can be tuned to operate by adjustment of the pH of the solvent system, so that the complexation process can be switched on and off at specific times.

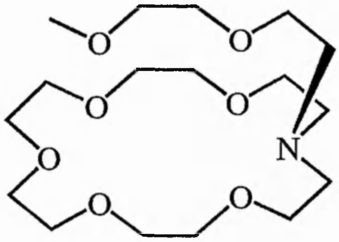
1.4 - Cryptands and Lariat Ethers

Lehn[14,15] has produced a class of macrocycles known as the cryptands **V** which forms an extension to the polyethers by joining an additional ether arm to two nitrogen atoms of an aza crown ring making a cage like molecule. Three possible configurations of the cryptands arise for each structure as the lone pairs on nitrogen can either be centred towards the cage (*i,i*), away (*o,o*) or alternate (*i,o*). The cryptates (metal complexes of the cryptands) stability constants for complexes with the alkali and alkaline earth metals are very high and these ligands form far more stable complexes with group I or II metals of the Periodic Table than do the crowns and the natural macrocycles. The potassium [2.2.2]cryptate **V** illustrates stability. It is about 10^4 times more stable than the potassium complex of valinomycin and around 10^5 times more stable than its potassium crown counterpart. The exceptionally high stablilities of the cryptates allow them to function as receptors for cations and models for alkali cation receptor proteins due to their slow dissociation rates[15].

Lariat ethers possessing only one pendant arm to aza crown ethers[16,17] **VI** have been produced in efforts to find macrocycles which do not bind metal ions as strongly as the cryptands, but more so than the crown ethers. The ether pendant arm allows for axial co-ordination to the cation. Tailoring the size and number of donor atoms on the arm will allow (for a particular metal) a compromise between thermodynamic stability of the complex and kinetic dissociation. This is a requirement for obtaining good working ionophoretic systems. Gokel has extended this work by producing conducting channels known as hydraphiles[18], formed by joining several aza-crowns that have in place of the lariat ether arm, a hydrocarbon chain.



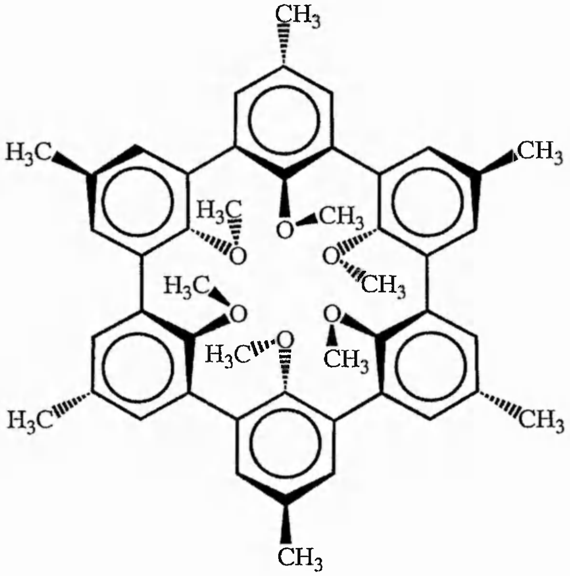
V



VI

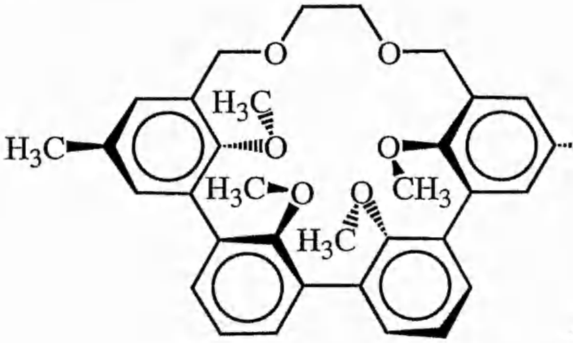
1.5 - Other Considerations of Macrocyclic Chemistry

In addition to the alkali metal complexing power of the cyclic polyethers, cryptands and lariat ethers and any of their complexes with ammonium salts, Cram[19] depicts other species with quite remarkable properties: the spherands, e.g. **VII** are preorganised hosts for only the guests Li^+ and Na^+ over other similar charged metals and their Gibbs free energies are highest, $-\Delta G^{\circ} > 96.3$ kJ mol^{-1} and 80.8 kJ mol^{-1} respectively for the picrate salts. A complex of host and guest in this case is referred to as an spheraplex. The fixed cavity of **VII** comprises 24 donor electrons and remains unsolvated during synthesis. This preorganisation of the host allows the guest to bind strongly as very little energy is expended in host reorganisation and desolvation, which must take place for both the polyethers and the cryptands.

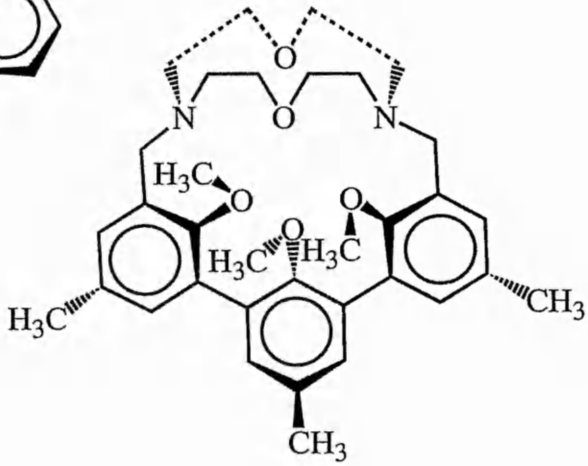


VII

Combinations of spherand and polyethers or cryptands to give hemispherands **VIII** and cryptaspherands **IX** respectively have been synthesised[19] in efforts to probe the metal complexing powers and ultimately to promote the discrimination of some metals over others.



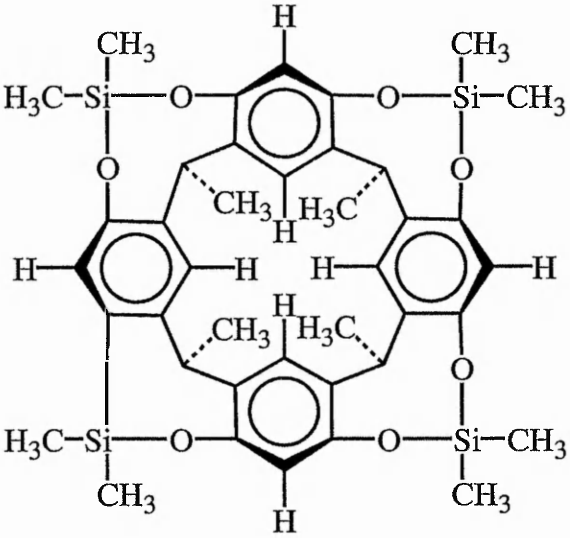
VIII



IX

In summary, the complexing ability of all of the variations of macrocycles tested falls into the following decreasing series: spherands > cryptaspherands > cryptands > corands (modified crowns).

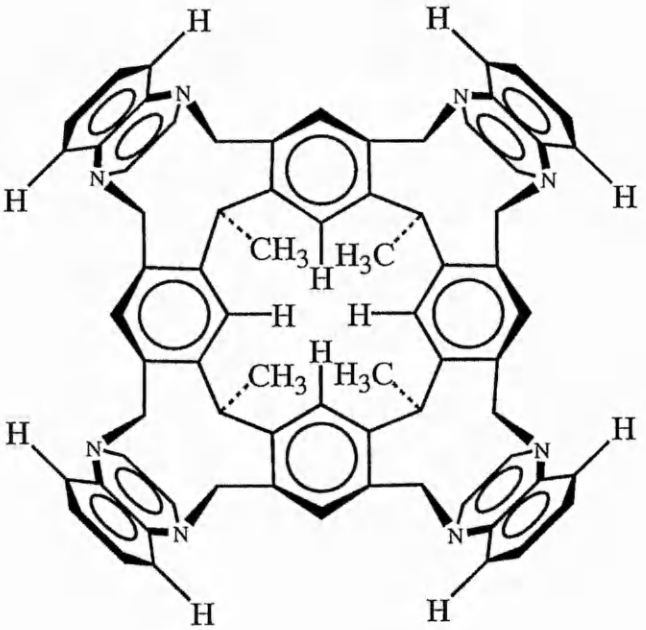
Cavitands are organic structures possessing concave cavities, visualised as bowl shaped, and have been found to occlude solvent molecules. For example a Gibbs free energy $-\Delta G^\circ$ of the order 8.4 kJ mol^{-1} has been observed between carbon disulfide and the cavitand **X**[19]. These are much smaller values when compared to the spherands complexing to metal ions.



X

Cavitand **XI** (page 8) crystallises with DMF[19] and is noted just to fit into the extended bowl shape category – it is described as vase shaped. Although the DMF molecule cannot be removed at high temperature and low pressure, it is of interest that it can be readily replaced with 1.5 mol of chloroform.

The examples given highlight the diversity of the field of macrocycles and there are still other intrinsic molecular architectures which have been designed and built to complex with cations, organic molecules, organic salts, or a combination of these. For example, the carcernands[19]; the cyclophanes[3]; the cyclodextrins[20] and the cyclo-based catenanes and rotaxanes[21], the cucurbiturils[22].



XI

1.6 - Construction of Macrocycles

For chain lengths of 12 or more, steric effects do not contribute significantly to the formation of rings. Ring closure (*intramolecular* reaction) is reliant on the internal entropy of the open chain. As the chain length increases, so does the number of degrees of freedom (the combinations of the various possible chain configurations) and therefore the less likely is the probability of two reactive ends of a chain meeting to form an enclosed loop. From this explanation, it is more likely that neighbouring molecules will react together to produce oligimers and eventually to form polymers (*intermolecular* reaction), whether straight chained or cyclic- Figure 1.

High dilution techniques favour ring closure, but a concentration of the order 10^{-3} mol dm^{-3} is necessary for the near elimination of polymerisation and is not practical in a large-scale synthesis due to the large volume of solvent required. High dilution can be overcome by feeding reagents gradually into the reaction mixture at low concentrations over a long period of time, but this is slow and therefore not an attractive method for easy synthesis of macrocycles.

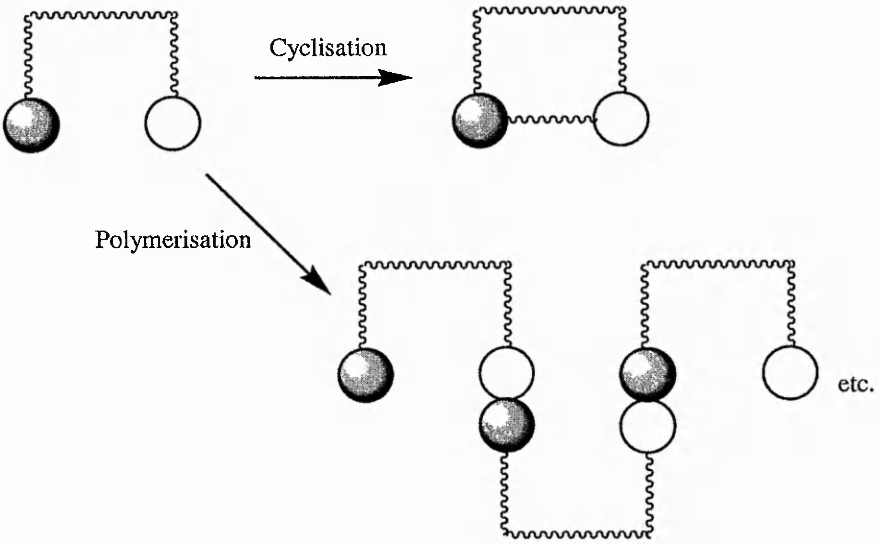
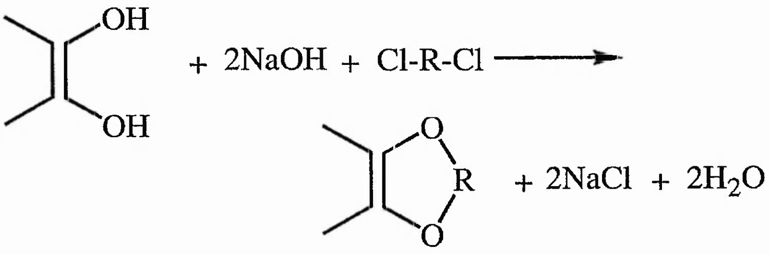


Figure 1

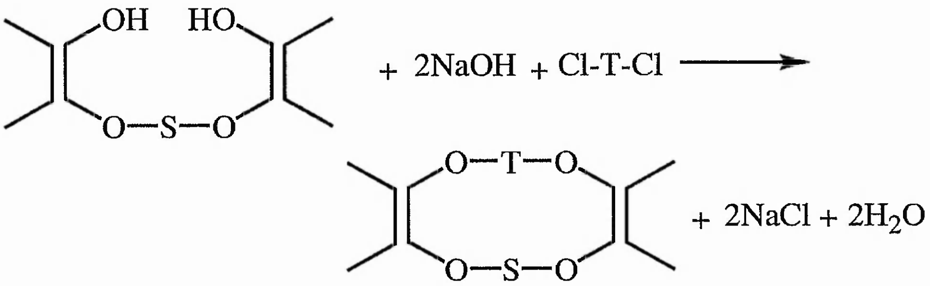
Bulky side groups help to reduce the number of degrees of freedom on substrates and therefore maximise the possibility of cyclisation occurring.

Normally the synthesis of macrocycles involves reaction of several large components, rather than the cyclisation of a single long chain. The methods **V** to **Z** described by Pedersen[8] for his cyclic polyethers – Figure 2 (page 10) can be taken to be general synthetic routes to any macrocycles; Pedersen[8] described **Method W** as ‘the most versatile for the preparation of compounds containing two or more benzo groups’:

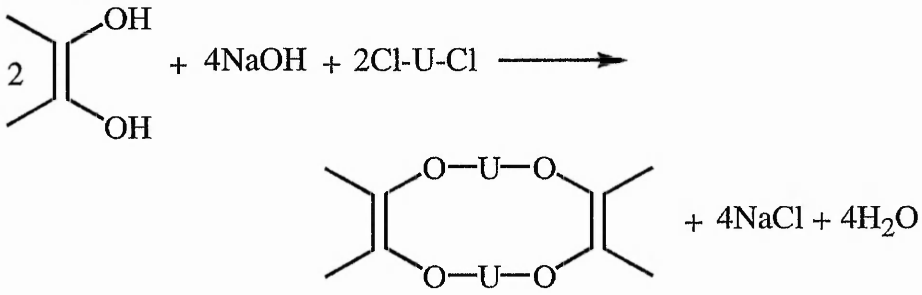
Method V



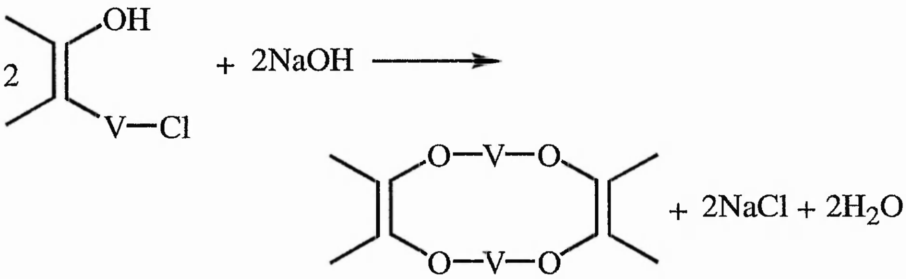
Method W



Method X



Method Y



Method Z is the dehydrogenation of the benzo containing polyethers to their cyclic hexyl derivatives in *p*-dioxane over a ruthenium dioxide catalyst.

Other macrocyclic systems have been produced by condensation reactions. These are termed *Schiff base* reactions and involve reaction between a primary amine and a carbonyl compound to form an imine function (reaction mechanism - Figure 3) and have been used more extensively than cyclisation other than at a donor atom.

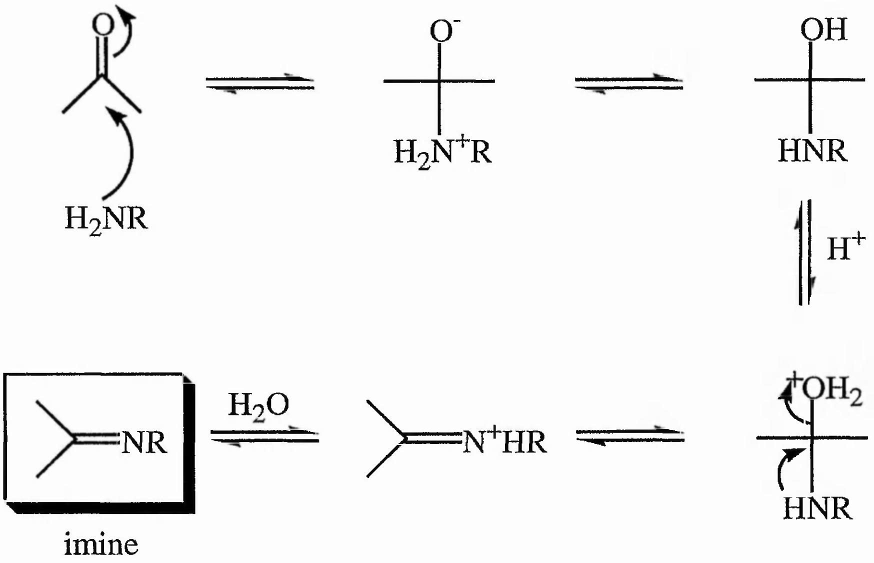
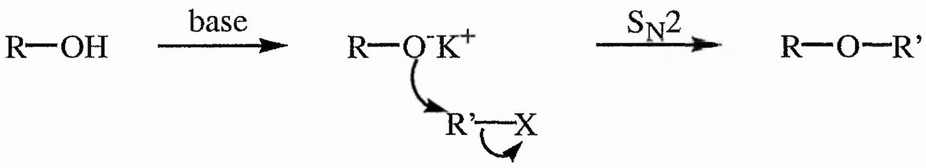


Figure 3

In addition, the Williamson Ether Synthesis[23], a process known since 1850 is a very common reaction of metal alkoxides and alkyl halides or tosylates producing ether linkages and assists in the construction of macrocycles (reaction mechanism – Figure 4).



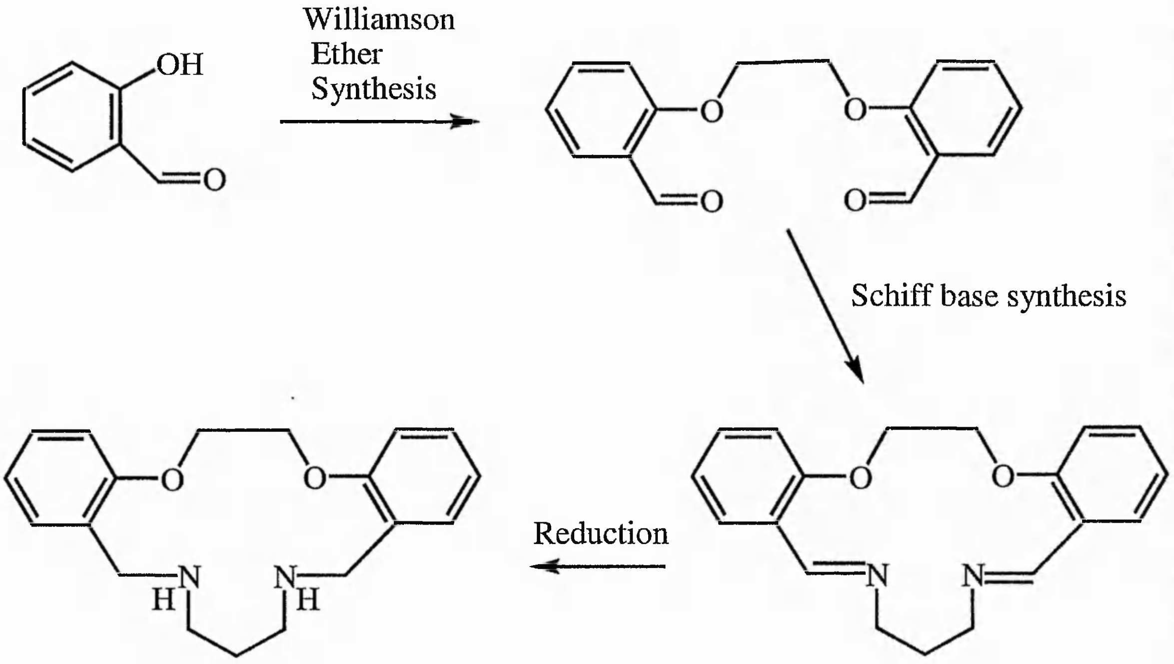
X = halide or tosylate
base, e.g. K_2CO_3

Figure 4

Metal templates are also very useful in the construction of macrocycles and are discussed later in this chapter.

1.7 - Mixed Nitrogen and Oxygen Macrocycles

Lindoy[24-28] has produced numerous macrocycles containing mixed donor atoms (mainly of N and O) and their complexes. These macrocycles, such as **XII** (Figure 5, below) were synthesised from two moles of salicylaldehyde by a Williamson ether synthesis of the phenolic groups and then ring closed to Schiff base products (subsequently reduced to the diamino products) by reacting a diaminoalkane to the carbonyl groups. Macrocycles of this type have proved more successful than the crown ethers in complexing to metals other than the alkali and alkaline earth metals, for example, macrocycle **XII** will readily complex with nickel(II)[24].



XII

Figure 5

Similar macrocycles to **XII** can be prepared with ring sizes of 14, 15, 16 and 17 and their interaction with transition metals Co(II), Cu(II), Zn(II) and Ni(II) has been investigated[29]. The results showed that of the four ions, Ni(II) and Cu(II) formed the most stable complexes, although only nickel showed differing stability over the series of macrocycles. This was concluded by thermodynamic studies to determine the stability of the metal complexes formed by the following reaction: (Figure 6)

$$M^{2+} + L \rightleftharpoons ML^{2+}$$

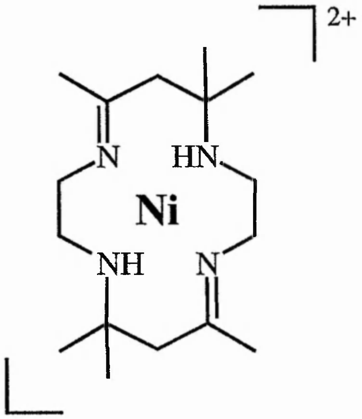
Figure 6

log *K* values for nickel(II) were 5.8 (highest) with macrocyclic ring size of 16, and approximately 3.5 (lowest) with ring size 17. X-ray crystallography was used to confirm the geometry adopted by the metal to the donor atoms in the cavity. Zn(II) (ZnI_2) adopted a tetrahedral geometry to a 15-membered macrocycle (O_2N_2) co-ordinating to only the nitrogen donor atoms and outside of the macrocyclic cavity. Conversely a Cu(II) was shown to co-ordinate to both the ether oxygens and the amine nitrogens albeit slightly above the ring cavity. These two examples show metals co-ordinating in different configurations and give an insight into the difficulty of designing macrocycles to suit particular metals with given oxidation states. The common approach has been to build a series of related macrocycles with increasing substitution and to identify where dislocations (the poorest metal ion to macrocycle configuration) occur both in the solution and solid state. Thereafter promising macrocycles may be further optimised for overall ring size, maximum substitution, type and number of donor atoms present to discriminate for a particular metal over others.

In the present work this approach was adopted by synthesising macrocycles with ring sizes of 14, 15, 16, 17, 18 and 19 incorporating two O and N donor atoms and ring sizes of 17, 19 and 20 incorporating three O and two N donor atoms.

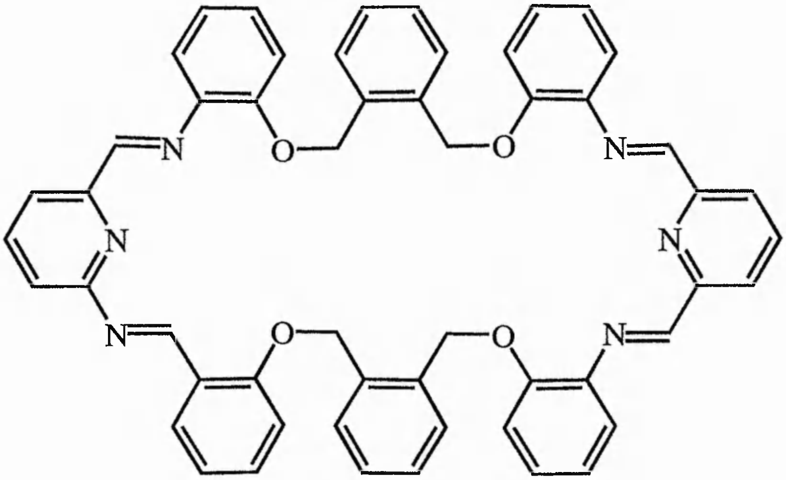
1.8 – The Template Effect

The role of metal ions in the construction of macrocycles has been documented since 1928, but was not specifically utilised until 1960 after Curtis[30-32] had identified an unexpected metal complex from the reaction of trisethylenediaminenickel(II) perchlorate and anhydrous acetone, producing both *cis* and *trans* isomers of species **XIII** (*trans* shown).



XIII

The use of metal ions in macrocyclic synthesis is common and both earlier and more recent examples can be found in the literature[33-36].



XIV

The macrocycle[36] **XIV** illustrates the diversity of ring systems that can be produced: it is a 34 membered ring and compared to the macrocycle **XII** (Figure 5) is large and incorporates two types of *normal* rings, benzene and pyridine. It is interesting that both macrocycles were built from simple units. The synthesis of **XII** is an example of a [1+1] condensation reaction. Conversely macrocycle **XIV** is formed by a Schiff base reaction between α,α′-bis(2-aminophenoxy)-o-xylene and pyridine-2,6-dicarbaldehyde. This is an example of a [2+2] condensation reaction as two moles of each starting material are used to form the product. However, this macrocycle can only be prepared in the presence of lead(II) perchlorate. Without the lead salt the reaction does not yield the desired product even using high dilution.

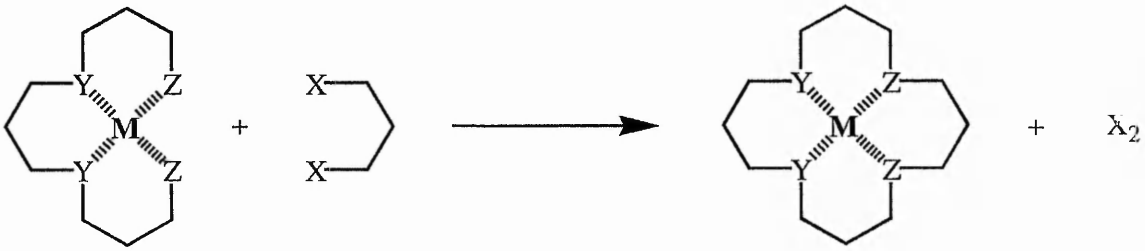


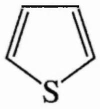
Figure 7

The metal ion of the salt can co-ordinate to the donor atoms of a suitable open-chained ligand, thus constraining potential reactive groups into position around the cation and enabling ring closure between the reactants (Figure 7). The template is paramount where steric effects would otherwise disfavour reaction leading to the formation of the macrocycle and this process is referred to as the *kinetic template effect.* In a reaction where the reactants are in equilibrium and there are few steric effects, the template serves to sequester the reactant in favour of macrocyclisation. This effect is known as the *thermodynamic template effect.* A recent example of this effect can be found in the literature[37].

As discussed earlier, templates also assist to eliminate polymerisation, which can lead to undesired by-products.

1.9 – Thiophene

Thiophene **XV** – a five-membered heterocyclic aromatic ring containing sulphur - is the most stable system to its corresponding counterparts, furan (containing an oxygen atom) and pyrrole (containing an nitrogen atom).



XV

This can be seen when the experimental heats of combustion of the three five-membered rings are compared with benzene[38]:

Benzene	3303 $kJmol^{-1}$
Thiophene	2562 $kJmol^{-1}$
Pyrrole	2420 $kJmol^{-1}$
Furan	2123 $kJmol^{-1}$

Thiophene is relatively stable to strong acidic conditions, as is benzene, but both furan and pyrrole are less stable.

The chemistry of thiophene is mainly limited to electrophilic substitution and this is favoured at the 2-positon of the ring over the 3-position. This is due to the lower energy involved in the transition state formed between the 2-position of thiophene and the electrophile – Figure 8[38] (page 17).

Further substitutions on mono substituted thiophenes are dependent on the nature of the constituents (their activating or deactivating of the ring electrons), but position 5 is largely the dominating position if the 2-position is already occupied and the 2-position dominates if the 3-position is first substituted.

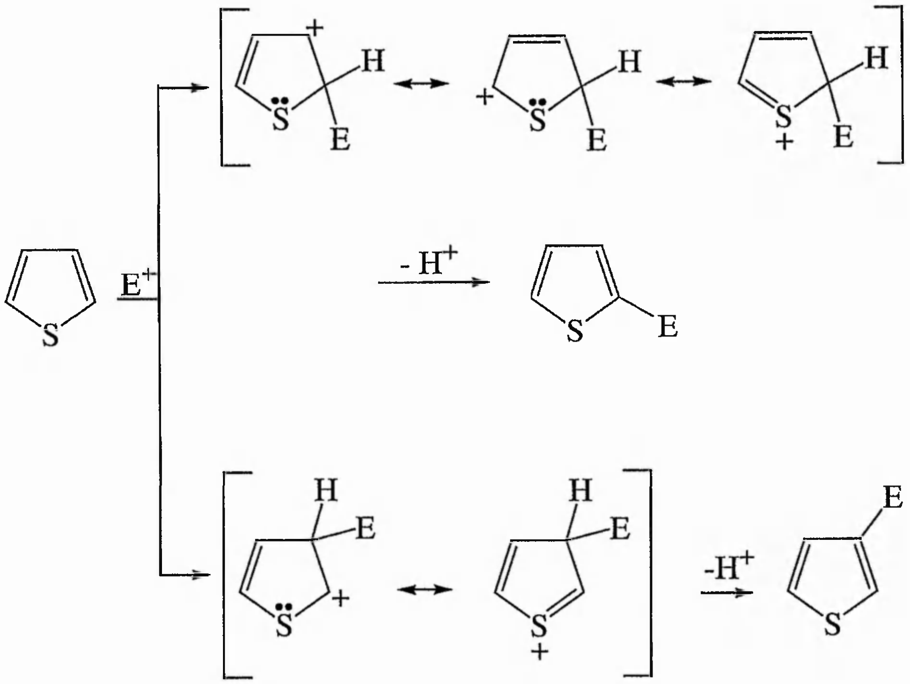


Figure 8

Furthermore, the preparation of some mono, di, tri and tetra substituted thiophenes may be carried out from aliphatic organic molecules in a one step process, which is easier and more convenient than their attempted preparation from thiophene itself[39]. As an example, 4-ethyl-2-methythiophene may be prepared from α-ethyllevulinic acid in the presence of a sulphide of phosphorus – Figure 9:

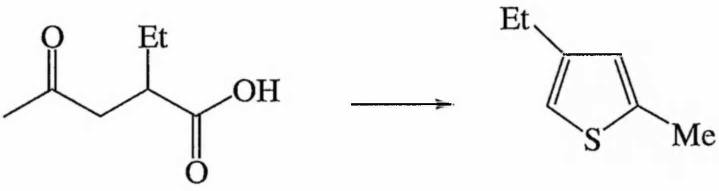


Figure 9

Substituted thiophenes[39] may also be formed by reaction of 1,2-difunctional compounds (α-diketones, α-keto-esters or oxalic esters) with esters of thioacetic acid. These reactions are usually performed in alcoholic solution with sodium present to form the alkoxide. For instance, benzil, an α-diketone, reacts with diethyl thiodiacetate in methanol with added sodium to produce after hydrolysis 3,4-diphenyl-2,5-thiophenedicarboxylic acid in a 74% yield[39] – Figure 10.

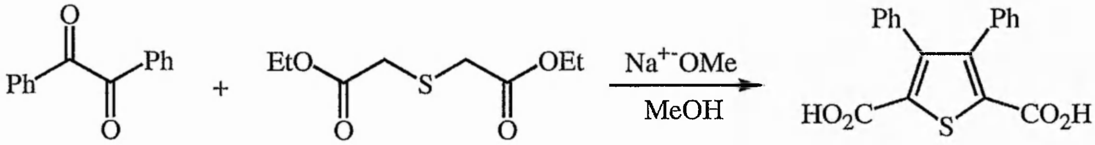


Figure 10

The free 2,5-thiophene-dicarboxylic acids are stable when hydrogen atoms, alkyl or aryl groups are connected at the 3 and 4 positions. The acids may also be readily decarboxylated to the free 3,4-disubstituted thiophene. However, if either the 3 or 4 position has a hydroxyl group attached, then hydrolysis of the ester groups to yield the 2,5-thiophenedicarboxylic acids is not always achievable. Both α-keto-esters and oxalic esters react in a similar manner to α-diketones to yield hydroxyl groups in the 3 or 4 position – Figure 11.

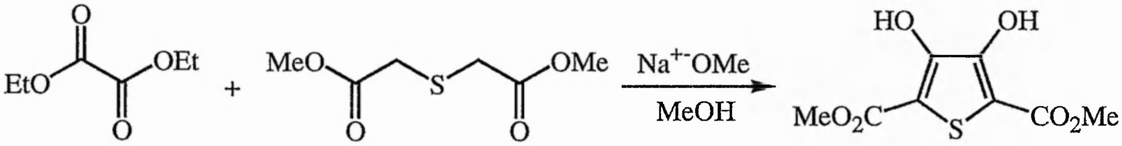


Figure 11

A one step procedure[40] to the synthesis of methyl 3-hydroxythiophene-2-carboxylate, the core starting material employed in this present work, is from the reaction of methyl 2-chloroacrylate and methyl thioglycollate in 2M methanolic sodium methoxide – Figure 12 (page 19).

Methyl 3-hydroxythiophene-2-carboxylate is commercially available[41].

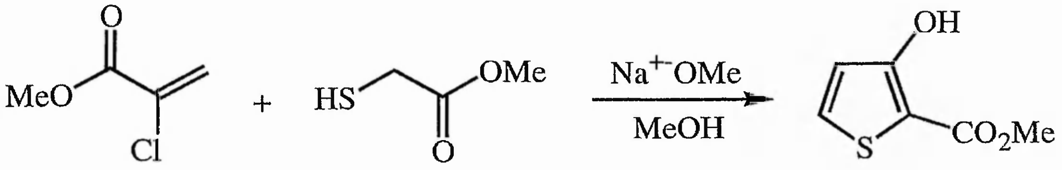
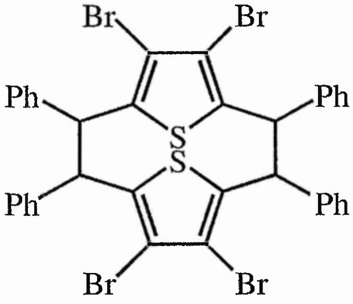


Figure 12

A key feature of thiophene is that it can be desulphurised with Raney nickel[42]. The reaction of substituted thiophene in a variety of positions, followed by desulphurisation, provides synthetic routes to a range of long chained aliphatic compounds that would otherwise prove extremely difficult to make.

1.10 - Heterocyclic macrocycles

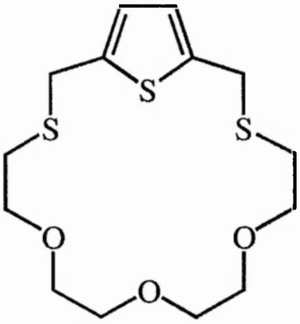
Meth-Cohn[43] has reported extensive work on macrocycles involving the thiophene ring system. Mainly, these were not compounds incorporating additional heteroatoms within the macrocycle, but macrocycles of varying ring size containing one or more thiophenes usually with the sulphur atom of thiophene pointing inwards. One example is the first thiophenophane **XVI** reported by Steinkopf:



XVI

A review in 1977 of heterocyclic macrocycles[44] shows that thiophene-based systems have been extensively studied.

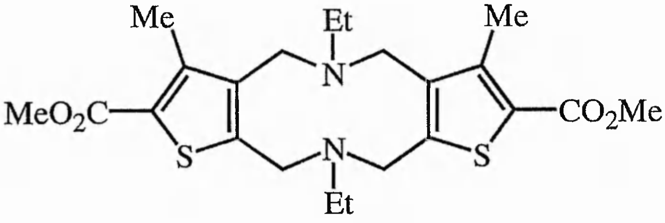
Most of the syntheses described have produced macrocycles anchored at both the *alpha* positions to the heterocyclic donor atom e.g. **XVII**. There are also numerous examples of macrocycles containing mixed heterocycles, again including the heterocycle donor atoms within large rings.



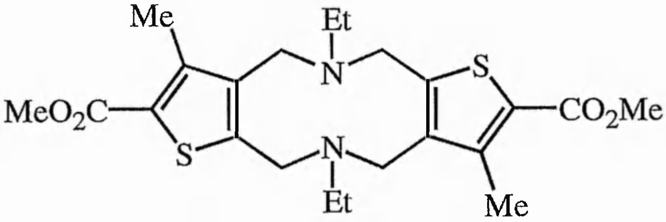
XVII

More recently, examples of thiophene-based macrocycles anchored at the 2 and 5 position of the heterocycle have been reported, a non-templated *Schiff base* synthesis of thiophene-2,5-dicarbaldehyde and several terminal diamino compounds of [2+2] macrocycles have been described[45-48], and reaction of thiophene-2,5-dicarbonyl chloride with 1,2-ethane diol or 2,5-dihydroxymethylthiophene in the presence of triethylamine has afforded [2+2] macrocycles including thia and oxa donors[49]. The latter reaction produces a macrocycle containing four thiophene units where all the S donor atoms are part of the ring.

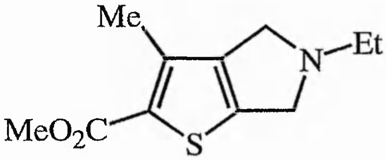
In contrast, and although 3,4-disubstituted thiophene macrocycles are known[50], 2,3-disubstituted macrocycles have received less attention. The syntheses of two isomeric forms (page 21) **XVIII** in low yield, 4% and **XIX**, yield 3% have been described from the reaction of methyl 2,3-bis(chloromethyl)-4-methylthiophene-5-carboxylate with ethylamine in acetonitrile, but the major product was **XX**, yield 37%.



XVIII

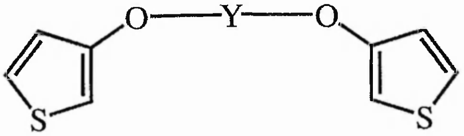


XIX



XX

Chaffin[51] has also described 2,3-disubstituted thiophene-based macrocycles of this type containing a number of mixed aza, oxa and thia donor atoms. 2,3-disubstituted thiophene-based macrocycles with ring sizes of 14 to 20, containing mixed donors, have been reported[52] and their extraction coefficients with alkali and alkaline earth metals and silver have been shown to be of higher orders than those of 18-crown-6 using the picrate extraction method of Pedersen[7]. These macrocycles were produced by firstly building ether bridges between two thiophene molecules **XXI** starting from methyl 3-hydroxy thiophene-2-carboxylate.



XXI

Y = $(CH_2)_{2, 3, 4, 5, 6 \text{ or } 10}$,
$(C_2H_4)_2O$, $(C_2H_4)_2S$ or
$(C_2H_4)_2O(CH_2)_2O$

Ring closure was achieved using the Mannich reaction with a mono-amino compound (ethylamine) or a diamino compound, such as piperazine, at normal dilution. The majority of the products produced were oils.

A few other ring systems of this type have since been reported[53] from the reaction with a diamino compound, *N,N′*-dibenzylethylenediamine.

The present work extends the synthesis of thiophene-based macrocycles by the use of the Mannich reaction with diamino compounds. The emphasis has been to produce crystalline thiophene-based macrocycles, which incorporate useful functional groups in the *para* position of the moiety *N,N′*-dibenzylethylenediamine. Functional groups attached in this position enable further reactions to be carried out on these macrocyclic compounds, for example, attachment to a polymer substrate, without the need to directly affect the ring cavity.

1.11 - The Mannich Reaction

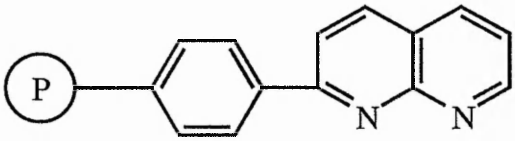
The Mannich reaction[54] is a versatile reaction for the attachment of a primary or secondary amine *alpha* to a carbon atom of pronounced acidity (3-alkoxy thiophene in this case) - Figure 13 (page 23). The condensation reaction, which involves formaldehyde, can be carried out in either acidic or basic media.

The reaction is thought to involve the reactive intermediate, the iminium ion. This species is formed in thermodynamic equilibrium and therefore the reaction is performed best in weakly acidic conditions. Strong acid media would render the free amine as its salt and therefore non-nucleophilic, thus suppressing the rate of reaction.

The mono-aminomethylation of methoxy thiophenes has been reported[55] in glacial acetic acid and this has formed the basis of formation of the thiophene-based macrocycles, via a double Mannich reaction, mentioned earlier[51].

1.12.1 - Immobilised chelating reagents

An example of chelating reagents bonding to brominated divinylbenzene resins has been reported by Valeria and Hendricker: the attachment[62,63] of 1,8-naphthyridine, poly(styryl-1,8-naphthyridine) **XXII**, 1,5-napthyridine and pyrido[2,3-b]pyrazine to brominated polystyrene-2% divinylbenzene copolymer beads. Some transition metal and lanthanide metal complexes (copper, iron, nickel and europium) of these resin-supported chelates were prepared, achieving 58% complexation for iron(III) chloride and 49% for copper(II) chloride with 1,8-napthyridine.



XXII

Prior to the work of Valeria and Hendricker, Neckers[64] had reported the polymer bound species bipyridine and its complexes with some transition metals. As in the previous example the brominated polymer had to first be synthesised before attachment of the chelating species - Figure 15.

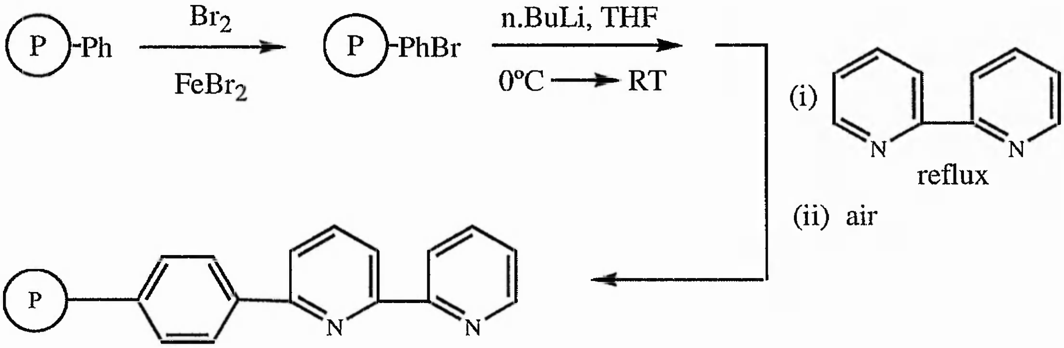


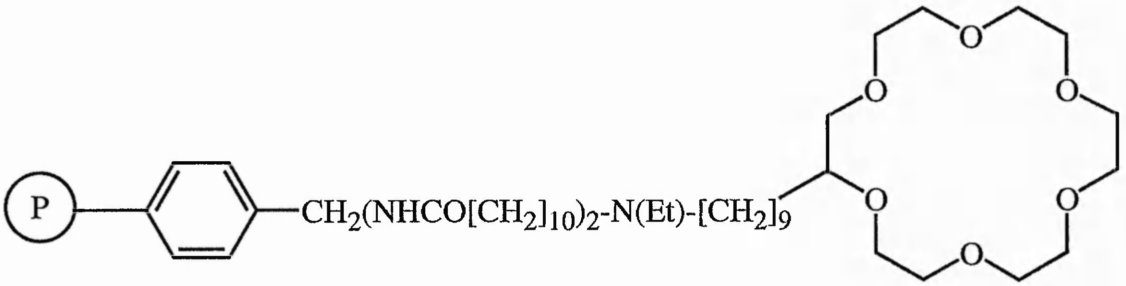
Figure 15

Polymeric supported diphosphine on a Merrifield resin, chloromethylated-1% divinylbenzene copolymer has been reported[65] and the complexes of nickel, rhodium and ruthenium with this substituted resin have been characterised by instrumental techniques such as UV-visible spectroscopy and metal EXAFS.

Both 3-formylsalicylic acid and 5-formylsalicylic acid have been attached to silica gel-bound amines[66]. In four immobilised chelating silica gel phases the selectivity at a given pH (about 5.5) for Fe(II) over Mg(II), Co(II), Ni(II), Cu(II) and Cd(II) was extremely high. The selectivity (obtained from batch equilibrium techniques) in the four phases for Fe(II) was 93.4-97.1%. Values for other metals were found to be less than 4%, with the exception of Cu(II) at 5.6-8.5%. Results were obtained by AAS at the appropriate wavelength for the metal under investigation. The back extraction of the metals Fe(II), Cu(II) and Pb(II) from the gels using EDTA was proved to be very useful in the recovery of the immobilised metals.

1.12.2 - Immobilised Macrocycles

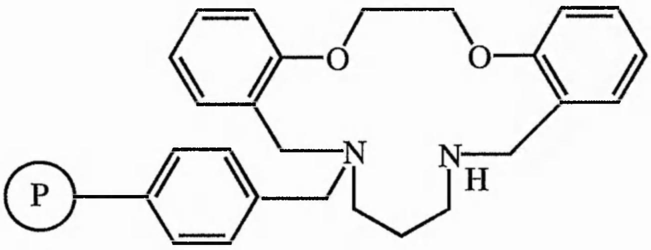
Some macrocyclic polyethers and cryptands have been successfully immobilised onto polymeric supports for use as heterogeneous phase-transfer catalysts. Tundo[67,68] synthesised both crowns and cryptands attached to chloromethylated divinylbenzene resins with long chain lengths separating polymer and macrocycle. It was found for the reaction of 1-bromo-octane to 1-iodo-octane using potassium iodide that for the rate of the reaction of the immobilised crown to be of the same order as that of the crown in a conventional phase-transfer reaction, a large spacer group between surface and crown was required. A spacer group of the order of 35 linear atoms **XXIII** gave the closest result to a similar phase-transfer reaction carried out without the use of the resin as a support. The large spacer was required for the macrocycle to ‘protrude’ into the liquid phase from the polymeric backbone. Shorter chains were not found to be consistent with faster rates and rates of reaction were also found to be dependant on polarity of the chosen reaction solvent.



XXIII

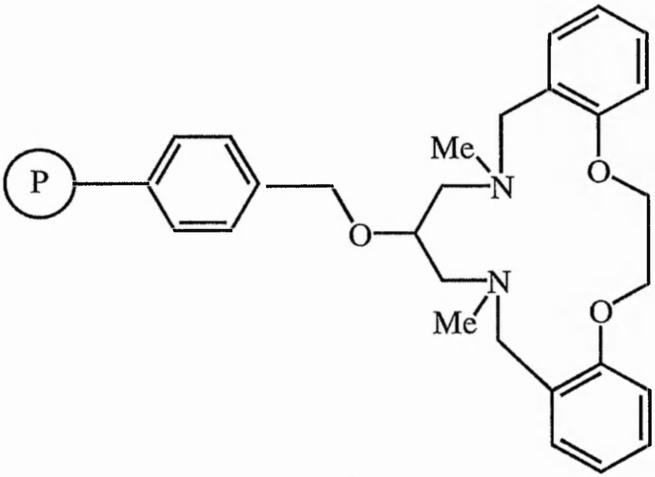
Other examples of polymer bound crowns, mixed donor crowns and cryptands and the use of polymer bound dibenzo-18-crown-6 in catalysis have been published[69]. This paper also reports application of crown ethers, bound or coated onto silica gel or polystyrene, to aid fast separations of alkali metal ions from mixtures by means of high-pressure liquid chromatography.

Lindoy[70] has supported several mixed dibenzo aza-oxa macrocycles on choromethylated divinylbenzene copolymers and carried out an investigation into the metal-ion binding properties of cobalt(II), nickel(II), copper(II) and zinc(II) using their nitrate salts. Binding to the resin was either by direct attachment to an amino group of the macrocyclic cavity or to a hydroxy group adjacent to the macrocyclic ring. **XXIV** and **XXV** (page 28) are typical.



XXIV

A high attachment of 0.66 mmol macrocycle per gram of functionalised polymer was determined for structure **XXIV** under the reaction conditions. **XXIV** was found to be able to load all four metals to a significantly greater extent than **XXV**. For instance, with copper(II) nitrate, 0.04 M of metal-ion concentration at equilibrium, **XXV** takes up only approximately 0.3 mmol metal per gram of resin, whereas **XXIV** takes up about three and a half times more metal. These results were obtained by batch analysis and the metal ion concentrations before and after the experiment were determined by EDTA titration or using atomic adsorption techniques. It is however important to point out that in this work it was evident that the metal-ion binding properties of the resin bound macrocycles were significantly altered from those of the free macrocycles. Such factors as the need to swell the polymer beads sufficiently for the metal ion salts to interact with the macrocycle and steric factors to do with the nature of the polymer were considered to be of significance in determining the degree of metal complexation.

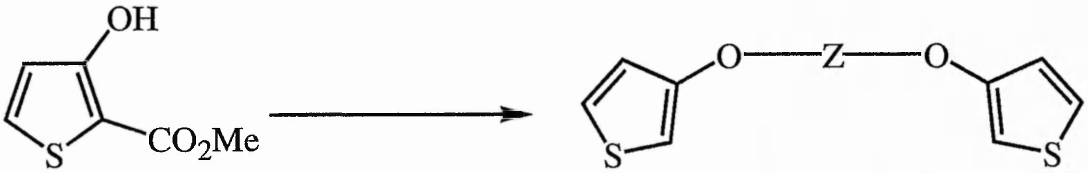


XXV

In the present research into thiophene-based macrocycles it will be shown that incorporating amine functionality with the amine group not directly bound to the macrocyclic ring, but coordinated through a benzyl spacer group, has been accomplished. In addition, other viable routes to thiophene-based macrocycles incorporating hydroxyl and protected amino functionality, together with their intermediates, are discussed (see Schemes Two and Three). Emphasis was given to the synthesis of a series of *para*-nitro substituted thiophene-based macrocycles of varying ring size and these products have formed the basis for preparation of bulk quantities of the final products - the *para*-amino substituted thiophene-based macrocycles. Such a route for preparation of large quantities of product is necessary if thiophene-based macrocycles appended to polymeric supports are to become of practical use, for example in the extraction of metals from solution or the uptake of metal salts on resin-supported materials.

EXPERIMENTAL

2.1 – The preparation of the starting materials, the α,ϖ-bis(3-oxythienyl)alkanes – Scheme One



1a Z = $(CH_2)_2$
1b $(CH_2)_3$
1c $(CH_2)_4$
1d $(C_2H_4)_2O$

Scheme One

Experiment 2.1.1

(**1a**) α,ϖ-bis(3-oxythienyl)ethane

To a mechanically stirred mixture of methyl 3-hydroxythiophene-2-carboxylate (50.10 g, 316.75 mmol) and potassium carbonate (24.00 g, 173.65 mmol) in DMF (250 cm^3) was added 1,2-dibromoethane (15.0 cm^3, 174.06 mmol) and the mixture was heated to approximately 100°C. After 5 hours the mixture was cooled slightly and poured into an excess of ice (~1 dm^3) with stirring. The precipitate was isolated at the pump and washed well with water. The wet solid, crude α,ϖ-bis(2-methoxycarbonyl-3-oxythienyl) ethane was saponified by refluxing in 4M aqueous sodium hydroxide (1.3 dm^3). After 4.5 hours the solution was cooled slightly and filtered through a glass frit into ice (excess). The filtrate was split into two portions and acidified with concentrated hydrochloric acid, isolated at the pump, washed well with water and dried (achieved by placing contents in a crystallizing dish and slowly evaporating the water on a warm surface). The dry compound, crude α,ϖ-bis(2-carbonyl-3-oxythienyl) ethane was mechanically stirred with copper(I) oxide (22.0 g) in pyridine (180 cm^3) and refluxed.

After 1 hour the mixture was transferred to a suitable flask (1 dm^3 round bottomed flask) and the solvent partially evaporated under reduced pressure. The residue was extracted repeatedly (Soxhlet apparatus) using DCM as solvent until no apparent colour was observed in the side arms of the apparatus. The solid apparent in the extract was isolated at the pump and washed with DCM (x2) and dried to yield a silvery beige coloured solid, fine flakes, 6.82 g. m.p. = 160.5-166.0°C (uncorrected). The filtrate was washed with 4M hydrochloric acid (x2) and saturated aqueous sodium hydrogen carbonate (x2), dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound. The crude solid was triturated using diethyl ether, isolated at the pump and washed with diethyl ether (x2) and dried to yield a brown-coloured very finely divided solid, 3.26 g. m.p. = 160.5-165.0°C (uncorrected). Total yield, 10.08 g, 28.2 %.

Lit.[51] m.p. = 156-159°C (crude)

Experiment 2.1.2

(1b) α,ϖ-bis(3-oxythienyl)propane

To a mechanically stirred mixture of methyl 3-hydroxythiophene-2-carboxylate (68.20 g, 431.18 mmol) and potassium carbonate (32.50 g, 235.15 mmol) in DMF (340 cm^3) was added 1,3-dibromopropane (24.0 cm^3, 235.48 mmol) and the mixture was heated to approximately 100°C. After 5 hours the mixture was cooled slightly and poured into an excess of ice (~0.5 dm^3) with stirring. The precipitate was isolated at the pump and washed well with water. The wet solid, crude α,ϖ-bis(2-methoxycarbonyl-3-oxythienyl) propane was saponified by refluxing in 50 % aqueous ethanol (1.25 dm^3) with potassium hydroxide (49.0 g). After 2 hours the solution was cooled slightly and filtered through a glass frit into ice (excess). The filtrate was split into two portions and acidified with concentrated hydrochloric acid, isolated at the pump, washed well with water and dried (achieved by placing contents in a crystallising dish and slowly evaporating the water on a warm surface). The dry compound, crude α,ϖ-bis(2-carbonyl-3-oxythienyl)propane was mechanically stirred with copper(I) oxide (57.2 g) in pyridine (450 cm^3) and refluxed. After 1 hour the mixture was cooled and transferred to a suitable flask (1 dm^3 round bottomed flask) and the solvent partially evaporated under reduced pressure. The residue was extracted repeatedly (Soxhlet apparatus) using

DCM as solvent until no apparent colour was observed in the side arms of the apparatus. The extracts were washed with 4M hydrochloric acid (x2) and saturated aqueous sodium hydrogen carbonate (x2), dried ($MgSO_4$) and the solvent evaporated off. The solid was purified by recrystallisation from ethanol (20 cm^3), isolation at the pump, washed with ethanol (3 x 25 cm^3) and dried providing the title compound as a light beige coloured finely divided solid, 29.8 g, 57.5 %. m.p. = 67.0-70.5°C (uncorrected).

Lit.[51] m.p. = 64-67°C

Experiment 2.1.3

(1c) α,ϖ-bis(3-oxythienyl)butane

To a mechanically stirred mixture of methyl 3-hydroxythiophene-2-carboxylate (50.10 g, 316.75 mmol) and potassium carbonate (26.60 g, 192.46 mmol) in DMF (250 cm^3) was added 1,4-dibromobutane (23.0 cm^3, 192.58 mmol) and the mixture was heated to approximately 100°C. After 5 hours the mixture was cooled slightly and poured into an excess of ice (~0.5 dm^3) with stirring. The precipitate was isolated at the pump and washed well with water. The wet solid, crude α,ϖ-bis(2-methoxycarbonyl-3-oxythienyl)butane was saponified by refluxing in 50 % aqueous ethanol (1.0 dm^3) with potassium hydroxide (36.10 g). After 2 hours the solution was cooled slightly and filtered through a glass frit into ice (excess). The filtrate was acidified with concentrated hydrochloric acid, isolated at the pump, washed well with water and dried (vacuum oven at T = 65°C for two days). The dry compound, crude α,ϖ-bis(2-carbonyl-3-oxythienyl)butane, was mechanically stirred with copper(I) oxide (51.20 g) in pyridine (430 cm^3) and refluxed. After 1 hour the mixture was cooled and transferred to a suitable flask (1 dm^3 round bottomed flask) and the solvent partially evaporated under reduced pressure. The residue was extracted repeatedly (Soxhlet apparatus) using DCM as solvent until no apparent colour was observed in the side arms of the apparatus. The extracts were washed with 4M hydrochloric acid (x2) and 12.5 % aqueous sodium hydroxide (x1), dried ($MgSO_4$) and the solvent evaporated off. The solid was purified by hot digestion from methanol (excess), cooled, isolation at the pump, washed well with methanol and dried to yield a brown coloured finely divided solid, 18.0 g, 44.7 %. m.p. = 103.0-105.0°C (uncorrected).

Lit.[51] m.p. = 104-105°C

Experiment 2.1.4

(1d) α,ϖ-bis(3-oxythienyl)diethyl ether

To a mechanically stirred mixture of methyl 3-hydroxythiophene-2-carboxylate (32.10 g, 202.93 mmol) and potassium carbonate (15.70 g, 113.60 mmol) in DMF (160 cm^3) was added diethyleneglycol di-*p*-tosylate (47.00 g, 113.39 mmol) and the mixture was heated to approximately 100°C. After 5 hours the mixture was cooled slightly and poured into an excess of ice (~0.5 dm^3) with stirring. The precipitate was isolated at the pump and washed well with water. The wet solid, crude α,ϖ-bis(2-methoxycarbonyl-3-oxythienyl)diethyl ether was saponified by refluxing in 80 % aqueous ethanol (0.70 dm^3) with potassium hydroxide (56.11 g). After 1 hour the solution was cooled slightly and filtered through a glass frit into ice (excess). The filtrate was acidified with concentrated hydrochloric acid, isolated at the pump, washed well with water and dried (vacuum oven at T = 70°C). The dry compound, crude α,ϖ-bis(2-carbonyl-3-oxythienyl)diethyl ether was mechanically stirred with copper(I) oxide (37.30 g) in pyridine (300 cm^3) and refluxed. After 1 hour the mixture was cooled and transferred to a suitable flask (1 dm^3 round bottomed flask) and the solvent partially evaporated under reduced pressure. The residue was extracted repeatedly (Soxhlet apparatus) using DCM as solvent until no apparent colour was observed in the side arms of the apparatus. The extracts were washed with 4M hydrochloric acid (x2) and saturated aqueous sodium hydrogen carbonate (x2), dried ($MgSO_4$) and the solvent evaporated off. Purified by recrystallisation from methanol, isolation at the pump, washing with methanol (x2) and dried to yield a beige coloured solid, 16.5 g, 60.2 %. m.p. = 60.5-62.0°C (uncorrected).

Lit.[51] m.p. = 58-60°C

2.2 - A Synthetic Route to [1+1] Thiophene-Based Macrocycles containing the Hydroxyl Functional group – Scheme Two (see page 34)

2.2.1 - Schiff Bases of *p*-hydroxybenzaldehyde

Experiment 2.2.1

(2a) *N,N´*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine
or (4,4′[1,2-ethanediylbis(nitrilomethylidene)]phenol

To a mechanically stirred solution of *p*-hydroxybenzaldehyde (20.11 g, 164.67 mmol) in dry ethanol (80 cm^3) was added ethylenediamine (6.0 cm^3, 89.75 mmol) in portions, maintaining the temperature of the reaction at about 20°C. After the addition the reaction mixture was allowed to stir for 2 hours at ambient temperature. The solid was isolated at the pump, washed with water (3 x 50 cm^3) and dried. Purification was by digestion in hot dry ethanol (80 cm^3), the solid being collected at the pump, washed with cold dry ethanol (2 x 30 cm^3) and dried to provide the title compound as a finely divided light beige solid, 15.65 g, 70.8 %. m.p. = 208.0-210.0°C (uncorrected); ν_{max}/cm^{-1}(KBr disc) 3423.8 (OH), 1638.9 (imine), 1606.1, 1587.1, 1516.7 (phenyl); ∂_H (270 MHz, DMSO) 3.81 (4H, s, **CH$_2$**), 6.78 (4H, d $J_{2(2'),3(3')}$ 8.6, 3(3′)Ph-**H**), 7.51 (4H, d $J_{2(2')3(3')}$ 8.6, 2(2′)Ph-**H**), 8.51 (2H, s, **HC**=N), 9.56 (2H, br, **OH**); ∂_C (67.8 MHz, DMSO) 61.4 (NCH$_2$), 115.3 (3(3′)Ph), 127.4 (1Ph), 129.5 (2(2′)Ph), 159.8 (4Ph), 161.3 (C=N)

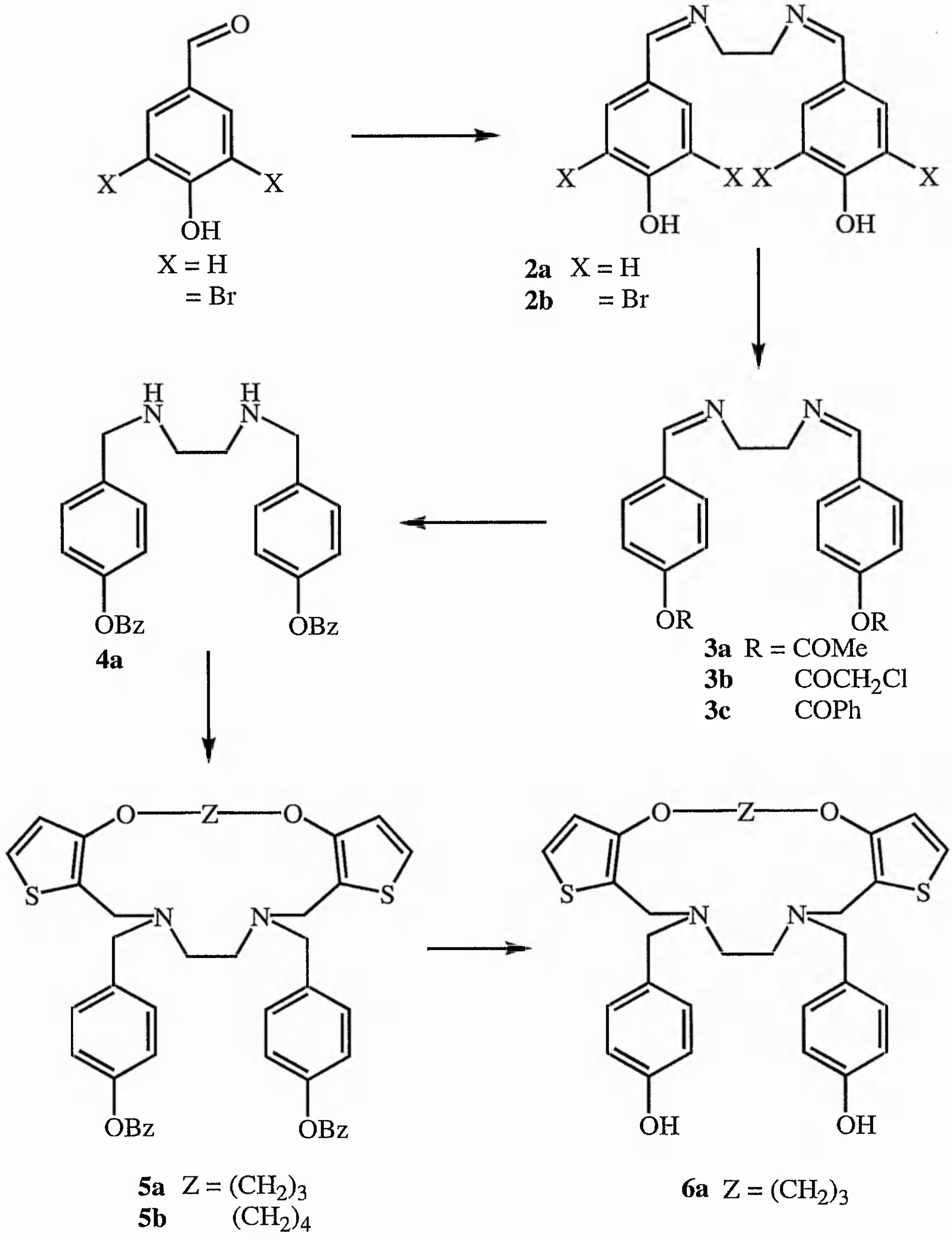
Lit.[71] m.p. = 212-213°C

Experiment 2.2.2

(2b) *N,N´*-bis-(3,5-dibromo-4-hydroxy-benzylidene)-ethane-1,2-diamine

To a magnetically stirred solution of 3,5-dibromo-4-hydroxybenzaldehyde (4.53 g, 16.18 mmol), at the reflux temperature, in dry ethanol (40 cm^3) was added ethylenediamine (0.6 cm^3, 8.98 mmol). After 1 hour the reaction mixture was cooled and the solid was isolated at the pump, washed with water (3 x 25cm^3), ethanol

continued page 35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X X
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OH
2a X = H
2b = Br
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OBz
OBz
4a
N
N
OR
OR
3a R = COMe
3b COCH2Cl
3c COPh
O
Z
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N
OBz
OBz
5a Z = (CH2)3
5b (CH2)4
O
Z
O
S
S
N
N
OH
OH
6a Z = (CH2)3

Scheme Two

Experiment 2.2.2 *continued*

(1 x 25 cm^3) and dried to constant weight in a desiccator ($CaCl_2$) providing the crude title compound as a finely divided light brown solid, 4.76 g, 100.8 %, m.p. = 259.5-261.0°C (uncorrected). A sample was hot digested in dry ethanol, cooled, isolated at the pump, washed with dry ethanol (2 x 5 cm^3) and dried for analysis, M.p.= 260.0-260.5°C; ν_{max}/cm^{-1} (KBr disc): 3433.8 (OH), 1650.9 (imine), 1576.5 & 1504.4 (phenyl); Microanalysis: Found: C, 33.14; H, 2.38; N, 5.42. $C_{16}H_{12}Br_2N_2O_2$ requires C, 32.91; H, 2.07; N, 4.80; m/z: Found $[M + H]^+$ 585.2, $C_{16}H_{12}Br_2N_2O_2$ requires 583.90.

2.2.2 - Protection of the Schiff Base *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine

Experiment 2.2.3

(3a) Attempted preparation of *N,N′*-bis-(4-acetoxy-benzylidene)-ethane-1,2-diamine

To a stirring suspension of *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine (0.52g, 1.94 mmol) and triethylamine (0.57 cm^3, 4.09 mmol) in dry DCM (15 cm^3) was added acetyl chloride (0.29 cm^3, 4.08 mmol) at 20°C After 2 hours, the organic layer was washed with water/saturated sodium chloride (1:1) (x5), saturated sodium chloride (x1), dried ($MgSO_4$) and the solvent evaporated off to obtain an orange oil (0.54 g, 79.4 % crude).

Experiment 2.2.4

(3b) Attempted preparation of *N,N′*-bis-(4-chloroacetoxy-benzylidene)-ethane-1,2-diamine

To a stirring suspension of *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine (2.02 g, 7.53 mmol) and triethylamine (2.20 cm^3, 15.78 mmol) in dry DCM (60 cm^3) was added chloroacetyl chloride (1.30 cm^3, 16.31 mmol) at 20°C. Product formation became apparent after 10 minutes by *tlc*. Signs of decomposition or formation of polymeric material were noted before 60 minutes. After 3.5 hours more chloroacetyl chloride (0.5 cm^3) was added. No reduction in starting material was noted by *tlc* after an extended period (6 hours), nor if the reaction mixture was refluxed for 30 minutes.

The suspension was filtered and the filtrate was evaporated. Polymeric material was removed by flash chromatography where only two compounds (one was starting material) were collected corresponding to the two spots seen on the *tlc* plate.

Experiment 2.2.5

(3c) *N,N'*-bis-(4-benzoate-benzylidene)-ethane-1,2-diamine

To a stirring suspension of *N,N'*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine (5.08 g, 18.93 mmol) and triethylamine (5.50 cm^3, 39.43 mmol) in dry DCM (150 cm^3) was added benzoyl chloride (4.50 cm^3, 38.77 mmol) in portions maintaining the temperature of the reaction at 15-20°C. After the addition the mixture was allowed to stir for 1 hour at ambient temperature. The organic phase was washed with water (5 x 50 cm^3), saturated aqueous sodium chloride (1 x 50 cm^3), dried (Na_2SO_4) and the solvent evaporated off. Purification was by digestion in dry hot ethanol (40 cm^3), the crystals were isolated at the pump and washed with dry ethanol (2 x 15 cm^3) and dried to provide the title compound as a white crystalline solid, 7.81 g, 86.6 %. m.p. = 181.0-182.0°C (uncorrected); *tlc*: R_f 0.47 [uv-active; light petroleum ether b.p. 40-60°C/ethyl acetate, (4:1)]; ν_{max}/cm^{-1}(KBr disc) 1731.0 (C=O), 1643.5 (imine), 1600.0, 1584.9, 1503.8 (phenyl); ∂_H (270 MHz/$CDCl_3$) 3.99 (4H, s, **CH_2**), 7.26 (4H, d $J_{2(2'),3(3')}$ 8.6, 3(3′)Ph-**H**), 7.51 (4H, dd *J* 7.3, 7.9, 3(3′)Ph′-**H**), 7.64 (2H, dd *J* 7.6, $J_{3(3'),4}$ 7.3, 4Ph′-**H**), 7.78 (4H, d $J_{2(2'),3(3')}$ 8.6, 2(2′)Ph-**H**), 8.20 (4H, d $J_{2(2'),3(3')}$ 7.3 2(2′)Ph′-**H**), 8.30 (2H, s, **HC=N**); ∂_C (67.8 MHz, $CDCl_3$) 61.6 (CH_2), 122.0 (3(3′)Ph), 128.6 (3(3′)Ph′), 129.3 and 130.2 (2(2′)Ph or 2(2′)Ph′, 133.7 (1Ph), 133.9 (4Ph′), 152.7 (4Ph), 161.5 (C=N), 164.9 (ester); Microanalysis: Found: C, 75.67; H, 5.02; N, 5.87. $C_{30}H_{24}N_2O_4$ requires C, 75.62; H, 5.08; N, 5.88; m/z: Found $[M + H]^+$ 477.2. $C_{30}H_{24}N_2O_4$ requires 476.5.

2.2.3 - The reduction of the protected Schiff Base, *N,N′*-bis-(4-benzoate-benzylidene)-ethane-1,2-diamine

Experiment 2.2.6

(4a) *N,N′*-bis-(4-benzoate-benzyl)-ethane-1,2-diamine

To a stirred suspension of *N,N′*-bis-(4-benzoate-benzylidene)-ethane-1,2-diamine (5.05 g, 10.60 mmol) in g.AcOH (25 cm^3) was added dimethylamine borane complex (DMAB) (1.56 g, 26.48 mmol) in g.AcOH (25 cm^3) in portions, maintaining the temperature of the reaction at about 20°C. After the addition the solution was allowed to stir for 90 minutes at ambient temperature, then basified to pH 14 using 4M sodium hydroxide solution (T < 40°C). The precipitate was extracted with DCM (3 x 30 cm^3). The organic layer was washed with saturated sodium chloride solution (1 x 50 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude off-white solid was purified by recrystallisation from ethanol, isolated at the pump (assisted with ethanol (20 cm^3)); and washed with ethanol (2 x 10 cm^3) to provide the title compound as a white crystalline solid, 3.03 g, 59.5 %; m.p. = 106.0-109.0°C. In a similar experiment, isolated crude solid was recrystallised from ethanol/petroleum ether and subsequently recrystallised twice from ethanol; m.p. = 113.0-114.0°C; ν_{max}/cm^{-1} (KBr disc) 3432.7 (N-H), 1726.6 (ester), 1598.1 & 1507.6 (phenyl); ∂_H (270 MHz/$CDCl_3$) 1.58 (2H, br. s, N**H**), 2.79 (4H, s, NC**H**$_2$), 3.81 (4H, s, C**H**$_2$N) 7.17 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′)Ph-**H**), 7.39 (4H, d $J_{2(2'),3(3')}$ 8.4, 2(2′)Ph-**H**), 7.50 (4H, dd J 7.2, 7.9, 3(3′)Ph′-**H**), 7.63 (2H, dd $J_{3(3'),4}$ 7.4, 4Ph′-**H**), 8.21 (4H, d $J_{2(2'),3(3')}$ 7.2, 2(2′)Ph′-**H**); ∂_C (67.8 MHz, $CDCl_3$) 48.8 (NCH_2), 53.4 (CH_2N), 121.6 (3(3′)Ph), 128.5 & 129.1 & 130.2 (2(2′)Ph or 2(2′)Ph′ or 3(3′)Ph′), 129.6 (1Ph), 133.5 (1Ph′), 138.2 (4Ph′), 149.8 (4Ph), 165.3 (ester); Microanalysis: Found: C, 74.21; H, 5.73; N, 5.48. $C_{30}H_{24}N_2O_4$ requires C, 74.98; H, 5.87; N, 5.83; m/z: Found $[M + H]^+$ 481.5. $C_{30}H_{24}N_2O_4$ requires 480.56.

Experiment 2.2.8

(5b) 14,17-bis-(4-benzoate-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene

To a stirred solution of *N,N'*-bis-(4-benzoate-benzyl)-ethane-1,2-diamine (8.05 g, 16.75 mmol) and 37 % aqueous formaldehyde solution (2.50 cm^3, 33.36 mmol) at ambient temperature, in g.AcOH (385 cm^3) was added α,ϖ-bis(3-oxythienyl)butane (3.85 g, 15.14 mmol). After 24 hours the solvent was reduced under reduced pressure; DCM (100 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated sodium hydrogen carbonate (200 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude oil was purified by flash chromatography [wt. 20:1; light petroleum b.p 40-60°C/ethyl acetate (3:1)] to provide the slightly impure title compound. Diethyl ether (excess) was added to the solid, filtered off and the crystals washed with diethyl ether. The solid was collected and digested in hot diethyl ether (excess), isolated at the pump and washed well with diethyl ether (excess x3) providing a cleaner white solid, 3.87 g, 33.7 %. A small sample was further purified by recrystallisation from acetonitrile, collected at the pump and washed with acetonitrile (x2) and diethyl ether (x3) to provide the pure title compound as a white solid. m.p. = 132.5-133.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3445.4 (OH), 3065.7(w) (Th-H), 1730.9 (ester), 1600.2 & 1506.7 (phenyl), 1559.1 (Th C=C); ∂_H (270 MHz, $CDCl_3$) 1.97 (4H, br.s, OCH$_2$C**H**$_2$), 2.70 (4H, s, NC**H**$_2$), 3.66 (4H, s, NC**H**$_2$Th), 3.68 (4H, s, NC**H**$_2$Ph), 4.10 (4H, br. s, OC**H**$_2$), 6.80 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.11 (2H, d $J_{4,5}$ 5.7, 5Th-**H**), 7.14 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3')Ph-**H**), 7.44 (4H, d $J_{2(2'),3(3')}$ 8.4, 2(2')Ph-**H**), 7.61 (2H, dd, J 7.4, 3(3')Ph'-**H**), 7.61 (2H, dd $J_{3(3'),4}$ 7.4, 4Ph'-**H**), 8.19 (4H, d $J_{2(2'),3(3')}$ 7.2, 2(2')Ph'-**H**); ∂_C (67.8 MHz, $CDCl_3$): 26.4 (OCH$_2$**C**H$_2$), 47.3 (NCH$_2$), 50.6 (NCH$_2$Th), 58.0 (NCH$_2$Ph), 70.9 (OCH$_2$), 116.6 (4Th), 118.4 (2Th), 121.3 (3(3')Ph), 122.5 (5Th), 128.5 & 129.6 & 129.7 & 130.2 (2(2')Ph or 2(2')Ph' or 3(3')Ph' or 1Ph), 133.4 (1Ph'), 137.6 (4Ph'), 149.7 (4Ph), 154.1 (3Th), 165.2 (ester); Microanalysis: Found: C, 66.62; H, 5.15; N, 3.43. $C_{44}H_{42}N_2O_6S_2$ requires C, 69.63; H, 5.58; N, 3.69; m/z: Found $[M + H]^+$ 759.3, $C_{44}H_{42}N_2O_6S_2$ requires 758.94.

Experiment 2.2.9

(6a) 13,16-bis-(4-hydroxy-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

A stirring solution of 13,16-bis-(4-benzoate-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene (0.38 g, 0.51 mmol) and KOH (0.11 g, 1.96 mmol) in 80 % ethanol (10 cm^3) was heated to reflux using a water bath. After 100 minutes the solution was cooled and the pH reduced to 8-9 by bubbling carbon dioxide through the solution. The mixture was filtered and the ethanol evaporated off from the filtrate. DCM was added and the organic layer was washed with water. 2M hydrochloric acid was added to the organic layer precipitating out a sticky solid. The mother liquor was decanted and the solid was back extracted with 2M sodium hydroxide and ethyl acetate. The organic phase was washed with saturated sodium chloride (x2), dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound as slightly off white coloured crystals, 0.16 g, 59.3 %. ν_{max}/cm^{-1} (KBr disc): 3422.0 (OH and N-H), 1733.9 (w) (ester), 1611.6 & 1513.3 (phenyl); NMR data – discussed in the Discussion Section 3.2.4.

2.3 - A Synthetic Route to [1+1] Thiophene-Based Macrocycles containing the Acetamido Functional Group – Scheme Three (see page 42)

Experiment 2.3.1

(7a) *N,N´*-bis-(4-acetamido-benzylidene)-ethane-1,2-diamine

To a magnetically stirred solution of 4-acetamidobenzaldehyde (10.06 g, 61.65 mmol), in ethanol (80 cm^3) was added ethylenediamine (2.50 cm^3, 37.40 mmol) and the mixture refluxed. After 1 hour the reaction mixture was cooled and the solid was isolated at the pump assisted with ethanol (80 cm^3), washed with ethanol (1 x 80 cm^3) and dried providing the crude title compound as a white solid, 9.33 g, 86.4 %. m.p. = (softens 254°C) 266.5-268.5°C (uncorrected). A sample was hot digested in ethanol, cooled, isolated at the pump, washed with ethanol (x2) and dried for analysis, m.p. = 266.0-267.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3305.0 & ~3250.0 (2° amide N-H), 3188.2

& 3115.4 (2° amide), 1689.8 or 1667.5 (amide carbonyl I), 1636.6 (imine), 1600.9 (phenyl), 1539.9 (amide II); Microanalysis: Found: C, 68.54; H, 6.40; N, 15.94. $C_{20}H_{22}N_4O_2$ requires C, 68.55; H, 6.33; N, 15.99; m/z: Found $[M + H]^+$ 351.4. $C_{20}H_{22}N_4O_2$ requires 350.42.

Experiment 2.3.2

(8a) *N,N′*-bis-(4-acetamido-benzyl)-ethane-1,2-diamine

To a mechanically stirred suspension of *N,N′*-bis-(4-acetamido-benzylidene)-ethane-1,2-diamine (4.12 g, 11.76 mmol) in g.AcOH (20 cm^3) was added solid dimethylamine borane complex (DMAB) (1.70 g, 28.85 mmol) in portions maintaining the temperature of the reaction at about 20°C. After addition the solution was allowed to stir for 1 hour at ambient temperature, then basified to pH 14 using 4M aqueous sodium hydroxide (T < 40°C). The solid was isolated at the pump, washed well with water and dried in a vacuum oven at 55°C, to provide the crude title compound as a white solid, 3.66 g, 87.8 %. m.p. = (softens 102°C) 105.0-109.0°C (uncorrected) (gas bubbles evolved); ν_{max}/cm^{-1} (KBr disc): 3273.1 br. (2° amine), 3121.5 (2° amide), 1670.3 (carbonyl amide I), 1605.8 (phenyl), 1547.9 (amide II); m/z: Found $[M + H]^+$ 355.6; also found adduct [2M+1] 709.4. $C_{20}H_{26}N_4O_2$ requires 354.45.

Experiment 2.3.3

(9a) 13,16-bis-(4-acetamido-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

To a stirred solution of *N,N′*-bis-(4-acetamido-benzyl)-ethane-1,2-diamine (2.00 g, 5.64 mmol) and 37 % aqueous formaldehyde solution (0.85 cm^3, 11.34 mmol) at ambient temperature, in g.AcOH (125 cm^3) was added α,ϖ-bis(3-oxythienyl)propane (1.23 g, 5.12 mmol). After 48 hours the solution was basified to pH 14 using 4M sodium hydroxide solution (T < 30°C) and the precipitate was isolated at the pump. The product was extracted into DCM (100 cm^3), washed with saturated sodium hydrogen carbonate (1 x 50 cm^3), dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound as a beige solid (foam), 2.85 g, 89.9 %. The crude solid was

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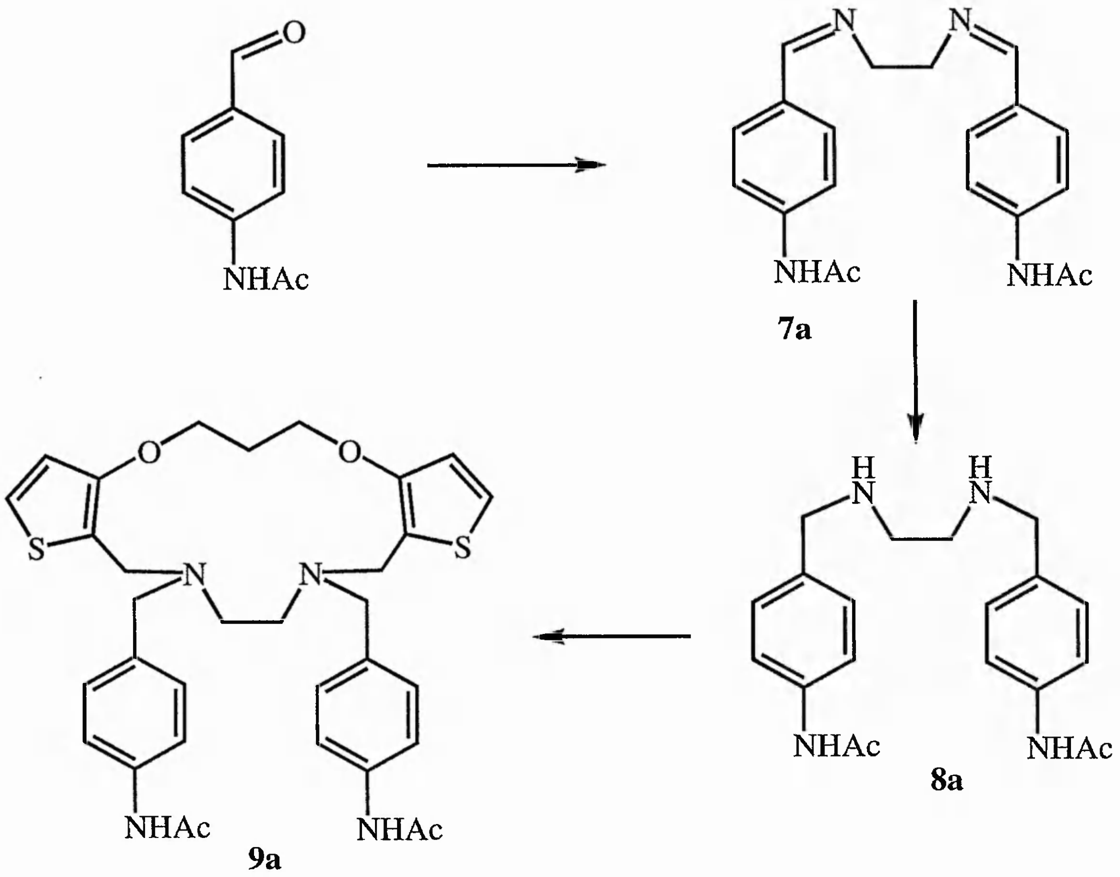

Scheme Three

Experiment 2.3.3 *continued*

purified by flash chromatography [wt. 30:1, light petroleum ether b.p 40-60°C/ethyl acetate/methanol (8:4:3)] to provide the slighty impure title compound as a light beige coloured solid (foam), 0.73 g, 23.1 %; m.p. = unable to determine (softens 82°C, obvious at 85°C; at ~94°C clear viscous oil (bubbles apparent); at ~115°C oil reduces in viscosity; no apparent change at ~150°C). ν_{max}/cm^{-1} (KBr disc): 3443.5 & 3302.2 (2° amide N-H), 3189.5 & 3120.5 (2° amide), 1664.1 (amide I), 1603.7 & 1513.0 (phenyl); ∂_H (270 MHz, $CDCl_3$) 2.16 (8H, s & q, $\mathbf{CH_3}$ & $OCH_2\mathbf{CH_2}$), 2.47 (4H, s, $N\mathbf{CH_2}$), 3.42 or 7.90 (2H, s, N-**H**) – D_2O shake not aquired, 3.56 (4H, s, $Th\mathbf{CH_2}N$), 3.76 (4H, s, $Ph\mathbf{CH_2}N$) 4.23 (4H, t, *J* 5.5, $O\mathbf{CH_2}$), 6.87 (2H, d $J_{4,5}$ 5.5, 4Th-**H**), 7.12 (2H, d $J_{4,5}$ 5.5, 5Th-H), 7.13 (4H, d, $J_{2(2'),3(3')}$ unknown, 2(2′)Ph-H), 7.31 (4H, d $J_{2(2'),3(3')}$ 8.5, 3(3′)Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 24.4 (CH_3), 29.8 (OCH_2CH_2) 48.2 ($ThCH_2N$), 49.3

(NCH_2), 58.4 ($PhCH_2N$), 68.0 (OCH_2), 117.4 (4Th), 119.1 (2Th), 120.1 (3(3′)Ph), 122.6 (5Th), 129.0 (2(2′)Ph, 135.8 (1Ph), 136.5 (4Ph), 154.0 (3Th), 168.8 (amide carbonyl); Microanalysis: Found: C, 63.15; H, 6.24; N, 8.67. $C_{33}H_{38}N_4O_4S_2$ requires C, 64.05; H, 6.19; N, 9.05; m/z: Found $[M + H]^+$ 619.5. $C_{33}H_{38}N_4O_4S_2$ requires 618.81.

2.4 - A Synthetic Route to [1+1] Thiophene-Based Macrocycles containing the Nitro Functional Group – Scheme Four (see page 45)

2.4.1 - Schiff Bases of *p*-nitrobenzaldehyde

Experiment 2.4.1
(10a) *N,N′*-bis-(4-nitro-benzylidene)-ethane-1,2-diamine

To a mechanically stirred suspension of 4-nitrobenzaldehyde (52.10 g, 344.76 mmol) in ethanol (315 cm^3) was added ethylenediamine (14.5 cm^3, 216.90 mmol) and the mixture refluxed. After 90 minutes the mixture was cooled and the solid isolated at the pump, washed with ethanol (2 x 200 cm^3) and diethyl ether (1 x 200 cm^3). The solid was purified by hot digestion in ethanol (250 cm^3), isolated at the pump and washed with ethanol (1 x 200 cm^3), diethyl ether (1 x 200 cm^3) and dried in a vacuum oven (~100°C) to provide the title compound as a finely divided beige coloured solid, 50.10 g, 89.1 %. m.p. = 202.0-203.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1639.9 (imine), 1601.8 (phenyl), 1520.0 & 1341.8 (nitro).

Lit.[72] m.p. = 200.5°C

Experiment 2.4.2

(10b) *N,N′*-bis-(4-nitro-benzylidene)-propane-1,3-diamine

To a mechanically stirred suspension of 4-nitrobenzaldehyde (50.0 g, 330.86 mmol) in ethanol (300 cm^3) was added 1,3-diaminopropane (17.5 cm^3, 209.63 mmol) and the mixture refluxed. After 90 minutes the mixture was cooled and the solid isolated at the pump, washed with ethanol (2 x 200 cm^3) and diethyl ether (1 x 200 cm^3). The solid was purified by hot digestion in ethanol (250 cm^3), isolated at the pump and washed with ethanol (1 x 200 cm^3), diethyl ether (1 x 200 cm^3) and dried in a vacuum oven (~100°C) to provide the title compound as a finely divided beige coloured solid, 49.4 g, 87.8 %. m.p. = 199.0-200.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1642.3 (imine), 1598.6 (phenyl), 1515.5 & 1342.4 (nitro).

Lit.[73] m.p. = 198-200°C

Experiment 2.4.3

(10c) *N,N′*-bis-(4-nitro-benzylidene)-butane-1,4-diamine

To a mechanically stirred suspension of 4-nitrobenzaldehyde (20.10 g, 133.01 mmol) in ethanol (120 cm^3) was added 1,4-diaminobutane (8.50 cm^3, 84.57 mmol) and the mixture refluxed. After 2 hours the mixture was cooled and the solid isolated at the pump, washed with ethanol (2 x 200 cm^3) and diethyl ether (1 x 200 cm^3). The solid was purified by hot digestion in ethanol (250 cm^3), isolated at the pump and washed with ethanol (1 x 200 cm^3), diethyl ether (1 x 200cm^3) and dried in a vacuum oven (~100°C) to provide the title compound as a brown coloured solid, 21.4 g, 90.8 %. m.p. = (softens 168°C) 169.5-171.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1642.2 (imine), 1600.5 (phenyl), 1515.6 & 1341.5 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.84 (4H, t, $NCH_2\mathbf{CH_2}$), 3.74 (4H, t, $N\mathbf{CH_2}$), 7.89 (4H, d $J_{2(2'),3(3')}$ 8.9, 2(2′) Ph-**H**), 8.27 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**), 8.38 (2H, s, **H**C=N); ∂_C (67.8 MHz, $CDCl_3$): 28.6 ($NCH_2\mathbf{CH_2}$), 61.6 ($N\mathbf{CH_2}$), 123.9 (3(3′) Ph), 128.7 (2(2′) Ph), 141.7 (4 Ph), 149.0 (1 Ph), 158.7 (C=N).

Lit.[74] m.p. = not quoted

Experiment 2.4.4

(10d) *N,N′*-bis-(4-nitro-benzylidene)-pentane-1,5-diamine

To a mechanically stirred suspension of 4-nitrobenzaldehyde (20.0 g, 132.35 mmol) in ethanol (120 cm^3) was added 1,5-diaminopentane (9.50 cm^3, 81.17 mmol) and the mixture refluxed. After 160 minutes the solution was cooled and the precipitate was isolated at the pump, washed with ethanol (2 x 50 cm^3) and diethyl ether (100 cm^3).

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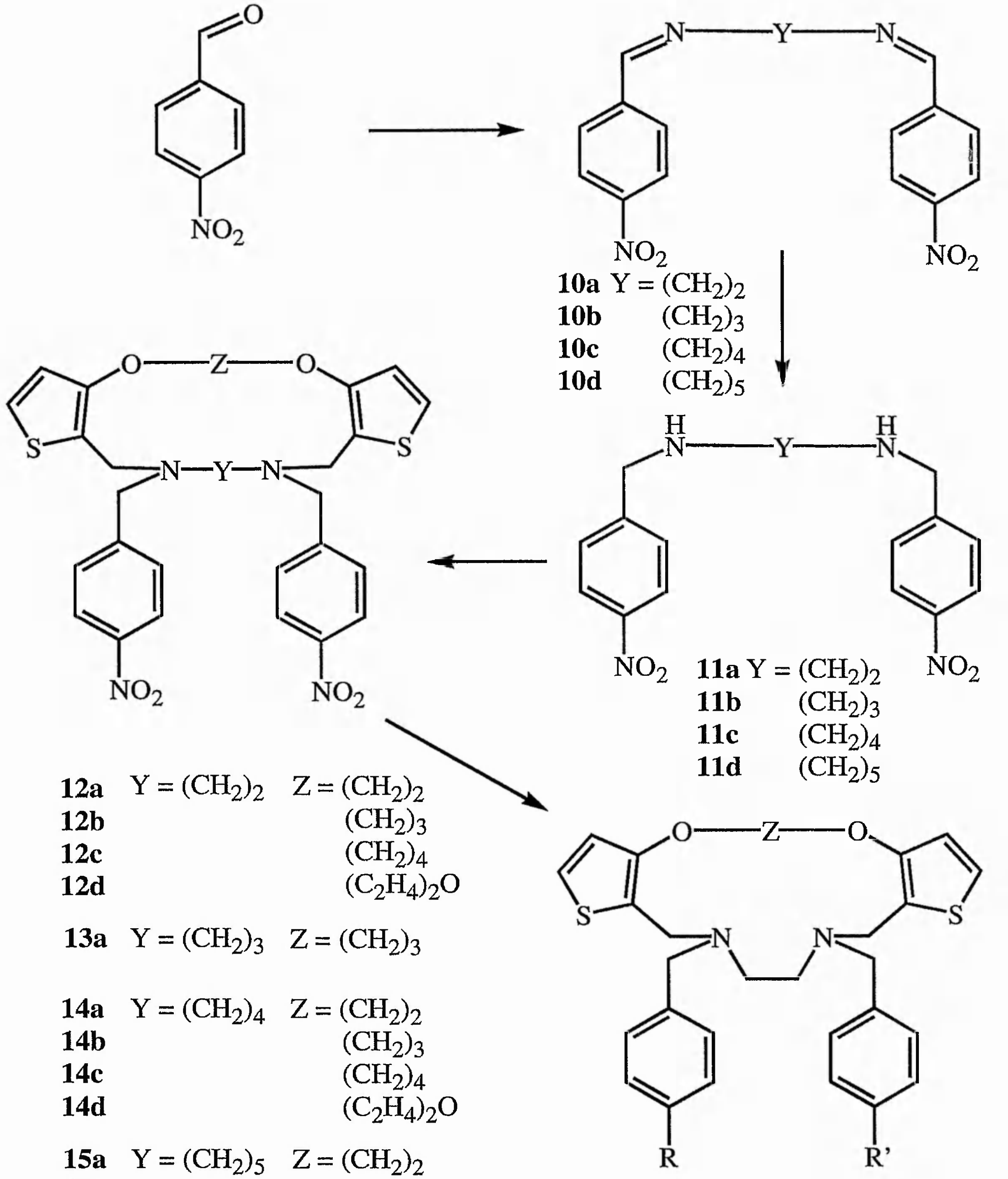


10a Y = $(CH_2)_2$
10b $(CH_2)_3$
10c $(CH_2)_4$
10d $(CH_2)_5$

11a Y = $(CH_2)_2$
11b $(CH_2)_3$
11c $(CH_2)_4$
11d $(CH_2)_5$

12a Y = $(CH_2)_2$ Z = $(CH_2)_2$
12b $(CH_2)_3$
12c $(CH_2)_4$
12d $(C_2H_4)_2O$

13a Y = $(CH_2)_3$ Z = $(CH_2)_3$

14a Y = $(CH_2)_4$ Z = $(CH_2)_2$
14b $(CH_2)_3$
14c $(CH_2)_4$
14d $(C_2H_4)_2O$

15a Y = $(CH_2)_5$ Z = $(CH_2)_2$
15b $(CH_2)_3$
15c $(CH_2)_4$
15d $(C_2H_4)_2O$

16a Z = $(CH_2)_3$, R = NO_2, R' = NH_2
16b Z = $(CH_2)_4$, R = NO_2, R' = NH_2
16c Z = $(CH_2)_3$, R = R' = NH_2
16d Z = $(CH_2)_4$, R = R' = NH_2

<u>**Scheme Four**</u>

Experiment 2.4.4 *continued*

The solid was dissolved in DCM (200 cm^3) and washed with water (2 x 200 cm^3), saturated aqueous sodium chloride (1 x 200 cm^3), dried (Na_2SO_4) and the solvent evaporated off to provide the crude title compound, 21.5 g, 88.2 %. m.p. = (softens 97°C (oily)) 114.5-115.5°C (uncorrected). A small sample of the crude product was further purified by recrystallisation from ethanol (x2) (hot filtration), isolation at the pump, washing with ethanol (x2) and dried to provide the title compound as a beige coloured solid, m.p. = 113.5-114.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1644.6 (imine), 1601.2 (phenyl), 1518.5 & 1342.6 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.49 (2H, q, $NCH_2CH_2\mathbf{CH_2}$), 1.80 (4H, q, $NCH_2\mathbf{CH_2}$), 3.70 (4H, t, $N\mathbf{CH_2}$), 7.88 (4H, d $J_{2(2'),3(3')}$ 8.7, 2(2′)Ph-**H**), 8.26 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′)Ph-**H**), 8.36 (2H, s, **HC**=N); ∂_C (67.8 MHz, $CDCl_3$): 25.1 ($NCH_2CH_2\mathbf{CH_2}$), 30.5 ($NCH_2\mathbf{CH_2}$), 61.8 ($N\mathbf{CH_2}$), 123.9 (3(3′) Ph), 128.7 (2(2′) Ph), 141.7 (1 Ph), 148.9 (4Ph), 158.5 (**C**=N); Microanalysis: Found: C, 61.82; H, 5.44; N, 15.18. $C_{19}H_{20}N_4O_4$ requires C, 61.95; H, 5.47; N, 15.21; m/z: Found $[M + H]^+$ 369.3. $C_{19}H_{20}N_4O_4$ requires 368.39.

2.4.2 - The Reduction of the Schiff Bases *N,N′*-bis-(4-nitro-benzylidene)-alkane-diamine

Experiment 2.4.5

(11a) *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine

To a mechanically stirred suspension of *N,N′*-bis-(4-nitro-benzylidene)-ethane-1,2-diamine (20.0 g, 61.29 mmol) in g.AcOH (80 cm^3) was added solid dimethylamine borane complex (DMAB) (9.00 g, 152.75 mmol) in portions, maintaining the temperature of the reaction at about 20°C. After addition the solution was allowed to stir for 90 minutes at ambient temperature, then basified to pH 14 using 4M aqueous sodium hydroxide (T < 40°C). An excess of water was added and the precipitate extracted with DCM (2 x 100 cm^3). The organic layer was washed with water (x2), saturated aqueous sodium chloride (x1), dried ($MgSO_4$) and the solvent evaporated off. The crude solid was recrystallised from methanol (11 cm^3), isolated at the pump (assisted with methanol (10 cm^3)), washed with methanol (2 x 20 cm^3) and dried to provide the title compound, 11.54 g, 57.0 %. m.p. = 80.0-82.0°C (uncorrected);

ν_{max}/cm^{-1} (KBr disc): 3422.0 (2° amine), 1600.9 (phenyl), 1508.3 & 1342.3 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.64 (2H, br. s, N**H**), 2.76 (4H, s, $NC\mathbf{H}_2$), 3.91 (4H, s, $NC\mathbf{H}_2Ph$), 7.50 (4H, d $J_{2(2'),3(3')}$ 8.9, 2(2′) Ph-**H**), 8.17 (4H, d $J_{2(2'),3(3')}$ 8.9, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 48.9 (NCH_2), 53.2 ($PhCH_2N$), 123.6 (3(3′) Ph), 128.6 (2(2′) Ph), 147.0 (4 Ph), 148.2 (1 Ph).

Lit.[75] m.p. = 78.0-78.5°C

Experiment 2.4.6

(11b) *N,N′*-bis-(4-nitro-benzyl)-propane-1,3-diamine

To a mechanically stirred suspension of *N,N′*-bis-(4-nitro-benzylidene)-propane-1,3-diamine (20.1 g, 59.06 mmol) in g.AcOH (80 cm^3) was added solid dimethylamine borane complex (DMAB) (8.70 g, 147.66 mmol) in portions maintaining the temperature of the reaction at about 20°C. After addition the solution was allowed to stir for 2 hours at ambient temperature, water (250 cm^3) was added and the solution basified to pH 14 using 4M NaOH (T < 40°C). The precipitate was extracted with DCM (150 cm^3) and washed with water (2 x 300 cm^3). 4M hydrochloric acid (200 cm^3) was added cautiously to the organic layer and the hydrochloride isolated at the pump and washed well with water (~1 dm^3). The hydrochloride was digested in hot methanol (50 cm^3) and DCM (50 cm^3), isolated at the pump and washed with DCM (x2). The material was then magnetically stirred with DCM (80 cm^3) and 2M sodium hydroxide (100 cm^3) until the solid dissolved. The two-phase system was filtered, the organic layer separated, dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound as an oil. Crystals were formed from evaporation of the oil in DCM on a large glass surface, 6.73 g, 33.1 % (hygroscopic). m.p. = (softens 60°C) 67.0-86.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3421.7 (2° amine), 1605.6 (phenyl), 1515.0 & 1346.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.66 (2H, br. s, N**H**), 1.74 (2H, q, $NCH_2C\mathbf{H}_2$), 2.72 (4H, t, $NC\mathbf{H}_2$), 3.90 (4H, s, $NC\mathbf{H}_2Ph$), 7.49 (4H, d $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 30.2 (NCH_2CH_2), 48.0 (NCH_2), 53.3 ($PhCH_2N$), 123.6 (3(3′) Ph), 128.6 (2(2′) Ph), 147.0 (4 Ph), 148.2 (1 Ph).

Lit.[76] m.p. = 175-178°C (hydrochloride)

Experiment 2.4.7

(11c) *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine

To a mechanically stirred suspension of *N,N′*-bis-(4-nitro-benzylidene)-butane-1,4-diamine (15.01 g, 42.36 mmol) in g.AcOH (90 cm^3) was added solid dimethylamine borane complex (DMAB) (6.23 g, 105.74 mmol) in portions, maintaining the temperature of the reaction at about 20°C. After addition the solution was allowed to stir for 2 hours at ambient temperature, then basified to pH 14 using 4M aqueous sodium hydroxide (T < 40°C). The precipitate was extracted into DCM (1 x 75 cm^3, 1 x 50 cm^3). 4M hydrochloric acid (100 cm^3) was added cautiously to the combined organic layers and the evolution of gas allowed to subside. The hydrochloride was isolated at the pump and washed well with acetone (3 x 100 cm^3). The material was then magnetically stirred with DCM (75 cm^3) and 2M sodium hydroxide (75 cm^3) until the solid had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), saturated aqueous sodium chloride (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound as a beige coloured solid, 10.58 g, 69.7 %. m.p. = (softens 57°C) 59.5-62.0°C (uncorrected). A small sample of the crude product was further purified by recrystallisation twice from ethanol, isolation at the pump, washed with ethanol (x2) and dried to provide the title compound as a beige coloured solid, m.p. = 61.5-63.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3436.0 (2° amine), 1598.1 (phenyl), 1512.3 & 1340.4 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.35 (2H, br. s, N-**H**), 1.58 (4H, spilt t, NCH_2**CH_2**), 2.65 (4H, t, N**CH_2**), 3.90 (4H, s, N**CH_2**Ph), 7.50 (4H, d $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 27.9 (NCH_2CH_2), 49.4 (NCH_2), 53.2 (NCH_2Ph), 123.6 (3(3′) Ph), 128.5 (2(2′) Ph), 147.0 (1 Ph), 148.4 (4 Ph); Microanalysis: Found: C, 60.25; H, 6.21; N, 15.72. $C_{18}H_{22}N_4O_4$ requires C, 60.32; H, 6.19; N, 15.63; m/z: Found $[M + H]^+$ 359.4. $C_{18}H_{22}N_4O_4$ requires 358.40.

Experiment 2.4.8

(11d) *N,N′*-bis-(4-nitro-benzyl)-pentane-1,5-diamine

To a mechanically stirred suspension of *N,N′*-bis-(4-nitro-benzylidene)-pentane-1,5-diamine (10.01 g, 27.17 mmol) in g.AcOH (60 cm^3) was added solid dimethylamine borane complex (DMAB) (4.01 g, 68.06 mmol) in portions, maintaining the temperature of the reaction at about 20°C. After addition the solution was allowed to stir for 2 hours at ambient temperature, then basified to pH 14 using 4M aqueous sodium hydroxide ($T < 40$°C). The precipitate was extracted into DCM (2 x 50 cm^3). 4M hydrochloric acid (100 cm^3) was added cautiously to the combined organic layers and the evolution of gas allowed to subside. The hydrochloride was isolated at the pump and washed well with acetone, DCM and acetone/DCM. The material was then magnetically stirred with DCM (50 cm^3) and 2M sodium hydroxide (50 cm^3) until the solid had dissolved. The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (1 x 100 cm^3), saturated aqueous sodium chloride (1 x 100 cm^3), dried ($MgSO_4$) and the solvent evaporated off to provide the crude title compound as a beige coloured solid, 6.65 g, 65.7%. m.p. = (softens 55°C) 57.0-59.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3425.9 (2° amine), 1605.0 (phenyl), 1517.7 & 1344.2 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.34 (2H, br. s, N**H**), 1.42 (2H, q, $NCH_2CH_2\mathbf{CH_2}$), 1.54 (4H, q, $NCH_2\mathbf{CH_2}$), 2.63 (4H, t, $N\mathbf{CH_2}$), 3.89 (4H, s, $N\mathbf{CH_2}Ph$), 7.50 (4H, d $J_{2(2'),3(3')}$ 8.9, 2(2′) Ph-**H**), 8.18 (4H, d $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 25.0 ($NCH_2CH_2\mathbf{CH_2}$), 30.0 ($NCH_2\mathbf{CH_2}$), 49.4 ($N\mathbf{CH_2}$), 53.3 ($Ph\mathbf{CH_2}N$), 123.6 (3(3′) Ph), 128.6 (2(2′) Ph), 147.0 (4 Ph), 148.4 (1 Ph); m/z: Found $[M + H]^+$ 373.2. $C_{19}H_{24}N_4O_4$ requires 372.42.

2.4.3 - Mannich Bases – [1+1] Thiophene-Based Macrocycles incorporating the nitro functional group:

2.4.3.1 - Macrocycles from *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine

Experiment 2.4.9

(12a) 12,15-bis-(4-nitro-benzyl)-2,5-dioxa-9,18-dithia-12,15-diaza-tricyclo[15.3.0.0^{6,10}]eicosa-1(17),6(10),7,19-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine (2.45 g, 7.42 mmol) and 37 % aqueous formaldehyde solution (1.10 cm^3, 14.68 mmol) at ambient temperature in g.AcOH (50 cm^3) was added a further amount of g.AcOH (100 cm^3) and α,ϖ-bis(3-oxythienyl)ethane (1.50 g, 6.63 mmol). After *ca.* 5 days the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. Purification was by trituration with acetonitrile (18.5 cm^3), isolation at the pump, washing with acetonitrile (4 x 5 cm^3), diethyl ether (2 x 5 cm^3) and drying to provide the title compound as a dark beige solid, 1.76 g, 45.7%. m.p. = (softens 177°C) 180.0-182.0°C (uncorrected). A sample was digested in hot acetonitrile (x2), isolated at the pump, washed with acetonitrile (x2) and dried for analysis. m.p. = 181.0-183.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3107.2(w) (Th-H), 1601.0 (phenyl), 1549.9 (Th C=C), 1508.4 & 1344.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 2.71 (4H, s, NC**H**$_2$), 3.72 (4H, s, NC**H**$_2$Th), 3.76 (4H, s, NC**H**$_2$Ph), 4.33 (4H, s, OC**H**$_2$), 6.85 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.16 (2H, d $J_{4,5}$ 5.4, 5Th-**H**), 7.54 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.14 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 47.0 (NCH_2Th), 50.0 (NCH_2), 58.2 (NCH_2Ph), 70.2 (OCH_2), 116.8 (4Th), 117.9 (2Th), 123.0 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 147.9 (4Ph), 154.1 (3Th); Microanalysis: Found: C, 57.64; H, 4.81; N, 9.47. $C_{28}H_{28}N_4O_6S_2$ requires C, 57.92; H, 4.86; N, 9.65; m/z: Found [M +H]$^+$ 581.1. $C_{28}H_{28}N_4O_6S_2$ requires 580.67.

Experiment 2.4.10

(12b) 13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine (3.05 g, 9.23 mmol) and 37 % aqueous formaldehyde solution (1.40 cm^3, 18.68 mmol) at ambient temperature in g.AcOH (200 cm^3), was added α,ϖ-bis(3-oxythienyl)propane (2.02 g, 8.41 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. Purification was by trituration with acetonitrile (12 cm^3), isolation at the pump, washing with acetonitrile (2 x 10 cm^3), diethyl ether (3 x 10 cm^3) and drying to provide the title compound as an off-white solid (tinge of green), 1.94 g, 38.8 %. m.p. = 147.5-149.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3108.2(w) (Th-H), 1604.8 (phenyl), 1553.9

(Th C=C), 1516.5 & 1343.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 2.21 (2H, q, $\mathbf{CH_2}$) 2.66 (4H, s, $N\mathbf{CH_2}$), 3.73 (8H, s, $N\mathbf{CH_2}Th$ & $N\mathbf{CH_2}Ph$), 4.25 (4H, t, $O\mathbf{CH_2}$), 6.90 (2H, d $J_{4,5}$ 5.6, 4Th-**H**), 7.17 (2H, d $J_{4,5}$ 5.6, 5Th-**H**), 7.51 (4H, d, $J_{2(2'),3(3')}$ 8.6, 2(2′) Ph-**H**), 8.13 (4H, d, $J_{2(2'),3(3')}$ 8.6, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 29.8 ($\mathbf{CH_2}$), 47.6 ($N\mathbf{CH_2}Th$), 49.9 ($N\mathbf{CH_2}$), 57.9 ($N\mathbf{CH_2}Ph$), 68.3 ($O\mathbf{CH_2}$), 117.5 (4Th), 117.8 (2Th), 122.9 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 147.8 (4Ph), 154.4 (3Th); Microanalysis: Found: C, 58.43; H, 5.07; N, 9.31. $C_{29}H_{30}N_4O_6S_2$ requires C, 58.57; H, 5.08; N, 9.42; m/z: Found $[M + H]^+$ 595.1. $C_{29}H_{30}N_4O_6S_2$ requires 594.70.

Crystals of this compound suitable for X-ray crystallography were grown from the slow evaporation of a DCM/acetonitrile solution (approximately 1:2 mixture of solvents). Comments on the structure of this compound in the crystalline state are mentioned in the latter part of the Discussion, section 3.7. The experimental data is presented in this chapter, section 2.8.

Experiment 2.4.11

(12c) 14,17-bis-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine (3.01 g, 9.11 mmol) and 37 % aqueous formaldehyde solution (1.40 cm^3, 18.68 mmol) at ambient temperature in g.AcOH (210 cm^3), was added α,ϖ-bis(3-oxythienyl)butane (2.10 g, 8.26 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. Purification was by trituration with acetonitrile (10 cm^3), isolation at the pump, washing with acetonitrile (2 x 5 cm^3), diethyl ether (2 x 5 cm^3) and drying to provide the title compound as an off-white solid (tinge of green), 1.65 g, 32.8 %. m.p. = 140.0-142.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3107.6(w) (Th-H), 1598.7 & 1560.5 (phenyl), 1552.0 (Th C=C), 1519.0 & 1345.0 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.99 (4H, s, $\mathbf{CH_2}$) 2.67 (4H, s, $N\mathbf{CH_2}$), 3.62 (4H, s, $N\mathbf{CH_2}Th$), 3.70 (4H, s, $N\mathbf{CH_2}Ph$), 4.11 (4H, s, $O\mathbf{CH_2}$), 6.81 (2H, d $J_{4,5}$ 5.3, 4Th-**H**), 7.12 (2H, d $J_{4,5}$ 5.6, 5Th-**H**), 7.54 (4H, d, $J_{2(2'),3(3')}$ 8.6, 2(2′)

Ph-**H**), 8.12 (4H, d, $J_{2(2'),3(3')}$ 8.6, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 26.4 (**C**H_2), 47.5 (N**C**H_2Th), 50.8 (N**C**H_2), 58.1 (N**C**H_2Ph), 70.7 (O**C**H_2), 116.5 (4Th), 117.0 (2Th), 122.8 (5Th), 123.5 (3(3′)Ph), 129.04 (2(2′)Ph), 147.0 (1Ph), 148.1 (4Ph), 154.4 (3Th); Microanalysis: Found: C, 59.34; H, 5.32; N, 8.96. $C_{30}H_{32}N_4O_6S_2$ requires C, 59.19; H, 5.30; N, 9.20; m/z: Found $[M + H]^+$ 608.8. $C_{30}H_{32}N_4O_6S_2$ requires 608.72.

Experiment 2.4.12

(12d) 15,18-bis-(4-nitro-benzyl)-2,5,8-trioxa-12,21-dithia-15,18-diaza-tricyclo[18.3.0.0^{9,13}]tricosa-1(20),9(13),10,22-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine (2.72 g, 8.23 mmol) and 37 % aqueous formaldehyde solution (1.30 cm^3, 17.35 mmol) at ambient temperature in g.AcOH (50 cm^3), was added a further amount of g.AcOH (150 cm^3) and α,ϖ-bis(3-oxythienyl)diethyl ether (2.03 g, 7.51 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. Purification was by trituration with acetonitrile (10 cm^3), isolation at the pump, washing with acetonitrile (1 x 5 cm^3), diethyl ether (2 x 5 cm^3) and drying to provide the title compound as an off-white (tinge of green) solid, 1.91 g, 40.7 %. m.p. = 152.5-154.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3101.7(w) (Th-H), 1603.6 (phenyl), 1552.1 (Th C=C), 1518.6 & 1343.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 2.70 (4H, s, NC**H**$_2$), 3.68 (4H, s, NC**H**$_2$Th), 3.80 (4H, s, NC**H**$_2$Ph), 3.84 (4H, m, OC**H**$_2$C**H**$_2$O), 4.18 (4H, m, OC**H**$_2$), 6.82 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.13 (2H, d $J_{4,5}$ 5.4, 5Th-**H**), 7.50 (4H, d, $J_{2(2'),3(3')}$ 8.9, 2(2′) Ph-**H**), 8.11 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 47.9 (N**C**H_2Th), 50.3 (N**C**H_2), 57.1 (N**C**H_2Ph), 67.0 (O**C**H_2**C**H_2O), 71.2 (O**C**H_2), 117.1 (4Th), 118.0 (2Th), 122.8 (5Th), 123.4 (3(3′)Ph), 129.2 (2(2′)Ph), 147.0 (1Ph), 148.0 (4Ph), 154.3 (3Th); Microanalysis: Found: C, 57.88; H, 4.98; N, 8.71. $C_{30}H_{32}N_4O_7S_2$ requires C, 57.68; H, 5.16; N, 8.97; m/z: Found $[M + H]^+$ 625.2. $C_{30}H_{32}N_4O_7S_2$ requires 624.72.

The preparation of **13a**, experiment 2.4.13 can be found later in this chapter, section 2.4.4 - page 59.

2.4.3.2 - Macrocycles from *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine

Experiment 2.4.14

(14a) 12,17-bis-(4-nitro-benzyl)-2,5-dioxa-9,20-dithia-12,17-diaza-tricyclo[17.3.0.0^{6,10}]docosa-1(19),6(10),7,21-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (2.02 g, 5.64 mmol) and 37 % aqueous formaldehyde solution (0.84 cm^3, 11.21 mmol) at ambient temperature in g.AcOH (115 cm^3), was added α,ϖ-bis(3-oxythienyl)ethane (1.15 g, 5.08 mmol). After 24 hours the solvent was evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off to obtain the crude title compound as a yellow/orange solid. m.p. = 161.5-166.5°C (uncorrected) opaque melt – continued heating to ~220°C (dark red); ν_{max}/cm^{-1} (KBr disc): 3108.2(w) (Th-H), 1603.6 (phenyl), 1551.0 (Th C=C), 1514.7 & 1344.7 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.50 (4H, s, $NCH_2\mathbf{CH_2}$), 2.39 (4H, br. t, $N\mathbf{CH_2}$), 3.77 (4H, s, $N\mathbf{CH_2}Th$), 3.83 (4H, s, $N\mathbf{CH_2}Ph$), 4.32 (4H, s, $O\mathbf{CH_2}$), 6.88 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.19 (2H, d $J_{4,5}$ 5.7, 5Th-**H**), 7.58 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.9, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 23.7 (NCH_2CH_2), 45.7 (NCH_2Th), 51.5 (NCH_2), 58.2 (NCH_2Ph), 70.1 (OCH_2), 115.5 & 115.7 (4Th or 2Th), 122.9 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 148.2 (4Ph), 154.7 (3Th); Microanalysis: Found (crude): C, 58.65; H, 5.28; N, 9.01. $C_{30}H_{32}N_4O_6S_2$ requires C, 59.19; H, 5.30; N, 9.20; m/z: Found $[M + H]^+$ 609.1. $C_{30}H_{32}N_4O_6S_2$ requires 608.72

Experiment 2.4.15

(14b) 13,18-bis-(4-nitro-benzyl)-2,6-dioxa-10,21-dithia-13,18-diaza-tricyclo[18.3.0.0^{7,11}]tricosa-1(20),7(11),8,22-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (2.03 g, 5.66 mmol) and 37 % aqueous formaldehyde solution (0.84 cm^3, 11.21 mmol) at ambient temperature in g.AcOH (120 cm^3), was added α,ϖ-bis(3-oxythienyl)propane (1.23 g, 5.12 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography (plug) [light petroleum ether b.p. 40-60°C/ethyl acetate (2:1)] and recrystallisation from acetonitrile (x2) (hot filtration), isolation at the pump, washing with acetonitrile (2 x 10 cm^3) and diethyl ether (2 x 10 cm^3) and drying to provide the title compound as a pale yellow finely divided crystalline solid, 1.64 g, 51.4 %. m.p. = 140.0-141.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): ~3100(w) (Th-H), 1596.7 (phenyl), 1556.2 (Th C=C), 1510.6 & 1341.4 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.38 (4H, br. q, NCH_2**CH_2**), 2.19 (2H, q, OCH_2**CH_2**), 2.41 (4H, t, NCH_2), 3.68 (4H, s, NCH_2Th), 3.72 (4H, s, N**CH_2**Ph), 4.22 (4H, t, O**CH_2**), 6.85 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.15 (2H, d $J_{4,5}$ 5.4, 5Th-**H**), 7.56 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.16 (4H, d, $J_{2(2'),3(3')}$ 8.9, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 24.0 (NCH_2CH_2), 30.1 (OCH_2CH_2), 47.5 (NCH_2Th), 52.4 (NCH_2), 58.3 (NCH_2Ph), 67.9 (OCH_2), 117.3 (4Th), 118.8 (2Th), 122.8 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 148.0 (4Ph), 154.1 (3Th); Microanalysis: Found: C, 59.86; H, 5.26; N, 9.09. $C_{31}H_{34}N_4O_6S_2$ requires C, 59.79; H, 5.50; N, 9.00; m/z: Found $[M + H]^+$ 623.3. $C_{31}H_{34}N_4O_6S_2$ requires 622.75.

Experiment 2.4.16

(14c) 14,19-bis-(4-nitro-benzyl)-2,7-dioxa-11,22-dithia-14,19-diaza-tricyclo[19.3.0.0^{8,12}]tetracosa-1(21),8(12),9,23-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (2.02 g, 5.64 mmol) and 37 % aqueous formaldehyde solution (0.84 cm^3, 11.21 mmol) at ambient temperature in g.AcOH (130 cm^3), was added α,ϖ-bis(3-oxythienyl)butane (1.30 g, 5.11 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography (plug) [light petroleum ether b.p. 40-60°C/ethyl acetate (2:1)] and recrystallisation from acetonitrile, isolation at the pump, washing with acetonitrile (2 x 5 cm^3) and diethyl ether

(2 x 5 cm^3) and drying to provide the title compound as a very pale yellow finely divided crystalline solid, 0.20 g, 5.57 % m.p. = 125.5-126.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): ~3100(w) (Th-H), 1603.5 (phenyl), 1551.9 (Th C=C), 1516.3 & 1344.9 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.52 (4H, br., NCH_2**CH_2**), 1.97 (4H, br., OCH_2**CH_2**), 2.48 (4H, br., N**CH_2**), 3.74 (8H, s, NCH_2Th & NCH_2Ph), 4.08 (4H, t, O**CH_2**), 6.84 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.13 (2H, d $J_{4,5}$ 5.4, 5Th-**H**), 7.58 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 24.9 (NCH_2CH_2), 26.6 (OCH_2CH_2), 46.9 (NCH_2Th), 52.8 (NCH_2), 57.7 (NCH_2Ph), 70.7 (OCH_2), 116.3 & 116.4 (4Th and 2Th), 122.6 (5Th), 123.5 (3(3′)Ph), 129.2 (2(2′)Ph), 147.0 (1Ph), 148.3 (4Ph), 154.6 (3Th); Microanalysis: Found: C, 60.36; H, 5.54; N, 8.89. $C_{32}H_{36}N_4O_6S_2$ requires C, 60.36; H, 5.70; N, 8.80; m/z: Found [M + H]$^+$ 637.1. $C_{32}H_{36}N_4O_6S_2$ requires 636.78.

Experiment 2.4.17

(14d) 15,20-bis-(4-nitro-benzyl)-2,5,8-trioxa-12,23-dithia-15,20-diaza-tricyclo[20.3.0.0^{9,13}]pentacosa-1(22),9(13),10,24-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (2.00 g, 5.58 mmol) and 37 % aqueous formaldehyde solution (0.84 cm^3, 11.21 mmol) at ambient temperature in g.AcOH (140 cm^3), was added α,ϖ-bis(3-oxythienyl)diethyl ether (1.37 g, 5.07 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The yellow crude product was purified by flash chromatography (plug) [light petroleum ether b.p. 40-60°C/ethyl acetate (2:1)]. A suitable solvent for recrystallisation would be acetonitrile, but due to lack of time further purification of this product was not carried out. The crude product was not sent for chemical analysis as previous work indicated that the results would not be meaningful without complete purification of the material.

2.4.3.3 - Macrocycles from *N,N′*-bis-(4-nitro-benzyl)-pentane-1,5-diamine

Experiment 2.4.18

(15a) 12,18-bis-(4-nitro-benzyl)-2,5-dioxa-9,21-dithia-12,18-diaza-tricyclo[18.3.0.0^{6,10}]tricosa-1(20),6(10),7,22-tetraene

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-pentane-1,5-diamine (0.37 g, 0.99 mmol) and 37 % aqueous formaldehyde solution (0.15 cm^3, 2.00 mmol) at ambient temperature in g.AcOH (20 cm^3) was added α,ϖ-bis(3-oxythienyl)ethane (0.21 g, 0.93 mmol). After 18-24 hours (time approximated) the solvent was partially evaporated under reduced pressure; DCM (35 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (100 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (50 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography [wt. 30:1, light petroleum ether b.p. 40-60°C/ethyl acetate (2:1)] and recrystallised from acetonitrile, isolated at the pump, washed with acetonitrile (x2) and diethyl ether (x2) and dried to provide the title compound as a slightly greenish solid, 0.14 g, 24.1 %. m.p. = 112.5-113.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3103.9(w) (Th-H), 1605.4 & 1509.7 (phenyl), 1550.2 (Th C=C), 1521.3 & 1345.4 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.25 (2H, q, $NCH_2CH_2\mathbf{CH_2}$), 1.50 (4H, q, $NCH_2\mathbf{CH_2}$), 2.44 (4H, t, $N\mathbf{CH_2}$), 3.77 (8H, s, $N\mathbf{CH_2}$Th & $N\mathbf{CH_2}$Ph), 4.31 (4H, s, $O\mathbf{CH_2}$), 6.86 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.17 (2H, d, $J_{4,5}$ 5.4, 5Th-**H**), 7.60 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 24.7 ($NCH_2CH_2CH_2$), 25.3 (NCH_2CH_2), 47.1 (NCH_2Th), 52.1 (NCH_2), 57.9 (NCH_2Ph), 70.6 (OCH_2), 116.5 (4Th), 117.4 (2Th), 122.8 (5Th), 123.5 (3(3′)Ph), 129.2 (2(2′)Ph), 147.0 (1Ph), 148.3 (4Ph), 154.2 (3Th); Microanalysis: Found: C, 59.94; H, 5.33; N, 8.83. $C_{31}H_{34}N_4O_6S_2$ requires C, 59.79; H, 5.50; N, 9.00; m/z: Found [M + H]$^+$ 623.3. $C_{31}H_{34}N_4O_6S_2$ requires 622.75

Experiment 2.4.19

(15b) 13,19-bis-(4-nitro-benzyl)-2,6-dioxa-10,22-dithia-13,19-diaza-tricyclo[19.3.0.0^{7,11}]tetracosa-1(21),7(11),8,23-tetraene

To a stirred solution of *N,N'*-bis-(4-nitro-benzyl)-pentane-1,5-diamine (2.02 g, 5.42 mmol) and 37 % aqueous formaldehyde solution (0.90 cm^3, 12.01 mmol) at ambient temperature, in g.AcOH (120 cm^3) was added α,ϖ-bis(3-oxythienyl)propane (1.17 g, 4.87 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography (plug) [light petroleum ether b.p. 40-60°C/ethyl acetate (2:1)] and recrystallised from acetonitrile (hot filtration), isolated at the pump, washed with acetonitrile (2 x 5 cm^3), diethyl ether (2 x 5 cm^3) and dried to provide the title compound as an off-white pale green solid, 1.22 g, 39.4 %. m.p. = (softens 63°C) 66 - >78° (uncorrected). A sample was further recrystallised from acetonitrile, isolated at the pump and washed with acetonitrile (x2) and dried. m.p. = (softens ~77°C) melts 79.5°C (gas bubbles evolved) – few gas bubbles at ~90°C (appears a clear melt) (uncorrected); ν_{max}/cm^{-1} (KBr disc): 3108.1(w) (Th-H), 1603.9.0 (phenyl), 1549.6 (Th C=C), 1513.0 & 1348.1 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.14 (2H, q, $NCH_2CH_2C\mathbf{H}_2$), 1.49 (4H, q, $NCH_2C\mathbf{H}_2$), 2.01 (s, impurity), 2.21 (2H, q, $OCH_2C\mathbf{H}_2$) 2.38 (4H, t, $NC\mathbf{H}_2$), 3.74 (4H, s, $NC\mathbf{H}_2Th$), 3.75 (4H, s, $NC\mathbf{H}_2Ph$), 4.18 (4H, t, $OC\mathbf{H}_2$), 6.86 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.16 (2H, d, $J_{4,5}$ 5.4, 5Th-**H**), 7.57 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 25.0 ($NCH_2CH_2CH_2$), 25.8 (NCH_2CH_2), 30.1 (OCH_2CH_2), 46.8 (NCH_2Th), 52.2 (NCH_2), 58.3 (NCH_2Ph), 67.9 (OCH_2), 116.9 (4Th), 117.8 (2Th), 123.0 (5Th), 123.5 (3(3′)Ph), 129.2 (2(2′)Ph), 147.0 (1Ph), 148.1 (4Ph), 154.4 (3Th); Microanalysis: Found: C, 60.73; H, 6.12; N, 8.60. $C_{32}H_{36}N_4O_6S_2$ requires C, 60.36; H, 5.70; N, 8.80; m/z: Found $[M + H]^+$ 637.3. $C_{32}H_{36}N_4O_6S_2$ requires 636.78.

Experiment 2.4.20

(15c) 14,20-bis-(4-nitro-benzyl)-2,7-dioxa-11,23-dithia-14,20-diaza-tricyclo[20.3.0.0^{8,12}]pentacosa-1(22),8(12),9,24-tetraene

To a stirred solution of *N,N'*-bis-(4-nitro-benzyl)-pentane-1,5-diamine (2.04 g, 5.48 mmol) and 37 % aqueous formaldehyde solution (0.80 cm^3, 10.67 mmol) at ambient temperature, in g.AcOH (125 cm^3) was added α,ϖ-bis(3-oxythienyl)butane (1.25 g, 4.91 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (2 x 100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography (plug) [light petroleum b.p. 40-60°C/ethyl acetate (2:1)] and recrystallised (twice) from acetonitrile, isolated at the pump, washed with acetonitrile (2 x 10 cm^3), diethyl ether (2 x 10 cm^3) and dried to provide the title compound as a pale green solid, 1.05 g, 32.8 %. m.p. = 109.0-110.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): ~3100(w) (Th-H), 1605.1 (phenyl), 1549.6 (Th C=C), 1519.8 & 1342.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.17 (2H, q, $NCH_2CH_2C\mathbf{H}_2$), 1.56 (4H, q, $NCH_2C\mathbf{H}_2$), 1.96 (4H, br., $OCH_2C\mathbf{H}_2$), 2.41 (4H, t, $NC\mathbf{H}_2$), 3.76 (4H, s, $NC\mathbf{H}_2Th$), 3.78 (4H, s, $NC\mathbf{H}_2Ph$), 4.07 (4H, br., $OC\mathbf{H}_2$), 6.83 (2H, d $J_{4,5}$ 5.4, 4Th-**H)**, 7.13 (2H, d, $J_{4,5}$ 5.4, 5Th-**H**), 7.58 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H)**, 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H);** ∂_C (67.8 MHz, $CDCl_3$): 25.1 ($NCH_2CH_2\mathbf{C}H_2$), 26.4 ($NCH_2\mathbf{C}H_2$), 26.6 ($OCH_2\mathbf{C}H_2$), 46.7 (NCH_2Th), 52.3 (NCH_2), 57.9 (NCH_2Ph), 70.9 (OCH_2), 116.3 (4Th), 116.3 (2Th), 122.6 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 148.3 (4Ph), 154.6 (3Th); Microanalysis: Found: C, 60.77; H, 5.69; N, 8.48. $C_{33}H_{38}N_4O_6S_2$ requires C, 60.90; H, 5.89; N, 8.61; m/z: Found $[M + H]^+$ 651.2. $C_{33}H_{38}N_4O_6S_2$ requires 650.81.

Experiment 2.4.21

(15d) 15,21-bis-(4-nitro-benzyl)-2,5,8-trioxa-12,24-dithia-15,21-diaza-tricyclo[21.3.0.0^{9,13}]hexacosa-1(23),9(13),10,25-tetraene

To a stirred solution of *N,N'*-bis-(4-nitro-benzyl)-pentane-1,5-diamine (2.04 g, 5.48 mmol) and 37 % aqueous formaldehyde solution (0.82 cm^3, 10.94 mmol) at ambient temperature, in g.AcOH (135 cm^3) was added α,ϖ-bis(3-oxythienyl)diethyl ether (1.35 g, 4.99 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. The crude product was purified by flash chromatography (plug) [light petroleum b.p. 40-60°C/ethyl acetate (2:1)] to yield a brown viscous oil, 2.16 g, 64.7 %. Attempts to induce crystallisation were not successful; *tlc* (one spot); IR spectroscopy (nujol): not successful (oil incompatible with nujol); ∂_H (270 MHz, $CDCl_3$) 1.20 (2H, q, $NCH_2CH_2\mathbf{CH_2}$), 1.52 (4H, q, $NCH_2\mathbf{CH_2}$), 2.42 (4H, t, $N\mathbf{CH_2}$), 3.74 (4H, s, $N\mathbf{CH_2}Th$), 3.77 (4H, s, $N\mathbf{CH_2}Ph$), 3.87 (4H, t, $OCH_2\mathbf{CH_2}$), 4.16 (4H, t, $O\mathbf{CH_2}$), 5.30 (DCM), 6.84 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.13 (2H, d, $J_{4,5}$ 5.4, 5Th-**H**), 7.58 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.17 (4H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 24.9 ($NCH_2CH_2CH_2$), 25.6 (NCH_2CH_2), 47.1 (NCH_2Th), 52.4 (NCH_2), 57.9 (NCH_2Ph), 70.3 (OCH_2CH_2O), 71.5 (OCH_2), 117.3 (4Th), 118.6 (2Th), 122.7 (5Th), 123.5 (3(3′)Ph), 129.1 (2(2′)Ph), 147.0 (1Ph), 148.3 (4Ph), 154.2 (3Th); Microanalysis: Found: C, 57.68; H, 5.87; N, 8.68. $C_{33}H_{38}N_4O_7S_2$ requires C, 59.44; H, 5.74; N, 8.40; m/z: Found $[M + H]^+$ 667.3. $C_{33}H_{38}N_4O_7S_2$ requires 666.80.

2.4.4 - Mannich Base – not incorporating Thiophene

Experiment 2.4.13

(13a) 1,3-bis-(4-nitro-benzyl)-hexahydropyrimidine

To a stirred solution of *N,N′*-bis-(4-nitro-benzyl)-propane-1,3-diamine (2.37 g, 6.88 mmol) and 37 % aqueous formaldehyde solution (1.00 cm^3, 13.34 mmol) at ambient temperature in g.AcOH (50 cm^3), was added a further quantity of g.AcOH (100 cm^3) and α,ϖ-bis(3-oxythienyl)propane (1.50 g, 6.24 mmol). After 24 hours the solvent was partially evaporated under reduced pressure; DCM (50 cm^3) was added and stirred well with saturated sodium hydrogen carbonate (200 cm^3). The organic layer was separated and washed with saturated aqueous sodium hydrogen carbonate (100 cm^3), dried ($MgSO_4$) and the solvent evaporated off. Diethyl ether (*ca.* 20 cm^3) was added and the crystals were allowed to slowly precipitate over 2 days. The crystals were isolated at the pump, washed with diethyl ether (3 x 5 cm^3) and dried to provide the title compound as a light beige coloured finely divided crystalline solid, 1.10 g, 44.9 %. m.p. = (softens 97°C) 98.0-99.0°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1598.3 (phenyl), 1510.2 & 1342.5 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.73 (2H, q, $NCH_2\mathbf{CH_2}$) 2.60 (4H, t, $N\mathbf{CH_2}CH_2$), 3.25 (2H, s, $N\mathbf{CH_2}N$), 3.67 (4H, s, $N\mathbf{CH_2}Ph$), 7.52 (4H, d, $J_{2(2'),3(3')}$ 8.7, 2(2′) Ph-**H**), 8.16 (4H, d, $J_{2(2'),3(3')}$ 8.9, 3(3′) Ph-**H**); ∂_C (67.8 MHz, $CDCl_3$): 22.4 ($NCH_2\mathbf{C}H_2$), 52.1 (NCH_2), 58.4 (NCH_2Ph), 75.3 (NCH_2N), 123.5 (3(3′)Ph), 129.4 (2(2′)Ph), 146.4 (1Ph), 147.2 (4Ph); Microanalysis: Found: C, 60.44; H, 5.50; N, 15.68. $C_{18}H_{20}N_4O_4$ requires C, 60.67; H, 5.66; N, 15.72; m/z: Found $[M + H]^+$ 357.1. $C_{18}H_{20}N_4O_4$ requires 356.38.

These results indicate that the expected formation of the Mannich base, 13,17-bis-(4-nitro-benzyl)-2,6-dioxa-10,20-dithia-13,17-diaza-tricyclo[17.3.0.$0^{7,11}$]docosa-1(19),7(11),8,21-tetraene was less favourable than formation of a six membered hexahydropyrimidine ring. See Discussion section 3.4.4.

2.4.5 - The Reduction of the Nitro Functional group(s):

2.4.5.1 - Initial Reduction attempts

Experiment 2.4.22

This experiment involved several attempts at the reduction of 13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.$0^{7,11}$]heneicosa-1(18),7(11),8,20-tetraene **12b** to the corresponding amine **16a** or **16c**. The majority of the attempted reduction methods involved the use of sodium hydrosulphide (NaHS): a method for the reduction of nitro arenes by negative divalent sulphur is known as the *Zinin Reduction*[77] method.

The following generated sodium hydrosulphide solutions were used in some of the attempted reductions:

Indicated by * approximately 2.4 g $Na_2S.9H_2O$ and 0.84 g $NaHCO_3$ in water (4 cm^3) to produce approximately 0.14 g cm^{-3} (2.5 mmol cm^{-3}) NaSH solution; or multiples of these quanities[77].

Indicated by# approximately 18 g $Na_2S.9H_2O$ and 6 g $NaHCO_3$ in methanol (74 cm^3) and water (50 cm^3) to produce approximately 0.03 g cm^{-3} (0.5 mmol cm^{-3})[78].

(i) **12b** (0.38 g, 0.64 mmol), MeOH (18 cm^3), NaHS* (1.5 cm^3, 5.9 eqv), reflux (1 hour)

No reaction was observed by *tlc*. This was probably because **12b** has little or no solubility in hot MeOH. Hot IPA appeared to give better solubility for **12b** over EtOH and MeOH.

(ii) **12b** (0.28 g, 0.47 mmol), IPA (4 cm^3), NaHS* (1.0 cm^3, 5.3 eqv), reflux (1 hour)

No reaction was observed after 1 hour by *tlc*. DCM and IPA were added in stages to help dissolve **12b**. After a further two hours no reaction was found by *tlc* and the experiment abandoned.

(iii) **12b** (0.25 g, 0.42 mmol), DMF (4 cm^3), NaHS* (1.0 cm^3, 6.0 eqv)

12b has good solubility in DMF. An exotherm was observed on addition of NaHS* to **12b** in DMF and a precipitate was formed. A control reaction was performed (*ie* no **12b**), this experiment also precipitated out a white solid, m.p. > 400°C (outside the temperature range of the melting point instrument), which dissolved readily in water and proved to not be organic material (no signals in ^1H & ^{13}C NMR (D_2O)). In the light of this side reaction DMF was deemed unsuitable as a solvent for this reaction.

(iv) **12b** (1.0 g, 16.82 mmol), py (20 cm^3), NaHS* (7.0 cm^3, 10.0 eqv)

12b has very good solubility in pyridine. In a first attempt the solution py/NaHS* (3.8 mmol) was stirred at ambient temperature for two hours: no reaction was observed by *tlc*. On increasing the temperature to reflux, this solution turned from brown to dark green. After ten minutes no starting material was observed by *tlc* and two spots (in addition to py) were found. More NaHS* (1.0 cm^3) and more py (2 cm^3) was added to ensure an excess of reducing agent after 50 minutes as it was thought partial reduction of **12b** might have occurred *ie* one remaining nitro group and one amino group on one molecule in addition to completed **16c**; heating thus continued for another 25 minutes or so. On work up, however only one base-line spot was seen (UV, also visible as a yellow spot) (elutant: light petroleum ether b.p. 60-80°C/ethyl acetate (1:2)). A crude brown solid was obtained (~70% yield), melting at ≈ 50-60°C suggesting the material was impure. Additional experiments using NaHS* (10 eqv) confirm the original reaction. Purification was unsuccessful by either recrystalisation or acidic extraction techniques. The crude product was eluted with a polar medium, MeOH/EtOAc/light petroleum ether 60-80°C (15:40:20) to show two spots at R_f 0.13 and 0.44. An IR spectrum of this crude product revealed that both amino (~3400, 3365.9 and 1621.7 cm^{-1}) and nitro (1515.7 and 1343.3 cm^{-1}) groups were present.

(v) **12b** (0.52 g, 0.87 mmol), 2,6-lutidine (10 cm^3), NaHS* (3.5 cm^3, 10 eqv), reflux

In light of the partial success using pyridine it was hoped that increasing the reaction temperature by the use of 2,6-lutidine (b.p. 143-145°C) might force the reaction to completion. Compound **12b** does not appreciably dissolve in 2,6-lutidine at ambient temperature but does so noticeably at reflux, however after 1 hour, no reaction was seen by *tlc*.

(vi) **12b** (0.25 g, 0.42 mmol), MeOH/toluene (10 cm^3 & 5 cm^3 respectively to aquire best solubility), NaHS* (3.0 cm^3, 3.8 eqv), reflux

A reaction time greater than eight hours at reflux (cooled and re-heated over two days) was required before the starting material disappeared (*tlc*). A crude yield of 57 % was obtained and the product had a melting point similar to that from the pyridine experiment (iv).

(vii) **12b** (0.12 g, 0.20 mmol), acetone/MeOH (10 cm^3 & 5 cm^3 respectively), NaHS* (1.5 cm^3, 4 eqv), reflux

The reaction did not go to completion even after 4 hours at the reflux temperature (re-heated over 2 days). However, some product was seen by *tlc*.

(viii) **12b** (0.36 g, 0.61 mmol), DMSO (10 cm^3), NaHS# (5.5 cm^3, 4.8 eqv), reflux

DMSO was used in this reaction and although it is a higher boiling solvent than pyridine, **12b** is less soluble in it. A methanolic solution of NaHS# (5 eqv, 5.5 cm^3) was refluxed with **12b** in DMSO [27 cm^3 g^{-1}]. Although starting material was reduced (*tlc*), several product spots were seen. Persistent heating did not prove successful in reducing to one product spot. On work-up a crude brown solid (73 % yield) was obtained. *tlc* showed different product spots under short and long UV wavelengths. The melting point temperature and proton NMR indicated that the desired product had not formed and DMSO as solvent was abandoned.

(ix) **12b** (0.20 g, 0.34 mmol), py (10 cm^3), NaHS (0.26 g, 4.64 eqv), reflux under nitrogen

Sodium hydrosulphide hydrate has a slight solubility in pyridine. An experiment was carried out to see if reaction with solid NaHS under anhydrous conditions would aid in reducing **12b**. An atmosphere of nitrogen was employed to prevent possible air oxidation of the sulphide ion. There was no apparent reaction (*tlc)* after 2.5 hours of heating. Continued heating, then work-up showed some product spots (*tlc*) in addition to starting material. This method was abandoned, as any reaction occurred too slowly to be of any use.

(x) **12b** (0.30 g, 0.50 mmol), py (2 cm^3), NaHS in water (0.2 cm^3, 5.8 mmol), reflux

Solid NaHS was dissolved (sonication) in water to produce a 1.64 g cm^{-1} solution. Refluxing this solution (11.6 eqv) with **12b** in pyridine, after 2 hours product spots were seen (*tlc*) in addition to starting material.

(xi) **12b** (0.30 g, 0.50 mmol), formic acid (10 cm^3), 5% Pd-C (0.09g), reflux

The starting material reduced after 50 minutes (*tlc*), but no solid product was obtained on work-up.

(xii) **12b** (0.05 g, 0.08 mmol), phenylhydrazine 97% (0.5 cm^3), reflux

12b partially dissolves in phenylhydrazine (used as both solvent and reagent here); it completely dissolves close to the reflux temperature. After 45 minutes of heating there was no reduction (*tlc*) in starting material and no apparent product spots were noted. This attempt at reduction was not as successful as the Zinin Reduction.

(xiii) **12b** (2.00 g, 3.36 mmol), hydrazine hydrate (1.65 cm^3, 33.85 mmol), graphite (2.0 g), pyridine (40 cm^3), reflux under nitrogen.

After one hour reaction products (*tlc*) (one main product) were seen, but starting material had not been reduced. At a reaction time of 2.5 hours there were signs that the starting material was being used up and two main products were apparent. At 3.5 hours, no starting material was observed (*tlc*) and the two main product spots (plus two others) were still seen. After a further 10 minutes, the reaction solution was filtered through a Celite pad into saturated sodium chloride solution and the Celite pad washed through with DCM. The organic layer was washed several times with water and evaporated under reduced pressure. The solid was purified by flash chromatography [light petroleum ether b.p. 40-60°C/ethyl acetate and ethanol (8:4:3)] to isolate the two main products (1) higher eluting – a yellow solid and (2) lower eluting – a beige solid. This reduction of the nitro group to the amino group was slower than the Zinin reductions previously attempted and this method was therefore not adopted.

2.4.5.2 - Preparation of mononitro/monoamino and diamino containing macrocycles

Experiment 2.4.23

(16a) 13-(4-amino-benzyl)-16-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

To a stirred solution of 13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene (1.51 g, 2.54 mmol), at ambient temperature, in pyridine (30 cm^3) was added the reducing agent, generated sodium hydrosulphide (10 cm^3, ~25 mmol) [9.62 g, 40 mmol of $Na_2S.9H_2O$ and 3.40 g, 40 mmol of sodium bicarbonate in water (16 cm^3)] and the mixture heated to reflux for 10 minutes at the point where the solution turned dark green. The reaction solution was quenched in salt/ice (150 cm^3) and the organics extracted with DCM (2 x 50 cm^3), dried ($MgSO_4$) and the solvent evaporated off under reduced pressure. The residue was purified by flash chromatography (plug) [petroleum ether b.p. 40-60°C/ethyl acetate/ethanol (6:3:1)] to provide the title compound as a yellow solid, 0.83 g, 58.0 %, [*tlc* one spot (R_f 0.52) in elutant - petroleum ether/ethyl acetate/ethanol (6:3:1). m.p. = undetermined – too great a temperature range to be determined; ν_{max}/cm^{-1} (KBr disc): 3444.3 & 3377.6 (amino), 3107.3(w) (Th-H), 1623.7 (amino), 1550.4 (Th C=C), 1515.6 & 1343.5 (nitro); ∂_H (270 MHz, $CDCl_3$) 2.18 (2H, q, $OCH_2\mathbf{CH_2}$), 2.60 (4H, m, $N\mathbf{CH_2}$), 3.51 (2H, s, $N\mathbf{CH_2}$Ph-NH_2), 3.59 (2H, s, $\mathbf{NH_2}$ [confirmed by D_2O shake]), 3.73 (6H, s, $N\mathbf{CH_2}$Th & $N\mathbf{CH_2}$Ph-NO_2), 4.23 (4H, m, $O\mathbf{CH_2}$), 6.85 (2H, d, $J_{2(2'),3(3')}$ 8.6, 3(3′) Ph(**H**)-NH_2), 6.88 (2H, split d, $J_{4,5}$ 5.3, 4Th-**H**), 7.07 (2H, d, $J_{2(2'),3(3')}$ 8.2, 2(2′) Ph(**H**)-NH_2), 7.15 (2H, d, $J_{4,5}$ 5.6, 5Th-**H**), 7.48 (2H, d, $J_{2(2'),3(3')}$ 8.9, 2(2′) Ph(**H**)-NO_2), 8.12 (2H, d, $J_{2(2'),3(3')}$ 8.6, 3(3′) Ph(**H**)-NO_2); ∂_C (67.8 MHz, $CDCl_3$): 29.8 ($OCH_2\mathbf{CH_2}$), 47.1 & 47.5 ($NO_2PhCH_2N\mathbf{CH_2}Th$ or $NH_2PhCH_2N\mathbf{CH_2}Th$), 49.1 & 49.7 ($NO_2PhCH_2N\mathbf{CH_2}$ or $NH_2PhCH_2N\mathbf{CH_2}$), 57.8 & 58.0 ($N\mathbf{CH_2}PhNO_2$ or $N\mathbf{CH_2}PhNH_2$), 67.9 & 68.2 ($O\mathbf{CH_2}$), 114.9 (3(3′)Ph-NH_2), 117.2 & 117.6 (4Th), 118.5 & 118.6 (2Th or 1PhNH_2), 122.6 & 122.8 (5Th), 123.4 (3(3′)PhNO_2), 129.1 (2(2′)PhNO_2), 129.9 (2(2′)PhNH_2), 145.2 (4PhNH_2), 146.9 (1PhNO_2), 148.1 (4PhNO_2), 154.1 & 154.2 (3Th); Microanalysis: Found (1): C, 60.85; H, 5.77; N, 9.82; Found (2): C, 61.29; H, 5.64; N, 9.29.

$C_{29}H_{32}N_4O_4S_2$ requires C, 61.68; H, 5.71; N, 9.92; m/z: Found $[M + H]^+$ 565.0. $C_{29}H_{32}N_4O_4S_2$ requires 564.72.

Experiment 2.4.24

(16b) 14-(4-amino-benzyl)-17-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene

To a stirred solution of 14,17-bis-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene (0.79 g, 1.30 mmol), at ambient temperature, in pyridine (16 cm^3) was added the reducing agent, generated sodium hydrosulphide (~5.4 cm^3, ~13.5 mmol) [4.76 g, 20 mmol of $Na_2S.9H_2O$ and 1.69 g, 20 mmol of sodium bicarbonate in water (8 cm^3)] and the mixture heated to reflux for 10 minutes at the point where the solution turned dark green. The reaction vessel was cooled in a salt/ice water bath and the contents partially evaporated under reduced pressure. The remaining wet residue was dissolved in DCM (30 cm^3), water (30 cm^3) was added and the contents magnetically stirred while the pH of the aqueous layer was adjusted to neutral by the addition of 2M hydrochloric acid (12 cm^3) in parts. A colour change was apparent. The two-phase system was filtered through a sintered glass funnel, the organic layer separated, washed with a 30 % sodium chloride solution (3 x water (50 cm^3)/saturated sodium chloride (20 cm^3)), dried ($MgSO_4$) and the solvent evaporated off under reduced pressure. The residue was purified by flash chromatography [wt. 30:1; petroleum ether b.p. 40-60°C/ethyl acetate (1:1)]; dissolved in DCM, filtered through a Celite pad and the solvent evaporated off under reduced pressure to provide the title compound as a yellow/orange solid, 0.28 g, 37.3 %, [*tlc* – predominately one spot (R_f 0.40) in elutant - petroleum ether b.p. 40-60°C/ethyl acetate/methanol (6:3:1)]; m.p. = undetermined - too great a temperature range to be determined; ν_{max}/cm^{-1} (KBr disc): 3449.8 & 3373.9 (amino), 3102.4(w) (Th-H), 1621.8 (amino), 1598.3 (phenyl), 1557.6 (Th C=C), 1515.0 & 1342.8 (nitro); ∂_H (270 MHz, $CDCl_3$) 1.96 (4H, br. s, $OCH_2\mathbf{CH_2}$), 2.63 (4H, s, $N\mathbf{CH_2}$), 3.49, 3.59, 3.65 & 3.72 (10H, s, $N\mathbf{CH_2}Ph\text{-}NH_2$, $Th\mathbf{CH_2}NCH_2Ph\text{-}NH_2$, $Th\mathbf{CH_2}NCH_2Ph\text{-}NO_2$, $N\mathbf{CH_2}Ph\text{-}NO_2$, inclusive of $\mathbf{NH_2}$ [confirmed by D_2O shake]), 4.09 (4H, split s, $O\mathbf{CH_2}$), 6.58 (2H, d, $J_{2(2'),3(3')}$ 8.2, 3(3′)Ph(**H**)-NH_2), 6.80 (2H, split d, $J_{4,5}$ 5.4, 4Th-**H**), 7.10 (4H, d, $J_{2(2'),3(3')}$ & $J_{4,5}$ 6.4 & 5.7, 5Th-**H** & 2(2′)Ph(**H**)-NH_2), 7.53 (2H, d, $J_{2(2'),3(3')}$ 8.4, 2(2′)Ph(**H**)-NO_2), 8.13 (2H, d, $J_{2(2'),3(3')}$ 8.7, 3(3′)Ph(**H**)-NO_2); ∂_C (67.8 MHz, $CDCl_3$): 26.3 & 26.5 (OCH_2CH_2), 47.5 (NCH_2Th), 50.1 & 50.7 ($NO_2PhCH_2NCH_2$ or $NH_2PhCH_2NCH_2$), 57.9 & 58.3 (NCH_2PhNO_2 or NCH_2PhNH_2), 70.7 & 70.9 (OCH_2), 114.9 (3(3′)Ph-NH_2), 116.5 & 116.6 (4Th), 117.5 & 118.4 (2Th or 1PhNH_2), 122.5 (5Th), 123.4 (3(3′)PhNO_2), 129.2 (2(2′)PhNO_2), 129.8 (2(2′)PhNH_2) 145.2 (4PhNH_2), 146.9 (1PhNO_2), 148.5 (4PhNO_2), 154.1 & 154.3 (3Th); Microanalysis: Found: C, 62.63; H, 6.21; N, 9.07. $C_{30}H_{34}N_4O_4S_2$ requires C, 62.26; H, 5.92; N, 9.68; m/z: Found $[M + H]^+$ 579.3. $C_{30}H_{34}N_4O_4S_2$ requires 578.74.

Experiment 2.4.25

(**16c**) 13,16-bis-(4-amino-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

To a stirred solution of 13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene (4.07 g, 6.84 mmol), at ambient temperature, in pyridine (60 cm^3) was added the reducing agent, generated sodium hydrosulphide (~50 cm^3, ~28 mmol) [17.98 g, 75 mmol of $Na_2S.9H_2O$ and 5.99 g, 71 mmol of sodium bicarbonate in methanol/water (74/50 cm^3)[78]] and the mixture heated to reflux for 10 minutes at the point where the solution turns orangey red. The reaction vessel was cooled in a salt/ice water bath and the contents partially evaporated under reduced pressure. The remaining wet residue was dissolved in DCM (80 cm^3) and water/salt. The organic layer was separated, dried ($MgSO_4$) and the solvent evaporated off. DCM was added to the crude compound and crystals precipitated over an extended period. The crystals were isolated at the pump, washed with DCM (x3) and dried to provide the title compound as a beige finely divided solid, 0.78 g, 21.3 %. m.p. = (softens 175°C) 176.0-178.0°C; ν_{max}/cm^{-1} (KBr disc): 3453.5 & 3396.3 (amino), 1624.2 (amino), ~1600 & 1521.2 (phenyl), 1557.9 (Th C=C); Microanalysis: Found: C, 58.63; H, 5.96; N, 9.36. $C_{29}H_{34}N_4O_2S_2$ requires C, 65.14; H, 6.41; N, 10.48; m/z: Found $[M + H]^+$ 535.1. $C_{29}H_{34}N_4O_2S_2$ requires 534.73.

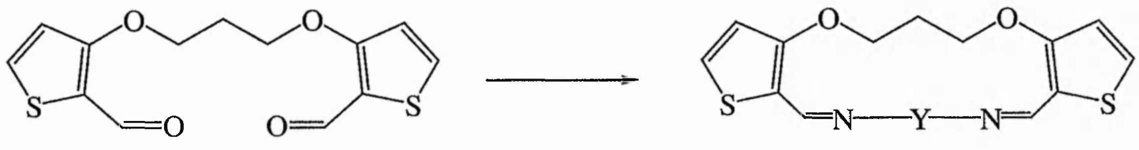
Experiment 2.4.26

(16d) 14,17-bis-(4-amino-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene

To a stirred solution of 14,17-bis-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene (0.16 g, 0.26 mmol), at ambient temperature, in pyridine (3 cm^3) was added the reducing agent, generated sodium hydrosulphide (1.1 cm^3, ~2.75 mmol) [4.86 g, 20 mmol of $Na_2S.9H_2O$ and 1.73 g, 20 mmol of sodium bicarbonate in water (8 cm^3)] and the mixture heated to reflux. After 4 hours the reaction vessel was cooled and refluxing re-commenced after 15 hours for 9.5 hours. The reaction contents were poured into solution and extracted with DCM (x2). The organic layer was washed with a 50 % sodium chloride solution (5 x water/saturated sodium chloride (1:1)), dried ($MgSO_4$) and the solvent evaporated off under reduced pressure to provide the crude title compound as a beige solid, 0.14 g, 100.0 %. m.p. = unable to determine (softens ~80°C, obvious at 86°C and oils out; ~97°C oil spreads (gas bubbles); 107°C partially clear; 120°C liquid formation; 160°C still opaque (gas bubbles); 180°C appears clear); ν_{max}/cm^{-1} (KBr disc): 3432.1 & 3372.0 (amino), 1616.9 (amino), 1589.3 & 1516.1 (phenyl), 1558.4 (Th C=C); Microanalysis: Found: C, 63.20; H, 6.40; N, 9.65. $C_{30}H_{36}N_4O_2S_2$ requires C, 65.66; H, 6.61; N, 10.21; m/z: Found $[M + H]^+$ 549.1. $C_{30}H_{36}N_4O_2S_2$ requires 548.76.

2.4 - [1+1] Schiff Base condensations applied to the preparation of Thiophene-Based Macrocycles – Scheme Five (see page 69)

Macrocyclic rings incorporating imine linkages via Schiff base formation have been shown$^{e.g\ 25}$ to complex to metal ions. A route to imine groups contained in thiophene-based macrocycles is therefore of intrinsic value. Also their reduced form could potentially lead to flexible unhindered rings where no bulky groups are directly attached to the donor atoms.



17a Y = $(CH_2)_2$
17b Y = $(CH_2)_5$

Scheme Five

Experiment 2.5.1

(17a) 2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.$0^{7,11}$]heneicosa-1(18),7(11),12(13),16(17),8,20-hexaene

To a stirred solution of α,ϖ-bis(2-formyl-3-oxythienyl)propane (2.00 g, 6.75 mmol) in ethanol (200 cm^3) at ambient temperature, was added ethylenediamine (0.5 cm^3, 7.48 mmol). After 52.5 hours the suspension was filtered off and washed with ethanol (2 x 10 cm^3), DCM (2 x 10 cm^3) and dried to provide the title compound as a light beige coloured finely divided solid, 1.87 g, 86.6 %. m.p. = (softens 205°C) 207.5-210.5°C (uncorrected); ν_{max}/cm^{-1} (KBr disc): 1618.5 (imine), 1542.4 (Th C=C); Microanalysis: Found: C, 55.47; H, 4.95; N, 8.31. $C_{15}H_{16}N_2O_2S_2$ requires C, 56.23; H, 5.03; N, 8.74; m/z: Found $[M + H]^+$ 321.3 (100%) and 641.2 (~25%). $C_{15}H_{16}N_2O_2S_2$ requires 320.43.

Experiment 2.5.2

(17b) 2,6-dioxa-10,22-dithia-13,19-diaza-tricyclo[19.3.0.$0^{7,11}$]tetracosa-1(21),7(11),12(13),19(20),8,23-hexaene

To a stirred solution of α,ϖ-bis(2-formyl-3-oxythienyl)propane (0.22 g, 0.74 mmol) in dry ethanol (25 cm^3) at ambient temperature, was added 1,5-diaminopentane (cadaverine) (0.1 cm^3, 0.85 mmol). After approximately one day, the solvent was evaporated off to yield a brown liquid. ν_{max}/cm^{-1} (liquid film): 1625.4 (imine), 1542.8 (Th C=C); ∂_H (270 MHz, $CDCl_3$) (tentative analysis of crude mixture) ~1.20 (t, cadaverine), ~2.50 (possible q, cadaverine), ~3.70 (br. s, cadaverine), 1.46 (2H possible q – not fully resolved, $NCH_2CH_2\mathbf{CH_2}$), ~1.66 (4H, possible q – not fully resolved), $NCH_2\mathbf{CH_2}$), ~2.68 (or ~2.50 - unknown) (2H, t, $OCH_2\mathbf{CH_2}$), 3.51 (4H, t, $N\mathbf{CH_2}$), 4.27 (4H, t, $O\mathbf{CH_2}$), 6.83 (2H, d $J_{4,5}$ 5.4, 4Th-**H**), 7.29 (2H, d, $J_{4,5}$ 5.4, 5Th-**H**), 8.40 (s, **HC=N**); ∂$_C$ (67.8MHz, $CDCl_3$): 18.2 (cadaverine), 24.4 ($NCH_2CH_2\mathbf{CH_2}$), 29.5 ($OCH_2\mathbf{CH_2}$), 30.7 ($NCH_2\mathbf{CH_2}$), 33.1 (unknown), 41.8 (unknown), 57.9 (cadaverine), 61.3 (NCH_2), 67.6 (OCH_2), 116.4 (4Th), 119.4 (2Th), 127.9 (5Th), 151.9 (3Th), 157.8 (C=N); m/z: Found $[2M + H]^+$ 726.2 (100%) and $[M + H]^+$ 363.5 (~17%). $C_{18}H_{22}N_2O_2S_2$ requires 362.5

2.6 - The Appendage of Thiophene-Based Macrocycles to a Polymeric Support – Scheme Six (see page 73)

Experiment 2.6.1

(18a) Polymer bound – 13,16-bis-(4-hydroxy-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

A small-scale attempt was made to append crude **6a** (Scheme Two – page 34) onto a 1 % cross-linked Merrifield resin using sodium hydride and dry THF:

To a stirred suspension of a chlorinated 1 % cross-linked Merrifield resin (1.0 mmol of Cl per gram of resin) (0.16 g) under nitrogen in dry THF (10 cm^3) was added a pre-pared solution of the sodium salt of 13,16-bis-(4-hydroxy-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene **6a** [NaH 60 % in oil (0.0067 g) was washed twice with petroleum ether b.p. 40-60°C and dried under nitrogen, then the crude macrocycle **6a** (0.086 g, 0.16 mmol) in THF (10 cm^3) was added with stirring]. After 23 hours of stirring at ambient temperature water was added to the reaction mixture, the polymer beads isolated at the pump and washed well with diethyl ether, DCM, more diethyl ether and dried for an extended period in a vacuum oven. A base-line diffuse reflectance (BDR) IR was conducted on the beads, but no significant changes to the Merrifield resin was noted. This experiment was not repeated on a larger scale with pure **6a** owing to the better success being achieved with the nitro-substituted macrocycles (Scheme Four – page 45).

Experiment 2.6.2

(18b) Polymer bound – 13-(4-amino-benzyl)-16-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

To a stirred mixture of 13-(4-amino-benzyl)-16-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene **16a** (0.178 g, 0.308 mmol) and 2 % cross-linked Merrifield resin (1.0 - 1.5 mmol Cl per gram of resin) (0.25 g) in DMF (2.40 cm^3) under an atmosphere of nitrogen was added *N*-ethyldiisopropylamine (0.059 cm^3, 0.341 mmol) and the mixture heated at approximately 100°C. After 8 hours the mixture was cooled and allowed to stir for a further 2.5 days. The polymer beads were isolated at the pump, washed with DMF (x2), DMF and methanol (4:1) (2 x 5 cm^3), DMF and methanol (1:1) (2 x 5 cm^3), DMF and methanol (1:4) (2 x 5 cm^3), methanol (x2). The brown polymer beads were dried* under reduced pressure at 65°C for 24 hours. Microanalysis: Found: C, 82.3; H, 6.89; N, 2.57. Presence of nitrogen here indicated that the macrocycle had been successfully linked to the polymer – see **18d** below. *drying pistol (methanol)

Experiment 2.6.3

(18c) Polymer bound - 14-(4-amino-benzyl)-17-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene

To a stirred mixture of 14-(4-amino-benzyl)-17-(4-nitro-benzyl)-2,7-dioxa-11,20-dithia-14,17-diaza-tricyclo[17.3.0.0^{8,12}]docosa-1(19),8(12),9,21-tetraene **16b** (0.214 g, 0.379 mmol) and 2 % cross-linked Merrifield resin (1.0 - 1.5 mmol Cl per gram of resin) (0.30 g) in DMF (3.00 cm^3) under an atmosphere of nitrogen was added *N*-ethyldiisopropylamine (0.072 cm^3, 0.416 mmol) and the mixture heated at approximately 100°C. After 8 hours the mixture was cooled and allowed to stir for a further 2.5 days. The polymer beads were isolated at the pump, washed with DMF (x2), DMF and methanol (4:1) (2 x 5 cm^3), DMF and methanol (1:1) (2 x 5 cm^3), DMF and methanol (1:4) (2 x 5 cm^3), methanol (x2). The brown polymer beads were dried* under reduced pressure at 65°C for 24 hours. Microanalysis: Found: C, 82.51; H, 6.95; N, 2.80. Presence of nitrogen here indicated that the macrocycle had been successfully linked to the polymer – see **18d** below. *drying pistol (methanol)

Experiment 2.6.4

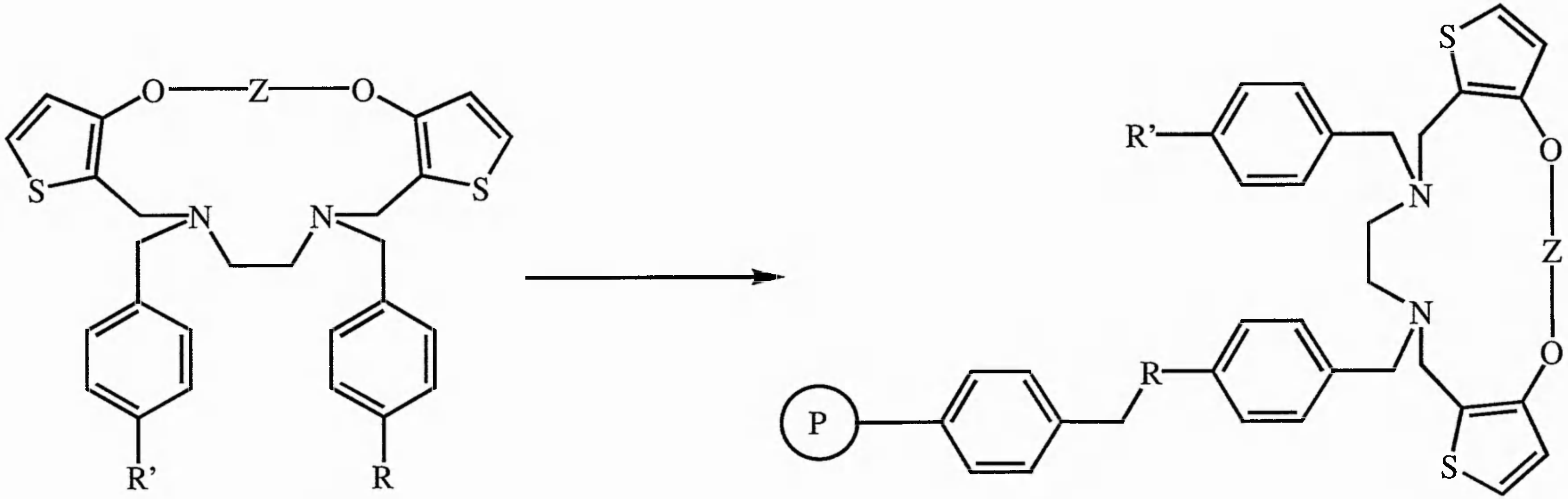
(18d) Polymer – BLANK

To a stirred mixture of 2 % cross-linked Merrifield resin (1.0 - 1.5 mmol Cl per gram of resin) (0.25 g) in DMF (2.40 cm^3) under an atmosphere of nitrogen was added *N*-ethyldiisopropylamine (0.059 cm^3, 0.341 mmol) and the mixture heated at approximately 100°C. After 8 hours the mixture was cooled and allowed to stir for a further 2.5 days. The polymer beads were isolated at the pump, washed with DMF (x2), DMF and methanol (4:1) (2 x 5 cm^3), DMF and methanol (1:1) (2 x 5 cm^3), DMF and methanol (1:4) (2 x 5 cm^3), methanol (x2). The off-white coloured polymer beads were dried* under reduced pressure at 65°C for 24 hours. Microanalysis: Found: C, 87.87; H, 7.33; N, 0.00. This experiment provides proof that no nitrogen is observed in the analysis of the polymer when the macrocycle is not present in the reaction mixture. It also shows that both potential sources of nitrogen (Hünigs base and/or DMF) are removed in the work-up of the polymeric reactions. *drying pistol (methanol)

Experiment 2.6.5

(18b′) Polymer bound – 13-(4-amino-benzyl)-16-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene

In initial attempts **16a** was loaded onto a chlorinated Merrifield resin (excess) for preliminary study (see section 2.7 – Metal-ion binding studies, experiment 2.7.3): To a stirred mixture of 2 % cross-linked Merrifield resin (1.0 - 1.5 mmol Cl per gram of resin) (1.42 g) and *N*-ethyldiisopropylamine (0.070 cm^3, 0.404 mmol) in DMF (7.0 cm^3) under an atmosphere of nitrogen was added a solution of 13-(4-amino-benzyl)-16-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene **16a** (0.198 g, 0.351 mmol) in DMF (1.4 cm^3). The mixture was heated at approximately 100°C, cooled and reheated etc. over several days until no further changes were apparent in aliquots determined by *tlc*. The mixture was cooled and the polymer beads were isolated at the pump, washed with DMF (2 x 10 cm^3), DMF and methanol (4:1) (1 x 10 cm^3), DMF and methanol (1:1) (1 x 10 cm^3), DMF and methanol (1:4) (1 x 10 cm^3), methanol (2 x 10 cm^3). The brown polymer beads were dried first in a vacuum dessicator (1 hour) then under reduced pressure in a drying pistol (ethanol) for three hours. Microanalysis (two analyses): Found: C, (1) 86.94, (2) 87.20; H, (1) 7.05, (2) 7.45; N, (1) 1.12, (2) 0.78.



6a Z = $(CH_2)_3$, R = R' = OH
16a Z = $(CH_2)_3$, R = NH_2, R' = NO_2
16b Z = $(CH_2)_4$, R = NH_2, R' = NO_2

18a Z = $(CH_2)_3$, R = O, R' = OH
18b Z = $(CH_2)_3$, R = NH, R' = NO_2
18c Z = $(CH_2)_4$, R = NH, R' = NO_2
18d Blank

Scheme Six

2.7 - Metal-Ion Binding Studies

Experiment 2.7.1

To a hot stirred solution of **14b** (13,18-bis-(4-nitro-benzyl)-2,6-dioxa-10,21-dithia-13,18-diaza-tricyclo[18.3.0.0^{7,11}]tricosa-1(20),7(11),8,22-tetraene) (0.20 g, 0.32 mmol) was added nickel(II) perchlorate (0.13 g, 0.36 mmol) in acetonitrile (1-2 cm^3). After one hour the reaction vessel was cooled and a solid precipitate formed. A *tlc* of the mother liquor revealed no change – only starting material was seen. The experiment indicated that the Ni(II) ion does not complex readily with this 17 membered, 2 oxygen atom and 2 nitrogen atom macrocycle.

Experiment 2.7.2

To test whether varying ring sizes of thiophene-based macrocycles would extract Zn(II) ions from an aqueous medium into an organic medium, the following solutions were produced:

Ring Size	Compound	Concentration	Molarity (M)	Solvent
-	$Zn(NO_3)_2.6H_2O$	0.7436 g 250 cm^{-3}	0.01	H_2O
15	**12b**	0.1489 g 25 cm^{-3}	0.01	DCM
17	**14b**	0.1555 g 25 cm^{-3}	0.01	DCM
18	**15b**	0.1587 g 25 cm^{-3}	0.01	DCM

Table 1

10 cm^3 of the solution of $Zn(NO_3)_2.6H_2O$ in water was shaken (vigorously on a mechanical shaker for 19 hours) against the following solutions: (a) 10 cm^3 of **12b** in DCM, (b) 10 cm^3 **14b** in DCM, (c) 10 cm^3 of **15b** in DCM and (d) 10 cm^3 of DCM. The two-phase systems were separated using phase separation filter paper (Whatman® 1PS Silicone Treated circles 185 mm, Cat No. 2200 185), collecting the aqueous layer. 5 cm^3 of the aqueous layer was titrated against EDTA solution (0.0139 M) using Eriochrome Black-T indicator and added pH 10 buffer. The following results were obtained (Table 2 – page 75). These are discussed later (Discussion section 3.8)

N⁰	Phase system	V (cm^3) aqueous	Titre 1 (cm^3)	Titre 2 (cm^3)	Ave. Titre (cm^3)
1	Zn(II) stock sol^{n}	5	3.50	3.55	3.53
2	Zn(II)/**12b**	5	3.30	3.35	3.33
3	Zn(II)/**14b**	5	3.45	3.30	3.38
4	Zn(II)/**15b**	5	3.40	3.40	3.40
5	Zn(II)/DCM	5	3.30	3.40	3.35

Table 2

Experiment 2.7.3

Initially, **16a** (0.2 g, 0.35 mmol) was reacted onto a 2 % cross-linked Merrifield resin (1.0 - 1.5 mmol Cl per gram of resin) (see experiment 2.6.5). This was approximately one third of a molecule of macrocycle per reactive site on the resin if assuming the lowest value of 1.0 mmol Cl per gram of resin. From two chemical combustion analyses, the nitrogen content of the substituted resin ranged between 0.78 - 1.12 % or 0.15 - 0.20 mmol macrocycle per gram of resin.

In order to test whether this resin with attached macrocycle (ring size 15) could remove Zn(II) metal ions from solution the following experiments were carried out:

(1) Appended resin (0.5 g, 0.1265 mmol) was shaken (vigorously on a mechanical shaker) with a 0.025 M $Zn(NO_3)_2.6H_2O$ in 9:1 ethyl acetate/methanol solution (10 cm^3) for 18 hours. Repeated for accuracy.

(2) Blank resin (0.5g) was shaken (vigorously on a mechanical shaker) with a 0.025 M $Zn(NO_3)_2.6H_2O$ in 9:1 ethyl acetate/methanol solution (10 cm^3) for 18 hours. Repeated for accuracy.

The initial amount of Zn(II) metal ion solution in the reaction mixture was at least twice that required to fully load the resin (assuming 1:1 complexation)[70]

For both experiments (1) and (2), the polymer resin was isolated at the pump and washed with 9:1 ethyl acetate/methanol solution (2 x 5 cm^3). To 5 cm^3 of the filtrate was added a pH 10 buffer (5 cm^3) and one drop of Eriochrome Black-T indicator. The solution was titrated against EDTA solution (0.0089 M) from a violet to an aqua blue colour and compared to the stock solution (0.025 M $Zn(NO_3)_2.6H_2O$ in 9:1 ethyl acetate/methanol) titre (3). The following results were obtained – Table 3.

Experiment	Titre 1 (cm^3)	Titre 2 (cm^3)	Ave. Titre (cm^3)
(1)	24.1	24.1	24.1
(2)	24.9	24.7	24.8
(3)	25.1	25.1	25.1

Table 3

2.8 - X-ray Crystallography

A suitable crystal of **12b** (13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene) was grown from the slow evaporation of a DCM/acetonitrile solution (approximately 1:2 mixture of solvents) and subjected to X-ray analysis. In a similar manner, crystals of **12c** were also grown. The latter crystals were decomposed by X-radiation and thus incompatible with this technique.

2.8.1 Data Collection

A yellow prismatic crystal of $C_{29}H_{30}N_4O_6S_2$ having approximate dimensions of 0.50 x 0.50 x 0.50 mm was mounted on a glass fibre with superglue. All crystallographic measurements were made on a Rigaku AFC7R diffractometer with graphite monochromated Mo-Kα radiation and a rotating anode generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range $39.25 < 2\theta < 39.84°$ corresponded to a primitive triclinic cell with dimensions:

a = 12.139(6) Å α = 101.60(4)° V = 1438(1) Å
b = 13.179(7) Å β = 90.49(4)°
c = 10.071(4) Å γ = 113.66(3)°

For Z = 2 and F.W. = 594.70, the calculated density was 1.37 g cm^{-3}. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group[79] was determined to be:

P-1 (#2)

The data were collected at a temperature of 20 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take-off angle of 6.0°. Scans of $(1.84 + 0.35 \tan \theta)^\circ$ were made at variable speeds. The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 0.3 mm and the crystal to detector distance was 235 mm. The computer-controlled slits were set to 3.0 mm (horizontal) and 3.0 mm (vertical).

2.8.2 - **Data Reduction**

Of the 5326 reflections that were collected, 5067 were unique ($R_{int} = 0.048$); equivalent reflections were merged. The intensities of three representative reflections were measured after every 200 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Mo-Kα radiation is 2.348 cm^{-1}. Azimuthal scans of several reflections indicated no need for an absorption correction. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was also applied.

2.8.3 - **Structure Solution and Refinement**

The structure was solved by heavy-atom Patterson methods and expanded using Fourier techniques[80]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[81] on F was based on 3457 observed reflections ($I > 3.00\sigma(I)$) and 371 variable parameters and converged (largest parameter shift was 0.04 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \,||F_o| - |F_c|| \,/\, \Sigma\, |F_o| = 0.047$$

$$R_w = [\Sigma\, w\, (|F_o| - |F_c|)^2 \,/\, \Sigma\, w\, F_o^{\,2}]^{1/2} = 0.045$$

The standard deviation of an observation of unit weight[82] was 2.39. The weighting scheme was based on counting statistics and included a factor ($p = 0.009$) to down weight the intense reflections. Plots of $\Sigma\, w\, (|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.28 and -0.37 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[83]. Anomalous dispersion effects were included in Fcalc[84]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[85]. The values for the mass attenuation coefficients are those of Creagh and Hubbell[86]. All calculations were performed using the teXsan[87] crystallographic software package of Molecular Structure Corporation. The results of the structure determination (atomic parameters, bond lengths, angles, torsion angles and deviations from the least squares planes) are presented in the following Tables 4 to 8 and in the Appendix.

Intensity Measurements

Diffractometer	Rigaku AFC7R
Radiation	MoKα (λ = 0.71069 Å) graphite monochromated
Attenuator	Zr foil (factor = 9.43)
Take-off Angle	6.0°
Detector Aperture	3.0 mm horizontal 3.0 mm vertical
Crystal to Detector Distance	235 mm
Voltage, Current	50 kV, 50 mA

Temperature	20.0°C
Scan Type	ω-2θ
Scan Rate	variable/min (in ω) (up to 4 scans)
Scan Width	$(1.84 + 0.35 \tan \theta)^{\circ}$
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 5326 Unique: 5067 ($R_{int} = 0.048$)
Corrections	Lorentz-polarization Secondary Extinction (coefficient: 2.29024e-007)

Structure Solution and Refinement

Structure Solution	Patterson Methods (DIRDIF92 PATTY)
Refinement	Full-matrix least-squares on F
Function Minimized	$\Sigma w (\lvert F_o \rvert - \lvert F_c \rvert)^2$
Least Squares Weights	$1/\sigma^2(F_o) = 4F_o^2/\sigma^2(F_o^2)$
p-factor	0.0094
Anomalous Dispersion	All non-hydrogen atoms
No. Observations ($I > 3.00\sigma(I)$)	3457
No. Variables	371
Reflection/Parameter Ratio	9.32
Residuals: R; R_w	0.047; 0.045
Goodness of Fit Indicator	2.39
Max Shift/Error in Final Cycle	0.04
Maximum peak in Final Diff. Map	0.28 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.37 $e^-/Å^3$

Table 4 - Fractional Atomic coordinates and Biso/Beq

atom	x	y	z	Biso/Beq
S(1)	0.19395(6)	0.18368(5)	0.29684(6)	4.44(2)
S(2)	-0.33555(5)	0.48944(6)	0.18667(6)	4.75(2)
O(1)	0.7673(2)	0.8161(2)	0.3664(2)	8.89(6)
O(3)	-0.0866(1)	0.1268(1)	0.0662(2)	4.40(4)
O(4)	0.4895(2)	0.9223(2)	0.6039(2)	7.56(6)
O(5)	-0.2636(1)	0.2306(1)	0.0567(2)	5.24(4)
O(7)	0.4005(2)	1.0248(2)	0.7032(2)	8.62(6)
O(8)	0.7110(2)	0.7845(2)	0.1550(2)	7.57(6)
N(1)	0.4018(2)	0.9451(2)	0.6155(2)	5.89(6)
N(9)	-0.0296(1)	0.5439(1)	0.2075(2)	2.77(4)
N(10)	0.1291(1)	0.4170(1)	0.2324(2)	2.68(4)
N(11)	0.6910(2)	0.7712(2)	0.2697(3)	5.34(6)
C(13)	-0.0321(2)	0.4811(2)	0.3124(2)	2.88(5)
C(14)	0.0848(2)	0.7350(2)	0.3538(2)	3.29(5)
C(15)	0.0032(2)	0.3816(2)	0.2661(2)	3.06(5)
C(16)	0.1462(2)	0.3218(2)	0.1426(2)	3.01(5)
C(17)	-0.0022(2)	0.1209(2)	0.1509(2)	3.25(5)
C(18)	0.3406(2)	0.5458(2)	0.3271(2)	2.62(4)
C(19)	0.4795(2)	0.6522(2)	0.1856(2)	3.62(5)
C(20)	0.2151(2)	0.4680(2)	0.3534(2)	2.96(4)
C(21)	0.1058(2)	0.2121(2)	0.1884(2)	3.06(5)
C(22)	0.5470(2)	0.6663(2)	0.4150(2)	4.56(6)
C(23)	-0.2720(2)	0.0549(2)	-0.0714(2)	4.91(6)
C(24)	-0.3444(2)	0.1171(2)	-0.0057(3)	5.04(6)
C(25)	0.4334(2)	0.5905(2)	0.4310(2)	3.91(5)
C(26)	-0.1963(2)	0.0286(2)	0.0217(2)	4.09(5)
C(27)	0.3653(2)	0.5775(2)	0.2044(2)	3.26(5)
C(28)	0.5681(2)	0.6944(2)	0.2907(2)	3.58(5)
C(29)	0.2929(2)	0.8756(2)	0.5217(2)	4.02(5)
C(30)	-0.0302(2)	0.6552(2)	0.2648(2)	3.80(5)
C(31)	-0.4349(2)	0.2742(2)	0.1464(3)	4.84(6)
C(32)	0.1863(2)	0.8849(2)	0.5499(2)	4.86(6)
C(33)	-0.2491(2)	0.4174(2)	0.1229(2)	3.02(5)
C(34)	0.0828(2)	0.8131(2)	0.4678(2)	4.09(5)
C(35)	0.0850(2)	0.0501(2)	0.2902(2)	4.64(6)
C(36)	0.2996(2)	0.8014(2)	0.4081(2)	4.45(6)
C(37)	-0.4577(2)	0.3660(2)	0.1902(2)	5.13(7)
C(38)	-0.0145(2)	0.0275(2)	0.2093(2)	3.96(6)
C(39)	0.1951(2)	0.7325(2)	0.3246(2)	4.33(6)
C(40)	-0.3147(2)	0.3046(2)	0.1067(2)	3.65(5)

Table 4 continued - Fractional Atomic coordinates and Biso/Beq

atom	x	y	z	Biso/Beq
C(41)	-0.1210(2)	0.4771(2)	0.0905(2)	2.93(4)
H(1)	0.1850	0.9407	0.6308	5.783
H(2)	0.0058	0.8187	0.4853	4.689
H(3)	0.3749	0.7952	0.3859	4.975
H(4)	0.1977	0.6808	0.2419	4.874
H(5)	0.4968	0.6745	0.1001	3.971
H(6)	0.6120	0.6980	0.4869	5.211
H(7)	0.4175	0.5698	0.5188	4.290
H(8)	0.3008	0.5456	0.1291	3.804
H(9)	0.2286	0.4117	0.3967	3.676
H(10)	-0.0502	0.6788	0.1819	3.676
H(11)	-0.0893	0.6542	0.3243	3.676
H(12)	-0.0041	0.3532	0.3551	3.676
H(13)	-0.1132	0.4489	0.3406	3.676
H(14)	-0.2497	0.0812	-0.1397	3.676
H(15)	0.1925	0.5210	0.4244	3.676
H(16)	0.0318	0.5408	0.3949	3.676
H(17)	0.1026	0.3039	0.0512	3.676
H(18)	0.2302	0.3524	0.1259	3.676
H(19)	-0.0428	0.3297	0.1813	3.676
H(20)	-0.0957	0.4127	0.0371	3.676
H(21)	-0.1191	0.5349	0.0280	3.676
H(22)	-0.5016	0.1900	0.1421	3.676
H(23)	-0.5357	0.3778	0.2331	3.676
H(24)	-0.091	-0.0504	0.1900	3.676
H(25)	0.0886	0.0088	0.3653	3.676
H(26)	-0.3333	-0.0168	-0.1359	3.676
H(27)	-0.2446	0.0152	0.1058	3.676
H(28)	-0.1877	-0.0425	-0.0107	3.676
H(29)	-0.4038	0.0689	0.0681	3.676
H(30)	-0.4092	0.1259	-0.0705	3.676

$$Beq = 8/3\ p2(U11(aa^*)2 + U22(bb^*)2 + U33(cc^*)2 + 2U12(aa^*bb^*)\cos g + 2U13(aa^*cc^*)\cos b + 2U23(bb^*cc^*)\cos a)$$

Table 5 – Anisotropic Displacement Parameters

atom	U11	U22	U33	U12	U13	U23
S(1)	0.0579(4)	0.0507(4)	0.0613(4)	0.0238(3)	-0.0094(3)	0.0128(3)
S(2)	0.0509(4)	0.0694(4)	0.0634(4)	0.0345(3)	0.0106(3)	0.0006(3)
O(1)	0.050(1)	0.117(2)	0.130(2)	-0.018(1)	-0.025(1)	0.053(1)
O(3)	0.0382(8)	0.0326(8)	0.086(1)	0.0065(7)	-0.0118(8)	0.0076(8)
O(4)	0.066(1)	0.091(2)	0.111(2)	0.018(1)	-0.026(1)	0.010(1)
O(5)	0.0332(9)	0.0367(9)	0.115(1)	0.0091(7)	-0.0051(9)	-0.0009(9)
O(7)	0.082(1)	0.102(2)	0.081(1)	-0.000(1)	-0.001(1)	-0.034(1)
O(8)	0.065(1)	0.087(1)	0.109(2)	-0.004(1)	0.023(1)	0.038(1)
N(1)	0.068(2)	0.061(1)	0.064(2)	-0.001(1)	-0.001(1)	0.008(1)
N(9)	0.0375(9)	0.0321(9)	0.0350(9)	0.0143(8)	0.0040(7)	0.0059(7)
N(10)	0.0278(9)	0.0299(9)	0.0381(9)	0.0069(7)	0.0020(7)	0.0048(7)
N(11)	0.041(1)	0.056(1)	0.093(2)	0.003(1)	0.001(1)	0.025(1)
C(13)	0.036(1)	0.041(1)	0.033(1)	0.015(1)	0.0068(9)	0.0101(9)
C(14)	0.047(1)	0.031(1)	0.046(1)	0.015(1)	0.003(1)	0.007(1)
C(15)	0.034(1)	0.036(1)	0.044(1)	0.0115(9)	0.0033(9)	0.0107(9)
C(16)	0.038(1)	0.036(1)	0.037(1)	0.0122(9)	0.0036(9)	0.0051(9)
C(17)	0.041(1)	0.038(1)	0.046(1)	0.019(1)	0.005(1)	0.005(1)
C(18)	0.033(1)	0.032(1)	0.034(1)	0.0148(9)	0.0019(9)	0.0040(9)
C(19)	0.042(1)	0.045(1)	0.048(1)	0.013(1)	0.008(1)	0.016(1)
C(20)	0.035(1)	0.039(1)	0.033(1)	0.0119(9)	0.0032(9)	0.0063(9)
C(21)	0.040(1)	0.035(1)	0.039(1)	0.016(1)	0.0038(9)	0.0042(9)
C(22)	0.038(1)	0.060(2)	0.060(2)	0.006(1)	-0.015(1)	0.014(1)
C(23)	0.056(2)	0.046(1)	0.066(2)	0.011(1)	-0.017(1)	-0.004(1)
C(24)	0.037(1)	0.044(1)	0.096(2)	0.009(1)	-0.010(1)	0.003(1)
C(25)	0.042(1)	0.057(1)	0.040(1)	0.010(1)	-0.004(1)	0.012(1)
C(26)	0.041(1)	0.033(1)	0.068(2)	0.007(1)	0.002(1)	-0.000(1)
C(27)	0.035(1)	0.043(1)	0.040(1)	0.011(1)	-0.0027(9)	0.007(1)
C(28)	0.032(1)	0.035(1)	0.063(2)	0.007(1)	0.001(1)	0.011(1)
C(29)	0.050(1)	0.040(1)	0.045(1)	0.003(1)	-0.000(1)	0.006(1)
C(30)	0.052(1)	0.043(1)	0.051(1)	0.025(1)	-0.002(1)	0.002(1)
C(31)	0.036(1)	0.069(2)	0.072(2)	0.011(1)	0.008(1)	0.023(1)
C(32)	0.064(2)	0.049(1)	0.049(1)	0.009(1)	0.014(1)	-0.007(1)
C(33)	0.035(1)	0.047(1)	0.035(1)	0.020(1)	0.0046(9)	0.007(1)
C(34)	0.049(1)	0.044(1)	0.055(1)	0.016(1)	0.014(1)	0.003(1)
C(35)	0.079(2)	0.049(1)	0.057(2)	0.029(1)	0.010(1)	0.022(1)

Table 5 continued – Anisotropic Displacement Parameters

atom	U11	U22	U33	U12	U13	U23
C(36)	0.047(1)	0.044(1)	0.071(2)	0.018(1)	0.004(1)	-0.002(1)
C(37)	0.042(1)	0.093(2)	0.059(2)	0.030(1)	0.015(1)	0.011(1)
C(38)	0.053(1)	0.036(1)	0.062(2)	0.018(1)	0.016(1)	0.013(1)
C(39)	0.049(1)	0.043(1)	0.062(2)	0.019(1)	0.000(1)	-0.010(1)
C(40)	0.031(1)	0.046(1)	0.057(1)	0.012(1)	-0.001(1)	0.012(1)
C(41)	0.037(1)	0.039(1)	0.033(1)	0.0141(9)	0.0053(9)	0.0074(9)

The general temperature factor expression:

$$Uij = exp(-2p2(a^{*}2U11h2 + b^{*}2U22k2 + c^{*}2U33l2 + 2a^{*}b^{*}U12hk + 2a^{*}c^{*}U13hl + 2b^{*}c^{*}U23kl))$$

All bond lengths up to 3 Å, intramolecular bond angles and torsion angles can be found in separate tables in the Appendix.

Tables 6a-d Selected Bond Distances (Å)

Table 6a - Ring cavity

atom 1	atom 2	distance	atom 1	atom 2	distance
N10	C16	1.480(4)	O5	C40	1.371(4)
C16	C21	1.500(4)	C40	C33	1.349(4)
C21	C17	1.360(4)	C33	C41	1.509(4)
C17	O3	1.364(4)	C41	N9	1.474(4)
O3	C26	1.423(4)	N9	C13	1.460(4)
C26	C23	1.488(5)	C13	C15	1.526(4)
C23	C24	1.501(5)	C15	N10	1.473(4)
C24	O5	1.425(4)			

Table 6b - Thiophene rings

L.H.S of molecule			R.H.S of molecule		
atom 1	**atom 2**	**distance**	**atom 1**	**atom 2**	**distance**
S1	C35	1.714(4)	S2	C37	1.713(4)
C35	C38	1.345(4)	C37	C31	1.339(5)
C38	C17	1.424(4)	C31	C40	1.433(4)
C17	C21	1.360(4)	C40	C33	1.349(4)
C21	S1	1.716(3)	C33	S2	1.727(3)

Table 6c - benzene rings

L.H.S of molecule R.H.S of molecule

atom 1	atom 2	distance	atom 1	atom 2	distance
C18	C25	1.382(4)	C14	C39	1.385(4)
C25	C22	1.375(4)	C39	C36	1.376(4)
C22	C28	1.373(5)	C36	C29	1.374(4)
C28	C19	1.360(4)	C29	C32	1.374(5)
C19	C27	1.383(4)	C32	C34	1.368(4)
C27	C18	1.381(4)	C34	C14	1.387(4)

Table 6d - Others

L.H.S of molecule R.H.S of molecule

atom 1	atom 2	distance	atom 1	atom 2	distance
N10	C20	1.453(4)	N9	C30	1.467(4)
C20	C18	1.519(4)	C30	C14	1.509(4)
N11	O1	1.212(4)	N1	O4	1.217(4)
N11	O8	1.215(4)	N1	O7	1.236(4)

Table 7 – Bond Angles (°) in the macrocyclic ring

atom 1	atom 2	atom 3	angle
N10	C16	C21	117.2(2)
C16	C21	C17	126.5(3)
C21	C17	O3	119.2(3)
C17	O3	C26	118.5(3)
O3	C26	C23	108.6(3)
C26	C23	C24	116.7(3)
C23	C24	O5	108.6(3)
C24	O5	C40	116.8(2)
O5	C40	C33	119.5(3)
C40	C33	C41	127.8(3)
C33	C41	N9	116.5(2)
C41	N9	C13	113.6(2)
N9	C13	C15	113.9(2)
C13	C15	N10	113.2(2)

Table 8a-c – Deviations from selected Least-Squares Planes (Å)

Table 8a - Least-Squares Plane through the ring cavity

Atoms Defining Plane	Distance	esd
O3	0.1292	0.0025
C26	-0.1079	0.0035
C23	0.6148	0.0039
C24	-0.0619	0.0042
O5	-0.0451	0.0028
C40	-0.4652	0.0034
C33	-0.0586	0.0030
C41	0.8575	0.0029
N9	0.2429	0.0023
C13	-0.9612	0.0028
C15	-0.7076	0.0030
N10	0.1387	0.0023
C16	0.7633	0.0029
C21	-0.1458	0.0030
C17	-0.4216	0.0032

Mean deviation from plane is 0.3814 Å; Chi-squared: 411870.7

Table 8b – Least squares plane through the ring donor atoms (O & N)

Atoms Defining Plane	Distance	esd	Additional Atoms	Distance	Additional Atoms	Distance
O3	0.0688	0.0025	C26	-0.1130	C41	0.7218
O5	-0.0840	0.0028	C23	0.6324	C13	-1.1436
N9	0.0563	0.0023	C24	-0.0473	C15	-0.8709
N10	-0.0611	0.0023	C40	-0.5136	C16	0.5907
			C33	-0.1514	C21	-0.2875
			C41	0.7218	C17	-0.5109

Mean deviation from plane is 0.0675 Å; Chi-squared: 2950.8

Table 8c – Least squares plane through the benzene rings

L.H.S of molecule R.H.S of molecule

Atoms Defining Plane	Distance	esd	Atoms Defining Plane	Distance	esd
C20	-0.0052	0.0029	C30	-0.0867	0.0034
C18	0.0244	0.0027	C14	-0.0061	0.0030
C25	0.0580	0.0035	C34	-0.0614	0.0034
C22	0.0109	0.0037	C32	-0.0041	0.0038
C28	-0.0267	0.0031	C29	0.0501	0.0033
C19	-0.0582	0.0032	C36	0.1399	0.0037
C27	-0.0317	0.0031	C39	0.1231	0.0037
N11	-0.0106	0.0034	N1	-0.0059	0.0035
O1	-0.0947	0.0037	O4	-0.2008	0.0033
O8	0.1112	0.0034	O7	0.1496	0.0037

Additional Atoms	Distance	Additional Atoms	Distance
N10	0.1086	N9	-0.7892

L.H.S - Mean deviation from plane is 0.0432 Å; Chi-squared: 2632.7

R.H.S - Mean deviation from plane is 0.0828 Å; Chi-squared: 9481.6

DISCUSSION

3.1 – Scheme One (page 29)

The preparation of the thiophene bridge products, α,ϖ-bis(3-oxythienyl)alkane, was first reported[52] from the starting material methyl 3-hydroxythiophene-2-carboxylate. In this work, isolation and characterisation of the intermediates, α,ϖ-bis(2-methoxycarbonyl-3-oxythienyl)alkane (formed by the Williamson ether synthesis of the appropriate alkylating agent to 2 moles of methyl 3-hydroxythiophene-2-carboxylate) and α,ϖ-bis(2-carbonyl-3-oxythienyl)alkane (produced by saponification of the latter compound in hot aqueous base) was performed. Subsequent decarboxylation of the dry saponified products using copper(I)oxide in refluxing pyridine led to the thiophene bridged products.

It has been determined by the present research that these thiophene-bridged compounds can be obtained without the need for purification at each intermediate stage and without significant loss of product. Table 9 shows the yields obtained from experiments 2.1.1 through to 2.1.4 and compares them to Chaffin's[51] results (calculated according to recorded yields at the intermediate stages)

Product name	Experiment	Yield (%)	Chaffin's Yield (%)
α,ϖ-bis (3-oxythienyl)ethane	2.1.1	28.2	59.7
α,ϖ-bis (3-oxythienyl)propane	2.1.2	57.5	55.3
α,ϖ-bis (3-oxythienyl)butane	2.1.3	44.7	47.5
α,ϖ-bis (3-oxythienyl)diethyl ether	2.1.4	60.2	77.6

Table 9

In addition, it has been shown that it is not necessary to dry the crude products obtained from the Williamson ether synthesis, but still essential to wash them thoroughly with water to remove as much DMF as possible before transferring the wet product to a suitably sized flask for the saponification reaction. The crude products from this stage were appreciably dried, but the use of bone-dry solvents and apparatus was not necessary. Overall, it has been shown on a large scale (30 to 70 g) that yields comparable (compare experiments 2.1.2 & 2.1.3) to those initially reported can be obtained satisfactorily by reducing the length of the process. Purification is only required at the final crude stage.

3.2 – [1+1] Thiophene-Based Macrocycles containing the Hydroxyl Functional group – Scheme Two (page 34)

Scheme two shows a synthetic route to thiophene-based macrocycles incorporating two hydroxyl groups. The phenolic groups were required so the macrocycle could be appended to a suitably functionalised polymeric substrate.

3.2.1 – Schiff Bases of *p*-hydroxybenzaldehyde

In initial attempts to synthesise Schiff base **2a** from *p*-hydroxybenzaldehyde and ethylenediamine in refluxing ethanol an oil was obtained which later solidified. This crude product was not identified and in the hope of obtaining the intended product the reaction was then tried in refluxing ethanol spiked with glacial acetic acid. As a weak acid (pKa 4.72) this should catalyse the reaction because an equilibrium involving the acid between strong base, ethylenediamine, and the weaker base, the carbonyl group, would be set up allowing free amine to react with the protonated carbonyl group (Figure 16 – page 89). This would not work however if a strong acid was used as the protonated base, the salt of ethylenediamine in this case would not be able to function as an nucleophile.

However, much as in the previous reaction, a crude solid was obtained. The product was impure, melting in the range 75-95°C.

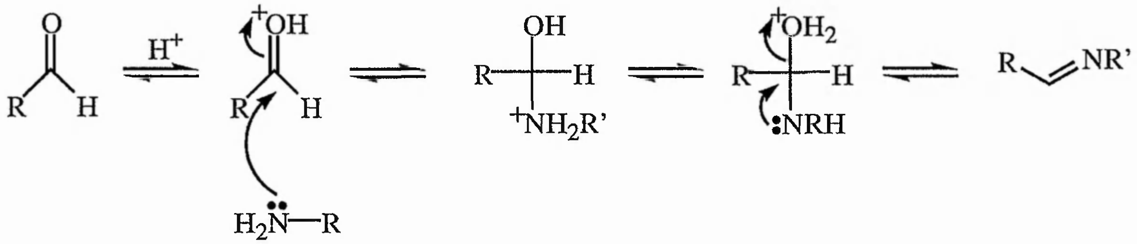


Figure 16

Billman[88] in the 1950's concentrated much effort on the formation of Schiff bases and their reduction to the respective amines. Attention was given to the synthesis of benzhydrylamines and structurally related compounds, $Ar_2 C = N\text{-}Ar'$. The isolation of the Schiff base utilised a moisture trap method to drive off formed water and a suitable catalyst, HBr or $ZnCl_2$. Yields were high, typically 70-80%.

Following Billman's moisture trap method (*p*-hydroxybenzaldehyde in toluene together with a catalytic quantity of 48% hydrobromic acid and adding ethylenediamine dropwise) using toluene as the solvent proved satisfactory in obtaining Schiff Base **2a**. Confidence that **2a** had been isolated was justified before spectroscopic experiments when its high melting point of 212-213°C[71] was determined. In optimising the experiment it was found that omitting the catalyst had little or no effect on the reaction. The yield was in excess of 100% and this was attributed to a hard visible impurity that could be removed by recrystallisation. Unfortunately a large amount of hot solvent (40 cm^3 g^{-1} toluene/*p*-hydroxybenzaldehyde) was required not only to dissolve the *p*-hydroxybenzaldehyde but also so that adding ethylenediamine to the substrate could be achieved without the solvent boiling vigorously (exothermic reaction). It was necessary to prevent the solvents boiling in order to reduce impurities, thought to be due to the reactants decomposing on the reaction vessel. The amount of solvent required was deemed too high for continued use of this preparative method and an alternative method was sought.

Since the solubility of *p*-hydroxybenzaldehyde is very high in ethanol, the reaction was carried out by controlling the exotherm at 20°C (experiment 2.2.1). This proved satisfactory as **2a** precipitated from ethanol (sparingly soluble). Although the yield (71%) after purification was slightly reduced compared to the moisture trap method of Billman, the ease and efficiency of obtaining the compound makes it the better method.

This preparation is similar to that used to obtain salen[89]. An extended reaction time was given to this reaction because thin layer chromatography examination to determine completion proved unsuitable since the R_f values of starting material and product were very similar in several different solvent systems.

The preparation of **2b** (experiment 2.2.2) was carried out using a similar reaction to **2a**, replacing *p*-hydroxybenzaldehyde with 3,5-dibromo-4-hydroxybenzaldehyde and working at the reflux temperature of ethanol. The analytical data strongly suggests the formation of product **2b**; a high sharp melting temperature of 260-260.5°C; IR spectrum stretch at 1651 cm^{-1} indicative of imine and a mass spectrum $[M+1]^+$ of 585.2 mass units agreeing within the limit of error to the expected value of 583.9 mass units. No NMR data was collected, as a suitable solvent was not found. However, the chemical combustion analysis for nitrogen was around twice the limit of error, ~0.6%.

The need to block the 3 and 5 positions on the benzene groups by bromine **2b** or the protection of the phenolic group of **2a** was necessary for ring closure to macrocycle using the Mannich reaction and this will be mentioned later.

3.2.2 – Protection of the Schiff Base *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine

Phenols can be protected using acid chlorides to give the corresponding esters.

Compound **2a** has little or no solubility in bench organic solvents (excluding the alcohols - sparing solubility). Acetic anhydride and **2a** in refluxing pyridine produced an oil and as crystalline product was desired it was sought to protect the hydroxyl function by the Schotten-Baumann reaction[90]. This reaction uses aqueous sodium hydroxide to remove the weakly acidic proton of a phenol to form the phenoxide ion, which in turn then reacts with the acid chloride to form the ester. Visually this reaction seemed to have worked. Starting material **2a** dissolved readily in base and the addition of benzoyl chloride produced a white solid almost instantly on shaking. An interesting feature of this reaction was that it could be monitored by cautiously smelling for the characteristic smell of any remaining benzoyl chloride. However IR spectroscopic analysis showed that the reaction had not worked as planned (Table 10, **1** – page 91).

KBr disc	2° amine ν_{max}/cm^{-1}	Amide I ν_{max}/cm^{-1}	Phenyl ν_{max}/cm^{-1}	Amide II ν_{max}/cm^{-1}
1	3295.5	1632.7	1603.8, 1579.4	1554.0
2	3296.6	1633.0	1603.8, 1579.3	1554.6

Table 10

A separate reaction of ethylenediamine and benzoyl chloride was investigated under the same conditions of the Schotten-Baumann reaction and established what had happened in the previous reaction. In fact the imine groups of **2a** had undergone hydrolysis[91] to the respective starting materials, *p*-hydroxybenzaldehyde and ethylenediamine and this is expected if one considers the chemistry of benzyl imines. The amine had then reacted with the acid chloride producing a secondary amide as a white solid – Figure 17 (aminolysis – reaction mechanism), Figure 18 (product). Its IR spectrum (Table 10, **2**) was also obtained.

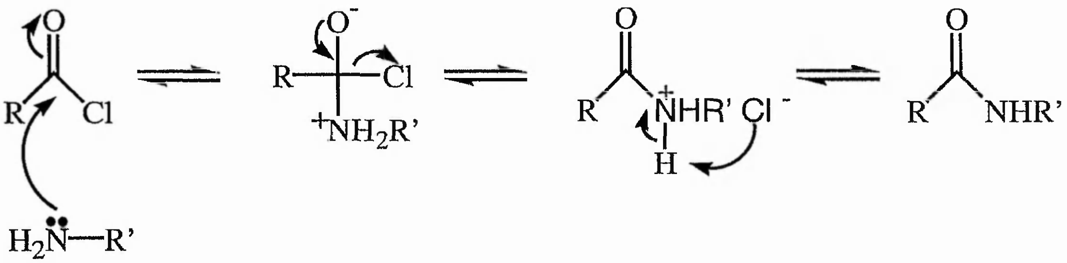


Figure 17

The fingerprint regions of both IR spectra also match and these data suggest that both products were the same, confirming that the intended protection of the phenol function had been unsuccessful. The solid state IR spectrum typical of secondary amide stretching is two bands seen in the region 3400 cm^{-1}. This was not observed, but a strong stretch at 3296 cm^{-1} was present. This may cast doubt on the proposed structure (Figure 18 – page 92) as a cyclic structure is more indicative of this data, however, the amide II stretch at 1554 cm^{-1} rules this possibility out. The secondary amide stretch may have been moved to a lower wave number by hydrogen bonding.

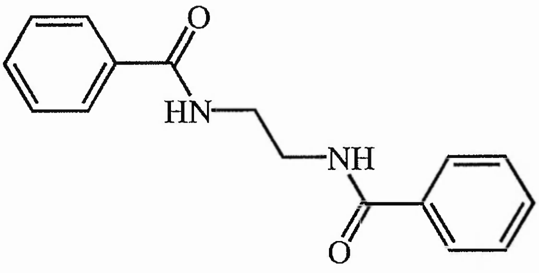


Figure 18 - *N,N′*-bis-(benzoate)-ethane-1,2-diamine

The starting material **2a** was found to have a very high solubility in DMF and by fortifying the solution with an organic base, triethylamine, the by-product hydrochloric acid could be removed allowing the reaction to proceed to completion and thus protect the hydroxyl function. The work up of this reaction proved tedious due to the need to remove the DMF. As compound **3c**, (identified from the DMF reaction) was soluble in DCM (low at circa 30 cm^3 g^{-1}) an attempt was made to carry out the reaction in DCM (experiment 2.2.5). The starting material had little or no solubility in DCM, but as a suspension with triethylamine in solution, benzoyl chloride was added whilst controlling the exothermic reaction at 15-20°C. Within ten minutes the reaction mixture went clear identifying product formation **3c** and after a short time lapse salt formation was obvious. This reaction proceeds in high yield (86%). All analytical data were in accordance with the proposed structure.

The protection of the phenol groups by groups other than benzoyl was also attempted in order to identify whether or not smaller protecting groups would favour higher yields in the future Mannich reaction. The acetylation of **2a** with acetyl chloride in DCM containing triethylamine (experiment 2.2.3) and, as mentioned earlier, with acetic anhydride in pyridine both yielded oils. This was unsatisfactory as the desired result was a crystalline, easily separable product. Chloroacetyl chloride was also tried as it would increase the molecular mass of the expected product and therefore might produce a crystalline product. However, although there was indication of product formation by *tlc* (experiment 2.2.4), production of polymeric material was evident in this reaction. This was likely to be due to the reaction of the ortho position (relative to the hydroxyl function) of *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine **2a** with the methine group of choroacetyl choride and the hydroxyl group of another molecule of *N,N′*-bis-

(4-hydroxy-benzylidene)-ethane-1,2-diamine **2a** to the carbonyl group of the same chloroacetyl chloride molecule, and so on. The chloroacetyl group was therefore also deemed unsatisfactory as a protecting group here. Of the various possibilities tried, benzoyl as the protecting group proved most useful in the isolation of a high yield crystalline compound.

3.2.3 – The reduction of the protected Schiff Base, *N,N′*-bis-(4-benzoate-benzylidene)-ethane-1,2-diamine

Billman explored many reducing reagents (sodium borohydride[92], lithium aluminium hydride[88], hydrogenation[93,94]) for the reduction of Schiff bases to their corresponding amines. One striking example of the reduction of imines is by the borane dimethylamine complex (DMAB) in glacial acetic acid[75]. Here Billman reported that the reaction was over in a matter of a few minutes and that glacial acetic acid enhanced the reactivity of the borane complex. This avoids the use of hydrogenation with a catalyst or harsh reducing agents like $LiAlH_4$. The ease of product isolation - add water and filter off the precipitate - enhances the attraction of the procedure.

The reaction was carried out on **3c** and proved to be successful as revealed by *tlc* by following Billman's method including a fifteen minute refluxing time. However, in numerous attempts at this reaction an oil was obtained and only once could this be crystallised from ethanol/water albeit in poor yield. In an attempt to obtain a crystalline product, the reducing agent pyridine borane complex[95-97], which also has enhanced reducing capabilities in glacial acetic acid, was used for the same imine reduction. This also reduced **3c** (shown by *tlc*), but by omitting the refluxing step a white crystalline compound formed on the addition of water. Repeating the reduction with DMAB and omitting the refluxing step also allowed the isolation of **4a** as a white crystalline solid. Thus it was concluded that it is detrimental to the isolation of **4a** if heat is applied. By modifying the method of Billman slightly by increasing the amount of glacial acetic acid, a visual monitoring of the reaction was made possible. The hard suspension of **3c** in glacial acetic acid that required manual breaking up eventually dissolved into solution as **4a** was formed. Experiment 2.2.6 made use of sodium hydroxide in the work-up to basify the aqueous layer to pH 14 with cooling – this is imperative in order to keep the product molecule intact and the strong base ensures any occluded acetic acid that remains (as identified by NMR in a separate reaction) in Billman's preparation is removed. Confirmation of the identity of the isolated solid **4a** is embedded in its analytical data and acylation of the benzoyl group(s) is ruled out. Firstly, it was shown by NMR that a doublet around 6.7 ppm was not present – presence of this doublet is usual for protons in the ortho position relative to a phenolic group[98] and can be seen in the spectrum of **2a**, *N,N′*-bis-(4-hydroxy-benzylidene)-ethane-1,2-diamine (experiment 2.2.1). These protons in **4a** have moved down field to 7.2 ppm. Further evidence that acyl transfer had not occurred was evident in the IR: the ester carbonyl stretch was found at 1727 cm^{-1} and there was no indication of typical amide group stretches. However, it was mentioned earlier that heating in weak acid destroyed the product and it is likely that a mixture of acylated and benzoylated product was formed[97] here producing oil. Also changes in the NMR aromatic region of the 2,2′ Ph protons from 7.8 ppm in the imine product **3c** to 7.4 ppm in the amine product **4a**; the absence of the imine proton at 8.30 ppm in **4a** along with the appearance of both a methine proton at 3.8 ppm and a broad singlet at 1.6 ppm; and the absence of the imine stretch at around 1640 cm^{-1} in the IR spectrum all suggest the proposed structure. However, the chemical combustion analysis of carbon was 0.77% lower than expected. It is not clear why the elemental analysis was outside the limits of error when the purity of the compound was reflected in its sharp melting point of 113-114°C. In addition the compound has a mass spectrum $[M+1]^+$ of 481.5 mass units and this was very convincing compared to a requirement of 480.56 mass units.

For the preparation of the Mannich base **5a** or **5b**, the need to protect the hydroxyl group of the phenol was mentioned earlier. This is critical if the Mannich reaction is intended only to proceed at the 2 and 2′ positions of α,ϖ-bis(3-oxythienyl)propane or butane. Without protecting the hydroxyl functions the ortho positions (relative to -OH) would be open to electrophilic attack by formaldehyde (Figure 19 – page 95 - shows the +M effect of *para* substituted phenol). This is undesired and protection of the group by forming an ester spreads the electronic charge of the oxygen over the carbonyl centre. The bromide imine **2b** was also produced in an effort to circumvent this problem as in this compound both the ortho positions are blocked. The reduction of **2b** using DMAB in glacial acetic acid was exothermic, but the material obtained was not the desired product and the route was therefore abandoned.

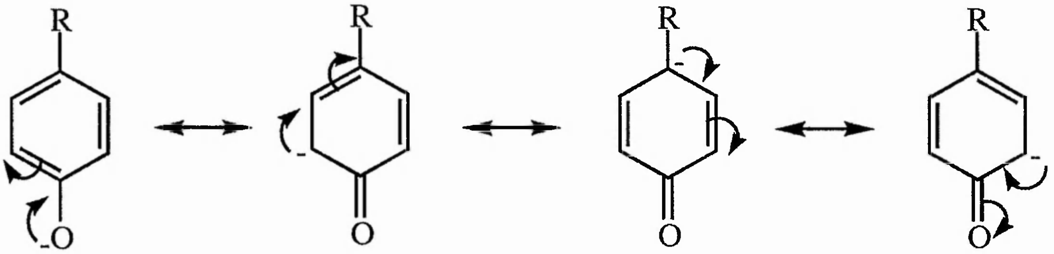


Figure 19

3.2.4 – [1+1] Thiophene-Based Macrocycles incorporating the benzoate and hydroxyl functional groups

The Mannich reaction leading to the formation of the thiophene-based macrocycle proceeds in the same way as those described in the introduction[52] (section 1.10 and 1.11). For the Mannich base, **5a**, the procedure adopted by Chaffin[51] was followed, except that ~ 150 cm^3 g^{-1} of glacial acetic acid to α,ϖ-bis(3-oxythienyl)propane was used instead of 25 cm^3 g^{-1}. It should be noted that an excess of reagents - 3 equivalents (not 2.2) of formaldehyde and 1.5 equivalents (not 1.1) - of **4a** was used. Nevertheless, the reaction appeared complete after 24 hours. At the crude stage a black oil was obtained. Much effort was spent on attempts to crystallise the oil without resorting to elaborate purification techniques. It was noted that when the crude product was dissolved in ethyl acetate, the addition of mineral acid caused an oil to drop out (under dry conditions the crude solid hydrochloride can also be obtained). Removal of the ethyl acetate and back extraction into DCM cleaned up the *tlc* of the product, leaving two spots - one on the base line. Then subjecting this oil to flash chromatography yielded 26% of a white crystalline solid, **5a**. The work up in experiment 2.2.7 was 'messy' and it was thought that steam distillation (in a further experiment) might facilitate the removal of the product from the polymeric material. Unfortunately this proved not to be the case, and purification by flash chromatography (without acidic extraction) proved to be the better method, giving a yield of 14%.

For the preparation of **5b** (experiment 2.2.8) from **4a** (1.1 equivalents), **1c** and formaldehyde (2.2 equivalents) in glacial acetic acid (100 cm^3 g^{-1} α,ϖ-bis(3-

glacial acetic acid by evaporation under reduced pressure allowed for larger quantities of Mannich base to be produced avoiding huge volumes of aqueous layer when directly basifying with sodium hydroxide. The use of saturated sodium hydrogen carbonate also avoided the emulsion problems associated with using strong base when extracting the organic material with DCM. Oil was still obtained at the crude stage, as was the case for compound **5a**. This was surprising as the reported[53] compounds prepared using the same thiophene-bridged compounds **1a** and **1b**, and *N*,*N'*-dibenzylethylenediamine (see Introduction, section 1.10) from the Mannich reaction under the same reaction conditions led to high yields of crystalline solids of 63 and 69% respectively. However, for the Mannich reaction between **1b** and *N*,*N'*-bis-(4-chloro-benzyl)-ethane-1,2-diamine, a reported yield of 36% of a crystalline solid was obtained.

In order to obtain pure product, it was necessary for the oil to be subjected to flash chromatography. A white solid precipitated from the target fractions collected. The slightly waxy solid was further cleaned up in diethyl ether, and purified by recrystallisation from acetonitrile. The yield of 34% was reasonable for cyclisation reactions, but rather low when compared to the earlier reactions using *N*,*N'*-dibenzylethylenediamine[53]. The analytical data was fully consistent with the proposed structure of **5b** and as discussed earlier for compound **4a**, the benzoyl-protecting group was still apparent in the NMR data. It was hoped that the chemical combustion analysis of **5b** would be closely matched to its theoretical value to further support the proposed structure **4a**, where the chemical combustion analysis for carbon was shown to be out by 0.77%. However, this was not the case: the hydrogen analysis was only marginally out, lower by 0.4%, but the carbon content of **5b** was lower than expected by 3%. Adding two molecules of water to the formula satisfies the carbon analysis, but leaves a 0.68% shortfall in the hydrogen content. Inclusion of acetonitrile was not supported by calculations. The compound was not significantly hygroscopic (no evidence visually), but may contain some cocrystallised water.

A small scale reaction, experiment 2.2.9 was conducted on compound **5a** to remove the benzoyl groups by hydrolysis in ethanolic solution using strongly basic conditions employing potassium hydroxide, creating **6a**. Although this compound, along with **5a**, have not been fully characterised, it is evident in the NMR spectra of crude **6a** that the protons at 8.2 ppm corresponding to the benzoyl group 2(2′)Ph′-H are absent. The crude product was not purified and shows a weak stretch in the IR spectra at 1734 cm^{-1} due to trace ester.

Although this seemed to be a viable route to the phenolic-based thiophene macrocycles, columning to obtain only very small quantities of protected Mannich base **5a** was a very lengthy procedure and the preparation of **6a** was therefore not repeated for purification and characterisation. This synthetic route was abandoned in favour of investigating routes to another suitable functional group, for linking to polymer substrates – the amino group.

3.3 – [1+1] Thiophene-Based Macrocycles containing the Acetamido Functional Group – Scheme Three (page 42)

Scheme three shows a three-step procedure to a thiophene-based macrocycle. The amide, *p*-acetamidobenzaldehyde is a commercially available product. The bisimine **7a** (experiment 2.3.1) was prepared in a similar manner to **2a** and **2b**. No NMR data was obtained, as a suitable solvent was not found. The reduction of **7a** to the amine **8a** (experiment 2.3.2) using DMAB was successful (no characteristic imine stretch in the IR spectrum), however, the insolubility of this amine in the available solvents led to it not being purified and no NMR data was collected. The Mannich reaction (experiment 2.3.3) leading to **9a**, using crude **8a** (1.1 equivalents), α,ϖ-bis(3-oxythienyl)propane **1c** and formaldehyde (2.2 equivalents) in glacial acetic acid (100 cm^3 g^{-1}) should proceed favourably between the two secondary amino groups and the 2 and 2′ positions of the thiophene-bridge respectively although it is noted[99] that amides can also undergo the Mannich reaction. After 48 hours, a crude solid (which foamed on evaporation of the organic solvent), 90% of the expected yield was isolated. This solid was difficult to purify by conventional methods and was therefore columned. A yield of 23% of **9a** was collected; another fraction containing **9a** and one other unidentified product was collected in 31% yield. The compound **9a** collected (one spot by *tlc*) was still slightly impure as could be seen by its melting point temperature range and microanalysis data. The IR and mass spectral data were in accordance with the expected functional groups and the theoretical mass. The ^{13}C NMR spectrum showed six easily identifiable sp^3

carbons in the region 24 – 69 ppm; eight sp^2 carbons were between 117 – 155 ppm and one at 169 ppm – the amide carbon. For the ^{1}H NMR all protons were identified and it appeared on close examination that both the methyl amide protons and the middle methine protons (quintet) of the thiophene bridge coincided at 2.16 ppm (integration holds). The coupling constant of the 2(2′)Ph was not found, but the protons were resonating in the region of the 5 and 5′ protons of thiophene. These data further support the proposed structure.

A *tlc* reaction - methanolic base hydrolysis of the impure **9a** - was conducted by persistent heating with an excess of sodium hydroxide (10 equivalents), then later the addition of potassium hydroxide. Although products were seen by *tlc*, starting material remained. The reaction time was also too long and completion could therefore not be guaranteed on a large scale. It is noted that base hydrolysis of acetylamides is sometimes extremely slow[90].

The attempt made to follow this reaction pathway to the *para*-acetamido thiophene-based macrocycles was conducted at the same time as attempts were being made on a chemical route to *para*-nitro thiophene-based macrocycles. The amide route was abandoned due to the better success of the nitro group pathway; this route will be discussed in section 3.4.

3.4 – [1+1] Thiophene-Based Macrocycles containing the Nitro Functional Group – Scheme Four (page 45)

3.4.1 – Schiff Bases of *p*-nitrobenzaldehyde

The preparation of the Schiff base **10a** (experiment 2.4.1), by the action of ethylenediamine (1.25 equivalents) on *p*-nitrobenzaldehyde (1 equivalent) in hot ethanol (6 cm^3 g^{-1}), similarly described by Eckstein and Lukasiewicz[72], caused solid product to precipitate from the medium. Indeed this preparation on a semi-large scale (20 to 50 g) enabled isolation of Schiff bases **10b** (experiment 2.4.2) and **10c** (experiment 2.4.3) using 1,3-diaminopropane and 1,4-diaminobutane respectively. Purification of **10a** to **10c** by digestion in hot ethanol gave their pure isolation in high yields: 89, 88 and 91% respectively. Schiff base **10d** was similarly prepared to the others using 1,5-

1,5-diaminopentane and yielded 88% (crude). NMR spectra could not be obtained for **10a** and **10b,** as a suitable solvent was not found. The increased solubility of the Schiff bases **10c** and **10d** (**10d** is soluble in hot ethanol) is marked by an increase in the aliphatic chain length and is reflected in the progressive lowering of the melting points in the series **10a**, **10b**, **10c** and **10d**: 203→200→171→114.5°C. Confidence in the isolation of these products was further supported by the disappearance of the carbonyl stretch of *p*-nitrobenzaldehyde in the IR spectrum and the appearance of the imine stretch at 1640 - 1645 cm^{-1}. Similar spectra were obtained for the compounds **2a, 2b** and **7a.** Further evidence for the isolation of **10d** is seen when comparing with the proton NMR spectrum of **10c**. Both spectra reveal the imine carbon at 158 ppm and the imine proton at 8.4 ppm. For **10d** the mass spectrum $[M+1]^+$ found is 369.3 and this is in good agreement with its theoretical mass value of 368.39.

3.4.2 – Reduction of the *N,N'*-bis-(4-nitro-benzylidene)-alkane-diamine Schiff Bases

The reductions of the four Schiff bases to their respective amines **11a**, **11b**, **11c** and **11d** (experiments 2.4.5 through to experiments 2.4.8) were conducted following Billman's[75] method as mentioned earlier (section 3.2.3). The reduction of **10a** $(O_2NArCH{=}NCH_2)_2$ is very exothermic and the compound appears to reduce much faster than **3c**, thus the additional refluxing time employed by Billman was substituted with a longer ambient reaction time. The difference in the exothermicity of the reactions must be attributed to the -M effect of the nitro group on the benzene ring. This effect will cause a significant amount of electron density on the sp^2 carbon of the imine to be pulled towards the direction of the benzene ring. The hydride ions from the borane complex then are electrostatically attracted more favourably to the imine carbon of **10a** compared to **3c**, hence the high exothermic reaction and shorter reaction time. Billman[75] described a proposed mechanism for this reaction (Figure 20 – page 100); Jones[101] postulated a similar mechanism for the reduction of carbonyls with trimethylamine borane catalysed with boron trifluoride.

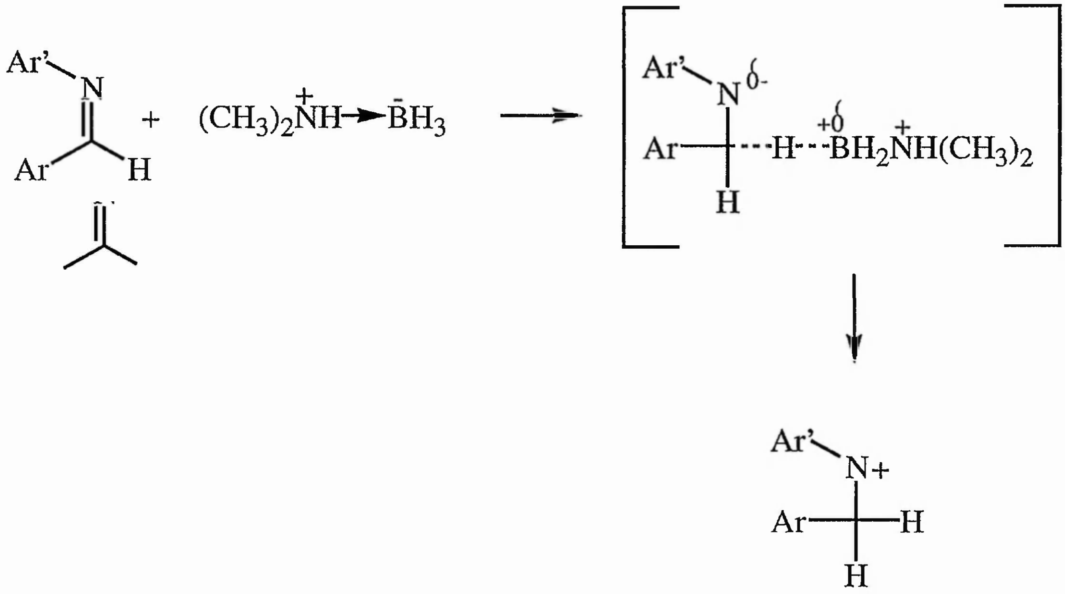
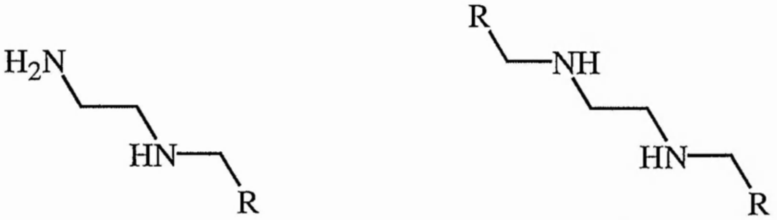


Figure 20

Repeating experiment 2.4.5 a number of times to bulk up the product under similar reaction conditions (sometimes DMAB was dissolved in glacial acetic acid and added dropwise), a solid was not always obtained at the crude stage. Production of an oil may have been due to the addition of old or diminished DMAB for the reduction. The addition of solid DMAB to the reaction mixture as opposed to dropwise addition of DMAB in glacial acetic acid helped to avoid loss of activity by decomposition of the complex in the solvent.

Eckstein and Lukasiewicz[72] also reduced the Schiff base $(O_2NArCH{=}NCH_2)_2$ to the diamine. In addition they prepared and reduced many differently substituted and disubstituted groups (fluoro, chloro, nitro, hydroxy and methoxy) of the moiety $ArCH{=}NCH_2CH_2N{=}CHAr$ in formic acid. Two products were isolated from their reaction (Figure 21 – page 101).

If absolutely dry conditions are not adhered to, and this was the case here in the reduction of **10a** in glacial acetic acid, then it is of no surprise that hydrolysis will occur to some extent, and in addition to formation of the structures A and B, full hydrolysis could also occur.



A **B**

Figure 21

Gleason[76] isolated *N*,*N'*-bis(*p*-nitro-benzyl)-1,3-diamino propane as its hydrochloride from the reduction of *N*,*N'*-bis(*p*-nitro-benzylidene)-1,3-diamino propane as a suspension in ethanol using sodium borohydride and passing HCl gas into the solution. Isolation of the dihydrochloride was also the preferred method in the current work to enable **11b**, **11c** and **11d** to be obtained from the crude stages of the DMAB reduction. The only modifications in the procedures employed were the slight variations of solvents used in the work-up of the reactions (experiments 2.4.6, 2.4.7 and 2.4.8). In the order of increasing solubility, methanol and water readily dissolve these hydrochlorides. A lower solubility was found using DCM (the NMR spectra of the hydrochlorides were all obtained in this solvent). Hence, the preferred method of preparation was that described in experiment 2.4.7 and this was applicable to the isolation of all four amine compounds. Acetone does not dissolve the hydrochlorides but helps to solubilise most impurities. This discovery helped to isolate the free amines as solids. Further purification was carried out for **11c** to characterise this product. **11d** was characterised as best as possible using the slightly crude product, as a suitable recrystallisation solvent could not be found. The yield of free amine **11b** was low owing to the use of methanol in the work-up. Methanol was initially used together with DCM as it facilitated the clean up of the hydrochloride although dissolving some of it. Peculiarly, this compound could only be crystallised by evaporation of the solvent (DCM) on a large glass surface. Water intake was visually evident by the caking of the solid and its sticky nature if the crystals of **11b** were exposed to the atmosphere for too long.

3.4.3 – [1+1] Thiophene-Based Macrocycles incorporating the nitro functional group

Initially, Mannich base **12b** was obtained from the reaction of α,ϖ-bis(3-oxythienyl)propane **1b**, *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine **11a** (1.1 equivalents), and formaldehyde (2.2 equivalents) in glacial acetic acid (100 cm^3 g^{-1}) over 24 hours using the sodium hydroxide work-up. This method was later modified for all the Mannich base reactions for the reasons described earlier (section 3.2.4). The compound **12b** was initially obtained at the crude stage from a mixture of DCM and diethyl ether. It was later found that triturating with acetonitrile aided crystal formation from the crude stage and considerably cleaned up the product from a brown colour to almost white. No further purification was necessary for this product. Cram[102] improved the isolation of 18-crown-6 by forming the complex with acetonitrile. X-ray crystallographic measurements (section 3.7) showed that no complex with acetonitrile was obtained in the current work. It is more likely that the macrocycle did not dissolve appreciably in acetonitrile but that the impurities did.

An experiment to determine optimum length of reaction time was conducted under the normal reaction conditions for the isolation of **12b** - Table 11.

Reaction time (hours)	Crude Yield (%)	Colour of pure compound	M.p (°C) of pure compound
24	93.9	Yellow	147.5-149.0
48	93.3	White	147.5-149.0
72	93.5	Light beige	147.5-149.0

Table 11

For the nitro-based Mannich bases a reaction time exceeding 24 hours is therefore not necessary, as the crude yields remain similar after this time. This will be discussed in more detail later (section 3.4.4).

The Mannich bases **12b**, **12c** and **12d** (experiments 2.4.10, 2.4.11 & 2.4.12) were all prepared under similar conditions, including their purification by precipitation from acetonitrile, but using different compounds to form the thiophene bridge. **12b** is a Mannich base comprising a 15 membered ring macrocycle with two oxygen and two nitrogen atoms; **12c** a similar 16 membered ring and **12d** a 17 membered ring containing an extra oxygen heteroatom (Figure 22).

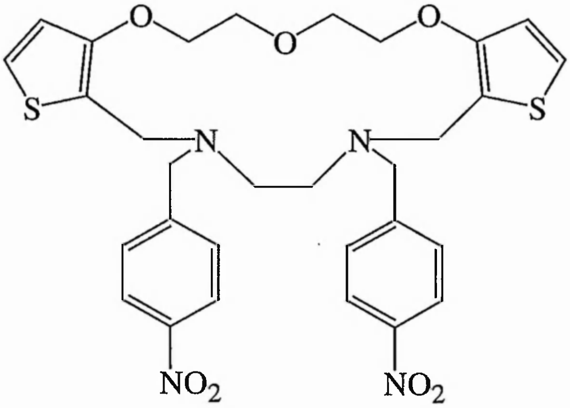


Figure 22

For the isolation of **12a,** the 14 membered ring macrocycle (experiment 2.4.9), an exhaustive reaction time of *circa* five days was allowed as α,ϖ-bis(3-oxythienyl)ethane did not dissolve[51] in glacial acetic acid to the same extent as the other thiophene-bridge compounds. A considerable darkening of the reaction mixture was noted over the reaction time. Further purification by hot digestion in acetonitrile was required.

Confidence in the structural assignment of these compounds is embedded in their analytical data. The eight signals in the region *circa* 117-154 ppm corresponding to the aromatic carbons in the ^{13}C NMR spectrum are common to and expected for all the Mannich bases; **12a** lacks one of the five aliphatic carbons that **12b, 12c** and **12d** have. In the proton NMR the two sets of doublets relate to thiophene and benzene. The coupling constant values of these doublets also support the fact that thiophene and benzene are incorporated in these compounds. Other consistencies in the proton NMR are found for all Mannich bases. The other important conclusive evidence was from the characteristic stretch around 1550 – 1552 cm^{-1} in the IR spectrum corresponding to the C=C of thiophene. This can be seen in the IR spectra of all four Mannich bases.

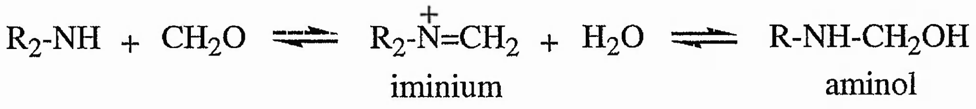
Further, unequivocal evidence of the structure was obtained for **12b** by X-ray crystallography and is discussed later (section 3.7). The moderate yields obtained for these compounds (Table 12) are disappointing compared to the high crude yields (Table 11) of **12b**.

Experiment	**Compound**	**Pure isolated Yield (%)**	**M.p (°C) of pure compound**
2.4.9	**12a**	45.7 (slightly impure)	181.0 - 183.5
2.4.10	**12b**	38.8	147.5 - 149.0
2.4.11	**12c**	32.8	140.0 – 142.0
2.4.12	**12d**	40.7	152.5 – 154.0

Table 12

These yields are also low when compared to the yields mentioned earlier in section 3.2.4 of 63% and 69% respectively when *N,N′*-dibenzylethylenediamine undergoes the Mannich reaction with α,ϖ-bis(3-oxythienyl)ethane or propane.

The reaction of formaldehyde and a secondary amine is an equilibrium reaction; both iminium and aminol are thought to exist – Figure 23.



$$R_2\text{-NH} + CH_2O \rightleftharpoons \underset{\text{iminium}}{R_2\text{-}\overset{+}{N}\text{=}CH_2} + H_2O \rightleftharpoons \underset{\text{aminol}}{R\text{-NH-}CH_2OH}$$

Figure 23

Yields from Mannich reactions involving *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine may be low in comparison as this diamine is most probably a weaker base than *N,N′*-dibenzylethylenediamine owing to the –M effect of the nitro group. A weaker base would tend to shift the equilibrium less to the right (towards the iminium ion) allowing free formaldehyde to react elsewhere.

It should be noted (Table 12) that the yield of **12d** is slightly higher but comparable to **12b** and **12c**. The increased yield of **12d** may be attributed to the internal template effect suggested by Chaffin[51] and owing to the additional heteroatom in **12d** which facilitates ring closure - Figure 24.

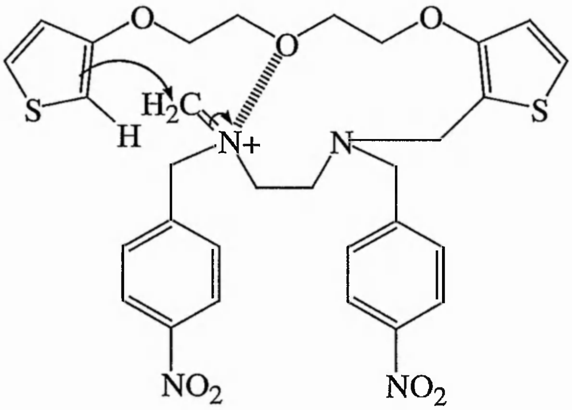


Figure 24

In the production of the macrocycles from *N,N′*-dibenzylethylenediamine[53] it was postulated that the high yields were due to the internal template effect operating via a heteroatom which is also common to the macrocycles prepared in the current work (see Figure 25).

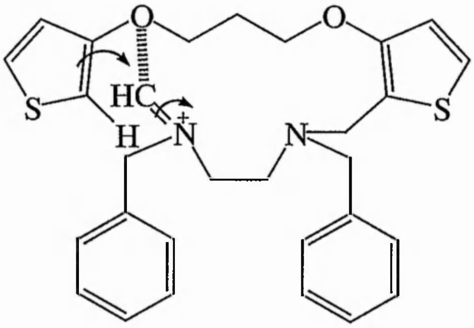


Figure 25

Alternatively, the increased yield of **12d** could be due to the reduced transannular action of the thiophene bridge caused by the additional heteroatom[103]. However, the data presented in Table 12 is not conclusive enough to suggest definitely that some special effect is operating in the preparation of **12d**.

It is also worthy of note that **12b** has a melting point temperature some 34°C lower than **12a**. The flexibility of the ring has significantly increased from **12a** to **12b** (this can be demonstrated using molecular models) and as expected - and exactly like the bisamines **11a, 11b, 11c** and **11d** - the melting temperature lowers. **12c** is more flexible still than compound **12b** and a 7°C lower melting point results. Interestingly, inclusion of the additional heteroatom in **12d** appears to increase the melting point to 5°C higher than **12b**. This coincides with the reduced transannular action which the heteroatom brings to the system[103]. Of course, these explanations are only hypothetical and variations in the true melting temperatures may instead be attributed to differences in the packing of the molecules within the crystal lattice.

The bisamines **11a** through to **11d** were prepared in order that macrocycles of varying ring sizes could be produced from the Mannich reaction with the various thiophene-bridged compounds **1a** to **1d**. Increasing the ring size is important to identify where metal to macrocycle ring dislocations occur along a series. This was mentioned in the Introduction (section 1.7).

The Mannich base, **13a** of Scheme Four is discussed in section 3.4.4

The thiophene-based macrocycles **14a** through to **14d** (experiments 2.4.14 to 2.4.17) were prepared in a similar manner to the previously mentioned macrocycles **12a** through to **12d**, except that *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (crude) was used instead of *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine. Similarly the preparations of macrocycles **15a** through to **15d** (experiments 2.4.18 to 2.4.21) used *N,N′*-bis-(4-nitro-benzyl)-pentane-1,5-diamine. It was found for the Mannich reaction of **14a-d** and **15a-d** that there was no significant darkening in the reaction medium or trace starting material after 24 hours, unlike the similar reactions to obtain **12a, 12b, 12c** or **12d**. Although some of the time the crude products were obtained as solids, it was quicker (and necessary to remove base-line (*tlc*) products) to pass the crude products through silica gel 60, followed by recrystallisation from acetonitrile. Some of the results of these preparations are presented in Table 13.

Experiment	**Compound**	**Ring Size**	**Isolated Yield**	**M.p (°C) of pure compound**
2.4.14	**14a**	16	low$^{\Upsilon}$	Crude
2.4.15	**14b**	17	51.4	140.0 – 141.5
2.4.16	**14c**	18	5.6*	125.5 –126.0
2.4.17	**14d**	19	-	-
2.4.18	**15a**	17	24.1*	112.5 – 113.5
2.4.19	**15b**	18	39.4	(note 1)
2.4.20	**15c**	19	32.8	109.0 – 110.0
2.4.21	**15d**	20	64.7$^{\#}$	oil

Table 13

$^{\Upsilon}$ recovered from column.

*True yields are not necessarily as low as indicated here. Loading to resin was done by adsorption onto silica gel 60 or uptake in DCM. Some difficulties were encountered here.

note 1: difficult to determine, owing to gas bubbles evolved on measurement.

$^{\#}$not true yield as DCM was occluded in the oil.

For the compounds **14a** through to **14d** (ring sizes of 16 to 19) the analytical data were in accordance with the proposed structures. **14a** was not purified and **14d** was isolated but not characterised. Evidence to suggest that these compounds are sensitive to light was noted from compound **14b**. If left for some time exposed to light the outer surface of the solid darkens.

Of the two compounds characterised, **14b** and **14c**, **14b** with a yield of 51% may be representative of the typical yield obtained using *N,N′*-bis-(4-nitro-benzyl)-butane-1,4-diamine (crude) under these conditions. This is considerably higher when compared to the isolated yield (39%) of **12b** which also contains the propane ether thiophene bridge, **1a**.

In the proton NMR of **14c**, where coupling of the aliphatic chains is expected, only unresolved signals appearing as broad singlets were found at the given operating temperature (22°C) of the instrument. This made *J* values difficult to assign. For **14b**, however, the ether protons were resolved, and only the NCH_2CH_2 quintet could not be fully resolved. The symmetrical compound **14b** and its increased flexibility assumed in DCM solution is probably the explanation of this broadening of the aliphatic chain proton signals at ambient temperature.

For the later series of Mannich bases **15a** to **15d** (ring sizes 17 to 20), with the exception of the OCH_2 (intended triplet) of compound **15c**, all signals in the proton NMR were resolved. None of these compounds possess the symmetry that occurs in **14b**. All analytical data suggests confirmation of the proposed structures of **15a** through to **15d**, except that the chemical combustion analysis for **15b** (experiment 2.4.19) was marginally out on the carbon and hydrogen analyses, by 0.37 and 0.42% respectively. An impurity was found in the proton NMR of this compound at 2 ppm. This could possibly be trace glacial acetic acid not fully neutralised in the work-up stage of the reaction, but it was more likely to be extraneous material as no correlating carbon signal was found for the acid. This unknown impurity has naturally affected the analysis. The melting point of this compound was also difficult to determine as gas bubbles evolved when heating near the melting point, perhaps indicating that the impurity vaporised at lower temperature than the true melting point of **15b** and then became trapped within the sample.

The brown viscous oil, **15d**, could not be crystallised. DCM was evident in the proton NMR at 5.3 ppm. Efforts to remove this occluded solvent using heat and high vacuum were not successful. The presence of DCM in the sample was likely to be why the chemical combustion analysis was lower than expected for carbon, by 1.76%. The viscosity of the oil made it difficult to obtain an IR spectrum. Nujol did not dissolve the oil.

Of the isolated crystalline compounds in Table 13, it should be noted that as the ring size increases, the melting point temperature falls.

3.4.4 - Examples of the Mannich Reaction leading to products other than the expected Thiophene-Based Macrocycles

Increasing the ring size by an additional carbon atom from 15 atoms in **12b** to 16 atoms in **13a** was sought (experiment 2.4.13). Slightly impure *N,N'*-bis-(4-nitro-benzyl)-propane-1,3-diamine was dissolved in about one third of the required amount of solvent, glacial acetic acid, and the required quantity of formaldehyde solution was added to this mixture. This was then followed by the addition of the remaining solvent and α,ϖ-bis(3-oxythienyl)propane solid. After 24 hours the crude oil was analysed by *tlc* in elutant 8:4:3 (petroleum ether b.p. 40-60°C/ethyl acetate/methanol). This revealed three major product spots at R_f values of 0.75 (α,ϖ-bis(3-oxythienyl)propane), 0.70 and 0.58. A trace product spot was also seen at R_f 0.51. Another *tlc* system (3:1 petroleum ether b.p. 40-60°C/ethyl acetate), much less polar, revealed additional faint spots. Trituration with acetonitrile did not assist precipitation of the expected macrocycle – Figure 26.

However, crystals appeared when the oil was dissolved in diethyl ether. These were allowed to slowly deposit, collected and washed with diethyl ether. No further purification was required. The pure product was eluted in the same solvent system as the crude (*tlc)* and only one spot at an R_f value of 0.59 was seen. The proton NMR data did not suggest the expected structure in Figure 26. No doublets of suitable *J* value corresponding to thiophene were shown – those indicating benzene were there.

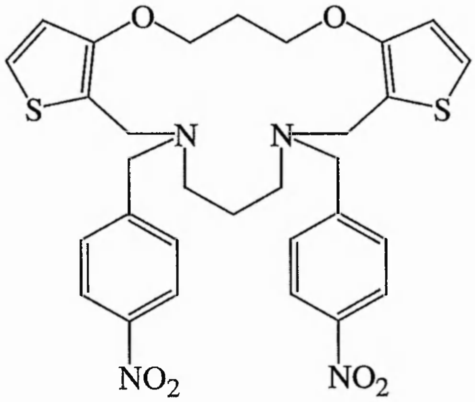


Figure 26

A singlet at 3.25 ppm and the absence of a NH broad signal in the spectrum was the only difference from the proton NMR of *N,N'*-bis-(4-nitro-benzyl)-propane-1,3-diamine **11b**. Likewise for the ^{13}C NMR a signal at 75 ppm was evident. Thus it was concluded that the following compound, 1,3-bis-(4-nitro-benzyl)-hexahydropyrimidine **13a** had been produced – Figure 27.

All other analytical data were in accordance with this structure. A yield of 45% was obtained based on *N,N'*-bis-(4-nitro-benzyl)-propane-1,3-diamine.

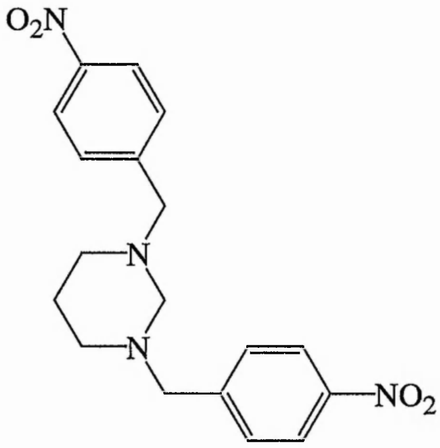


Figure 27

Reactions to form six membered rings by ring closure of a straight chain usually proceed favourably if the linear chain is not heavily substituted with bulky groups leading to steric hinderance in ring formation. Bulky groups aside, six membered rings are not significantly strained once formed. The short distance from the head to the tail of the straight chain favours cyclisation over polymerisation with the correct dilution. Conversely, five membered rings and smaller rings can be formed but are under increased strain when compared to six membered rings. The strain is greatest of all in three membered rings. Larger rings are not by comparison strained at all, yet the likely success of ring formation is low over polymerisation as the probability of head meeting tail is reduced due to the increased number of degrees of freedom.

In the reaction under consideration, *N,N'*-bis-(4-nitro-benzyl)propane and formaldehyde solution were mixed together in a low volume of solvent prior to the intended indeed biased the reaction towards formation of the hexahydropyrimidine ring, with the result that the expected product (Figure 26) could only be produced in low yield, if at all. However, even if a large volume of solvent were initially used, it might still be expected that the hexahydropyrimidine ring would form. This is because initial condensation forms an iminium ion at either nitrogen centre, hence cyclisation to the six membered ring would be highly favourable over subsequent diiminium ion reaction to the α,ϖ-bis(3-oxythienyl)propane. In light of the above discussion, the production of **13a** was favourable. It has however, not been ruled out that the macrocycle in Figure 26 was formed at low yield during the reaction. The *tlc* of the crude suggested other product formation along with the presence of starting material. Although not isolated, it is very likely that the product at an R_f of 0.70 was the desired compound illustrated in Figure 26. However, as **13a** was produced in a 45% yield, the amount of any other product would necessarily be very low. One concludes that a competitive cyclisation reaction of *N,N'*-bis-(4-nitro-benzyl)propane to form a six membered ring is more favourable over formation of a sixteen membered ring with α,ϖ-bis(3-oxythienyl)-propane-1,3-diamine.

Krässig[104] produced a five membered ring, an imidazolidine ring from formaldehyde in the following reaction – Figure 28.

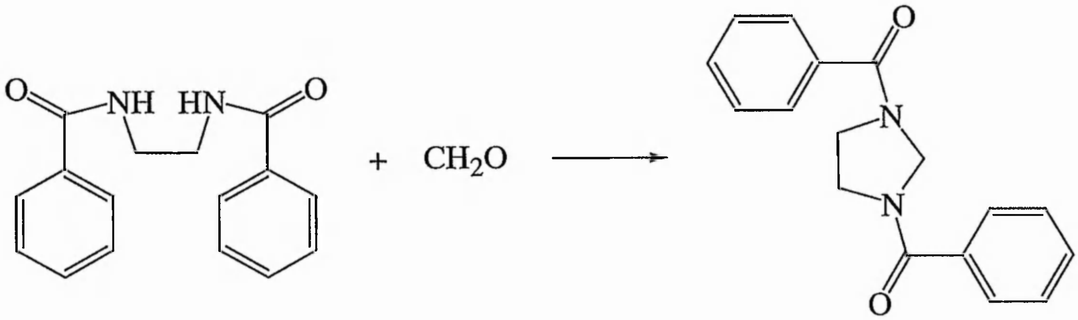


Figure 28

Both Eckstein and Lukasiewicz[72], and Billman[93,94] produced substituted imidazolidine rings from the bisamines $ArCH_2NCH_2CH_2NCH_2Ar$ and the appropriate aldehyde. It is therefore not surprising that the six membered ring **13a** was formed. Also, for the preparations **12a** through to **12d** it may be inferred that it is highly likely that some five membered imidazolidine ring would form as a by-product. Even after 24 hours, trace amounts of the starting material (thiophene-bridge compound) are seen by *tlc* amongst a host of other unidentified products as well as the intended macrocycles (observed for **12b** and **12d**).

The compound *N,N′*-bis-(4-nitro-benzyl)-ethane-1,2-diamine **11a** slowly dissolves in glacial acetic acid. Setting up the equilibrium towards the iminium ion by the addition of formaldehyde shortens the time required for **11a** to dissolve. Dissolution is much quicker if performed in a low volume of solvent, and then the solvent may be topped up to the required volume prior to the addition of a thiophene-bridge compound for the Mannich reaction. Experiments 2.4.9 and 2.4.12 to produce both **12a** and **12d** respectively were carried out in this manner. In addition, compound **12b** was produced by this procedure as well as by the method recorded in the Experimental section – experiment 2.4.10 where formaldehyde solution was added to the reaction medium at high volume. No significant gain in yield was noted in either method.

Other experimental evidence highlights a pattern of ring closure of the nitrogen-containing moiety in the Mannich reactions employed in this study. For example:

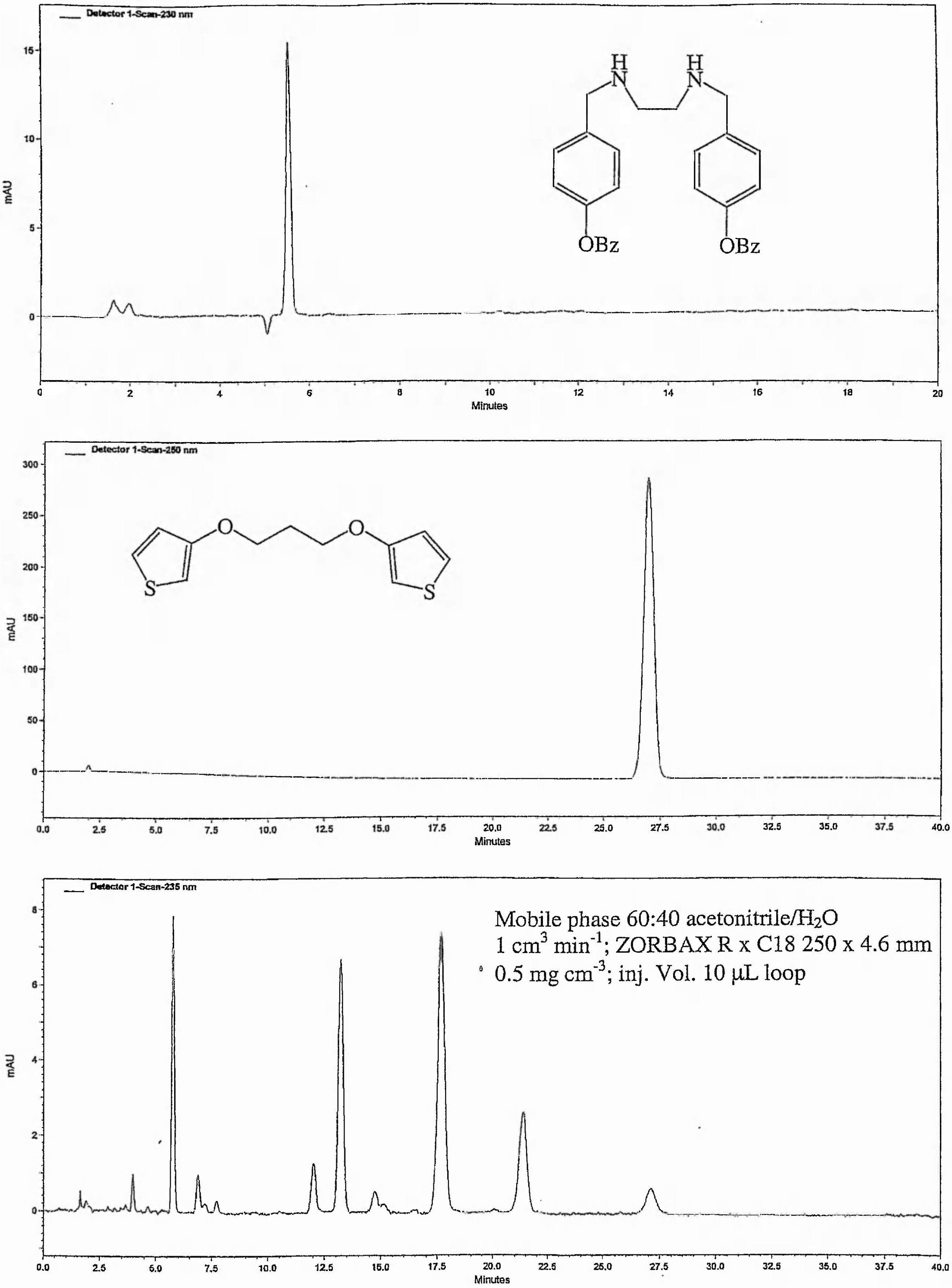
In a separate reaction, α,ϖ-bis(3-oxythienyl)propane **1b** (1.0 equivalents) and formaldehyde (2.2 equivalents) in glacial acetic acid (150 cm^3 g^{-1}) were stirred for *circa* three days. A dark brown solution with some black solid was obtained. A *tlc* revealed a few trace and base line products. No starting material was apparent. In another identical experiment, protected amine, *N,N′*-bis-(4-benzoate-benzyl)-ethane-1,2-diamine **4a** (1.1 equivalents) of Scheme Two was substituted for the α,ϖ-bis(3-oxythienyl)propane. After *circa* three days the remaining colourless solution revealed (*tlc*) only base-line spots, correlating to either products or starting material. The results of these two reactions will become more revealing as the discussion proceeds.

The earlier discussion of experiment 2.2.7 to produce Mannich base **5a** highlighted the fact that it was obtained as a black oil at the crude stage after a reaction time of 24 hours (it should be mentioned that in the preparation of crude **5b**, where the equivalents of reagents were added in the suggested ratios[51], an oil was obtained). This crude oil **5a** was subjected[105] to separation by HPLC. Even though the equivalents of reactants are in excess, α,ϖ-bis(3-oxythienyl)propane was still evident in the crude product - see Figure 29 (page 114) . Three other main constituents were eluted at retention times of 13.25, 17.75 and 21.5 minutes. They were not identified by any other means of instrumentation except UV spectroscopy. One of these compounds was the Mannich base **5a**; the other two were not identified. It is possible that the five membered ring, the imidazolidine may prove to be one of the two unknown constituents.

This could be further investigated by LC-MS or the product mixture could be separated by chromatography and its contents determined by NMR spectroscopy.

In the production of **9a** (experiment 2.3.3) - Scheme Three, two fractions were collected, one containing **9a** and the other both **9a** and an unidentified product. This was discussed earlier (see section 3.3). The unknown product and **9a** were subjected to gas chromatography[106] in the hope of supporting the argument that an imidazolidine ring formation was competing in the reaction. The unknown product, however, could not be identified by this technique.

For the preparation of compounds **14a** through to **15d**, as previously mentioned, no significant darkening of the reaction medium was noted after 24 hours. In fact a 24-hour reaction time was only employed here so that comparisons could be made with other Mannich bases. For the reaction to produce **15c** it was noted by *tlc* that after about 20 hours, no starting material was present. It was not noted at what time during the reaction all the α,ϖ-bis(3-oxythienyl)butane was used up. It was then observed in the production of compound **15d** via the Mannich reaction that no starting material was seen by *tlc* after about 4 hours. It was concluded from this that a reaction time of the order 4 hours or less was the requirement for those Mannich reactions leading to macrocycles. This was interesting, as probably the reaction medium could be increased to about five or six times the dilution (by syringe pump or otherwise) to obtain, theorectically, far greater yields, avoiding oligomers (chained or cyclic) or polymers over the 24-hour period.



Mobile phase 60:40 acetonitrile/H_2O
1 cm^3 min^{-1}; ZORBAX R x C18 250 x 4.6 mm
0.5 mg cm^{-3}; inj. Vol. 10 μL loop

Figure 29

The observations above indirectly confirm that in using *N,N′*-bis-(4-substituted-benzyl)-ethane-1,2-diamine units in the Mannich reaction a smaller ring or other product(s) are being formed. If the five membered ring is formed another equilibrium (Figure 30) in addition to the one for production of the macrocycle is set up and this will eventually consume the secondary amine starting material and one mole of formaldehyde, hence the α,ϖ-bis(3-oxythienyl)alkane bridge will not all be used up. The excess formaldehyde, after both the imidazolidine (minor product) (or another compound) and macrocycle (major product) had been produced, would eventually condense and thus polymerise the excess α,ϖ-bis(3-oxythienyl)alkane, hence the disappearance (*tlc*) of α,ϖ-bis(3-oxythienyl)alkane and the progressive darkening of the solution after 24 hours. The evidence described above indicates this is a likely explanation for both the formation of by-products and the progressive darkening of some reaction mixtures.

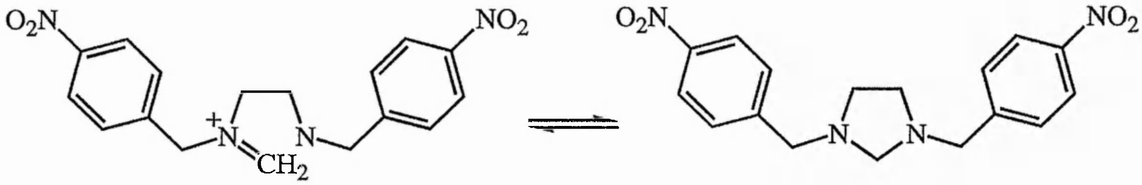


Figure 30

3.4.5 – Reduction of the Nitro Functional Group(s)

Examples of reductions of arene nitro groups to amino groups in the literature are plentiful[107]. Notably, the use of metals such as Zn, Sn or Fe to reduce the nitro group in strong acid is common. Transformation from the nitro group to the amino group is not a single mechanistic step, but proceeds through several intermediate stages such as hydroxylamine and others. Some reducing agents enable these intermediates to be isolated, however, due to their high reductive potential, the use of metals in mineral acids always pushes the reaction to completion. The mechanism is as follows[100] (Figure 31 – page 116):

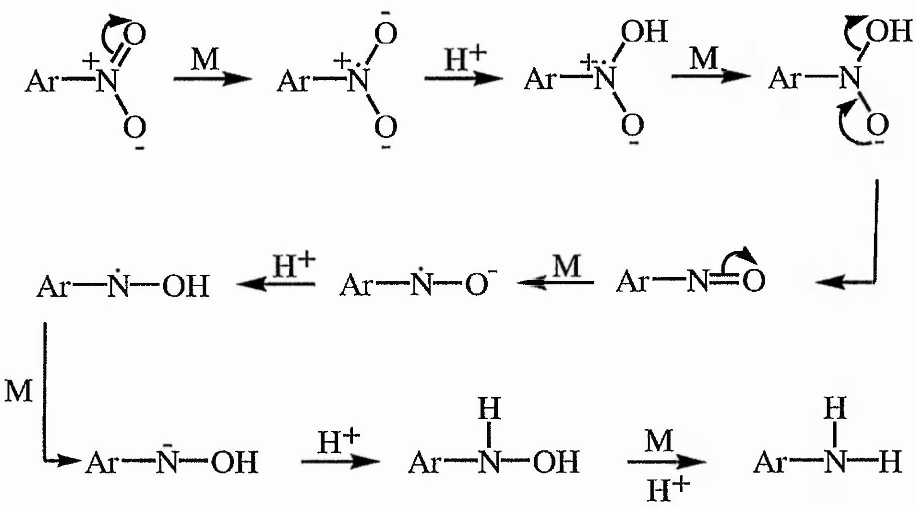


Figure 31

However, the use of metals in mineral acid was not an option in this present work. The use of hot mineral acid would be very likely to cleave the thiophene ether linkage of the thiophene-based macrocycles[91]. This was not desired. An alternative reaction using sulphides (or poly sulphides)[100] is known as the *Zinin Reduction*[77]. This involves the use of sodium hydrosulphide (NaHS) which can be generated by the action of sodium sulphide nonahydrate and sodium bicarbonate in water (following equation).

$$Na_2S + NaHCO_3 \rightleftharpoons Na_2CO_3 + NaHS$$

The stoichiometry of the Zinin reduction of arene nitro compounds follows the equation:

$$4\ RC_6H_4NO_2 + 6\ S^{2-} + 7\ H_2O \rightleftharpoons 4\ RC_6H_4NH_2 + 3\ S_2O_3^{2-} + 6\ OH^-$$

Ensuring an excess of water and alkali are present should maximise the chances of the reduction towards the amino group. Although the review[77] by Porter reports the possibility that the disulphide ion is responsible for the reduction, the actual mechanism is unclear, although it is known that intermediates are formed during the reaction.

Hodgson[108] suggests a mechanism of alkaline sulphide reduction, explaining that it is the oxidation of the sulphur atom by the nitro group rather than the reduction of the nitro group by the sulphide ion.

For the reduction of macrocycle **12b** (Figure 32) it was found that pyridine as solvent gave the best results.

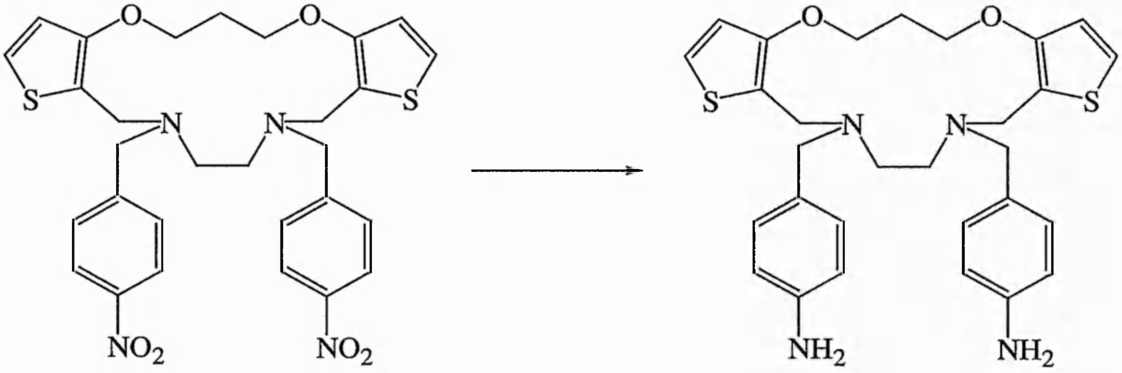


Figure 32

The experiments 2.4.22 (i) through to (x) identified the success of pyridine as solvent over other possibilities:

(i) Alcohol is the common solvent for reductions of this type. However, **12b** does not dissolve appreciably in alcohols.

(ii) The use of DCM to help dissolve **12b** with IPA did not facilitate reaction.

(iii) DMF was an unsuitable solvent. A possible side reaction was suggested[109] and this was found to have occurred. The inorganic material isolated from a control experiment *i.e.* containing no **12b** could have been $Na_2S_2O_3$. It was ruled out that it was sodium carbonate as no signal was present in the ^{13}C NMR. If the inorganic solid could be proved to be $Na_2S_2O_3$ then DMF may have been reduced in the reaction, however this was not investigated further.

(iv) Pyridine readily dissolves **12b**. It was noted from this experiment that heat, as a driving force was necessary. The colour change of the solution from brown to dark green was apparent at high temperature and the reduction of the nitro group resulted in ten minutes or less. The major products (two spots seen by *tlc*) were (as revealed by IR spectroscopy) a mixture of both the mononitro-mono amino compound **16a** and the diamino compound **16c** (Scheme Four).

(v) Lutidine as solvent was inferior to pyridine.

Idoux[110] had found for the reduction of dinitrobiphenyls that methanol alone only partially solubilised these compounds. Methanol/acetone was better; methanol/toluene was superior in solubilising and thus increasing the yield of the products. Further experiments using these solvents were carried out:

(vi) & (vii) Both methanol/acetone and methanol/toluene appeared of practical use, yet the reaction time was too long compared with that time required when using pyridine.

(viii) DMSO as solvent was not found to give better results than pyridine.

(ix) & (x) NaHS in pyridine under anhydrous conditions and NaHS in water added to pyridine were not as successful as using NaHS generated from sodium hydrosulphide and sodium bicarbonate in water. This was likely to be because no added/generated alkali was present. Hojo *et al* investigated the 'kinetics of the reduction of nitrobenzenes by sodium disulphide'[111]. These authors showed that the rate constant in 40% methanol was 2.41 times faster in the presence of 0.5 M sodium hydroxide than in 0.1 M added sodium hydroxide.

(xi) Using formic acid for *insitu* hydrogenation with 5% Pd-C appeared not to be as successful as the Zinin reduction (iv).

(xii) Phenylhydrazine in pyridine did not appear successful in the reduction of the nitro groups to the amino groups in the time allocated.

(xiii) Hydrazine hydrate and graphite[112] was successful in the reduction of the nitro groups to the amino groups. The reduction was a lot slower than the Zinin reduction (iv) as it took about 3.5 hours for the starting material **12b** to be consumed. On separation of the two main products, the higher eluting compound (*tlc*) had a similar wide melting temperature range to the mono-nitro/mono-amino compound **16a**: this proved that the solid compound isolated from experiment 2.4.23 did not have occluded sulphur in it affecting the melting point; the lower eluting compound (*tlc*) of melting temperature ~197-203°C might have been **16c**, but conflict between the two melting temperatures was noted. This experiment was not pursued further due to the success of (iv).

Pyridine has been used previously as solvent for the reduction of nitro arenes using the Zinin reduction method[113] or using hydrogen sulphide[114]. As the reduction in pyridine using aqueous NaHS seemed to be successful, this method was used to isolate the compound **16a**, in which only one nitro group has been reduced. Firstly, **16a** was prepared so that there would only be one reactive site on the molecule for attachment to a suitably functionalised resin. Secondly, the full reduction of **12b** under the conditions employed took up to 8 hours. It was not clear why initial reduction to the mononitro-monoamino compound **16a** was fast (10 minutes or less), yet its full conversion was very time consuming. Some diamino compound (as seen from *tlc* and experiment 2.4.25) was also present after 10 minutes. Whether the excess amount of generated NaHS (~10 equivalents) in the equilibrium had been reduced significantly by air oxidation or the solubility of **16a** was affected in the changing medium is not known.

Experiments 2.4.23 and 2.4.24 were used to isolate **16a** and **16b** respectively. The differences in the work-up procedures mentioned in the experimental section were tried in efforts to identify better/quicker conditions of isolation. These compounds were slightly impure: melting point temperatures were not recorded as the solids oiled out over a large temperature range; their chemical combustion analysis were marginally incorrect compared with the expected values for the pure compounds. IR spectroscopy revealed that both the nitro and amino groups were present. Additional data was in accordance with the proposed structures. Furthermore, for compound **16a,** in the proton NMR spectrum, one can see additional signals in the aromatic region when compared to the dinitro compound **12b**. These are the two sets of doublets at 6.58 and 7.07 ppm corresponding to the ortho and meta protons relative to the amino group. Interestingly the 4-positon proton of thiophene at 6.88 ppm gave three signals, instead of the expected doublet. Two coupling constants *J,* both 5.28 ppm were noted. This proton position may be split owing to an imbalance in the electron density of the molecule. Turning attention to the ^{13}C spectra it can be seen that there are two closely grouped signals at 67.9 and 68.2 ppm due to the OCH_2 carbons. Also it can be seen that the methine groups bridging the thiophene bridge and the dibenzylethylenediamine moiety are in slightly different electronic environments; the other two sets of carbon atoms flanking the tertiary amines are significantly split at 49.1 and 49.7 ppm, and 47.1 and 47.5 ppm. It is concluded from this data that the two groups, the nitro group (-M effect) and the amino group (+M effect) are having a profound effect on the remaining atoms in the molecule, either increasing or reducing the electron density. This is seen on the opposite side of the molecule *i.e.* the OCH_2 signals are affected. It should not however be ruled out that the molecule may exist in an asymmetrical molecular conformation.

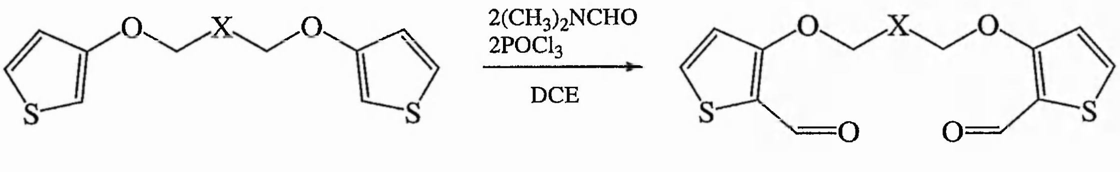
A similar argument to the above can be made for **16b**.

Efforts to produce the diamino compounds **16c** and **16d** were not completely successful. However, experiments 2.4.25 and 2.4.26 did succeed in isolating the diamino compounds. The solids obtained, in particular **16c,** were good finely divided crystalline solids, unlike compounds **16a** and **16b** (the half reduced compounds), which had flaky plate-like crystals.

In experiment 2.4.25 to obtain **16c**, four equivalents of methanolic NaHS were used and 21% of product was isolated within ten minutes of the reaction starting. **16c** and **16d** were not purified, as no suitable solvent could be found. Similar problems attended the NMR analysis. The chemical combustion analysis for **16c** did not support the molecular formula however the IR data and the mass spectrum were in accordance with the proposed structure. Further work, for example X-ray crystallography is necessary here to fully characterise these compounds. If the compounds were found to have the expected structures, they would make suitable candidates for studying attachment to resins. This is because they are easily isolated and scale-up of the quantities should not present too many problems.

3.5- [1+1] Schiff base condensations – Scheme Five (page 69)

Schiff base reactions leading to macrocycles have been reported in the literature and in many cases confer ease of formation. For macrocycles containing thiophene, some Schiff base reactions have been carried out using 2,5-diformylthiophene and a range of diamino compounds[45-48]. The Vilsmeier-Haack formylation method of the thiophene bridge, α,ϖ-bis(3-oxythienyl)alkane has been described[51] - Figure 33 – page 121.

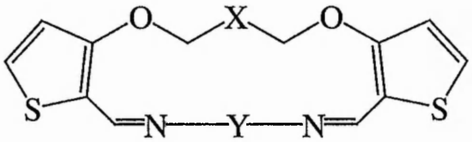


X = CH_2
X = CH_2OCH_2

Figure 33

Attempts have been made to produce macrocycles from α,ϖ-bis(2-formyl-3-oxythienyl)alkane and a diaminoalkane. Chaffin[51] reported some success reacting formylated thiophene bridge compounds containing additional heteroatoms with ethylenediamine, 1,6-diaminohexane or 2,2′-oxybis(ethylamine) (Figure 34) to produce macrocycles. Solubility and purification problems were however encountered and this work appeared to cease.

Sloman[115] further investigated both formylated thiophene bridge compounds of Figure 33 to attempt the formation of Schiff base macrocycles by reaction with ethylenediamine *insitu* using metal ion templates. Some success was achieved in adding a metal salt to both the aldehyde and diaminoalkane (in a 2:1 ratio) after pre-heating. A mixture of Schiff-base complex [1+1] macrocycle and an open chain [2+2] complex (from incomplete reaction) was suggested to have formed. It was also reported in this work that macrocyclic diimines could not be isolated without hydrolysis occurring if a template was not employed.



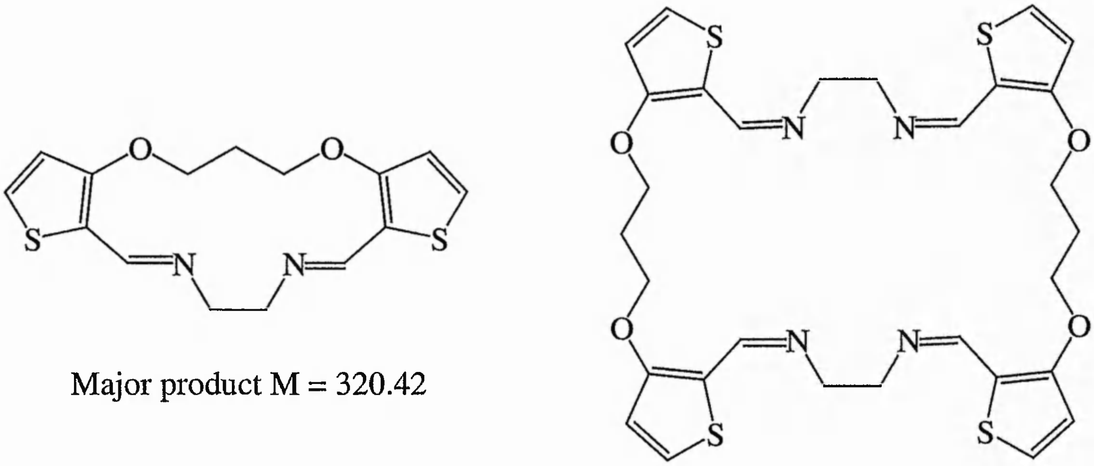
X = CH_2OCH_2
X = $CH_2O(CH_2)_2OCH_2$
X = CH_2SCH_2

Figure 34

Experiment 2.5.1 to produce **17a** (Scheme Five of experimental section 2.5) gave a beige coloured crystalline solid which appeared to be very stable when exposed to the atmosphere. The reaction was completed in 52.5 hours or less at ambient temperature.

The starting material partially dissolved in ethanol and had good solubility in DCM. Hence, product isolation was confirmed before analysis, as the product solid did not dissolve in DCM. No suitable solvent was found for purification or for NMR analysis. In the IR spectrum, the appearance of imine stretch at 1618 cm^{-1} and the fact that there was no carbonyl stretch further proved the proposed structure. The C=C of thiophene was found at 1542 cm^{-1}. The mass spectrum showed the parent ion $[M+1]^+$ at 321.3 mass units (100%) and some [2+2] dimer was also evident at 641.2 mass units (25%) - Figure 35.

The product (not further purified) was only slightly impure as could be seen by the chemical combustion analysis: C content was incorrect by 0.76% and the nitrogen by 0.43%. The conclusive evidence suggests strongly that macrocycles of this sort can be readily produced without employing metal templates using the method shown in Scheme Five. An attempt made at reduction of this compound in dry boiling ethanol with sodium borohydride was unsuccessful due to solubility problems.



Major product M = 320.42

Minor product M = 640.85

Figure 35

Experiment 2.5.2 to produce **17b** (Scheme Five) also appeared to have been successful. Increasing the aliphatic chain length between the two nitrogen groups by using 1,5-diaminopentane (cadaverine) was intended to increase the solubility of the Schiff base. The IR spectrum was in line with the proposed structure – imine stretch at 1625 cm^{-1}

and no carbonyl stretch. The product **17b** isolated as a brown liquid, but the NMR spectrum suggested some cadaverine was still present. In the proton NMR, signals corresponding to the imine (8.4 ppm), thiophene and aliphatic hydrocarbons appear to be present. The mass spectrum shows two main peaks corresponding to $[M+1]^+$ at 363.5 mass units (~17%) and $[2M+1]^+$ at 726.2 mass units (100%). Either the adduct was formed in the ion trap of the instrument or, more likely, the dimer was produced under these reaction conditions. This could be overcome by increasing the dilution of the reaction medium. No further work was carried out to rid this compound of the excess cadaverine (b.p. 178-180°C) or fully purify it owing to time constraints.

It has been shown above that Schiff base macrocycles containing thiophene can be prepared and are not susceptible to hydrolysis in their preparation. Varying the aliphatic chain lengths between the two oxygens and the two nitrogens should overcome solubility problems for their reduction. If difficulties continue to arise, their reduction to the corresponding diamino products may be possible by partial suspension in a suitable solvent for hydrogenation over a catalyst.

The diamino thiophene based macrocycles were desired as products, as it has been reported in the literature[24] that an array of metal complexes of similar macrocycles containing benzene have been readily produced. The benzene-based macrocyclic metal complexes were subjected to potentiometric analysis[29] and it was possible to identify easily where dislocations along the series of macrocycles occurred.

3.6 - Thiophene-Based Macrocycles Attached to a Polymeric Support – Scheme Six (page 73)

The appendage of the mononitro-monoamino macrocycles **16a** and **16b** to a polymeric resin, a 2 % cross-linked chlororinated divinylbenzene (1.0 – 1.5 mmol Cl per gram of resin) (Merrifield resin) is detailed in experiments 2.6.2 and 2.6.3 respectively (Scheme Six). (Merrifield resins were mentioned earlier in the Introduction section 1.12). The experimental procedures were similar to those employed by Lindoy[70] *et al* except that the base used was a non-nucleophilic base, *N*-ethyldiisoproplyamine (Hünig's base) instead of triethylamine.

Initially it was sought to identify whether attachment to the resin was possible (experiment 2.6.5). Assuming minimum chlorides per gram resin (1.0 mmol Cl per gram of resin), four times as much resin (1.4 g) to macrocycle was used in order to be able to follow reaction by *tlc*. Indeed, having swelled the resin in DMF with added Hünig's base and reacted it with the macrocycle (0.35 mmol) at 100°C, the eluting starting material spot (*tlc*) started to diminish with the emergence of a lower eluting spot (thought to be the salt). After continuous re-heating over a further four days and no apparent change in *tlc* the resin was cleaned up by washing with DMF, DMF-MeOH (concentration gradient) and MeOH, and was dried under reduced pressure to yield a brown coloured resin, compared with the initial white/cream colour of the Merrifield resin.

To determine whether or not the macrocycle had reacted onto the polymer a differential[116] scanning solid state IR spectrum was run; comparison of the blank Merrifield resin with the reacted resin showed a reduction in the H-C-Cl bending vibration at 1266.7 and 1267.0 cm^{-1} respectively when compared to other unaltered peaks in each spectrum. It was expected that some free chloro groups would still be present on the macrocycle appended resin as this was in large excess in the reaction. To further prove macrocyclic attachment, chemical analysis was obtained on the resin. Nitrogen content of 1.12% and 0.78% in two analyses correspond to between 0.15 - 0.20 mmol macrocycle per gram of resin. Bearing in mind a ratio of a quarter of macrocycle to polymer Cl groups was used in the first instance, it would be expected that a higher content of macrocycle to resin could be achieved. Thus the experiments 2.6.2 through to 2.6.4 were carried out.

For the experiments 2.6.2, 2.6.3 and 2.6.4 (experiment 2.6.4 was a blank run *i.e.* no macrocycle and was a parallel reaction of 2.6.2) the chemical combustion analysis was obtained (Table 14 – page 125):

Element	**Experiment (compound)**		
	2.5.2 (17b)	**2.5.3 (17c)**	**2.5.4 (blank)**
C	82.30	82.51	87.87
H	6.89	6.95	7.33
N	2.57	2.80	0.00

Table 14

Although it has been suggested that nitrogen analysis of this type on polymeric supports is subject to uncertainty[64], the nitrogen content on the blank polymer was zero (Table 14), yet the others are 2.57 and 2.80% for **18b** and **18c** respectively. It was necessary to prove that no nitrogen content was present in the blank run polymer because of the conditions employed. Both DMF and Hünig's base could have been the source of nitrogen if they had not been fully removed in the preparation. The analysis gives confidence that the nitrogen content for products **18b** and **18c** must have come from the macrocycle, hence confirmation that attachment to the resin was achieved. Based on these results, the nitrogen percentage indicates 0.46 and 0.50 mmol of macrocycle per gram of resin for **18b** and **18c** respectively. These are moderately high results when compared to Lindoy *et al* [70] who recorded values of between 0.21 and 0.66 mmol of macrocycle per gram of resin for various appended macrocycles using the same polymeric support under almost identical conditions.

Further evidence to support attachment of the macrocycles to the resin comes from the brown colour of the resin after reaction. The polymer beads after the blank reaction carried out with no macrocycle present remained almost white, although slightly darker than the commercially available resin of a white/cream colour.

A differential scanning solid state IR spectrum was obtained from all three polymers. Compared with a similar spectrum of unreacted Merrifield resin no significant change was seen in the polymer produced from the blank reaction. For both **18b** and **18c**, the stretches below 1500 cm^{-1} tended to broaden out, while this region for both the unreacted Merrifield resin and the resin from the blank reaction were sharper and better defined. The broadening cannot easily be explained, but inference from this data suggests there has been a change in the structure of the Merrifield resins reacted with macrocycle.

Merrifield resin was used as an example system to identify whether the macrocycles obtained in this work could be attached to polymeric supports. This clearly appears to be the case. The reason for these experiments was to investigate if metal uptake would be achievable by macrocycles of this type on polymeric supports (see later, section 3.8). Before reaction can take place, a divinylbenzene resin (DVB), like Merrifield resin needs to be considerably swelled in an appropriate aprotic solvent. This would be necessary if the attached thiophene-based macrocycles were to be reached by a surrounding solution and ultimately utilised as extracting agents. However, if a practical application of these macrocycles were required – such as the extraction of toxic metals from effluent – then the use of other more hydrophilic resins as supports would have to be investigated. Lindoy *et al*[117] have used macrocycles attached to silica gel for metal binding studies. However, linkages to silica gel are susceptible to hydrolytic cleavage as the Si-O-C bond is highly polarised[118]. Inorganic polymer supports with appended organic molecules overcome this problem as they contain Si-O-Si-C bonds that are more stable to electrophiles and nucleophilic reagents[118] - Figure 36.

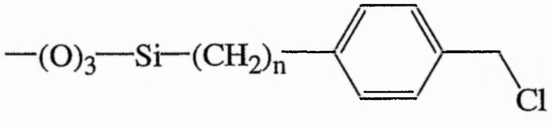


Figure 36

Resins of this type would serve to attach the macrocycles synthesied in this work, as they are Merrifield-type silanised glass supports. The organic part (Figure 36) is identical to the DVB resin used in this study, but the hydrophilic nature of the inorganic polymer overcomes the difficulty of using DVB resins for metal-ion binding studies in aqueous media.

3.7 - X-ray Crystallography data

Crystal Structure of **12b**

The crystal structure of **12b** was solved by the technique of X-ray crystallography. The structure is of triclinic geometry and two molecules exist in the unit cell. The fractional atomic coordinates and the anisotropic displacement parameters are presented in Tables 4 and 5 respectively of the experimental section. Additional tables of selected parameters are given in the experimental section 2.8 in order to aid discussion of the nature of the crystal structure. The structural geometry of **12b** (Figure 37 – see page 128) confirms the evidence of the other analytical methods reported previously. The X-ray analysis of **12b** in turn supports the proposed structures of all the macrocycles synthesised in the present work.

Tables 6a through to 6d of bond lengths, split the molecule into two halves (L.H.S and R.H.S) and four sections. Of the four sections, the bond lengths of the ring cavity are presented in Table 6a. The other three sections are the comparison (bond lengths) of the thiophene rings (Table 6b), the benzene rings (Table 6c) and the bridging atoms between the ring cavity and benzene rings, and the nitro groups (Table 6d). Table 7 presents the bond angles in the macrocyclic ring cavity.

The ring cavity circumference is about 21.70 Å. There are subtle differences in the bond lengths when comparing each half of the cavity. The largest differences of 0.013 Å are for C26-C23, C23-C24 and N9-C13, C15-N10. The smaller differences of 0.002 Å are for O3-C26, C24-O5. Steric strain is likely to be the major cause of these differences owing to the unsymmetrical geometry the molecule adopts.

Thiophene rings

The two substituted thiophene rings are seen not to be planar with respect to the macrocycle ring cavity, but are both tilted to the same side away from the plane of the N and O atoms (Figure 40 – page 137). Below is a schematic view of the substituted thiophene rings in **12b** (Structure 1) and comparisons of these bond lengths are made

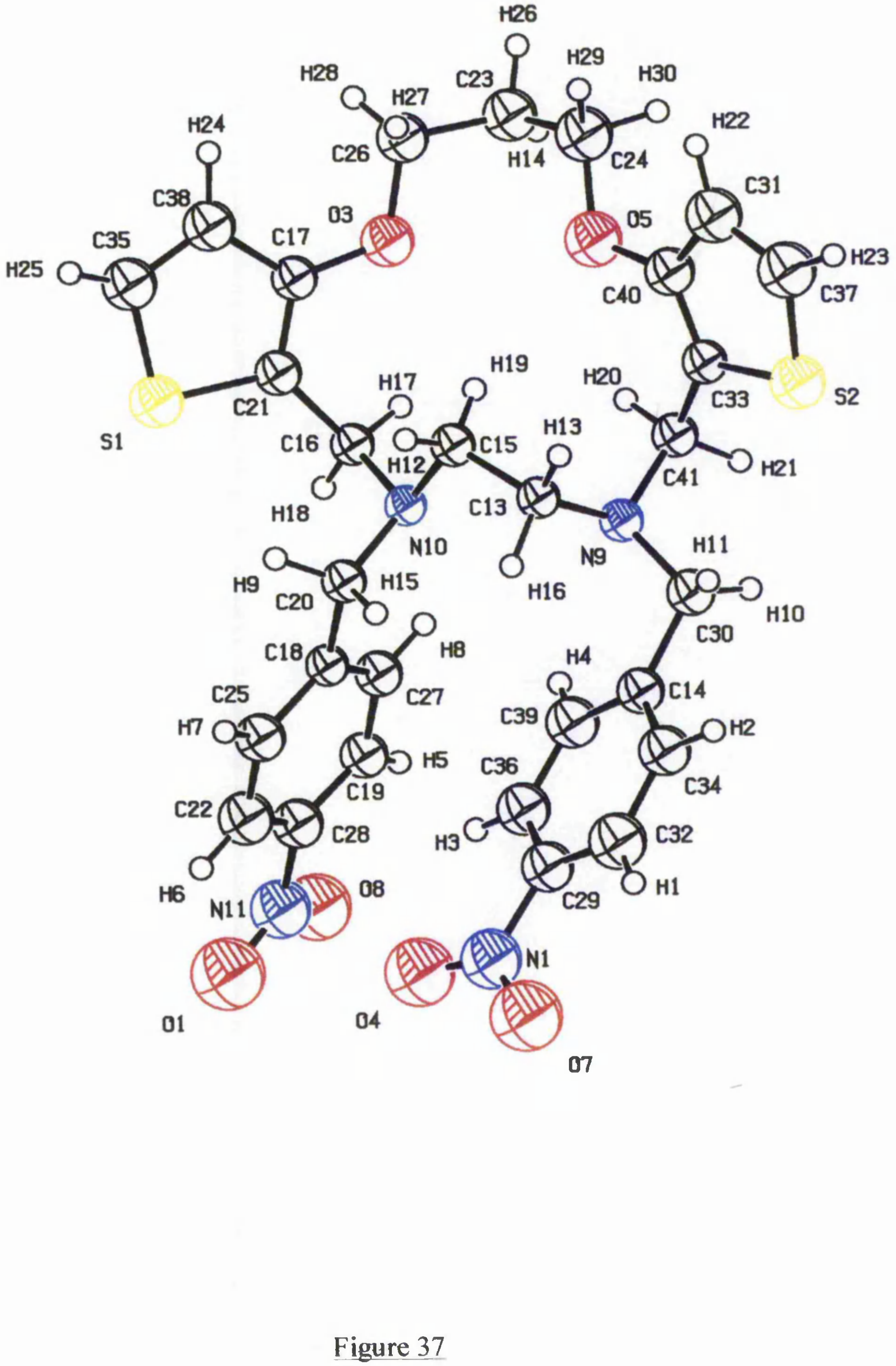
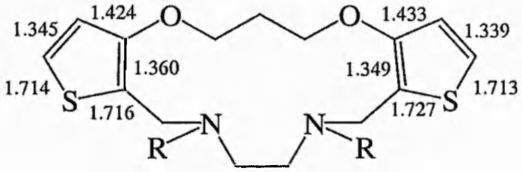
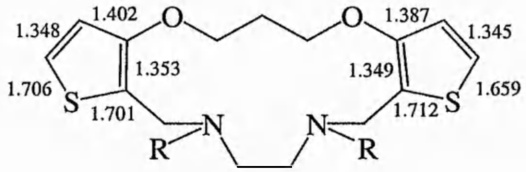

H26
H28
H27
C23
H29
H30
H22
H24
C26
H14
C24
C31
C38
O3
O5
C35
C17
H23
H25
C40
C37
H19
H17
H20
C21
C33
S2
S1
C16
H12
C15
H13
C41
H21
C13
H18
N10
N9
H11
H9
H15
H16
H10
C20
C30
C18
H8
H4
C25
C27
C14
H7
C39
H2
H5
C36
C34
C19
C22
C28
C32
H3
H1
C29
O8
H6
N11
N1
O1
O4
O7

Figure 37

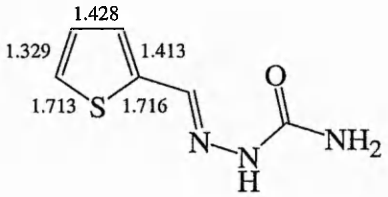
with a similar thiophene-based macrocycle[53] (Structure 2), a 2-substituted thiophene[119] (Structure 3) and the experimental results for thiophene[120].



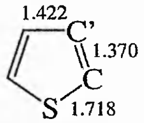
Structure 1 R = p-$O_2NC_6H_4$



Structure 2 (R = C_6H_5)



Structure 3



Thiophene

Considerations of steric hinderance constraints of the substituents connected to the macrocycle rings should not be disregarded when simplifing the argument of bond length being directly related to electronic effects in the thiophene ring.

Good agreement of the crystal structure **12b** (Structure 1) is made with Structure 2 for the thiophene C=C bond lengths. All other bond lengths are considerably longer than Structure 2. This is rather surprising as both direct 2,2′ substituents are the same. These differences will be discussed later. The two thiophene S-C and C-C bond lengths of **12b** (Structure 1) are more closely matched to those in the mono substituted thiophene (Structure 3) and thiophene itself than to those in Structure 2.

For both the structures 2 and 3 a short S···N contact has been observed. The S···N (where both atoms are sp^2 hybridised) distance of 3.037(6) Å reported by Koziol, Palenik and Palenik[119] for structure 3 is considerably shorter than the sum of the sulphur and nitrogen van der Waals radii of 3.45 Å. Also the reported angle of 121.9(3)° between the S-C-C (going from S to N) and the torsion angle –3.0(7)° (S-C-C-N) strengthen the argument that an interaction between the sulphur and nitrogen atoms occurs in these systems. In comparison, Halfpenny and Sloman[53] obtained for sp^3 nitrogen in structure 2 a value of 3.115(4) Å (N2···S2) and 3.328(4) Å (N1···S1). These values are only marginally higher than Palenik[119] and co-workers obtained for sp^2 nitrogen. Both these examples suggest a non-bonded S···N interaction would be possible in **12b** (Figure 37) where the distances between adjacent sulphur and nitrogen atoms are 3.638(4) Å (S1···N10) and 3.484(4) Å (S2···N9). Also on the L.H.S the bond angle (S1-C21-C16) is 123.5(2)° (compare C17-C21-C16 of 126.5(3)°) and the torsion angle (S1-C21-C16-N10) is –85.33°; on the R.H.S the bond angle (S2-C33-C41) is 122.7(2)° (compare C40-C33-C41 of 127.8(3)°) and the torsion angle (S2-C33-C41-N9) is 70.0(3)°. The large intramolecular distances S1···N10 and S2···N9, the external bond angles together with the large torsion angles indicate that non-bonded interactions between the sulphur and nitrogen atoms are not in fact present in **12b**. This may appear odd in light of the two previous examples, however other electronic considerations within the molecule may explain the apparent lack of non-bonded interaction between sulphur and nitrogen.

At first glance, nothing appears unusual about the structural geometry of compound **12b**. However, in the previously reported[53] X-ray structure of a similar thiophene-based macrocycle, Structure 2, it was found that the macrocycle ring was not planar and that there was considerable distortion in the ring cavity. The benzene groups were pushed apart to the point that the methine constituents of the ethyl bridge between the nitrogens in the macrocycle ring were opposite to one another, above and below the N-N plane. This was not the case for **12b** (Figure 37 and 40) as the ethyl group is clearly on one side of the ring cavity and the benzene rings are comparatively close together. The bond lengths in the two benzene rings of **12b** are quoted in Table 6c (page 84). There are only subtle differences in these two sets of bond lengths. The bond lengths around the bridging methine groups, namely C30 and C20, between the two nitrogen atoms and the benzene rings (Table 6d – page 84)) agree to 0.004 Å on the L.H.S and R.H.S of the molecule.

The two nitro groups (bond lengths – Table 6d) appear to be orientated in such a way as to accommodate an electrostatic attraction between O4 and N11 and this causes the benzene rings to be relatively close together. The distance between O4···N11 is 4.757(6) Å however. This is the shortest distance between the two nitro groups. The sum of the van der Waals radii of N and O is 2.90 Å and therefore it is unlikely a non-bonded contact is active between the nitro groups. The puzzling conformation, with respect to the close distance exhibited between the two benzene groups may be explained elsewhere.

On inspection of the hydrogen atom distances from one benzene (R.H.S) to the adjacent benzene ring it was noted that the shortest distance was between H4···C27 at 2.857(3) Å. Other distances were: H4···C19 (3.626(4) Å), H4···C18 (3.159(4) Å), H3···C28 (3.196(4) Å) and H3···C19 (3.109(4) Å). Taking the value[121] of the half-thickness of an aromatic nucleus to be 1.70 Å, the sum of the van der Waals radii for H4···benzene is 2.90 Å. Taking into account the van der Waals radius error, only reliable[121] to 0.05 or 0.10 Å per atom, the H4···C27 distance is close enough to suggest an interaction is possible between these atoms. Strong hydrogen bond interactions of this sort for acidic C-H groups have recently been shown to occur involving aromatic rings. As examples: an inclusion guest, dichloromethane, bonds (H···ring centroid distances) at a distance of 2.46 Å to the aromatic phenyl group of a aluminium fused bis-*p*-tert-butylcalix[4]arene[122]; an intramolecular hydrogen bond of 2.43 Å between a purine ring and a phenyl group has been found in a organorhodium compound[123]. Although, in the crystal structure of **12b**, the (H4···C27) interaction is much longer, and therefore the bond must be correspondingly weaker, it may account for the close proximity of the two benzene rings. The -M effect of the nitro groups pulls electron density away from the hydrogen atoms and causes them to become weakly acidic. The attraction between H4···π may therefore be counted as electrostatic rather than a 'true' hydrogen bond. The distances between H8···N10 and H4···N9 are 2.492(3) and 2.594(3) Å respectively and this is much lower than the sum of the van der Waals radii (2.70 Å). This distance of 2.492(3) Å is quite likely to correspond to a 'strong' hydrogen bond, the reduced electron density around H8 facilitating the interaction to N10. The torsion angle (N10-C20-C18-C27) is only 8.9(4)° again indicating a non-bonded contact. For the H4···N9 non-bonded interaction the torsion angle (N9-C30-C14-C39) is 34.2(4)°. This torsion angle is much higher than the other non-bonded contact between H8···N10, but still acceptable[53] for a weak hydrogen bond. The lone pairs of the nitrogen atoms in **12b** are pointing along the remaining axis of the tetrahedron. These lone pairs both appear to be orientated in the direction of the hydrogens in the adjacent benzene rings. It may be concluded that the H8···N10 and the H4···N9 interactions are the true underlying non-bonded contacts causing the two benzene rings to be in close proximity. The slight distortion of the R.H.S benzene ring may be a compromise to maximise the strong hydrogen bond and minimise both repulsive and steric effects, enabling the ethyl bridge between the two nitrogen atoms to remain on one side of the cavity plane. The H4···π cloud interaction mentioned previously could also be a contributing factor. This further explains why there is lack of an S···N interaction described earlier. The bond lengths in the thiophene ring would naturally be different from those in a structure displaying an S···N interaction, or differences in the substituents attached to the thiophene ring.

In structure 2, which has H in place of the NO_2 groups, the benzene groups are far apart. This is likely to be due to the repulsive effects between the iso-π electron clouds of the benzene rings and to the lack of any interaction between the nitrogen and the phenyl hydrogen atoms.

The least-squares planes through the atoms of both nitrobenzene groups are given in Table 8 (page 85). On the L.H.S nitrobenzene the atoms are effectively planar, with the exception that the nitro group oxygen atoms are slightly (~ ± 0.1 Å) away from the plane. The neighbouring nitrogen atom from the macrocycle ring (N10) is close (~ 0.1 Å) to the benzene ring plane and this also accounts for the attraction between H8···N10 mentioned earlier. Conversely, with respect to the R.H.S nitrobenzene group, larger deviations from the least-squares plane are noted. In the benzene ring itself, C36 and C39 are about 0.13 Å above the plane, hence towards the adjacent benzene ring. The oxygen atoms on the nitro group are more distorted out of this plane (up to ± 0.2 Å) and the bridging methine group (C30) is ~ 0.87 Å away. Together with the fact that the nitrogen atom from the macrocycle ring (N9) is below the plane by ~ 0.79 Å, these differences further confirm the distortion on the R.H.S nitrobenzene group to the L.H.S.

The observed configuration of the nitrobenzene groups may also, to some extent, if existing in solution lead to an explanation of the observation made in the reduction of the nitro group to the amino group by the Zinin reduction. It was noted, in a large excess of reducing agent that one nitro group in compound **12b** was reduced to the amino group in 10 minutes or less (some diamino was also formed), yet the other nitro group took much longer to convert. In a hypothetical explanation, if, in the mononitro-monoamino compound, a stronger H···π interaction occurs than the one described above because more electron density is associated with the aniline moiety, then the nitro group remaining may well be less accessible to the incoming disulphide ion. Attack by the disulphide ion (or more likely attack by the nitro group on the disulphide ion[108]) may thus preferentially be favoured only on one side of the molecule.

The Macrocyclic Cavity

Table 8a (page 85) gives the deviations from the least-squares plane through the atoms in the macrocyclic cavity of **12b**. As it can be seen, with reference to the X-ray structure (Figure 37), large deviations from the mean (~ ± 0.9 Å) are present in the cavity. Defining a plane through the four donor atoms (Table 8b) shows that these atoms are in good planar approximation (~ ± 0.075 Å). The other atoms in the ring cavity are above or below the plane by at least 0.1 Å (C13 of the ethyl bridge between the two nitrogen atoms is –1.14 Å away from this plane), with the exception of C24. This may be observed in Figure 40 – page 137

A method[124] to obtain a good estimate of the hole size in a macrocyclic cavity available to a metal ion (assumed spherical) has been used with considerable accuracy relative to the experimental results. The hole size (R_H) is estimated by firstly defining the centroid (CE) of the donor[124] atoms from X-ray diffraction (in both the free macrocycle and any complexed macrocycle). It is then necessary to correct the hole size by subtracting the mean distance of the donor atoms' radii (values obtained from a range of experimental results of donor atom to metal bonds) to give the bond cavity (R_A) available to the metal ion. As an example, donor set O_2N_2 macrocycle **XII** (see Figure 5 of Introduction section 1.7) of ring size 15 (it has two independent molecules in the asymmetric unit[125]) has R_H = 2.09 and 2.15 Å. On complexation with nickel(II) chloride to give **[XII]**NiCl, R_H was estimated to be 2.09 Å and the bonding cavity, R_A = 1.35 Å . The 'goodness of fit', R_A/R_P (where R_P is the Pauling covalent radius of the metal) of 0.97 was shown to coincide well with thermodynamic and kinetic stabilities.

Hence, such a procedure was applied to the free macrocycle **12b**. Although it is stressed[124] that not in all cases will the relative hole size in the free ligand reflect that in the complexed one, it is nonetheless a good indicator.

Figure 38 shows in Ångstroms the relative positions of the donor atoms (the bite sizes of the cavity) in the O_2N_2 set of **12b** taken from the X-ray crystallographic measurements.

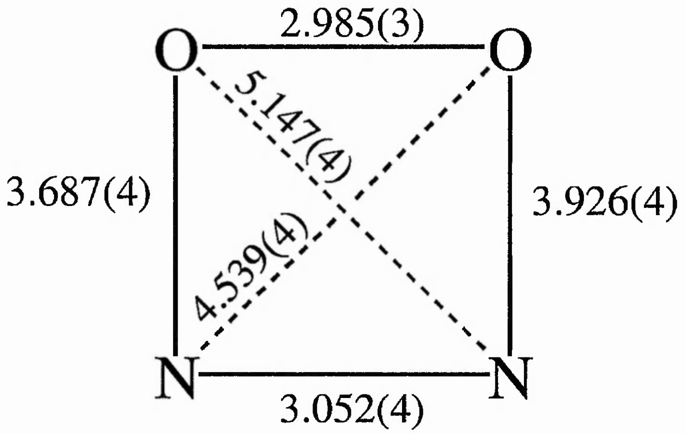


Figure 38

Correcting this cavity for the available hole size gives R_H = 2.43 Å. The mean donor radius of the O_2N_2 set is 0.74 Å (where sp^3 N is 0.72 Å and O(ether) is 0.76 Å in estimated covalent radii of high-spin Ni(II) complexes[124]). This would give an effective bond cavity of 1.69 Å for compound **12b** – Figure 39 – page 135.

The Pauling covalent radius for high-spin Ni(II) is 1.39 Å. The goodness of fit (R_A/R_P) is thus 1.22 (if R_A is assumed to be the same on complexation) in **12b**. This value leads to the consideration that the ring cavity is too large for a nickel(II) ion. It should not readily be accepted from the above calculation that **12b** will not complex to nickel(II). A conformational change in the geometry of the molecule may well occur to accommodate nickel, at least in solution. Very recent solution NMR studies[126] have demonstrated that compound **12b** does complex with nickel(II) (and copper(II)), but that the metal salt counterion plays an important role in the complex formation which was previously established by Coomber[127]. If a lowering of energy on complexation can be accomplished, solid complexes of nickel(II) and **12b** may be achievable, if not, then **12b** is likely to conform to its original solid state geometry and on crystallisation expel the nickel ion from the cavity as it is too large to accommodate it.

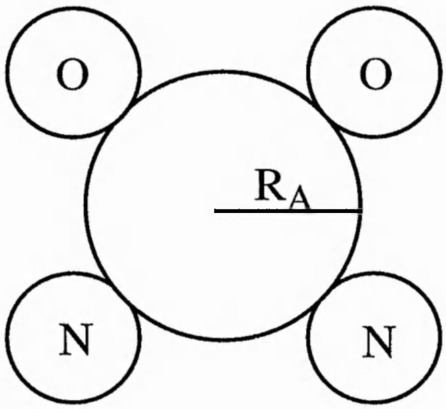


Figure 39

The large cavity is likely to be due to steric hinderance as described earlier for the position of some of the atoms contained in compound **12b**. If it is assumed that the average bonding radii of the donor atoms in question do not significantly differ from those obtained using radii from nickel complexes in the literature and that complexation is simplified to equate a good fit to cavity size then the first row transition metals do not appear to be good candidates for forming solid complexes with **12b**.

3.8 - Metal-Ion Binding Studies

There are numerous methods presented in the literature[e.g 10,29] for obtaining experimental evidence about metal-ion binding to macrocyclic ligands. In this present work, metal complexation behaviour was investigated by experiments 2.7.1 to 2.7.3 and the preliminary results are discussed below. Further work is needed in order to fully evaluate methods for complex preparation and to calculate thermodynamic properties of the metal-ion macrocyclic complexes.

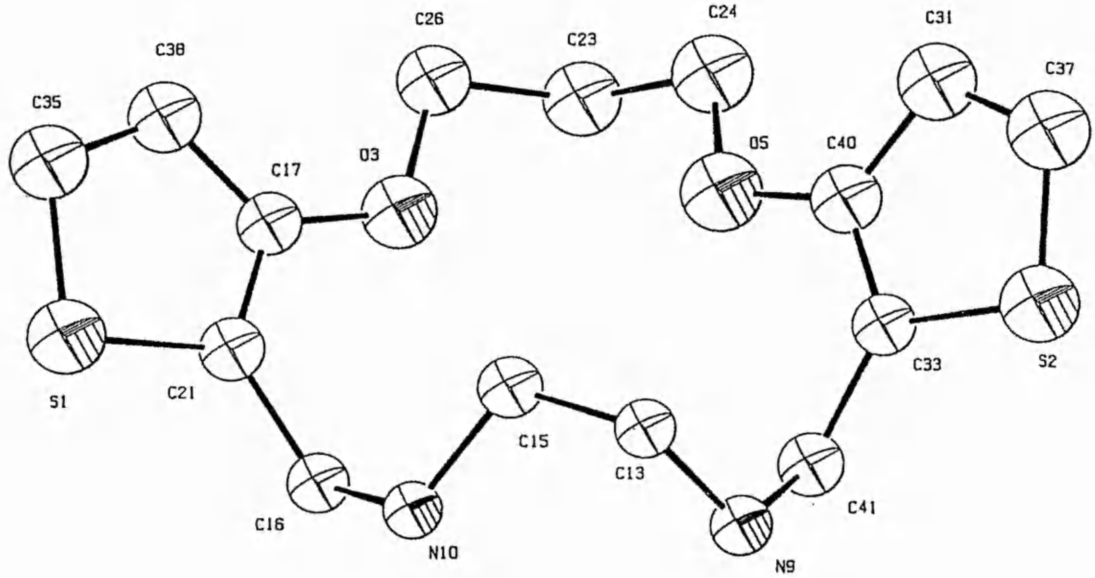
The solubility nature of compounds **12a-d** restricted the ease of conducting experiments to produce metal ion complexes. Their poor solubility in alcoholic solvents such as methanol or ethanol, which dissolve some metal salts readily, meant that partition methods were required in which the macrocycle dissolved in DCM (the compounds readily dissolve in this solvent) was shaken with the metal salt dissolved in water. Coomber[127] has shown that this method may be problematic due to transfer of metal to the DCM layer independent of complex formation. However time constraints precluded more accurate complexation studies in the present work.

Two-phase experiments for **12a-d** and nickel nitrate hexahydrate solution were vigorously shaken for an extended period of time. Comparison of the aqueous layer metal content (total 4 ppm) against standards (ranging from 1 – 5 ppm) by AAS led to the conclusion that no nickel(II) had been extracted by the macrocycles **12a-d** across the DCM/aqueous interface. Since the AAS measurements were only accurate to 2 ppm there may have been some error in this work. Also, although no metal had appeared to complex to the macrocycles under investigation, as previously stated the effect of the counterion is very important in complexation of a metal ion to a macrocycle, yet this was not investigated due to lack of time.

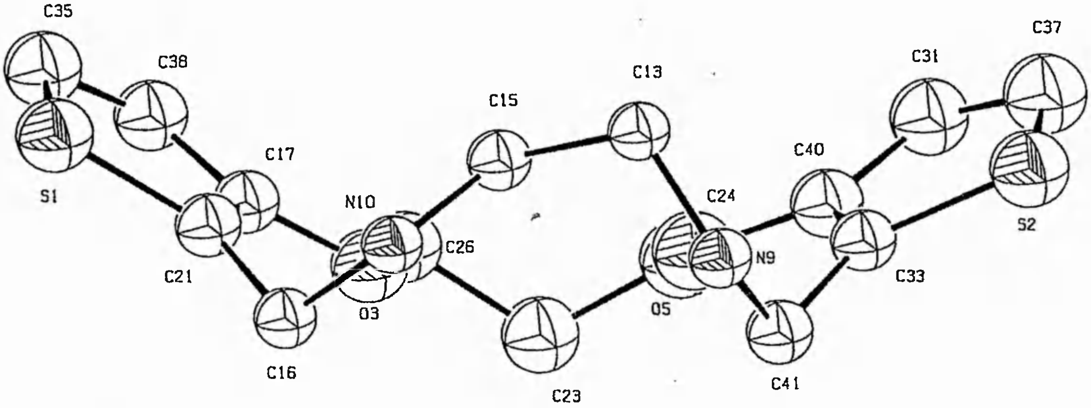
Compound **14b** is similar in nature to **12a-d**, but can be dissolved in hot acetonitrile. Experiment 2.7.1 was carried out in an attempt to see if this tetravalent macrocycle of ring size 17 would complex with nickel(II) perchlorate. No colour change was observed on cooling, the precipitate seemed likely to be **14b;** no additional products were seen (*tlc*) other than soluble **14b**. It can therefore be concluded that this macrocycle does not form a complex with nickel(II) under these conditions. The nickel ion has however previously been shown[29] to complex to a similar O_2N_2 donor benzene-based macrocycle of ring size 17.

The concentration of zinc remaining in water before and after extraction by varying ring sized (15 to 18 atoms) macrocycles (**12b**, **14b** and **15b**) in DCM was investigated. The results presented for experiment 2.7.2 (Table 2 – page 75) show for the titres 2 through to 5 that zinc is removed from the aqueous layer during the extraction process as the titre volumes are lower than 1 (the stock solution). Since experiment 5 had no macrocycle present, it may be concluded from these results that the macrocycles **12b**, **14b** and **15b** are not complexing with zinc during the extraction process, but that zinc has a finite solubility in DCM.

It is clear that both nickel and zinc nitrates (hard anions) were not being extracted by the macrocycles in these two-phase systems. Many possible reasons may account for why this is so:



View of macrocycle ring perpendicular to a plane through the N and O atoms



View of macrocycle ring in the plane of the N and O atoms

Figure 40

Izatt and co-workers[128] in their work appending polyaza macrocycles to silica gel stated that 'major problems are encountered in using macrocycle ligands in solvent extraction and liquid membrane systems', such as, 'loss of extraction effectiveness when low concentrations of metal ions are involved', and, 'the relatively slow kinetics of extraction'.

In the discussion of the crystal structure of **12b** (ring size 15), it was inferred that a nickel(II) ion was likely to be too small to readily complex to the available sized cavity. It has been established for similar O_2N_2 donor macrocycles[124] that a 0.04 – 0.05 Å increase in the radius of the macrocyclic cavity occurs on addition of a methylene group into the ring. Compound **14b** (ring size 17) will have a larger cavity than **12b** and it therefore would not be expected that a nickel(II) ion should readily complex with **14b**. From experiment 2.7.1, this is confirmed.

The zinc ion (Pauling covalent radius[121] ~ 1.48 Å) would also be too small for complexation to the macrocycles examined in this work (if it is assumed that the mean zinc(II) to donor atom radius is not significantly different to that of nickel(II)). However the zinc(II) ion is somewhat larger than nickel(II) and it is possible that if counterion effects had been examined, formation of a complex might have been achieved under modified conditions.

The evidence from the preliminary metal-ion binding studies suggests strongly that larger cations such as manganese(II) (Pauling metallic radius[121] ~ 1.6 Å) or some from the first very long period (Lanthanide series) of the Periodic Table may be more suited to complex formation with the macrocycles synthesised in this report. If, for instance, the manganese(II) ion did complex well to compound **12b**, then it would allow **12b** to discriminate over smaller ions, such as nickel(II) or zinc(II) in an extraction process. Also, **12b** may facilitate in the removal of the toxic Mn(II) ion from oxidation reactions using potassium permanganate.

In view of the more recent solution NMR work quoted above, other variables need to be considered and experimentally evaluated before making the general assumption that the cavities of the macrocycles synthesised are too large for most first row transition metals of the Periodic Table. Izatt et al[128] also suggested that one way to overcome the difficulties mentioned earlier in two-phase extraction processes was to attach macrocyclic ligands to solid supports. Morcellet et al[129] have also adopted this approach and have extracted metal ions from water with tetrapyrazolic macrocycles bound both to Merrifield resins and to silica gel. Both Alldredge et al[130] and Izatt et al[131] have on a pilot scale tested silica gel-bound macrocycles for heavy metal extraction.

Using the conditions employed by Lindoy[70] *et al* the macrocycle **16b** was appended to a Merrifield resin and was investigated for zinc extraction (experiment 2.7.3). As previously mentioned (section 3.6), initially a fairly low percentage of macrocycle **16b** was loaded onto a 2% cross-linked Merrifield resin (1.0 – 1.5 mmol Cl per gram of resin) to give approximately 0.15 – 0.20 mmol macrocycle per gram of resin. This resin in a binary solvent (ethyl acetate and methanol 9:1) was mixed with an excess of zinc(II) nitrate solution (in the binary solvent) and shaken on a mechanical shaker for 18 hours. Titrations on the remaining zinc(II) solution indicated the following: some zinc(II) was adsorbed onto the polymer surface – compare titres 2 and 3 of Table 3 (page 76) or, less likely, lost in the clean up stage of the polymer beads. Zinc(II) was taken up by the macrocycle – compare titres 1 and 2 of Table 3. It can be calculated that under these conditions between 6 – 8% of zinc(II) ions were extracted by the resin-attached macrocycle. However, this resin was not fully laden with macrocycle. Extrapolation to 0.5 mmol macrocycle per gram of resin (see section 3.6) could potentially lead to uptake of 20% of the metal in the zinc(II) nitrate solution under the conditions used. This is indeed encouraging as a preliminary indication of the extraction potential of macrocycles of this type. Other metal ions would naturally also have to be investigated.

It was shown in experiment 2.7.2 that no zinc was taken up by macrocycle **12b** using the two-phase extraction process, yet experiment 2.7.3 does indicate zinc uptake by the resin-supported **16b**. This implies that experiment 2.7.2 may not have had the optimum conditions for metal uptake by the free macrocycle and further investigation is required to establish what those might be. The work of Labat and Coomber mentioned earlier does indicate in solution that the metal counterion may have an important effect but due to lack of time only zinc(II) nitrate was used in these experiments.

The experiments described above serve only to indicate that formation of metal-ion to macrocycle complexes does to some extent occur both in the free and supported macrocycles in solution. Further exploration into the nature of these macrocyclic systems and their interaction with metal ions is required to obtain a more comprehensive understanding.

CONCLUSIONS

Conclusions and Future Work

The compounds, α,ϖ-bis(3-oxythienyl)alkane (where alkane is ethane, propane, butane or diethyl ether), largely referred to in this thesis as starting materials, were required in order to extend the chemistry of thiophene-based macrocycles produced via the Mannich reaction. As these starting materials are not obtainable commercially, their accessibility from methyl 3-hydroxythiophene-2-carboxylate was required quickly, easily and in bulk quantities. The work described in this thesis (section 3.1) has greatly improved synthetic methods originally described by Chaffin[51] to enable production on a semi-large scale (starting with around 50 g of methyl 3-hydroxythiophene-2-carboxylate). The procedure was significantly shortened and comparatively good yields were also obtained (see Table 9, section 3.1).

It has been reported elsewhere[53,115] that thiophene-based macrocycles produced via the Mannich reaction from the starting materials, α,ϖ-bis(3-oxythienyl)propane and *N*,*N*′-dibenzylethylenediamine were crystalline products obtained in high yield. The work presented here extended these types of crystalline thiophene-based macrocycles to give a wide range of ring sizes and incorporate functional groups in the *para*-position of the dibenzylenediamine moiety.

For the synthesis of thiophene-based macrocycles incorporating a functional group for attachment to a suitably functionalised polymeric support, several routes were examined.

The route starting from *p*-hydroxybenzaldehyde (Scheme Two) to obtain thiophene-based macrocycles incorporating the hydroxyl function was tried first. Attempts to obtain crystalline material other than by chromatography were exhaustive. Macrocyclic compounds of this type posses several interesting features which may lead to their isolation in due course. Firstly, they have a phenolic group which could be easily appended to a chlorinated resin. Secondly, they have two hydroxyl benzyl arms, which may (if unrestricted) adopt axial coordinates, chelating to metal ions complexed in the macrocyclic cavity. One possible disadvantage of these types of macrocycles in their usage is the acidic nature of the phenolic group which may interfere with the basic ligand sites (zwitterionic).

The requirements to obtain solid macrocycles were intended in order to avoid elaborate purification methods. This was paramount from the outset as practical applications were envisaged for these thiophene-based macrocycles. It was previously mentioned (section 3.8) that pilot scale test results of silica gel-bound macrocycles for metal ion separations had been reported[130,131]. So procedures towards production of bulk quantities of thiophene-based macrocyles were considered a high priority.

In exploration to obtain thiophene-based macrocycles which incorporate suitable functionality for attachment to a polymeric support, two routes starting from *p*-acetamidobenzaldehyde (Scheme Three) or *p*-nitrobenzaldehyde (Scheme Four) were considered. Ultimately, the amino group was required from both these syntheses as this group could facilitate further reaction, hence attachment to a chlorinated Merrifield resin. Of the two routes investigated, the macrocycles containing the acetamido group were not as accessible as those incorporating the nitro group. The thiophene-based macrocycle **12b** (see Scheme Four) was simply obtained by precipitation (using acetonitrile), resulting in a yield of a little less than 40%. No further purification was required. Confidence in the structure assignment of this compound was obtained from X-ray crystallographic measurements (see later). In the light of the success of the isolation of **12b**, this route was pursued. Further success was accomplished as the ring size was expanded from 15 (**12b**) to 16 (**12c**) and to 17 (**12d**) by the reactions involving *N*,*N*′-bis-(4-nitro-benzyl)-ethane-1,2-diamine and the starting materials α,ϖ-bis(3-oxythienyl)butane and diethyl ether respectively. Furthermore, a better work-up procedure, which gave scope for increasing quantities was implemented over previous reported methods (see section 3.2.4).

Favouring this route to thiophene-based macrocycles incorporating the nitro group, other O_2N_2 and O_3N_2-donor macrocycles of varying ring size were synthesised. The chain length between the two tertiary amine groups was expanded. This meant synthesising *N*,*N*′-bis-(4-nitro-benzyl)-alkane-diamine (where alkane is propane-1,3, butane-1,4 or pentane-1,5) on a semi-large scale. These solid compounds proved troublesome to obtain earlier on, but subsequent procedures have led to their isolation with ease. Indeed, the Mannich reaction of both *N*,*N*′-bis-(4-nitro-benzyl)-butane-1,4-diamine and *N*,*N*′-bis-(4-nitro-benzyl)-pentane-1,5-diamine with the starting α,ϖ-bis(3-oxythienyl)alkanes has led to an extension of the family of thiophene-based macrocycles incorporating the nitro function (see Scheme Four).

In summary a range of O_2N_2 and O_3N_2-donor thiophene-based macrocycles incorporating the nitro group of ring sizes 14 to 19 and, 17, 19 and 20, respectively comprising of three variations in the chain length between the tertiary amines have been synthesised.

The X-ray crystallographic measurements on 13,16-bis-(4-nitro-benzyl)-2,6-dioxa-10,19-dithia-13,16-diaza-tricyclo[16.3.0.0^{7,11}]heneicosa-1(18),7(11),8,20-tetraene (**12b**) are presented in the experimental section 2.8. An account of the geometry of the crystal structure can be found in the Discussion section 3.7 together with the size of the available bonding cavity (hole size) for the metal ions. The key feature of the crystal structure's geometry is the close proximity of the benzene rings (see Figure 37 – page 128). This can be accounted for by the observed intramolecular non-bonded contacts between the nitrogen atoms in the macrocycle ring and the nearest hydrogen atom in each adjacent benzene ring. These hydrogen bond distances of 2.49 – 2.59 Å are much less than the sum of the N and H van der Waals radii (2.70 Å). In addition a weak attraction occurs between the π cloud of one benzene ring and an adjacent hydrogen atom from the other benzene ring. The two nitro groups may also have an extremely weak non-bonded interaction to one another as the atoms are orientated correctly for this to occur. In this compound there is no interaction between the sulphur atom of thiophene and the nitrogen atom in the macrocyclic ring. This is rather surprising as this type of interaction has been observed in several previous structure determinations of 2-substituted thiophenes.

In the Mannich reaction to obtain the macrocyclic product from α,ϖ-bis(3-oxythienyl)propane and *N*,*N*′-bis-(4-nitro-benzyl)-propane-1,3-diamine, the main product isolated was 1,3-bis-(4-nitro-benzyl)-hexahydropyrimidine. This clearly demonstrated that competitive ring formation was occurring in the construction of demonstrated that competitive ring formation was occurring in the construction of thiophene-based macrocycles of this type using the Mannich reaction. Furthermore, this discovery coupled with other observations (see section 3.4.4) during the production of macrocycles synthesised in this present work aids to the understanding of ring formation via the Mannich reaction.

The likelihood[91] of dealkylation at the alkoxide of these thiophene-based macrocycles using acidic conditions led to the use of the *Zinin* reduction[77] for the conversion of the nitro groups into the amino groups. The reduction was accomplished in pyridine as solvent as other attempted solvent media were either incompatible with the target compounds or the reductions were too slow (section 3.4.5). It was found, employing basic conditions and the use of the disulphide dianion[77] that conversion from the dinitro thiophene-based macrocycles to the mononitro-monoamino thiophene-based macrocycles was achievable in ten minutes or less at elevated temperature. Filtration through silica was necessary for their isolation. The diamino thiophene-based macrocycles could be obtained from solution by precipitation, but, for the target compounds isolated, purification posed problems. Nonetheless, other pure diamino thiophene-based macrocycles with larger ring sizes are assumed to be readily achievable by this method. To have a range of thiophene-based macrocycles obtainable in potentially bulk quantities would be the appropriate synthetic direction to pursue based on previously mentioned aims.

Mononitro-monoamino compounds of ring sizes 15 and 16 were attached (section 3.5) to a polymeric support (a chlorinated Merrifield resin). These results offer a modest value of around 0.5 mmol macrocycle per gram of polymer. The relatively non-polar polymeric support chosen for these experiments merely served to indicate that these thiophene-based macrocycles could successfully be bound onto polymers. It was found possible to reduce all the thiophene-based macrocycles containing the nitro group synthesised in this work to either the mononitro-monoamino or the diamino macrocycles and subsequently to attach them to a Merrifield resin.

A limited number of metal-ion binding experiments were carried out on thiophene-based macrocycles incorporating the nitro group (section 3.8). From the methods used, no conclusive evidence was found to evaluate the extraction potential of these macrocycles (various ring sizes) for the nickel(II) or zinc(II) ions. The approximate bonding cavity (hole size) of **12b** (uncomplexed) was calculated[124] from the X-ray crystallographic data. The hole size was calculated to be too large to accommodate a high spin nickel(II) ion. However, more recent work[126] indicates that a nickel complex does form in solution. Counterion effects have also been shown to be important in complex formation and these were not investigated in this work. Further experimental investigation is required to properly evaluate the metal-ion binding properties of these thiophene-based macrocycles.

For a polymer bound macrocycle of ring size 15, it has been concluded (section 3.8), based on metal-ion complexation studies of a similar system with lower macrocyclic loading (0.15 – 0.20 mmol macrocycle per gram of resin) that a 20% extraction of zinc(II) nitrate is possible using the higher loaded resin.

It would be of further interest to apply these ring systems to silica gel[117,128] or Merrifield-type silanised glass[118] supports. The chemistry for macrocyclic attachment is much the same for these latter two supports as for the less polar polymeric resin. The solution compatibility of hydrophilic-based supports with appended thiophene-based macrocycles makes them more suited for utilisation on a practical scale[130,131]. A study of the differences between free macrocycles and macrocycles appended to hydrophilic supports is now necessary.

The benzyl groups incorporated in the thiophene-based macrocycles reported in this work serve as a short spacer group for attachment to a polymeric support. Attachment via a spacer allows the ring cavity of the macrocycles to remain untouched. Yet, the bulky nature of the benzyl groups may interfere with metal-ion complexation by distorting the ring cavity and enlarging its ‘natural’ size. Also, tertiary amines are less basic than secondary ones and the binding strength of the ring cavity for metal-ion interaction will be reduced. In order to circumvent some of these envisaged difficulties, thiophene-based macrocycles of the type described in section 3.5 were further investigated following results previously reported[51,115]. The formation of Schiff bases from α,ϖ-bis(2-formyl-3-oxythienyl)propane and ethylenediamine or 1,5-diaminopentane (cadaverine) was achievable with ease and without the use of metal ion templates. These compounds showed no signs of decomposition (*via* hydrolysis) in air.

Their reduction to secondary amines has yet to be accomplished. These systems could potentially open up a new interesting area of research for comparison to similar macrocycles[29] not containing thiophene. The metal-ion binding studies of these systems both ‘free’ and bound to hydrophilic supports would also be of considerable interest.

Appendix - A1 – Additional X-ray data

Table 15 - Intramolecular distances to 3 Å

- H positions were fixed hence atom-H bond has no esd

atom 1	atom 2	distance	atom 1	atom 2	distance
S1	C16	2.835(3)	S1	C17	2.527(4)
S1	C21	1.715(3)	S1	C35	1.714(4)
S1	C38	2.543(4)	S1	H6	2.88
S1	H9	2.83	S1	H18	2.98
S1	H25	2.39	S2	C31	2.540(4)
S2	C33	1.727(3)	S2	C37	1.713(4)
S2	C40	2.522(4)	S2	C41	2.841(3)
S2	H23	2.39	O1	O8	2.136(5)
O1	N11	1.212(4)	O1	C22	2.732(5)
O1	C28	2.316(4)	O1	H6	2.43
O1	H24	2.84	O3	O5	2.985(3)
O3	C16	2.920(4)	O3	C17	1.364(4)
O3	C21	2.350(4)	O3	C23	2.364(4)
O3	C26	1.423(4)	O3	C38	2.492(4)
O3	H14	2.66	O3	H17	2.57
O3	H19	2.53	O3	H24	2.84
O4	O7	2.154(5)	O3	H28	2.04
O4	C29	2.311(5)	O4	N1	1.217(4)
O4	H3	2.48	O4	C36	2.729(5)
O5	C24	1.425(4)	O5	C23	2.376(4)
O5	C33	2.349(4)	O5	C31	2.499(4)
O5	C41	2.948(4)	O5	C40	1.371(4)
O5	H19	2.63	O5	H14	2.55
O5	H22	2.89	O5	H20	2.49
O5	H30	1.99	O5	H29	2.16
O7	C29	2.316(4)	O7	N1	1.235(4)
O7	H1	2.43	O7	C32	2.735(5)
O7	H29	2.83	O7	H27	2.69
O8	N11	1.215(4)	O7	H30	2.92
O8	C28	2.308(4)	O8	C19	2.707(4)
O8	H24	2.47	O8	H5	2.41
N1	C29	1.462(4)	O8	H28	2.97
N1	C36	2.442(5)	N1	C32	2.450(6)
N1	H3	2.64	N1	H1	2.62

Table 15 continued

atom 1	atom 2	distance	atom 1	atom 2	distance
N9	C14	2.471(4)	N9	C13	1.460(4)
N9	C30	1.467(4)	N9	C15	2.504(4)
N9	C39	2.886(4)	N9	C33	2.536(4)
N9	H4	2.59	N9	C41	1.474(4)
N9	H11	2.05	N9	H10	1.96
N9	H16	2.04	N9	H13	2.02
N9	H20	2.06	N9	H19	2.72
N9	H21	2.06	N9	H20	2.94
N10	C15	1.473(4)	N10	C13	2.504(4)
N10	C18	2.489(4)	N10	C16	1.480(4)
N10	C21	2.544(4)	N10	C20	1.453(4)
N10	H8	2.49	N10	C27	2.857(4)
N10	H12	2.05	N10	H9	2.07
N10	H16	2.69	N10	H15	2.07
N10	H18	1.97	N10	H17	2.04
N10	H21	2.83	N10	H19	1.94
N11	C22	2.454(5)	N11	C19	2.442(5)
N11	H5	2.60	N11	C28	1.475(4)
N11	H24	3.00	N11	H6	2.60
C13	C30	2.428(4)	C13	C15	1.526(4)
C13	C41	2.455(4)	C13	C33	2.963(4)
C13	H12	1.97	C13	H11	2.62
C13	H15	2.75	C13	H13	0.97
C13	H19	2.11	C13	H16	1.07
C14	C29	2.754(5)	C13	H20	2.74
C14	C32	2.399(5)	C14	C30	1.509(4)
C14	C36	2.411(5)	C14	C34	1.387(4)
C14	H2	2.04	C14	C39	1.385(4)
C14	H10	2.17	C14	H4	2.04
C14	H16	2.50	C14	H11	1.94
C15	C20	2.428(4)	C15	C16	2.434(4)
C15	H9	2.87	C15	C21	2.950(4)
C15	H13	2.03	C15	H12	1.03
C15	H16	2.13	C15	H15	2.56
C15	H19	0.98	C15	H17	2.71
C16	C17	2.555(4)	C15	H20	2.77
C16	C21	1.500(4)	C16	C20	2.439(4)
C16	H9	2.60	C16	H8	2.82
C16	H17	0.99	C16	H12	2.90

Table 15 continued

atom 1	atom 2	distance	atom 1	atom 2	distance
C16	H19	2.37	C16	H18	0.96
C17	C21	1.360(4)	C16	H21	2.90
C17	C35	2.292(5)	C17	C26	2.395(5)
C17	H17	2.64	C17	C38	1.424(4)
C17	H24	2.20	C17	H19	2.94
C17	H28	2.64	C17	H27	2.69
C18	C20	1.519(4)	C18	C19	2.406(4)
C18	C25	1.382(4)	C18	C22	2.405(4)
C18	C28	2.750(4)	C18	C27	1.381(4)
C18	H8	2.05	C18	H7	2.05
C19	C22	2.390(5)	C18	H9	2.01
C19	C27	1.383(4)	C18	H18	2.75
C19	H5	0.96	C19	C25	2.748(5)
C20	C25	2.503(4)	C19	C28	1.360(4)
C20	H7	2.65	C19	H8	2.05
C20	H15	1.02	C20	C27	2.543(4)
C20	H18	2.54	C20	H8	2.71
C21	C38	2.335(4)	C20	H12	2.48
C21	H12	2.97	C20	H16	2.76
C21	H18	2.08	C21	C35	2.474(5)
C22	C25	1.375(4)	C21	H9	2.85
C22	C28	1.372(4)	C21	H17	2.02
C22	H7	2.04	C21	H19	2.82
C23	C26	1.488(5)	C22	C27	2.754(4)
C23	H26	1.03	C22	H6	0.96
C23	H28	2.10	C23	C24	1.501(5)
C23	H30	2.21	C23	H14	0.83
C24	C31	2.901(6)	C23	H27	2.02
C24	H14	1.89	C23	H29	2.18
C24	H26	2.03	C24	C26	2.544(5)
C24	H29	1.14	C24	C40	2.381(5)
C25	C27	2.371(4)	C24	H22	2.78
C25	H6	2.05	C24	H27	2.53
C25	H9	2.61	C24	H30	1.07
C26	C38	2.899(5)	C25	C28	2.359(5)
C26	H24	2.71	C25	H7	0.98
C26	H27	1.04	C25	H15	2.69
C26	H29	2.80	C26	H14	2.08
C27	H4	2.86	C26	H26	2.10

Table 15 continued

atom 1	atom 2	distance	atom 1	atom 2	distance
C27	H8	0.98	C26	H28	0.98
C28	H5	2.02	C27	C28	2.360(4)
C29	C32	1.374(5)	C27	H5	2.05
C29	C36	1.374(4)	C27	H18	2.69
C29	H1	2.05	C28	H6	2.03
C30	C34	2.518(5)	C29	C34	2.364(5)
C30	C41	2.458(4)	C29	C39	2.359(5)
C30	H4	2.67	C29	H3	2.07
C30	H11	0.94	C30	C39	2.523(5)
C30	H16	2.50	C30	H2	2.66
C31	C33	2.340(5)	C30	H10	1.01
C31	C40	1.433(4)	C30	H13	2.76
C31	H22	1.07	C30	H21	2.54
C31	H29	2.84	C31	C37	1.339(5)
C32	C34	1.368(4)	C31	H5	2.87
C32	C39	2.745(5)	C31	H23	2.24
C32	H2	2.05	C31	H30	2.73
C33	C40	1.349(4)	C32	C36	2.399(5)
C33	H8	2.79	C32	H1	0.99
C33	H20	2.08	C33	C37	2.483(5)
C34	C36	2.761(5)	C33	C41	1.509(4)
C34	H1	2.06	C33	H13	2.59
C34	H11	2.46	C33	H21	2.11
C34	H25	2.94	C34	C39	2.375(5)
C35	H24	2.12	C34	H2	0.98
C36	C39	1.376(4)	C34	H12	2.97
C36	H4	2.04	C35	C38	1.345(4)
C37	H5	2.86	C35	H25	1.03
C37	H22	2.11	C36	H3	0.97
C38	H1	2.74	C37	C40	2.292(5)
C38	H25	2.11	C37	H7	2.86
C38	H28	2.78	C37	H23	1.10
C39	H4	0.97	C38	H24	1.05
C40	C41	2.567(4)	C38	H27	2.90
C40	H22	2.24	C39	H3	2.04
C40	H30	2.48	C39	H16	2.75
C41	H10	2.41	C40	H20	2.64
C41	H13	2.63	C40	H29	2.79
C41	H20	1.06	C41	H8	2.98

Table 15 continued

atom 1	atom 2	distance	atom 1	atom 2	distance
C41	H21	1.08	C41	H11	2.86
C41	H20	2.90	C41	H19	2.77

Table 16 – Bond Angles (°)

atom 1	atom 2	atom 3	angle	atom 1	atom 2	atom 3	angle
C21	S1	C35	92.4(2)	C33	S2	C37	92.4(2)
C17	O3	C26	118.5(3)	C24	O5	C40	116.8(2)
O4	N1	O7	122.9(4)	O4	N1	C29	119.0(4)
O7	N1	C29	118.1(4)	C13	N9	C30	112.0(2)
C13	N9	C41	113.6(2)	C30	N9	C41	113.4(2)
C15	N10	C16	111.0(2)	C15	N10	C20	112.1(2)
C16	N10	C20	112.5(2)	O1	N11	O8	123.3(4)
O1	N11	C28	118.8(4)	O8	N11	C28	117.9(3)
N9	C13	C15	113.9(2)	C30	C14	C34	120.8(3)
C30	C14	C39	121.3(3)	C34	C14	C39	118.0(3)
N10	C15	C13	113.2(2)	N10	C16	C21	117.2(2)
O3	C17	C21	119.2(3)	O3	C17	C38	126.8(3)
C21	C17	C38	114.0(3)	C20	C18	C25	119.2(3)
C20	C18	C27	122.5(3)	C25	C18	C27	118.2(3)
C27	C19	C28	118.8(3)	N10	C20	C18	113.7(2)
S1	C21	C16	123.5(2)	S1	C21	C17	110.0(2)
C16	C21	C17	126.5(3)	C25	C22	C28	118.4(3)
C24	C23	C26	116.7(3)	O5	C24	C23	108.6(3)
C18	C25	C22	121.5(3)	O3	C26	C23	108.6(3)
C18	C27	C19	121.1(3)	N11	C28	C19	118.9(3)
N11	C28	C22	119.1(3)	C19	C28	C22	122.0(3)
N1	C29	C32	119.5(3)	N1	C29	C36	118.9(3)
C32	C29	C36	121.6(3)	N9	C30	C14	112.3(3)
C37	C31	C40	111.5(3)	C29	C32	C34	119.1(3)
S2	C33	C40	109.5(2)	S2	C33	C41	122.7(2)
C40	C33	C41	127.8(3)	C14	C34	C32	121.2(3)
S1	C35	C38	112.0(3)	C29	C36	C39	118.2(3)
S2	C37	C31	112.1(3)	C17	C38	C35	111.7(3)
C14	C39	C36	121.8(3)	O5	C40	C31	126.1(3)

Table 16 continued

O5	C40	C33	119.5(3)	C31	C40	C33	114.4(3)
N9	C41	C33	116.5(2)				

Table 17 – Torsion Angles (°)

atom 1	**atom 2**	**atom 3**	**atom 4**	**angle**
S1	C21	C16	N10	85.3(3)
S1	C21	C17	O3	178.9(2)
S1	C21	C17	C38	0.0(3)
S1	C35	C38	C17	0.1(4)
S2	C33	C40	O5	179.9(2)
S2	C33	C40	C31	-0.8(4)
S2	C33	C41	N9	70.0(3)
S2	C37	C31	C40	-0.8(4)
O1	N11	C28	C19	173.9(4)
O1	N11	C28	C22	-7.0(5)
O3	C17	C21	C16	-2.0(5)
O3	C17	C38	C35	-178.9(3)
O3	C26	C23	C24	-81.7(4)
O4	N1	C29	C32	166.8(4)
O4	N1	C29	C36	-12.4(6)
O5	C24	C23	C26	70.2(4)
O5	C40	C31	C37	-179.6(3)
O5	C40	C33	C41	0.9(5)
O7	N1	C29	C32	-13.2(5)
O7	N1	C29	C36	167.5(4)
O8	N11	C28	C19	-7.3(5)
O8	N11	C28	C22	171.7(4)
N1	C29	C32	C34	-174.7(3)
N1	C29	C36	C39	176.7(3)
N9	C13	C15	N10	64.1(3)
N9	C30	C14	C34	-145.8(3)
N9	C30	C14	C39	34.2(4)
N9	C41	C33	C40	-111.1(4)
N10	C16	C21	C17	95.8(4)
N10	C20	C18	C25	-173.6(3)
N10	C20	C18	C27	8.9(4)
N11	C28	C19	C27	178.0(3)

Table 17 continued

atom 1	atom 2	atom 3	atom 4	angle
C13	N9	C30	C14	67.0(3)
C13	N9	C41	C33	50.6(3)
C13	C15	N10	C16	-159.0(2)
C13	C15	N10	C20	74.2(3)
C14	C30	N9	C41	-162.7(3)
C14	C34	C32	C29	-2.9(6)
C14	C39	C36	C29	-1.2(6)
C15	N10	C16	C21	-52.5(3)
C15	N10	C20	C18	-157.1(2)
C15	C13	N9	C30	-164.0(2)
C15	C13	N9	C41	65.9(3)
C16	N10	C20	C18	76.9(3)
C16	C21	S1	C35	-179.0(3)
C16	C21	C17	C38	179.0(3)
C17	O3	C26	C23	178.7(3)
C17	C21	S1	C35	0.0(3)
C18	C25	C22	C28	-2.1(6)
C18	C27	C19	C28	0.1(5)
C19	C27	C18	C20	177.3(3)

A2 – Nomenclature

The naming of the thiophene-based macrocycles synthesised in this thesis is the same adopted by Chaffin[51]. Table 18 (page 155) details the basic numerical terms[51]. Naming follows these steps: (a) the largest ring is the parent and numbering starts from the most important bridgehead; (b) number adjoining rings; (c) priority of heteroatoms is in the series O > S > N; (d) number and position of any multiple bonds

As an example the generation of a thiophene-based macrocycle by the naming procedure is given for **15d** (Figure 41):

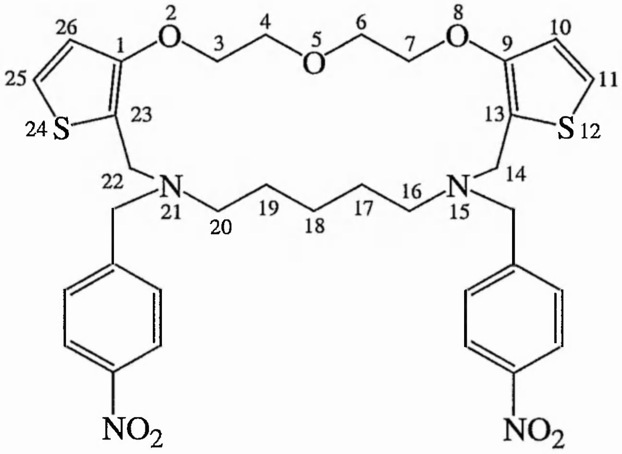


Figure 41

(a) 26-membered ring (HEXACOSA)

(b) Three (TRICYCLO); junction points 9,13 & 1,23

(c) O at 2, 5 & 8; S at 12 & 24; N at 15 & 21

(d) Four double bonds between 1 & 23, 9 & 13, 10 & 11, 25 & 26

Named as:

15,21-bis-(4-nitro-benzyl)-2,5,8-trioxa-12,24-dithia-15,21-diaza-tricyclo[21.3.0.0^{9,13}]hexacosa-1(23),9(13),10,25-tetraene

Number	Term	Number	Term	Number	Term
1	mono/hen*	7	hepta	20	icosa^
2	di/do*	8	octa	30	triaconta
3	tri	9	nona	40	tetraconta
4	tetra	10	deca	50	pentaconta
5	penta	11	undeca		
6	hexa	12	dodeca#		

Table 18

*	hen or do used when more than one numerical term e.g. 22 is docosa.
#	numbers after 12 are identified as two numerical terms e.g. 13 is trideca.
^	the letter ‘i’ is removed in numerical combination e.g. 23 is tricosa; Chemical Abstracts and Beilstein use ‘eicosa’ instead of ‘icosa’ – this is used in this thesis.

REFERENCES

1 D. K. Cabbiness & D. W. Margerum, *J. Am. Chem. Soc.*, **91**, 6540-6541, (1969)

2 F. P. Hinz & D. W. Margerum, *Inorganic Chem.*, **13**, 2941-2949, (1974)

3 L. F. Lindoy, *'The Chemistry of Macrocyclic Ligand Complexes'*, Cambridge University Press (Cambridge), (1989)

4 A. Lüttringhaus and K. Ziegler, *Annali di chimica*, **528**, 155-161, (1937)

5 R. Adams and L. N. Whitehill, *J. Am. Chem. Soc.*, **63**, 2073-2078, (1941)

6 C. J. Pedersen, *Angew. Chem. Int. Ed. Engl.*, **27**, 1021-1027, (1988)

7 C. J. Pedersen, *Proceedings of the Federation of American Societies for Experimental Biology*, **27**, Nov-Dec, 1305-1309, (1968)

8 C. J. Pedersen, *J. Am. Chem. Soc.*, **89**, 7017-7036, (1967)

9 C. J. Pedersen & H. K. Frensdorff, *Angew. Chem. Internat. Edit.*, **11**, 16-25, (1972)

10 R. M. Izatt, J. S. Bradshaw, S. A. Nielsen, J. D. Lamb and J. J. Christensen, *Chem. Rev.*, **85**, 271-339, (1985)

11 D. J. Sam & H. E. Simmons, *J. Am. Chem. Soc.*, **94**, 4024-4025, (1972)

12 C. L. Liotta, H. P. Harris, M. McDermott, T. Gonzalez and K. Smith, *Tetrahedron Lett.*, **28**, 2417-2420 (1974)

13 C. W. McDaniel, J. S. Bradshaw and R. M. Izatt, *Heterocycles*, **30**, 665-705, (1990)

14 J. M. Lehn, *Structure and Bonding*, **16**, 1-69, (1973)

15 J. M. Lehn, *Accounts of Chemical Research.*, **11**, 49-57, (1978)

16 G. W. Gokel, D. M. Dishong & C. J. Diamond, *J. Chem. Soc., Chem. Comm.*, 1053-1054, (1980)

17 R. A. Schultz, D. M. Dishong, C. J. Diamond & G. W. Gokel, *J. Am. Chem. Soc.*, **104**, 625-626, (1982)

18 G. W. Gokel, *J. Chem. Soc., Chem. Commum.*, 1-9, (2000)

19 D. J. Cram, *Science*, **240**, 760-767, (1988)

20 J. Szejtli, *Chem. Rev.*, **98**, 1743-1753, (1998)

21 S. A. Nepogodiev & J. F. Stoddart, *ibid.*, **98**, 1959-1976, (1998)

22 J. Kim, I-S. Jung, S-Y. Kim, E. Lee, J-K. Kang, S. Sakamoto, K. Yamaguchi & K. Kim, *J. Am. Chem. Soc.*, 122, 540-541, (2000)

23 J. McMurry, *'Organic Chemistry'*, Brooks/Cole Publishing Company, 3rd Edition, 671, (1992)

24 L. G. Armstrong, P. G. Grimsley, L. F. Lindoy, H. C. Lip, V. A. Norris, R. J. Smith, *Inorganic Chemistry*, **17**, 2350-2352, (1978)

25 L. G. Armstrong, L. F. Lindoy, M. McPartlin, G. M. Mockler & P. A. Tasker, *Inorganic Chemistry*, **16**, 1665-1669, (1977)

26 K. R. Adam, L. F. Lindoy, H.C. Lip, J. H. Rea, B. W. Skelton & A. H. White, *J. Chem. Soc., Dalton Trans.*, 74-79, (1981)

27 K. R. Adam, K. P. Dancey, A. J. Leong, L. F. Lindoy, B. J. McCool, M. McPartlin & P. A. Tasker, *J. Am. Chem. Soc.*, **110**, 8471-8477, (1988)

28 K. R. Adam, S. Donnelly, A. J. Leong, L. F. Lindoy, B. J. McCool, A. Bashall, M. R. Dent, B. P. Murphy, M. McPartlin, D. E. Fenton & P. A. Tasker, *J. Chem. Soc., Dalton Trans.*, 1635-1643, (1990)

29 L. F. Lindoy, '*Synthesis of Macrocycles - The Design of Selective Complexing Agents*', Progress in Macrocyclic Chemistry Volume 3, Edited R. M. Izatt & J. J. Christensen, John Wiley & Sons, Inc., 53-92 (1987)

30 N. F. Curtis, *J. Chem. Soc.*, 4409-4413 (1960)

31 N. F. Curtis & D. A. House, *Chemistry and Industry* 1708-1709 (1961)

32 N. F. Curtis, Y. M. Curtis & H. K. J. Powell, *J. Chem. Soc.* (A), 1015-1018, (1966)

33 G. A. Melson & D. H. Busch, *Proceedings-Chem. Soc.*, 223-224, (1963)

34 E. C. Constable, C. Sacht, G. Palo, D. A. Tocher & M. R. Truter, *J. Chem. Soc., Dalton Trans.*, 1307-1312, (1993)

35 G. A. Lawrance, M. Maeder & E. N. Wilkes, *Rev. Inorg. Chem.*, **13**, 199-232, (1993)

36 D. E. Fenton, R. W. Matthews, M. McPartlin, B. P. Murphy, I. J. Scowen & P. Tasker, *J. Chem. Soc., Dalton Trans.*, 3421-3427 (1996)

37 H. Adams, D. E. Fenton & S. J. Ryan, *Inorg. Chem. Commun.* 2, 52-54 (1999)

38 L. A. Paquette, '*Principles of Modern Heterocyclic Chemistry*', W. A. Benjamin, Inc., 104, (1968)

39 D. E. Wolf & K. Folkers, '*Organic Reactions*', John Wiley & Sons, Inc. (NY), **VI**, 410-468, (1951)

40 P. R. Huddleston & J. M. Barker, *Synth. Comm*, **9**, 731-734, (1979)

41 Laporte Fine Chemicals, Four Ashes, Wolverhampton

42 G. R. Pettit & E. E. van Tamelen, '*Organic Reactions*' John Wiley & Sons, Inc. (NY),**12**, 356-529, (1962)

43 O. Meth-Cohn, *Quart. Rep. Sulfur. Chem.*, **5**, 129-150, (1970)

44 G. R. Newkome, J. D. Sauer, J. M. Roper and D. C. Hager, *Chem. Rev.*, **77**, 513-597 (1977)

45 N. A. Bailey, M. M. Eddy, D. E. Fenton, G. Jones, S. Moss & A. Mukhopadhyay, *J. Chem. Soc., Chem. Comm.*, 628-630 (1981)

46 N. A. Bailey, M. M. Eddy, D. E. Fenton, S. Moss & A. Mukhopadhyay, *J. Chem. Soc., Dalton Trans.*, 2281-2288 (1984)

47 D. E. Fenton & R. Moody, *J. Chem. Soc., Dalton Trans.*, 219-220 (1987)

48 H. Adams, N. A. Bailey, S. R. Collinson, D. E. Fenton, J. C. Hawley & S. J. Kitchen, *J. Organo. Chem.*, **550**, 7-20, (1998)

49 B. Oussaid, B. Garrigues, A. M. Caminade & J. P. Majoral, *Phosphorus, Sulphur and Silicon*, **73**, 41-47, (1992)

50 D. J. Zwanenburg & H. Wynberg, *J. Org. Chem.*, **34**, 333-339 (1969)

51 J. D. E. Chaffin, *Ph.D Thesis*, The Nottingham Trent University, (1995)

52 J. M. Barker, J. D. E. Chaffin, J. Halfpenny, P. R. Huddleston & P. F. Tseki., *J. Chem. Soc., Chem. Commun.*, **23**, 1733-1734 (1993)

53 J. Halfpenny & Z. S. Sloman, *J. Chem. Soc., Perkin Trans. 1*, 1877-1879 (2000)

54 F. F. Blicke, '*Organic Reactions*', John Wiley & Sons, Inc., **1**, 303-341, (1942)

55 J. M. Barker, P. R. Huddleston & M. L. Wood, *Synth. Comm.*, **5**, 59-64, (1975)

56 P. Comba, N. F. Curtis, G. A. Lawrance, A. M. Sargeson, B. W. Skelton & A. H. White, *Inorg. Chem.*, **25**, 4260-4267 (1986)

57 N. W. Alcock & P. A. Tasker, *J. Chem. Soc., Chem. Comm.*, 1239-1240 (1972)

58 A. V. Bordunov, J. S. Bradshaw, V. N. Pastushok & R. M. Izatt, *Synlett*, 933-948 (1996)

59 S. J. Shuttleworth, S. M. Allin & P. K. Sharma, *Synthesis*, 1217-1239, (1997)

60 R. B. Merrifield, *J. Am. Chem. Soc.*, **85**, 2149-2154, (1963)

61 R. B. Merrifield, *Science*, **150**, 178-185, (1965)

62 N. S. Valera & D. G. Hendricker, *Polymer*, **21**, 597-598, (1980)

63 *Idem.*, *ibid.*, **22**, 1007-1009, (1981)

64 R. J. Card & D. C. Neckers, *J. Am. Chem. Soc.*, **99**, 7733-7734, (1977)

65 N. R. Champness, W. Levason, R. D. Oldroyd & D. J. Gulliver, *J. Organo. Chem.*, **465**, 275-281, (1994)

66 M. E. Mahmoud, E. M. Soliman, *Talanta*, **44**, 15-22, (1997)

67 M. Cinouini, S. Colonna, H. Molinari, F. Montanari & P. Tundo, *J. Chem. Soc.*, *Chem. Comm.*, 394-396, (1976)

68 H. Molinari, F. Montanari & P. Tundo, *ibid.*, 639-641, (1977)

69 E. Blasius & K. P. Janzen, *Pure & Appl. Chem.*, **54**, 2115-2128, (1982)

70 R. S. Paredes, N. S. Valera & L. F. Lindoy, *Aust. J. Chem.*, **39**, 1071-1079, (1986)

71 L. N. Ferguson & I. Kelly, *J. Am. Chem. Soc.*, **73**, 3707-3709, (1951)

72 Z. Eckstein & A. Lukasiewicz, *Bull. Acad. Pol. Sci. Ser. Sci. Chim.*, **7**, 789-796, (1959)

73 J. Strumillo and A. Kotelko, *Acta. Pol. Pharm.*, **24**, 271-274, (1967)

74 Beilstein Registry number 5126882

75 J. H. Billman & J. W. McDowell, *J. Org. Chem.*, **26**, 1437-1440, (1961)

76 C. E. Frosst & Co, *GB Patent* 987438, (1961)

77 H. K. Porter, '*Organic Reactions*', John Wiley & Sons, Inc. (NY), **20**, 455-481, (1973)

78 B. S. Furniss, A. J. Hannaford, P. W. G. Smith & A. R. Tatchell, '*Vogel's Textbook of Practical Organic Chemistry*', 5th Ed., Longmann Scientific & Technical, Harlow (England), 895, (1989)

79 'International Tables for X-ray Crystallography', **I**, The Kynoch Press, Birmingham (England), (1969)

80 DIRDIF94: P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, R. de Gelder, R. Israel & J. M. M. Smits. The DIRDIF-94 program system, Technical Report of the Crystallography Laboratory, University of Nijmegen (The Netherlands), (1994)

81 Least Squares function minimized:

$\sum w(|F_o|-|F_c|)^2$ where

$w = 1/[\sigma^2 (F_o)] = [\sigma^2_c (F_o) + p^2F_o^2/4]^{-1}$

$\sigma_c(F_o)$ = e.s.d. based on counting statistics

p = p-factor

82 Standard deviation of an observation of unit weight:

$[\sum w(|F_o|-|F_c|^2/N_o-N_v)]^{1/2}$

where: N_o = number of observations
N_v = number of variables

83 D. T. Cromer & J. T. Waber, 'International Tables for X-ray Crystallography', **IV**, The Kynoch Press, Birmingham (England), Table 2.2 A (1974).

84 J. A. Ibers & W. C. Hamilton, *Acta Crystallogr.*, **17**, 781-782, (1964).

85 D. C. Creagh & W. J. McAuley, 'International Tables for Crystallography', Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.6.8, 219-222 (1992).

86 D. C. Creagh & J.H. Hubbell, 'International Tables for Crystallography', Vol C, (A.J.C. Wilson, ed.), Kluwer Academic Publishers, Boston, Table 4.2.4.3, 200-206 (1992).

87 teXsan for Windows: Crystal Structure Analysis Package, Molecular Structure Corporation (1997).

88 J. H. Billman & K. M. Tai, *J. Org. Chem.*, **23**, 535-539, (1958)

89 A. T. Mason, *Chem. Ber.*, **20**, 267-277, (1887)

90 *e.g.* A. I. Vogel, '*A Text Book of Practical Organic Chemistry*', 3rd Ed., Longman, Green & Co. Ltd (London), (1959)

91 P. R. Huddleston, *personal communication*

92 J. H. Billman & A. C. Diesing, *J. Org. Chem.*, **22**, 1068-1070, (1957)

93 J. H. Billman, J-Y. C. Ho & L. R. Caswell, *ibid.*, **22**, 538-539, (1957)

94 *Idem.*, *ibid.*, **17**, 1375-1378, (1952)

95 R. O. Hutchins, K. Learn, B. Nazer & D. Pytlewski, *Organic Prep. and Procedures Int.*, **16**, 335-372, (1984)

96 A. Pelter, R. M. Rosser & S. Mills, *J. Chem. Soc., Perkin Trans. 1*, 717-720, (1984)

97 D. S. Kemp, J. A. Grattan & J. Reczek, *J. Org. Chem.*, **40**, 3465-3466, (1975)

98 D. H. Williams & I. Fleming, '*Spectroscopic methods in organic chemistry*' 5th Ed., The McGraw-Hill Companies (London) (1995)

99 J. March, '*Advanced Organic Chemistry – Reactions, Mechanisms, and Structure*', 3rd Ed., John Wiley & Sons, 800, (1985)

100 *Idem., ibid.*, 1103-1104, (1985)

101 W. M. Jones, *J. Am. Chem. Soc.*, **82**, 2528-2532, (1960)

102 L. M. Harwood & C. J. Moody, '*Experimental Organic Chemistry – Principles and Practise*', Blackwell Scientific Publications, 686-687, (1989)

103 B. Dietrich, P. Viout & J. M Lehn, '*Macrocyclic Chemistry – Aspects of Organic and Inorganic Supramolecular Chemistry*', VCH, (1993)

104 V. H. Krässig, *Makromol. Chem.*, **17**, 77-130, (1955)

105 HPLC analysis performed by R. Cooper, Laporte R & D, Middlesbrough

106 Gas chromatography performed by A. T. Franklin, The Nottingham Trent University

107 R. C. LaRock, 'Comprehensive Organic Transformations', VCH (NY), 412-415, (1989)

108 H. H. Hodgson, *J. Soc. Dyers. Colour*, **59**, 246-247, (1943)

109 M. Chalton, *personal communication*

110 J. P. Idoux, *J. Chem Soc.* (C), 435-437, (1970)

111 M. Hojo, V. Takagi & Y. Ogata, *J. Am. Chem. Soc.*, **82**, 2459-2462, (1960)

112 B. H. Han, D. H. Shin & S. Y. Coh, *Tetrahedron Lett.*, **26**, 6233-6234, (1985)

113 O. L. Brady, J. N. E. Day & C. V. Reynolds, *J. Chem Soc.*, 2264-2266, (1929)

114 H. H. Hodgson & S. Birtwell, *J. Chem Soc.*, 75-77, (1944)

115 Z. S. Sloman, *Ph.D Thesis*, The Nottingham Trent University, (1999)

116 J. I. Crowley & H. Rapoport, *Acc. Chem. Res.*, **9**, 135-144, (1976)

117 V. Dudler, L. F. Lindoy, D. Sallin & C. W. Schlaepfer, *Aust. J. Chem.*, **40**, 1557-1563, (1987)

118 W. Parr & K. Grohmann, *Tetrahedron Lett.*, 2633-2636, (1971)

119 A. E. Koziol, R. C. Palenik & G. J. Palenik, *J. Chem. Soc., Chem. Commun.*, 226-227, (1988)

120 W. R. Harshbarger & S. H. Bauer, *Acta Crystallogr.*, **B26**, 1010-1020, (1970)

121 L. Pauling, '*The Nature of the Chemical Bond*', 3rd Ed., Cornell University Press (NY), 260, (1980)

122 J. L. Atwood, S. G. Bott, C. Jones & C. L. Raston, *J. Chem. Soc., Chem. Commun.*, 1349-1351, (1992)

123 A. Gavaglioni & R. Cini, *J. Chem. Soc., Dalton Trans.*, 1149-1158, (1997)

124 K. Henrik, P. A. Tasker & L. F. Lindoy, *Progress in Inorganic Chem.*, **33**, 1-58, (1985)

125 P. A. Tasker, J. Trotier & L. F. Lindoy, *J. Chem. Research*, 328-329, (1981)

126 G. Labat, *personal communication*

127 D. C. Coomber, *Ph.D Thesis*, The Nottingham Trent University, (1998)

128 R. M. Izatt, R. L. Bruening, B. J. Tarbt, D. Griffin, M. L. Bruening, K. E. Krakowiak & J. S. Bradshaw, *Pure & Appl. Chem.*, **62**, 1115-1118, (1990)

129 S. Radi, A. Ramdani, Y. Lekchiri, M. Morcellet, G. Crini, L. Janus & B. Martel, *J. Appl. Polymer Sci.*, **78**, 2495-2499, (2000)

130 R. L. Alldredge & G. M. Lochhead, *Abstr. Pap. Am. Chem. Soc.*, Apr. 14-19th, **201**, (1991)

131 R. M. Izatt, R. L. Bruening & M. B. Borup, *Wat. Sci. Tech.*, **23**, 301-308, (1991)