Synthesis and Characterisation of Novel α-Functionalised Phosphoryl Derivatives

The appendix (published articles) has been redacted at the request of the university.

Abstract

This thesis focuses on the synthesis and study of α-aminoalkylphosphinic acids, α-aminoalkylphosphonic acids and macrocycles containing these sub-units.

There are two broad types of macrocyclic systems that are targeted:

(i) C-functionalised α-aminophosphonic acids; and

(ii) N-functionalised α-aminophosphonic acids

A novel N-functionalised macrocycle ring that includes four pendant methylenephosphonates with embedded pyridine has been successfully prepared. The strategy employed involved the synthesis of the macrocycle prior to addition of the pendant arms. However, the synthesis of analogous systems containing thiophene failed principally due to the very poor solubility of the intermediate Schiff base.

The N-functionalised macrocycle with embedded pyridine was synthesised via the Mannich reaction. The protonation behaviour of this macrocycle has been followed by ^{31}P and ^{1}H NMR spectroscopy. The initial protonation pattern of the N-functionalised macrocycle is rather like its corresponding macrocyclic amine. The proton NMR spectrum of its lanthanum (III) complex in aqueous solution indicates that the complex adopts only one of the five possible configurations, SSSS/RRRR. The crystal structure of the novel N-functionalised macrocycle shows an extended hydrogen-bonded structure in the solid state. The macrocycle has an unusual conformation with the pendant arms alternating 'up' and 'down' around the ring. The La^{3+} complex has a unique ten-co-ordinate geometry with all pendant arms co-ordinated to the La^{3+} ion, which is in the plane of the six-macrocyclic nitrogen donors.

The synthesis of C-functionalised macrocycles with embedded pyridine or thiophene involved a strategy in which the macrocyclisation occurred after the phosphonic acid groups were introduced. The synthesis proved to be problematic in both the thiophene and pyridine systems. In the case of the pyridine system the synthetic route was achieved to the penultimate step at which point the key macrocyclisation step failed to occur. In the case of the thiophene systems problems arose during the deprotection step, which prevented progress with this synthetic route.

Another aspect of this thesis was to investigate synthetic procedures aimed at thiophene bis [α-aminoalkylphosphinic] acids. During this work a reaction of 2,5-thiophenedialdehyde with Ph_2CHNH_2 and hypophosphorous acid yields novel α-hydroxy- or α-amino-methylphosphinic derivatives depending on reaction conditions: the X-ray structure analysis of diphenylmethylammonium 5-formyl-2-thienyl (hydroxy) methylphosphinate provides the first direct structural information on the α-hydroxyalkylphosphinate class of compounds. Key compounds prepared in the course of this work were submitted for screening in anti-cancer programmes and in no case was significant anti-cancer activity observed.

Mahesh Jayantilal Sanganee, BSc (Hons), CChem MRSC

This thesis has been submitted to the University of North London for the degree of Doctor of Philosophy.

February 2001

DEDICATION

This thesis is dedicated to Mummy and to the memory of my dearest Papa

ACKNOWLEDGEMENTS

I wish to express my sincere thanks to my supervisor Dr Annie Bligh for her advice, guidance, and with her continuing support during the course of this work.

I would also like to thank GlaxoSmithKline (GSK) for the provision of laboratory and library facilities in the past at Dartford and now at Stevenage site. Thanks also go to the spectroscopy team and my colleagues at GSK for helpful discussions.

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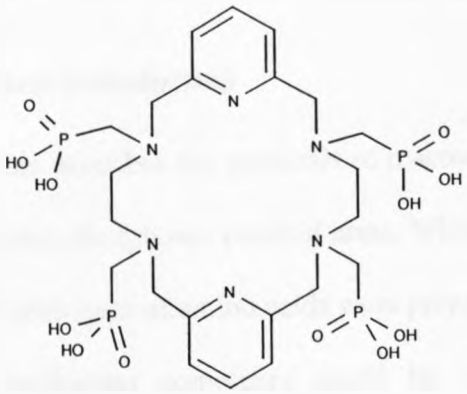
I am also grateful to Professor Mary McPartlin and Mr Thomas M.Woodroffe for their X-ray crystallographic determination and Carlos Geraldes for his protonation studies.

Contents

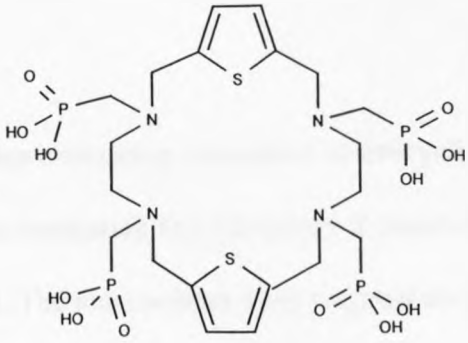
Abbreviations

NMR	nuclear magnetic resonance
m.p.	melting point
IR	infra-red
LSIMS	liquid secondary ion mass spectrometry
MRI	magnetic resonance imaging
CT	computerised tomography
DMSO	dimethylsulfoxide
DMF	*N,N*,-dimethylformamide
Ph	phenyl
Bn	benzyl
Et	ethyl
Py	pyridine
THF	tetrahydrofuran
TMEDA	*N,N,N'N'* tetramethylethylenediamine
EDTA	ethylenediaminetetraacetic acid
DOTA	1,4,7,10-tetraazacyclododecane-*N,N',N'',N''*-tetraacetic acid

Compound Abbreviations



N6TPH8



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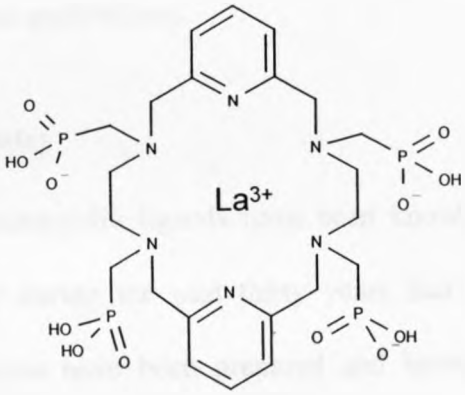
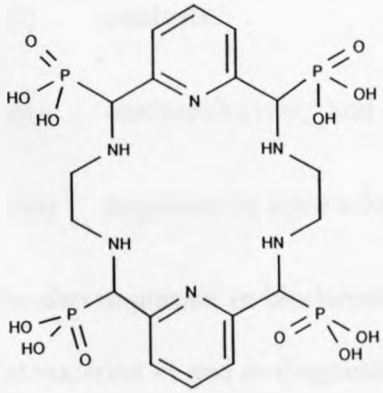


[La(N6TPH5)]



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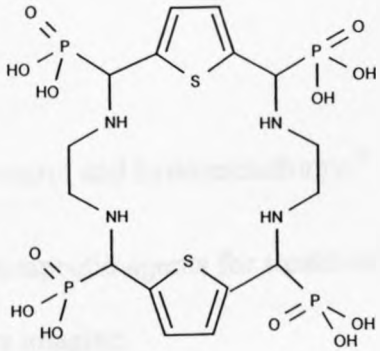


N4S2TPH8_1

Chapter 1

INTRODUCTION

1.1 A General Introduction

This thesis describes the synthesis of macrocycles containing embedded heterocyclic systems bearing phosphorus pendant arms. Whilst investigating this chemistry a range of phosphorus analogues of amino acids were prepared. The macrocycles were targeted such that their lanthanum complexes could be studied as NMR contrast agents. The phosphorus amino acid ligands are also of interest because of their importance in both biological and non-biological applications.

1.2 Macrocyclic Chemistry

Metal complexes of macrocyclic ligands have been known for more than seventy years. However, it is only during the past thirty years that a large number of new macrocyclic ligand complexes have been prepared and investigated because of their importance in chemical areas as:

(i) catalysts;[1]

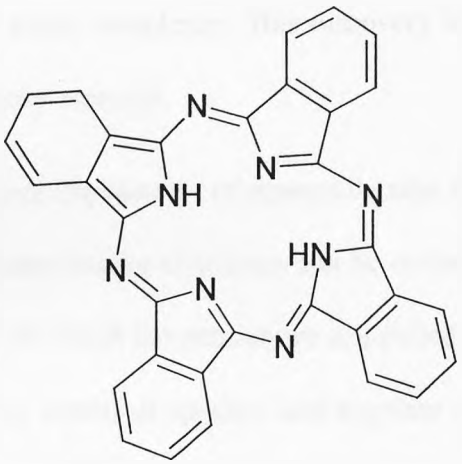
(ii) semiconductors;[2] and

(iii) sequestering agents for use in pollution control and hydrometallurgy.[3]

They are also important in biochemical areas both as therapeutic agents for treatment for metal intoxication or and as diagnostic agents for tumour imaging.

Macrocyclic ligands consist of an organic framework of carbon and heteroatoms arranged in a cyclic manner. A commonly accepted definition of a macrocyclic ligand is that it contains at least three donor atoms and the macrocyclic ring should consist of a minimum of nine atoms.

Prior to 1960, the phthalocyanine **(1),** a highly conjugated macrocycle that bears a strong resemblance to the natural porphyrin system, was the only well-established synthetic cyclic ligand.



(1)

Phthalocyanines, and related derivatives, have been used as:

(i) semiconductors;[4]

(ii) catalysts for use in chemical transformations;[5] and

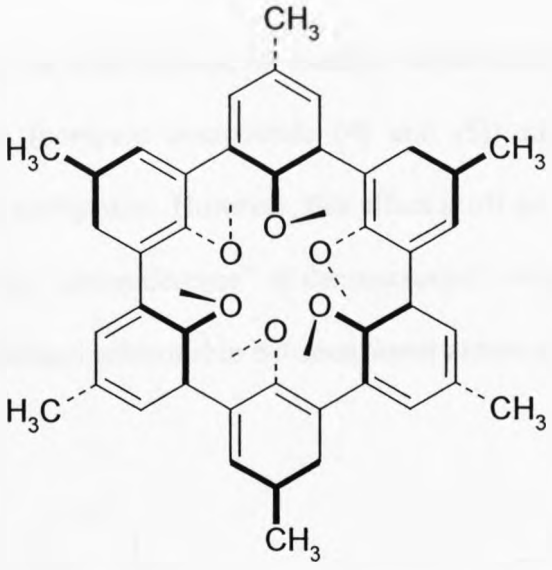
(iii) colouring agents as used in the dyes industry.[6]

Since 1960 a rapid interest in macrocyclic chemistry has resulted in a large number of macrocycles being prepared. In addition, the importance of metal ions in biological systems has become more apparent. The research involving the syntheses of macrocycles has concentrated on the preparation of natural macrocycles (e.g. corrins, porphyrins) as well as 18-crown-6 related compounds. Indeed the importance of synthetic macrocycles was recognised by the awarding of Nobel prizes in 1987 to:

(i) C.J Pedersen[7] for his discovery of crown ethers. The unique property of the crown ethers is to preferentially bind to alkali and alkaline earth metal ions to form stable complexes. This discovery lead to a completely new area of chemistry research.

(ii) J.M Lehn[8] drove the concept of supermolecular chemistry into the field it is today. Supermolecular chemistry can be defined as chemistry "beyond the molecule" in which the entities are compelled as a result of association of two or more chemical species held together by intermolecular forces. Lehn is now unofficially regarded as the "father of supermolecular chemistry."

(iii) D. J Cram[9] whose key contribution to this field was his treatise on the "principle of preorganisation." A typical example of a preorganised cavity involves macrocycle **(2),** which forms very stable complexes with small alkaline actions (Li^+, Na^+).

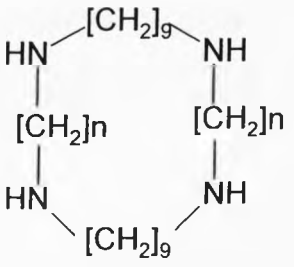


(2)

1.2.1 The Macrocyclic Cavity

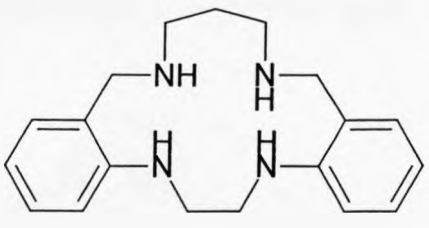
The chelation environment (hole size, donor field) offered by macrocyclic ligands is highly dependant on:

(i) the number of atoms in the macrocyclic ring, for example tetraza macrocycles of type **3**;



(3)

(ii) the nature of the donor atoms, for example replacement of a sulphur atom for nitrogen (compare compounds **(4)** and **(5)**) may be expected to decrease the cavity size. However, this effect is off set by a corresponding increase in the "circumference" of the macrocyclic ring. As such there is no straightforward relationship between donor atoms and cavity size.



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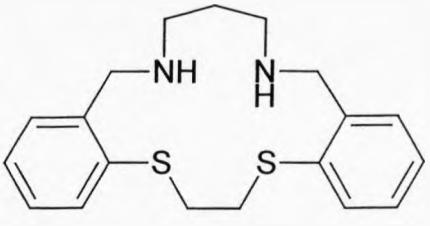


(5)

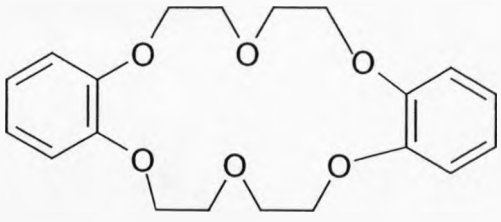
(iii) Hybridization of the donor atoms, going from an sp^3-amine donor atom to an sp^2 imine donor leads to a reduction of the macrocyclic hole size. Because of the high s-orbital character, the sp^2 hybrids are not as diffuse as sp^3 hybrids and hence their overlap with appropriate metal orbitals leads to a decrease in the corresponding metal-nitrogen bond length.

All of these factors contribute to defining the selectivity towards metal ions and the properties exhibited by such complexes.

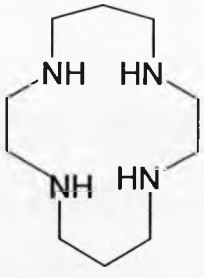
1.2.2 Synthetic Macrocycles

There are five different types of macrocycles; these can be categorised according to the types of donor atoms incorporated into the macrocyclic ring itself these are:

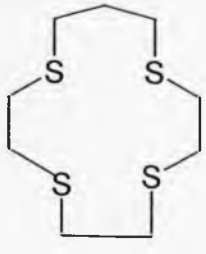
(i) oxygen donor (crown ethers)



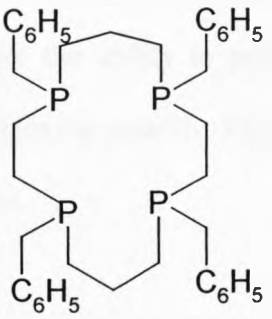
(ii) nitrogen donor (aza macrocycles)

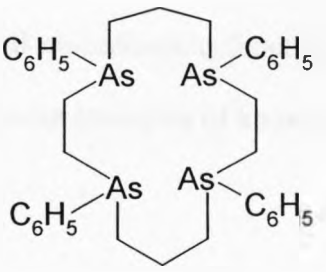


(iii) sulphur donor (thioethers)

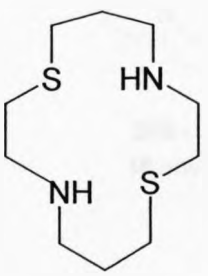


(iv) phosphorus and arsenic donors





(v) mixed-donor ligands



The macrocyclic ligands with nitrogen, sulphur, phosphorus and/or arsenic donors have considerable affinity for transition and other heavy metal ions and generally form less stable complexes with alkali and alkaline earth metals. In contrast oxygen incorporated macrocycles such as crown ethers show strong complexing ability towards alkali and alkaline earth metals.

1.2.3 Macrocyclic Ligands with Pendant Functional Groups

There has been increasing interest in synthesis of macrocycles with pendant arms, because they have the ability to provide additional co-ordinating functions and hence enhance the complexing stability. **Figure 1** shows some examples of known macrocycles with pendant arms.

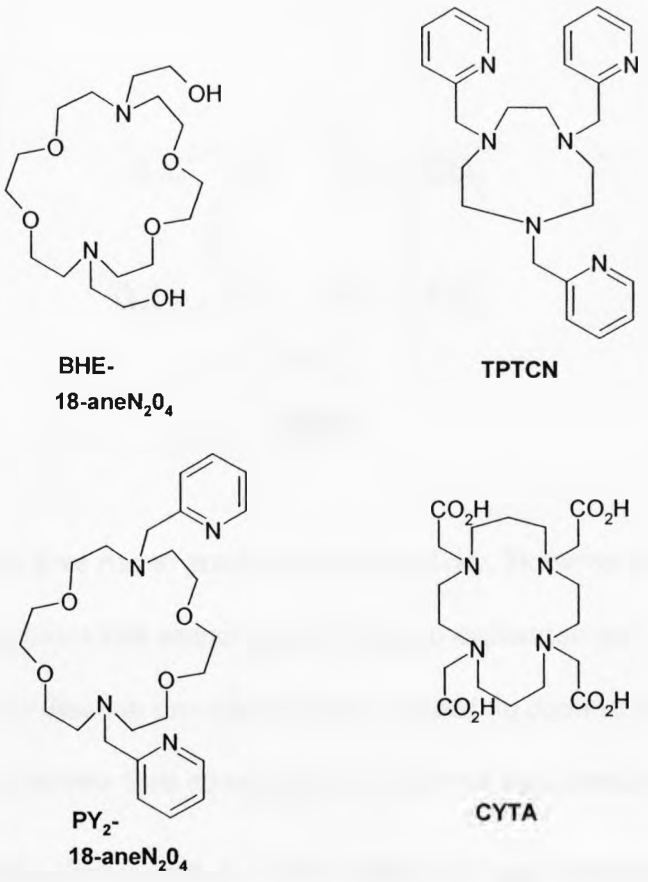
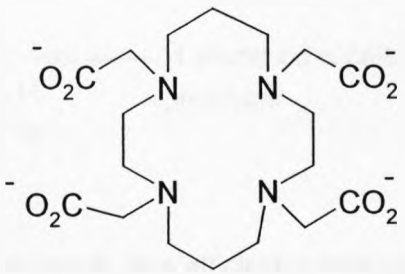


Figure 1: Examples of known macrocycles with pendant arms

Ligands that have neutral oxygen donors (alcohols and ethers) on pendant groups on macrocycles have been synthesised in abundance.[10,11] The effect of hydroxyethyl groups on metal ion size selectivity patterns appears to be identical with the effect in

other situations where groups bearing neutral oxygen donors are added to existing ligands.

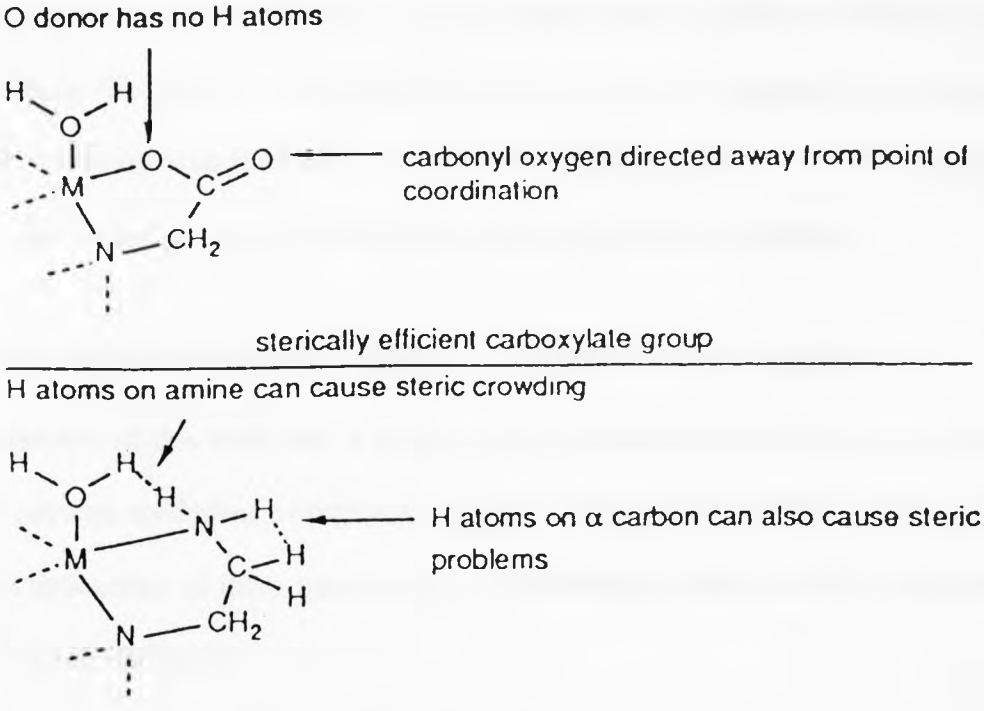
A large amount of work has also been reported[12,13] on the complexing properties of N-acetate-substituted macrocycles. An area of considerable interest has been tetraazamacrocycles with four added N-acetates **(TETA)**.[12]



TETA

These ligands can give rise to greater metal selectivity. However this does present a problem for some metal ions that cannot expand their co-ordination number to meet the potential octadentate co-ordination provided by these ligands. In contrast complexation of large metal ions that can expand their co-ordination number to eight binds very strongly.

In general the carboxylates such as **CYTA (Figure 1)** are sterically more efficient than amine donors (or alcohols), this allows for efficient co-ordination of other donor groups present. The origin of the greater steric efficiency of the carboxylate donor than the amine donors is shown diagrammatically below.



Many other types of donor groups have been attached to macrocycles as pendant groups. Among these are pyridyl groups,[14,15] phenolate groups,[16] and 2-aminoethyl groups.[17,18] There is insufficient evidence to say that these groups do or do not produce selectivities or stable complexes. There is some evidence also to indicate that the pyridyl group is sterically more demanding than the carboxylate group. For example in the crystal structure of **[Fe (TPTCN)]$^{2+}$** (**TPTCN** is shown in **Figure 1**) the Fe(II)-N bonds of the macrocycle ring are not particularly short.[15] The phenolate group as a pendant group may very well be sterically efficient in the same way as a carboxylate group, since its donor atom is oxygen without any attached hydrogens or other atoms.

Macrocycles with pendant arms that have a pyridine-functionality such as **(TPTCN)** were reported by Tsukube[19] to show specific binding affinity for the hard Na^+ cation whereas the parent macrocyclic polyamines are well recognised as potential ligands of soft heavy transition metal cations. This unique property of **(TPTCN)** makes them Na^+ carriers and is therefore suitable for effective membrane transport.

1.2.4 Macrocycles Containing Pyridine or Thiophene as Donor Ligands

The objective of this work was to prepare novel thiophene and pyridine macrocycles with four pendant methylene phosphonate groups and to investigate the structures and aqueous complexation of these macrocycles with lanthanide metal ions. The complexes produced will be studied for:

(i) their biological activities;

(ii) their potential as magnetic resonance imaging agents; and

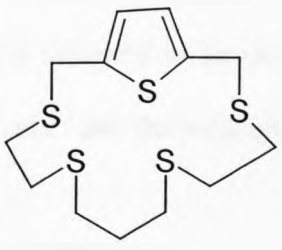
(iii) as chelators in radiopharmaceutical applications.

In addition the aim was to synthesise and characterise compounds containing α-aminophosphinic acid functional groups. These compounds will be of interest because of their potential anti-bacterial, herbicidal and fungicidal activities.

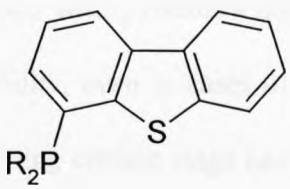
1.2.4.1 Thiophene as Donor Ligands

Thiophene is not considered a strong donor ligand. However, thiophene is known to be a reasonable ligand for group II cations particularly in their low oxidation state. There are a number of different examples in which thiophene has been shown to act as a ligand. For example:

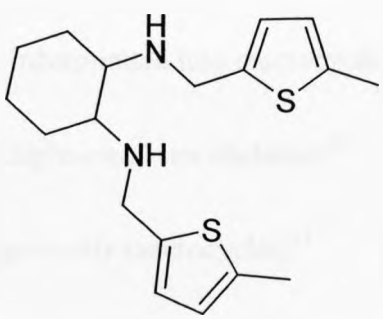
(i) Ruthenium (II) complex [20] of :



(ii) Copper (II) complex [21] of:



(iii) Silver (I) complex[22] of:



In general thiophene-sulphur metal distances are within Van der Waals contact distance, indicating some partial bonding between sulphur and metal.

Metal complexes of thiophene are of interest since the interaction of these aromatic heterocycles with metal is assumed to be central to the mechanisms of both catalytic desulfurisation of fossil fuels[23] and the poisoning of nobel metal catalysts.[24]

1.2.4.2 Pyridine as Donor Ligands

Pyridine is known to be a good donor ligand. This is expected, as there is a lone pair on nitrogen, which is not part of the aromatic sextet and is available for metal co-ordination. This, combined with pyridine's high dipole moment relative to alkylamines, increases its donating ability, even in cases of co-ordinating non-π-bonding metals.[25] In addition, pyridine-containing chelate rings have lower ring strain than analogous chelate rings formed from alkyl amines.[26]A wide variety of metal ions are known to form complexes with pyridine based ligands. These ranges from alkali metals,[27] alkali earth metals,[28] transition metals,[29] heavy metals,[30] and lanthanides.[31]

Pyridine has been incorporated into macrocyclic polyaza ligands to provide:

(i) multiple-metal ion chelators;[32]

(ii) large-cavity macrocycles;[33]

(iii) cryptands;[34] and

(iv) components of an ion-selective electrode.[35]

Nelson pioneered the work on the pyridine containing macrocycles based on template synthesis, which is generally high yielding. In general the macrocycles were

prepared by reacting 2,6-diacetylpyridine (DAP) with diamine in equimolar amounts in the presence of a metal salt. The importance of the metal ion is shown by the fact that in its absence only viscous oils are obtained, these having indefinite composition and properties suggestive of an oligomeric/polymeric constitution. The macrocycles were isolated as crystalline complexes of the metal ion used as a template in their formation. Further details on the mechanism to pyridine-containing macrocycles is presented in section 2.2

1.2.5 Lanthanide Macrocyclic Complexes

Since the discovery of the lanthanide elements, the co-ordination chemistry of the trivalent lanthanide (III) ions has received considerable attention with the level of this attention increasing in recent years.[36] This research is active research because of their applications in fundamental and applied sciences for example as:

(i) contrast agents in magnetic resonance imaging;[37,38]

(ii) phosphors (in television screens) and lasers;[39]

(iii) catalysts in the transesterification of RNA;[40] and

(iv) NMR shift reagents.[41,42]

This work primarily targets compounds that will be tested as contrast agents. The following section provides more detail in this field.

1.2.5.1 Magnetic Resonance Imaging (MRI) Contrast Agents

The development of MRI techniques as a clinical diagnostic tool has promoted the need for a new class of pharmaceuticals. This need arose from the fact that separation of tumour from oedema was frequently better with contrast enhanced CT-X-ray than with unenhanced MRI. The MRI contrast agent would be administered to a patient in order to enhance the image contrast between normal and disease tissue and/or indicate the status of organ function or blood flow.

The MRI contrast agents (paramagnetic compounds) reduce the proton relaxation times of the water protons. It is the effect on the water protons that is detected not the agent itself. Since paramagnetic compounds possess at least one unpaired electron a net magnetic moment is created in the paramagnetic species due to the unpaired electron spins. The net magnetic moment of an electron spin is of a magnitude 657 times that of a proton. It is, therefore, apparent that an electron is nearly 500,000 times more effective than a proton (relaxation is equal to the square of the magnetic moment, i.e. 657^2). Additionally, since some paramagnetic species may have more than one unpaired electron, such as the gadolinium (III) ion with seven unpaired electrons, the relaxation efficiency of that paramagnetic species is dramatically increased.

The use of paramagnetic ions as agents for enhancing the relaxation of water protons has been reported since the late 1940s.[43,44] Since the contrast in MRI is generated by variations in the relaxation times, there is therefore considerable interest in agents developed to alter these relaxation times to increase the image contrast. For the metal complex to be a successful contrast agent it must satisfy certain criteria.[45]

(i) To produce strong relaxation effects, the paramagnetic ion should preferably have a high electron spin number, S, and a long electron spin relaxation time.

(ii) The distance between the paramagnetic ion and the protons that it is relaxing should be minimal, that is the ion, whether complexed or not, should bind directly to the water molecules. It is important, therefore, that when designing a paramagnetic complex to ensure that water is not totally excluded from direct access to the metal ion.

(iii) Toxicity is an important feature to be considered since the use of free ions is extremely hazardous. However, complexes of ions with chelating agents such as **EDTA** and **DTPA** are safer than the aqua ion because the metal ion is held strongly by these ligands and is prevented from interacting with enzyme or membrane systems. Administrations of the metal in the form of a chelate has a second advantage in that the chelating ligand can be specially designed to overcome problems associated with poor solubility of some free metal ions at physiological pH. This also enables the agent to travel within lipophilic/hydrophobic and lipophobic/hydrophilic media in the body.

(iv) It would be desirable to target a contrast agent to specific sites of interest. The nature of the ligand is of importance.

Although **[Gd (DTPA)($H_2$0)]** $^{2-}$ is the best contrast agent in use to date as far as toxicity is concerned, the chelate itself exhibits low relaxivity, and, due to its non

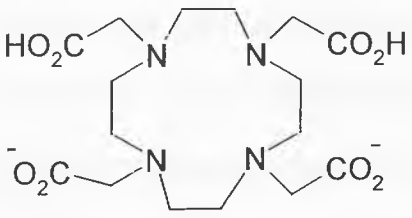
planarity, does not allow for maximum co-ordination of water to the metal ion compared to the free Gd^{3+} aqua ion. For these reasons there is significant room for improvement in the development of contrast agents taking into consideration better relaxivities and specificity.

Recent advances on contrast agents are based on relatively planar macrocyclic ring structures due to the high stability associated with these compounds, the increased accessibility of the water molecules and hence enhanced relaxivity.

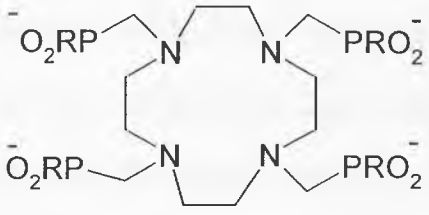
Most efforts to date have focused on symmetric macrocycles consisting of two identical aromatic head units, mainly pyridines,[46,47] furans,[48,49] and phenols.[50,51] The complexes of 18- or 22-membered hexaaza donor ligands have received special attention because of their unique inertness towards metal release in solution, even under conditions that would result in the immediate decomposition of most other lanthanide complexes.

1.2.5.2 Structure and Stability of Lanthanide Complexes

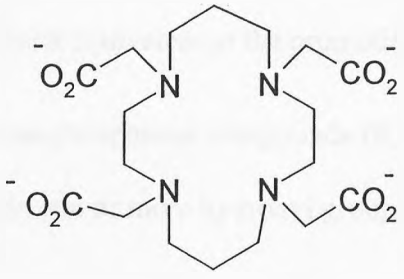
The most common co-ordination numbers of lanthanide ions are eight and nine. In order to form a stable complex in aqueous solutions the ligand must have donor atoms that satisfy the demands of hard, polarising lanthanide ions. Thus among the neutral donors amine nitrogen is preferred to ether oxygen and amongst the hard anionic donor's carboxylates, phosphonates and phosphinates are preferred groups. Thus compounds such as **DOTA**,[52] **N4TPT(CH_3)** and **N4TPT(CH_2Ph)**[53] **(Figure 2)** form well-defined 1:1 complexes with all of the lanthanide ions that possess high formation constants and are kinetically inert with respect to acid or metal ion.



DOTA



N4TPT(R=CH_3)
N4TPT(R= CH_2Ph)



TETA

Figure 2: Some examples of compounds that form stable complexes with lanthanide ions

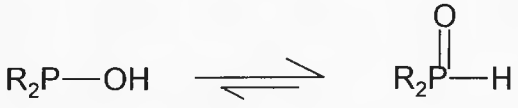
The nature of the anionic donor is also important, and the more acidic phosphinates [**N4TPT(CH_3), N4TPT(CH_2Ph)**] form complexes that tend to resist protonation and hence exhibit excellent kinetic stability in acidic media.[54]

The majority of stable lanthanide complexes are formed with octadentate ligands and the most common geometry exhibited is the square antiprism and the dodecahedron.[55] The latter geometry is known for the terbium complex of 1,4,8,11-tetraazacyclotetradecane-1, 4,8,11-tetraacetate or **TETA**. The former is more commonly observed, and occurs[53] in the isostructural complexes of Y, Gd and Eu with **N4TPT(CH_2Ph)** where the angle of twist around the four-fold axis is only 29° which is well short of that found in an idealised antiprism (45°).

1.2.6 Phosphorus Chemistry

The electronic structure of the phosphorus atom is $1s^2\ 2s^2 2p^6 3s^2 3p^3$, the bonding electrons of phosphorus can be represented by $3p_x^1 3p_y^1 3p_z^1$, which in turn leads to the formation of trivalent compounds similar to the nitrogen atom. The energy to promote an electron from the 3s to the 3d levels in phosphorus is considerably large (1780 kJ mol^{-1}) and therefore is not available in normal chemical reactions unless the energy gain from their use is at least equivalent to the promotion energy involved.

Trivalent-phosphorus compounds (R_3P, where R can be hydrogen, alkyl, alkoxy etc) that contain one or more hydroxyl group exist largely in the phosphoryl form **(6)**:



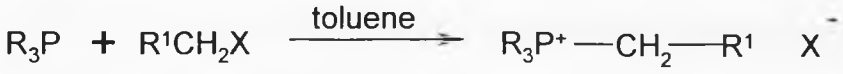
(6)

This is because of the strength of the P-O bond allowing the phosphorus to be pentavalent.

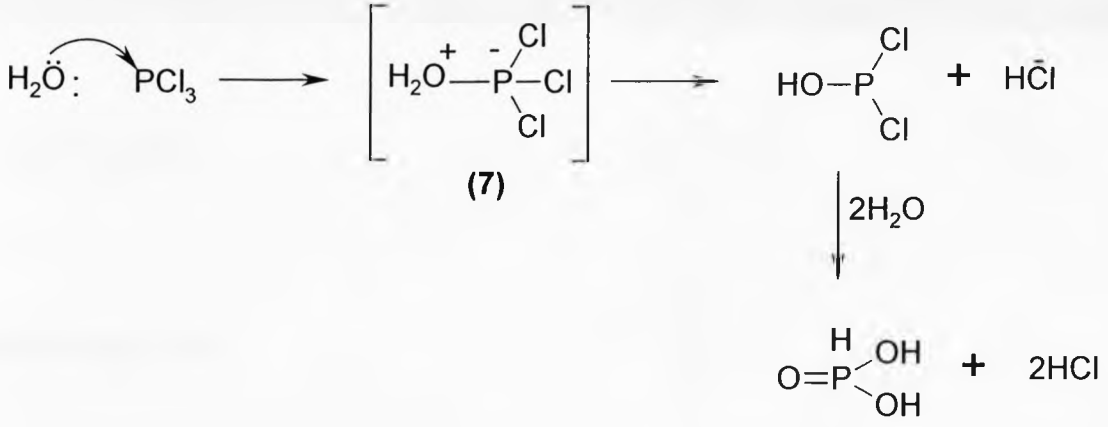
1.2.6.1 Reactivity of Trivalent Phosphorus

Trivalent phosphorus compounds can exhibit a range of reactivity exemplified by:

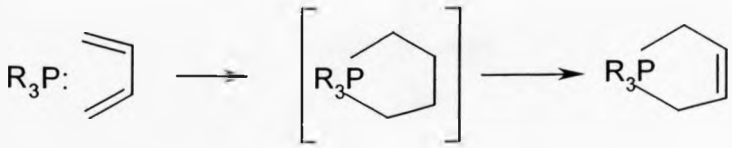
(i) its high nucleophilic character since the compounds contain a lone pair of electrons, a best known example of this is the formation of phosphonium salts with alkyl halides:



(ii) its electrophilic character, since phosphorus has empty d-orbital which allows many of its compounds to show electrophilic character by stabilising the intermediates in reaction with nucleophiles. For example in phosphorus trichloride the involvement of d-orbitals leads to stabilisation of the intermediate **(7)**:



(iii) its ability to exhibit dienophilic characteristics, for example, addition of phosphorus compounds with dienes are important routes to phosphorus heterocycles, e.g.



1.2.6.2 Reactivity of Pentavalent Phosphorus

The P=O bond occurs commonly in phosphorus compounds of which phosphorus oxy-acids merit discussion because of their relevance to the chemistry reported in this chapter. **Table 1** shows some examples of phosphorus oxy-acids.

The acids are strong [pK_1 (0.8-2.3)] and are often encountered as reagents. For example polyphosphoric acid which provides high acidity is used as a dehydrating agent.

Table 1: Examples of phosphorus oxy-acids

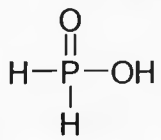
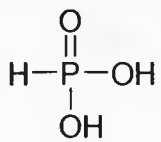
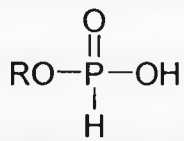
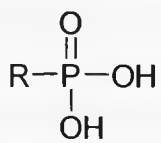
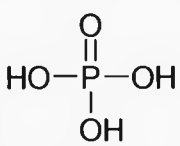
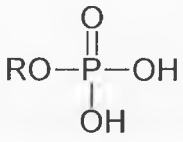
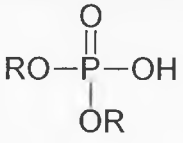
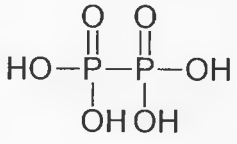
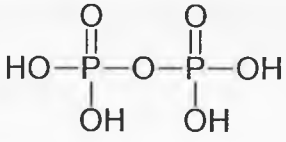
Acid	Formula
Phosphinic Acid	
Phosphorous Acid	
Monoalkyl Phosphite	
Alkanephosphonic Acid	
Phosphoric Acid	

Table 1-*continued*

Acid	Formula
Monoalkyl phosphate	
Dialkyl phosphate	
Hypophosphoric acid	
Pyrophosphoric acid	

The reactivity of phosphorus oxy-acids, is in many ways, analogous to that of the carboxylic acids as they form derivatives of type: acid chloride, esters, amides, anhydrides etc. The reactions of all these types of derivatives can be separated into two types: those, which involve reaction at the phosphorus atom, and those, which do not.

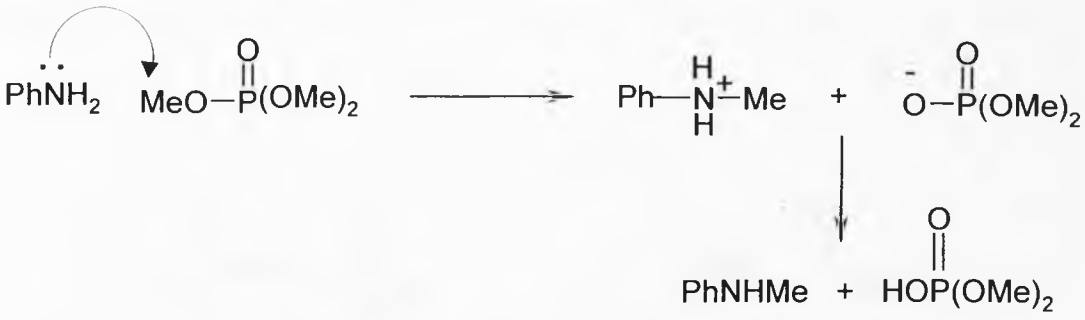
In reactions that involves an attack at the phosphorus atom, the phosphorus atom acts as an electrophile, as represented below:

The most studied phosphoryl compounds have been: (i) esters (X=OR), (ii) halides (X= halide); and (iii) amides ($X=NR_2$). Common nucleophiles include alcohols, water and amines. For example:

These types of reactions are extremely important because living organisms rely on them for both energy conversion and protein synthesis.

However, in reactions, which do not involve attack on the phosphorus atom, the phosphorus atom although not involved at the reaction site, modifies its reactivity.

For example, trimethyl phosphate reacts with aniline via an S_N2 mechanism, which involves a phosphorus oxy-anion as the leaving group, **Scheme 1**.



Scheme 1

1.3 Phosphorus Based Amino Acid Analogues

There is growing interest in the field of phosphorus analogues of amino acids, due to them having utility in both biological and non-biological applications as:

(i) substrates or inhibitors of enzymes involved in the metabolism of amino acids;[56,57]

(ii) metal-complexing agents which may control the uptake or removal of metal ions in living systems;[58,59]

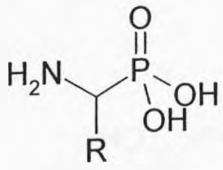
(iii) industrial chemicals, e.g. in water treatment, as sequestering agents;[60] and

(iv) in pollution control and metal extraction.[61]

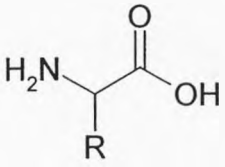
1.3.1 α-Aminoalkylphosphonic Acids

α-Aminoalkylphosphonic acids are structurally similar to α-amino acids except that an additional hydroxyl group is bonded to the phosphorus which makes the phosphonic acid groups more acidic than the equivalent carboxylic acid groups. In

addition the phosphorus atom is tetrahedral as opposed to the trigonal planar carbon atom.



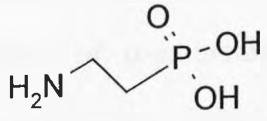
α-Aminophosphonic Acid



α-Amino Acid

1.3.1.1 Biological Activity and Natural Occurrence of α-Aminophosphonic acids

The first naturally occurring α-aminophosphonic acid to be isolated was 2-aminoethylphosphonic acid **(8)** by Horiguch and Kondatsu[62,63] from the ciliated protozoan.

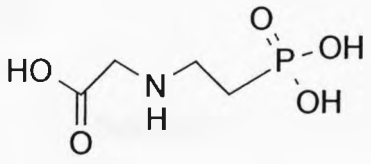


(in non-zwitterionic form)

(8)

The biological activity of α-aminoalkylphosphonic acids is such that it competes in biological processes with naturally occurring amino acids for the active site of the enzyme, because of its structural similarity to amino acids. This work has been reviewed in a comprehensive article by Kafarski and Lejczak.[64]

The synthetic derivative *N*-(phosphonoethyl) glycine **(9)**[65] is often referred to as glyphosate. Interest in these classes of compounds has increased rapidly because of their uses as herbicides within the agrochemical industry.



(9)

1.3.1.2 Synthesis of α-Aminoalkylphosphonic Acids

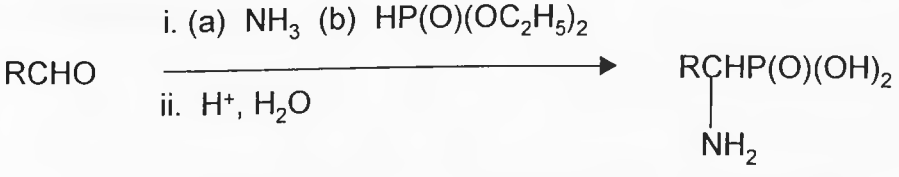
Schwarzenbach[66] proposed one of the first methods of preparing α-aminomethylphosphonic acid, from the reaction of the amine with chloromethylphosphonic acid in alkaline solution. This methodology was not suitable for general-purpose synthesis of α-aminomethylphosphonic acid because the reaction requires a temperature of 80 °C for several days **(Scheme 2)**.

$$RNH_2 + 2ClCH_2P(O)(OH)_2 + 2NaOH \longrightarrow RN(CH_2P(O)(OH)_2)_2 + 2NaCl$$

Scheme 2

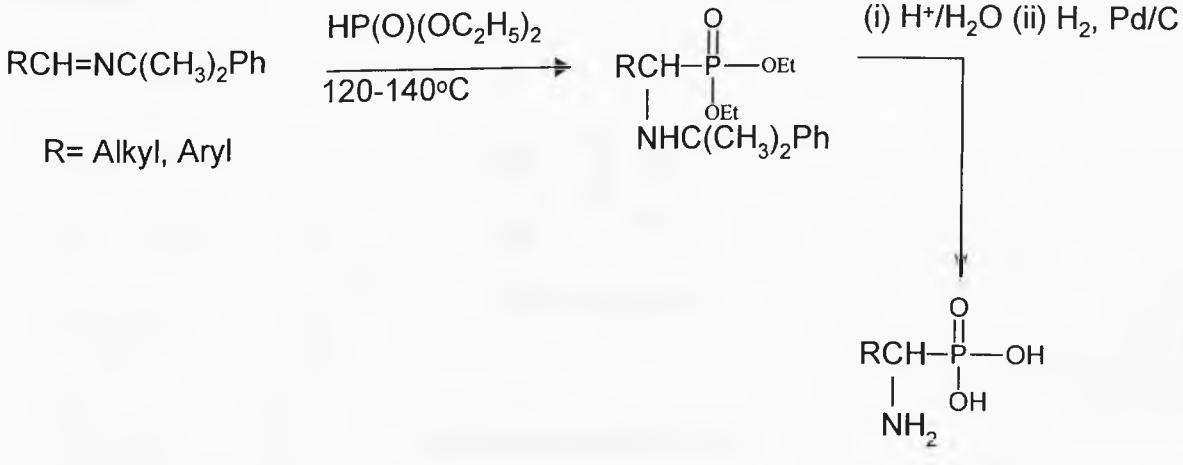
Kabachnik and Medved[67] described an alternative procedure for the preparation of α-aminophosphonic acids, which involved the addition of ammonia and diethyl phosphite

to either aldehydes or ketones, followed by the hydrolysis of the addition product **(Scheme 3)**. The reported yield by this method was generally low with a poor product purity profile.



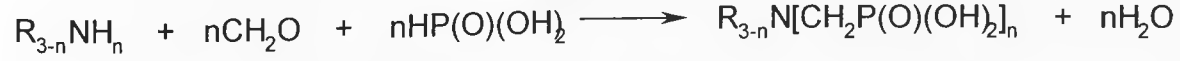
Scheme 3

Tyka[68] developed a general method of synthesis, which involved the addition of dialkyl phosphite to the Schiff base prepared from a benzylamine and a suitable carbonyl compound. Acid hydrolysis followed by the removal of the "*N*-benzyl group" by hydrogenolysis gave α-aminophosphonic acid in 61% yield **(Scheme 4)**.



Scheme 4

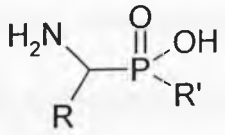
Moedritzer[69] developed a direct method for the preparation of α-aminophosphonic acid in high yields with good purity profile. Mannich type reaction conditions were employed using phosphorous acid, formaldehyde and an amine as reactants **(Scheme 5)**.



Scheme 5

1.3.2 α-Aminoalkylphosphinic Acids

Further to α-aminophosphonic acids, α-aminophosphinic acids are also structural analogues to α-amino acids, where a phosphinic acid group has replaced the carboxylic acid group.



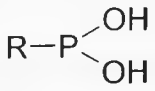
R^1= H or alkyl

α-Aminophosphinic Acid

The homologous series of α-aminophosphinic acids also exist where R^1 is alkyl, however these type of substituted compounds are not the focus of this thesis.

The α-aminophosphinic acids are also referred to as α-aminophosphonous acids but phosphonous implies that the phosphorus is in a tervalent state **(Figure 3)** so the term phosphinic acid[70] is more correct and is in accord with the IUPAC nomenclature.

Phosphonous Acid



Phosphinous Acid

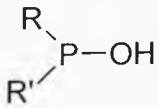
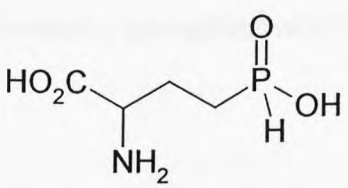


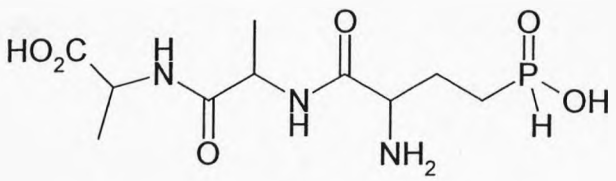
Figure 3: Tervalent Phosphorus

1.3.2.1 Biological Activity and Natural Occurrence of α-Aminophosphinic Acids

Examples of naturally occurring α-aminophosphinic acids are rare. The first naturally occurring compounds with hydrogen as substituent on phosphorus, **(10)** and **(11)** were recently isolated from bacteria (*Streptomyces hygroscopicus*).[71]



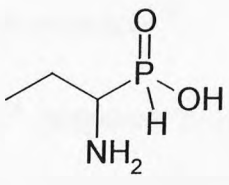
(10)



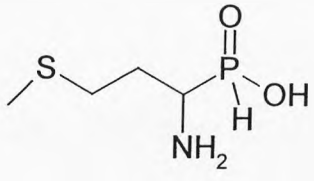
(11)

The interest in α-aminophosphinic acids arose from their physiological activities as potential antibacterial agents,[72,73] pesticides,[74] neuroactive compounds and anticancer drugs.[75]

Two examples include, α-aminoisobutylphosphinic acid **(12)** and α-amino-γ-methylthiopropylphosphinic acid **(13)**, which are biologically active α-aminophosphinic acids. They were found to be effective reversible inhibitors of the tRNA aminoacylation reaction of L-valine and L-methionine.[76]



(12)

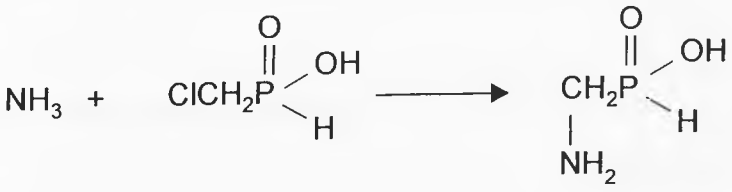


(13)

In general, the biological activity of α-aminophosphinic acids arose from their competition with their amino acid analogues for active sites of enzymes or cell receptors.

1.3.2.2 Synthesis of α-Aminoalkylphosphinic Acids

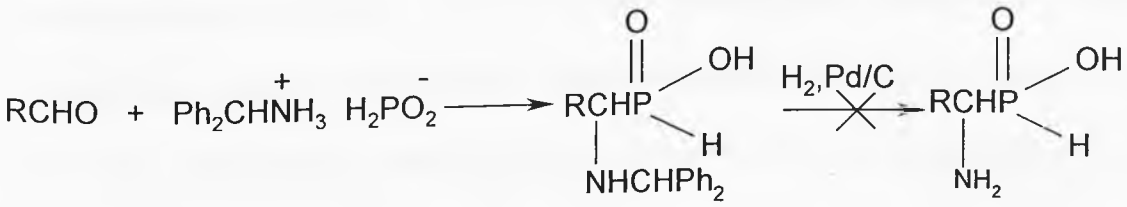
The glycine analogue was the first reported example of the α-aminoalkylphosphinic acid, which was prepared by the ammonolysis of chloromethylphosphinic acid **(Scheme 6)**.



Scheme 6

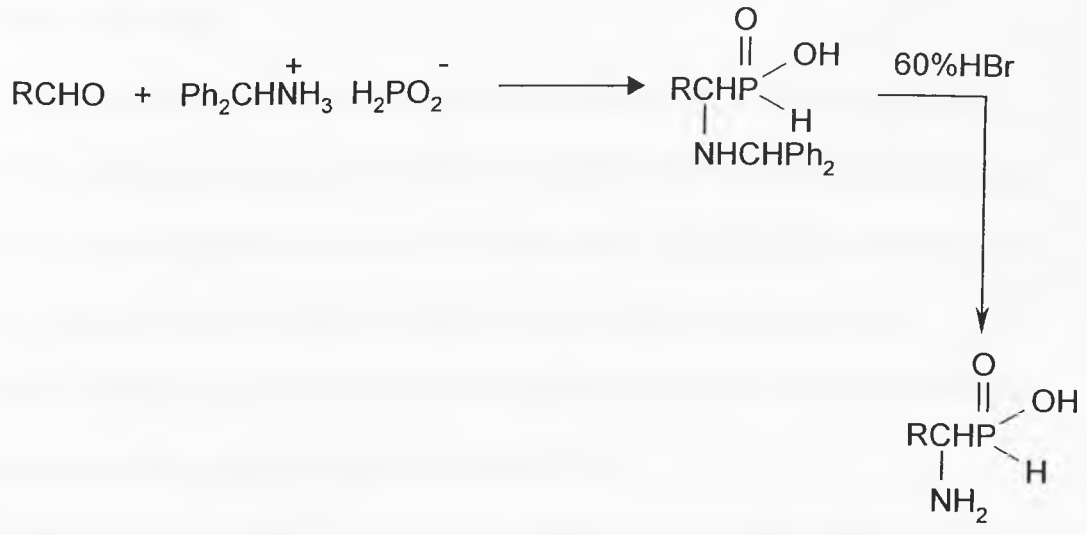
The analogues of α-aminoalkylphosphinic acid of other common amino acids such as alanine, valine, methionine were prepared by treating the corresponding oximes with hypophosphorous acid.[77]

Schmidt[78] proposed a general method for the preparation of *N*-substituted aminophosphinic acids by treating an equimolar mixture of aqueous hypophosphorous acid and benzyl amine with an aldehyde. Schmidt discovered that the final debenzylation by catalytic hydrogenolysis fails due to catalytic poisoning **(Scheme 7)**.



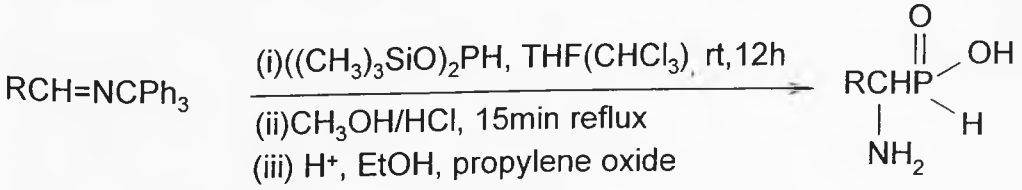
Scheme 7

Dingwall and co-workers[79] developed Schmidt's method further, the aldehyde is condensed with aqueous hypophosphorous acid and diphenylmethylamine hydrochloride in one-pot at high temperature. The debenzylation to remove the labile protecting group is carried out with refluxing 60% hydrobromic acid **(Scheme 8)**.



Scheme 8

More recently the use of bis (trimethylsilyl) phosphonite[80] as the phosphorus fragment has been another variation on the α-diphenylmethylamine theme. Taking this one step further the addition of the same bis (trimethylsilyl) phosphonite to trityl protected imine has been used to prepare α-aminophosphinic acids. The advantage here is the α-trityl group may be easily cleaved to form the free α-aminophosphinic acid **(Scheme 9)**.



Scheme 9

1.4 Aims of this thesis

The aims of this work were to synthesize and study both C-functionalised/N-functionalised macrocyclic rings that include four pendant methylenephosphonates with embedded pyridine/thiophene heterocycles. In the case of C-functionalised macrocycles the general strategy was to prepare phosphorus functionalised subunits and then macrocyclize, whereas, in the case of N-functionalised macrocycles the macrocyclisation precedes incorporation of the phosphorus functionalities.

The formed macrocycles were to be studied for their protonation behaviour as well as their complexing ability with lanthanide ions, in order to evaluate them as MRI contrast agents.

Another important aspect of this work was to submit some of the key intermediates for biological testing as compounds of similar classes have shown interesting biological profiles.

Chapter 2

Synthesis of Novel Hexaaza Macrocycle with Methylenephosphonate Pendant Arms and its Lanthanum (III) Complex

2.1 Introduction

Cyclic polyaza [81,82] compounds have attracted much attention in the areas listed below:

(i) in medicine because of their chelating affinity for metals of the first transition series;

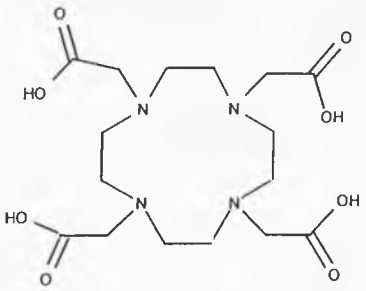
(ii) for recognition of small molecules e.g. as oxygen carriers and therefore intermediates in the oxidation of various substrates by molecular oxygen; and

(iii) in organic chemistry e.g. as complexing agents of alkali metals.

The incorporation of functionalised pendant co-ordinating arms on cyclic polyaza compounds can provide additional co-ordinating functions and hence complexing stability. Examples of reported pendant arms are methylenecarboxylate,[83] methylenepyridyl,[84] hydroxyalkyl,[85] methylenephosphonate[86] and methylenephosphinate.[87]

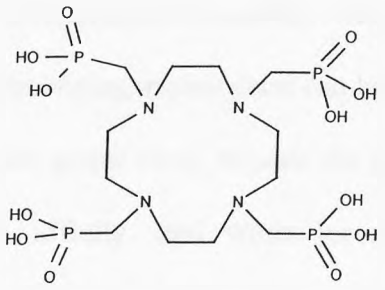
There is growing interest in polyazamacrocyclic carboxylates as chelating agents for metal ions[88] and their comparison with the corresponding polyazamacrocyclic phosphonates. Polyazamacrocycles with acetate pendant arms such as 1,4,7,10-

tetraazacyclododecane-N,N',N",N"'-tetraacetic acid **(N4H4)** have been shown to form stable complexes with the trivalent lanthanide cations in aqueous solution.[89]



N4H4

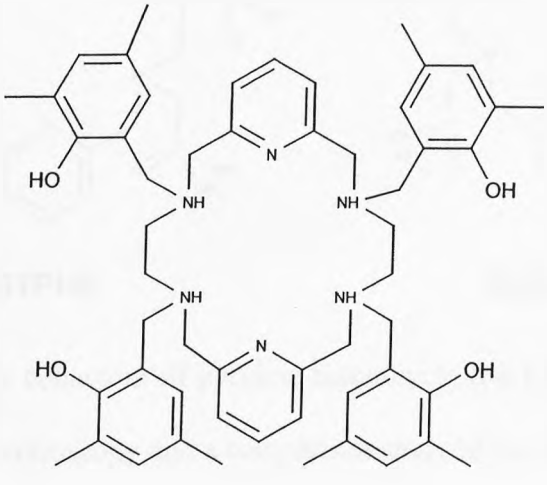
In 1989 the N-methyl-D-glucamine [1-deoxy-1-(methylamino)-D-glucitol] salt of **[Gd(N4H4)(H_2O)]** - (DOTAREM) became the second magnetic resonance imaging (MRI) contrast agent available on the pharmaceutical market, and is an alternative to **[Gd(DTPA)(H_2O)]^2**-(Magnevist) (H5DTPA = diethylenetriaminepentaacetic acid). The lanthanide complexes of a second related tetraaza macrocycle with methylenephosphonate pendant arms, 1,4,7,10-tetraazacyclododecane-N, N' ,N", N"'-1,4,7, 10-tetrakis(methylenephosphonic acid) **(N4TPH8)**, have been studied in some detail with regard to their solution and magnetic properties,[90,91] and as high resolution NMR shift reagents for proteins,[92,93] as well as shift reagents for *in vivo* ^{23}Na NMR spectroscopy.[94,95]



N4TPH8

Also it has been shown by Sherry[96] that phosphorus-containing polyazamacrocyclic compounds complexed to a metal ion, have MRI enhancement effects. As such phosphorus containing macrocycles are an important class of compounds and synthetic route to these deserves investigation.

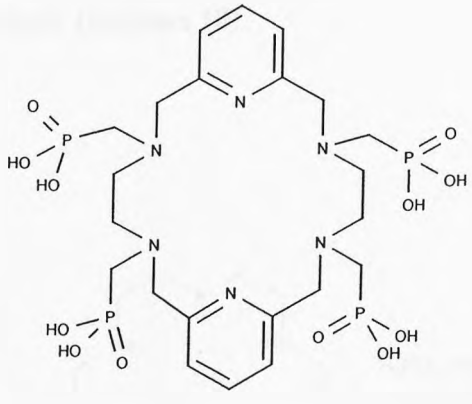
Bligh[31(b)] in 1997 reported the synthesis of the gadolinium complex of a novel 18-membered hexaazamacrocycle containing two pyridyl groups with 2-hydroxy-3,5-dimethylbenzyl pendant arms **(N6H4)**, and its potential as a MRI agent.



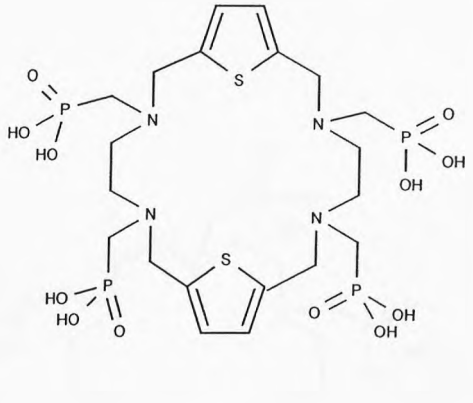
N6H4

18-Membered hexaazamacrocycle embedded with pyridine ring systems have been reported. [25,97] Pyridine-containing macrocycles can bind metal ions more effectively than the corresponding aliphatic amine ones, because the pyridine group has high dipole moments and lower proton affinity, and when incorporated through 2- and 6-aminomethyl groups, provide chelate rings with lower ring strain.[26]

In this study to design better ligands for use as magnetic resonance imaging agents[37,38] and for extracting metal ions from aqueous solution.[61] This chapter describes the synthesis of the first 18-membered macrocycle containing two pyridine rings and with functionalised phosphonate pendant arms (**N6TPH8**). Also described is an attempted synthesis of the thiophene analogue (**N4S2TPH8**), a totally unexplored area of chemistry. However, thiophene has been studied as a chelating agent and aspects of this chemistry are described in the section 1.2.4.1.



N6TPH8



N4S2TPH8

The protonation behaviour of pyridine macrocycle (**N6TPH8**) has been followed by ^{31}P and ^{1}H NMR spectroscopy and a comparison study of the NMR spectroscopic data obtained is made with the ligand (**N4TPH8**).[98]

Also described in this chapter is:

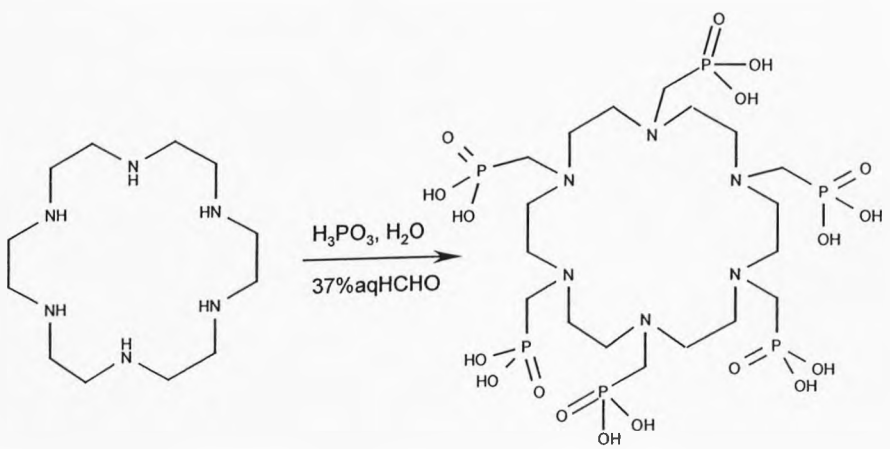
(i) the synthesis of the novel lanthanum complex **[La(N6TPH5)]**;

(ii) the solution and solid state ^{1}H NMR of the lanthanum complex **[La(N6TPH5)]**; and

(iii) a comparison of the X-ray structure of the free ligand **(N6TPH8)** with the lanthanum complex **[La(N6TPH5)]**.

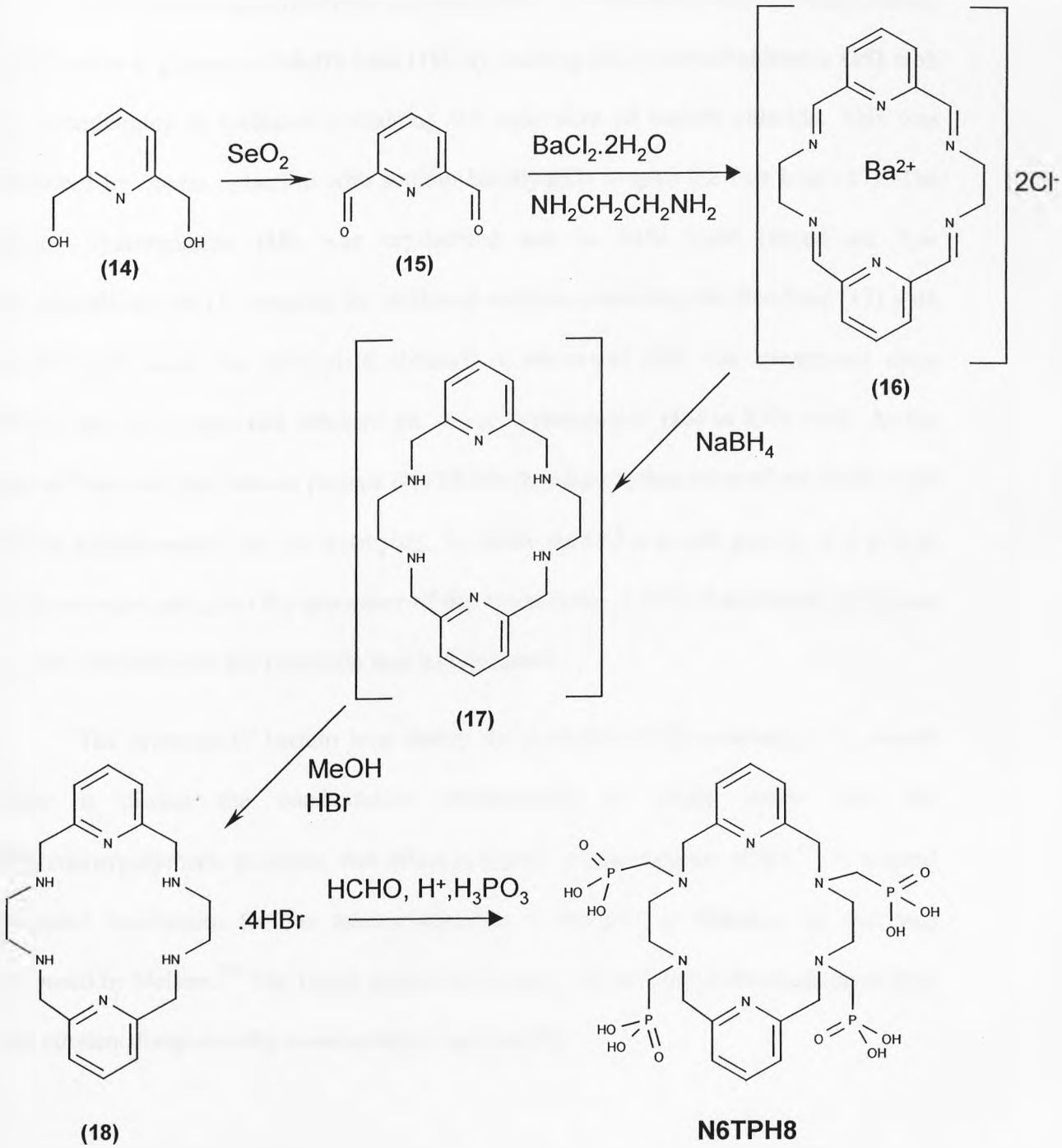
2.2 Synthesis of Hexaazamacrocycle N6TPH8

Prior to this work only one reported example of an 18-membered hexaazamacrocycle containing phosphonate pendant arms on the nitrogen atom had been reported in the literature.[99] The preparation of this compound involved treating a mixture of the saturated hexaazamacrocycle, phosphonic acid and water with 37% aqueous formaldehyde **(Scheme 10)**.



Scheme 10

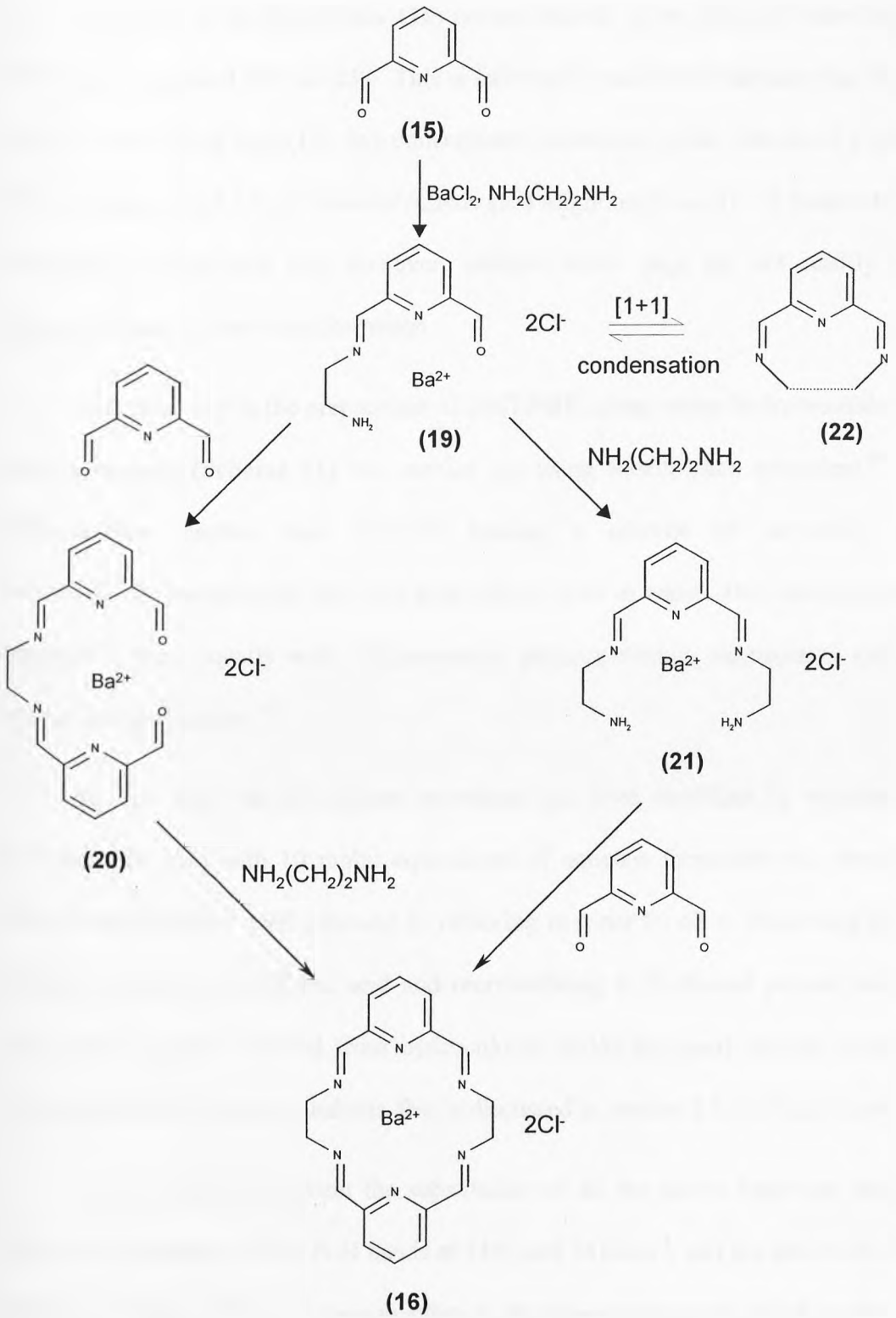
The synthetic route leading to (**N6TPH8**) is outlined below **(Scheme 11)**. Preparation of amine hydrobromide **(18)** was based on Jackel's procedure[25] starting with compound **(15).** 2,6-Pyridinedialdehyde **(15)** was prepared using Luing[100] methodology. 2,6-Pyridinemethanol **(14)** was oxidised to compound **(15)** in quantitative yield using selenium dioxide as the oxidant. The ^{1}H NMR of compound **(15)** showed a characteristic aldehyde signal at δ 10.1 ppm and signals at δ 8.3 and 8.2 ppm correspondences to hydrogen at the 4-position and 3,5-position of the pyridine, respectively.


SeO2
BaCl2.2H2O
NH2CH2CH2NH2
Ba2+
2Cl-
NaBH4
MeOH
HBr
.4HBr
HCHO, H+,H3PO3
(14)
(15)
(16)
(17)
(18)
N6TPH8

Scheme 11

2,6-Pyridinedialdehyde **(15)** (see section 4.7.2) was used in the next step without purification to prepare a Schiff's base **(16),** by reacting 2,6-pyridinedialdehyde **(15)** with ethylenediamine in methanol containing 0.5 equivalent of barium chloride. This was followed by *in-situ* reduction with sodium borohydride to give the free base **(17)**. The amine hydrobromide **(18)** was crystallised out in 34% yield (based on 2,6-pyridinedialdehyde) by treating the methanol solution containing the free-base **(17)** with hydrobromic acid. The poor yield obtained of compound **(18)** was unexpected since Jackel and co-workers had obtained the amine hydrobromide **(18)** in 83% yield. As the aim of this work had been to prepare **(N6TPH8)** therefore optimisation of the yield to the amine hydrobromide was not attempted. ^{1}H NMR showed a simple pattern of 4 sets of peaks as expected given the symmetry of the macrocycle. A lack of aldehydic and imine signals indicated that the reduction step had occurred.

The presence of barium ions during the synthesis of the macrocycle is crucial since it directs the condensation preferentially to cyclic rather than the oligomeric/polymeric products, this effect is known as the template effect.[101] A general accepted mechanism for the macrocyclisation is depicted in **Scheme 12**, and was proposed by Nelson.[101] The initial product of reaction of the 2,6-pyridinedialdehyde **(15)** and ethylenediamine is the monocarbonyl species **(19)**.


(15)
BaCl2, NH2(CH2)2NH2
2Cl-
[1+1]
condensation
Ba2+
(19)
(22)
NH2(CH2)2NH2
2Cl-
Ba2+
(21)
(20)
NH2(CH2)2NH2
2Cl-
Ba2+
(16)

Scheme 12

Synthesis of the Schiff base **(16)** occurs initially in an intermolecular fashion to give either compound (**20**) or (**21**). This is followed by an intermolecular ring closure to give the target Schiff base **(16)**. In a concentrated solution or in the absence of a metal ion ethylenediamine and 2,6-pyridinedialdehyde **(15)** might react in a [1+1] fashion to give a 9-membered macrocycle **(22)** however, medium sized rings are not readily formed because of intra *vs* inter bond formation.

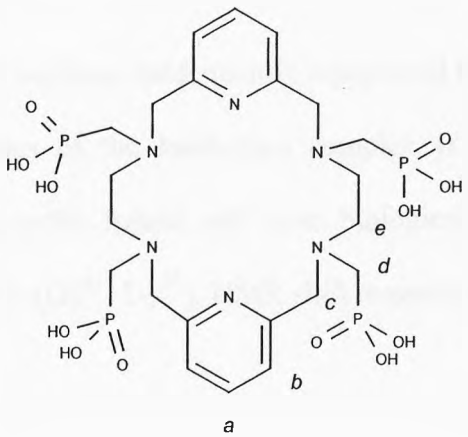
The final step in the preparation of (**N6TPH8**) using amine hydrobromide **(18)** as starting material **(Scheme 11)** was carried out using Moedritzer's procedure.[69] It is a Mannich-type reaction that involved heating a mixture of secondary amine, formaldehyde, phosphorous acid and hydrochloric acid in water. This reaction has been reported to work equally well with ammonia, primary amines, functionally substituted amines and polyamines.[102]

In this work the Moedritzer procedure has been modified by treating amine hydrobromide **(18)** with 10 molar equivalents of aqueous formaldehyde, phosphorous acid and hydrochloric acid, followed by refluxing in water for 62 h. Dissolving the crude product in dilute hydrochloric acid and recrystallising it in ethanol proved successful. Only those crystals obtained from hydrochloric acid/isopropanol mixture were found suitable for X-ray structure analysis, this is discussed in section 2.5.2 of this chapter.

In the infrared spectrum the substitution of all the amino hydrogen atoms was shown by the absence of the N-H bands at 3465 and 3415cm^{-1}, and the presence of strong bands at 1158 and 1074 cm^{-1} corresponding to the phosphoryl group which confirmed the successful synthesis of the ligand (**N6TPH8**). The mass spectrum of the macrocyclic

ligand (**N6TPH8)** had a parent ion at m/z 703 corresponding to $[M+H]^+$ and a base peak at m/z 623 indicating that one HPO_3 group had been lost from the parent structure.

Table 2: **^{1}H NMR data for (N6TPH8)**



Chemical Shift ppm	Coupling Constant/Hz	Chemical/Magnetic nuclei	Multiplicity	Assignment
8.1	8.0	2	t	a
7.6	8.0	4	d	b
4.9	-	8	s	c
4.1	-	8	s	e
3.3	7.5	8	d	d

The pyridyl proton at position *a* is *ortho* coupled to the chemically equivalent protons at position *b*, giving rise to a doublet centred at 8.1 ppm. Consequently, the

pyridyl protons at position *b* are *ortho* coupled to proton at position *a*, giving a doublet at δ 7.6 ppm. Also noteworthy is the doublet at δ 3.3 ppm due to the methylene phosphonate protons coupled to the phosphorus atom (J_{HP}=7.5 Hz), consisting of an AX spectrum (X is the ^{31}P nucleus).

Compound **(N6TPH8)** has been subsequently complexed to the lanthanum metal. It is anticipated that analogues of the lanthanum complex **[La (N6TPH5)]** of this potentially decadentate macrocyclic ligand will have biological application including their use as MRI contrast agents (Gd^{3+}, Dy^{3+}), NMR shift reagents (Dy^{3+}, Tm^{3+}) and bone palliative agents (Sm^{3+}).

2.3 Synthesis of Lanthanum complex of (N6TPH8)

The macrocyclic chelate **(N6TPH8)** forms a 1:1 stable complex with La^{3+} ions. The **[La (N6TPH5)]** complex is the first lanthanide macrocyclic complex with four co-ordinated pendant arms. This was prepared by adding lanthanum oxide to the refluxing solution of **(N6TPH8)** in water. The crude product was recrystallised from dilute hydrochloric acid (pH 2.5) to give **(N6TPH8)** as white crystals in 69% yield. The crystals obtained in this way were found to be suitable for X-ray analysis.

The mass spectrum of the **[La (N6TPH5)]** complex has a parent ion at m/z at 839 corresponding to $[M+H]^+$. The ^1H NMR spectrum of the neutral **[La (N6TPH5)]** complex together with its solid state characteristics suggest that the ligand adopts one of five possible stereochemical configurations about the nitrogen atom i.e. the SSSS/RRRR configurations. The proton NMR spectrum consists of an apparent triplet, (actually dd) at δ 7.75 and a doublet at 7.26 (J_{HH} 7.5 Hz) corresponding to the pyridine protons. The

methylene protons adjacent to the pyridine ring, c and c', (see **Figure 4**) yield an AB pattern at δ 3.70 and 4.69 with a geminal coupling of 10.9 Hz and similarly the protons, d and d', give an AB pattern at δ 3.28 and 3.50 with a geminal coupling of 15.3 Hz consistent with the ligand maintaining its four-fold symmetry upon complex formation in solution. The methylene phosphonate protons, e and e', show two signals (J_{HP} 7.50 and J_{HH} 17.0 Hz), consisting of the AB part of a ABX spectrum (X is the ^{31}P nucleus). The assignments of the proton signals and the verification of the geminal couplings were based upon a two-dimensional homonuclear correlation (COSY), **Figure 4**.

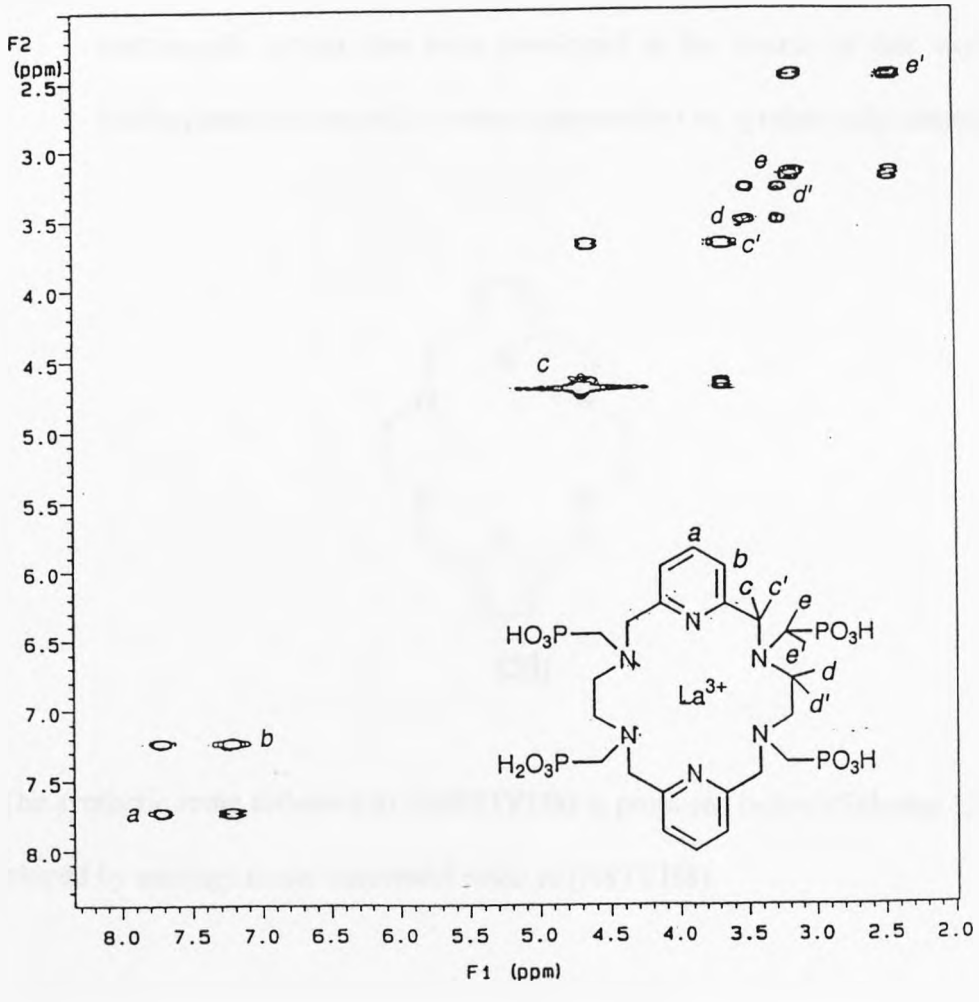


Figure 4: Two-dimensional COSY spectrum of **[La (N6TPH5)]**

2.4 Attempted Synthesis of Tetraazadithiomacrocycle (N4S2TPH8)

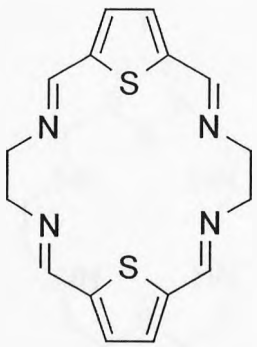
As discussed in Section 2.1 a second macrocyclic system was targeted for synthesis/studies in which the pyridine ring was replaced with the thiophene.

The reasons why the thiophene systems were of interest includes:

(i) macrocyclic tetraazabisthiophenes, e.g. compound (**23**) are unknown in the literature;[103]

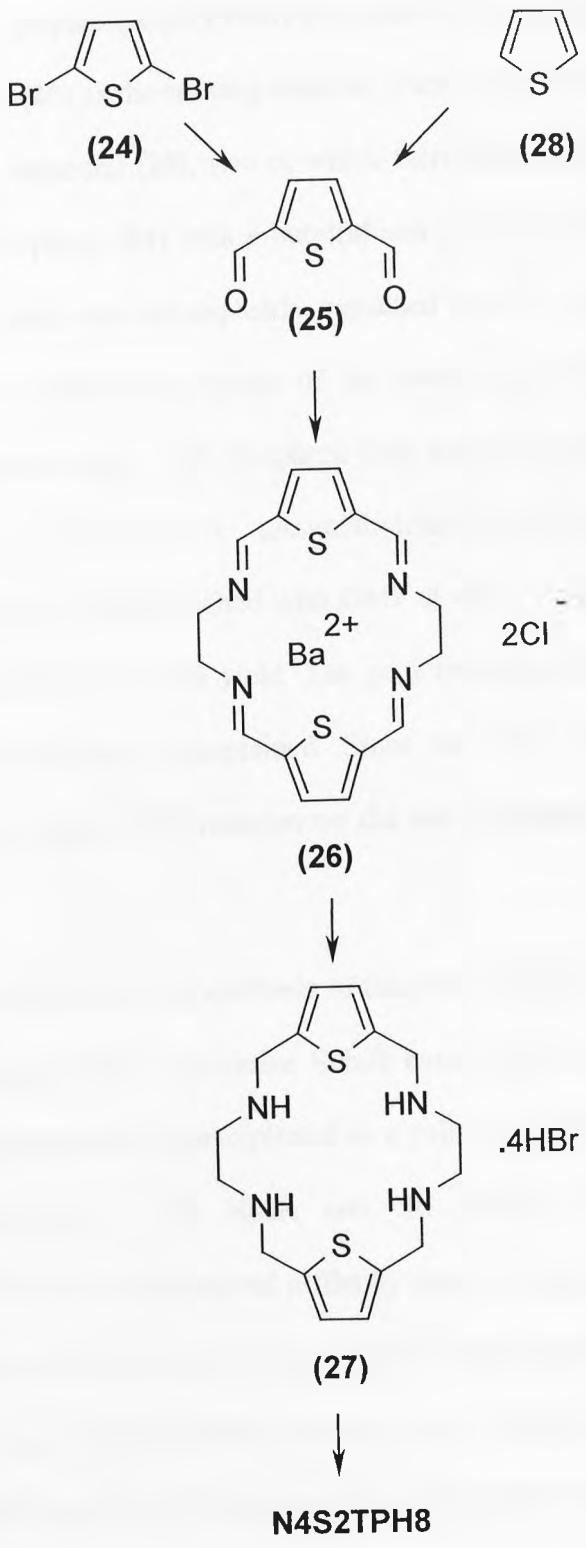
(ii) there is evidence that thiophene are chelating agents; [20-22] and

(iii) given that a facile synthetic route to the analogous bis pyridine macrocyclic system has been developed in the course of this work the bisthiophene macrocyclic systems appeared to be synthetically accessible.



(23)

The synthetic route followed to (**N4S2TPH8**) is proposed below **(Scheme 13)** and was developed by analogy to the successful route to (**N6TPH8**).


Br
S
Br
(24)
S
(28)
S
O
O
(25)
S
N
N
Ba 2+
N
N
S
2Cl -
(26)
S
NH
HN
NH
HN
S
.4HBr
(27)
N4S2TPH8

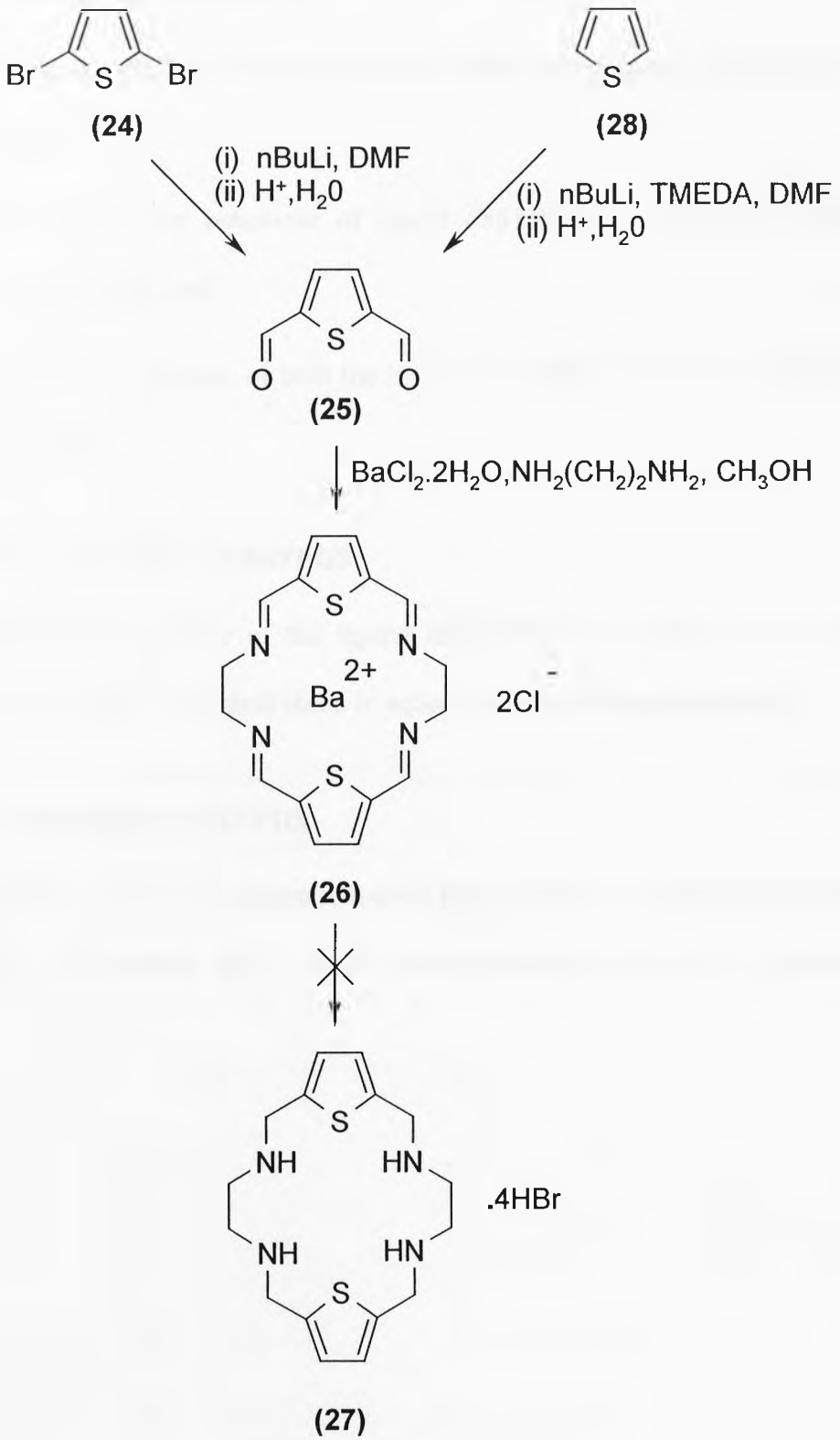
Scheme 13

In an attempt to prepare (**N4S2TPH8) (Scheme 13),** it was required to have the 2,5-thiophenedialdehyde **(25)** as the starting material. There are several reported methods for the preparation of compound **(25),** two of which were tried, in the present work.[104] Reacting 2,5-dibromothiophene **(24)** with *n*-butyllithium at -65 °C in dry ether that gave the dilithiated species which was subsequently quenched with N, N-dimethylformamide (DMF) to afford orange needle-like crystals of the dialdehyde in consistently 33-39% yield. Feringa's[105] method started with thiophene **(28)** which was lithiated in refluxing hexane, in the presence of *N,N,N'N'* tetramethylethylenediamine (TMEDA). The dilithiated intermediate was then quenched with DMF at -40°C. This, followed by acid work-up, gave the dialdehyde in 22% yield. The poor isolated yield of the dialdehyde from both the methods remains unexplained. Since we were interested in defining conditions for the latter stages of the reaction we did not investigate these reactions any further.

The method employed for the synthesis of thiophene Schiff base **(26)** was similar to that used for the preparation of pyridine Schiff base **(16)** depicted in **Scheme 11.** During the reaction compound **(26)** precipitated as a yellow solid that was subsequently isolated and characterised by ^{1}H NMR and IR. Initially ^{1}H NMR structural characterisation of Schiff base **(26)** proved difficult, simply because the Schiff base had only limited solubility in all common solvents. Fenton[103] who had first claimed to prepare Schiff base **(26)** using a non-template procedure had previously reported the low solubility of the Schiff base. The ^{1}H NMR spectrum of the Schiff base **(26)** was obtained in deuterated trifluoroacetic acid which if left standing for a period of time resulted in the hydrolysis of Schiff base **(26)** to the 2,5- thiophenedialdehyde **(25).**

The reduction of Schiff base **(26)** to the hydrobromide salt **(27)** has proved difficult. A variety of conditions were investigated, these being listed in section 5.8 however in all cases only starting material was recovered. This was probably due to both poisoning of catalyst by the sulfur, and problems with lack of solubility of the Schiff base.

Synthetic work described in this chapter has led to the synthesis of a novel **(N6TPH8)** macrocycle. However, the analogous thiophene macrocycle **(N4S2TPH8)** could not be prepared for the reasons as discussed above. **Scheme 14** summarises the current position of this attempted synthetic route. Showing both successful and unsuccessful reactions.


Br
S
Br
(24)
S
(28)
(i) nBuLi, DMF
(ii) H+,H20
(i) nBuLi, TMEDA, DMF
(ii) H+,H20
S
O
O
(25)
BaCl2.2H2O,NH2(CH2)2NH2, CH3OH
S
N
N
2+
Ba
N
N
S
2Cl-
(26)
S
NH
HN
NH
HN
S
.4HBr
(27)

Scheme 14

2.5 Physical Properties of N6TPH8

Having prepared the hexaazamacrocycle **(N6TPH8)** we are now in the position to study the following:

(i) the protonation behaviour of ligand (**N6TPH8)** by ^{31}P and ^{1}H NMR spectroscopy; and

(ii) the crystal structure of both the ligand (**N6TPH8**) and its lanthanum (III) complex.

2.5.1 Protonation Behaviour of N6TPH8

The protonation sequence of the ligand (**N6TPH8)** was followed by the pH dependence of its ^{1}H and ^{31}P chemical shifts in aqueous solution **(Figure 5 and 6)**.

2.5.1.1 Proton NMR Study of N6TPH8

In all spectra the splitting pattern remained the same over the entire range of pH **(Figure 5)**. This is accounted for by rapid proton exchange between all protonated species.

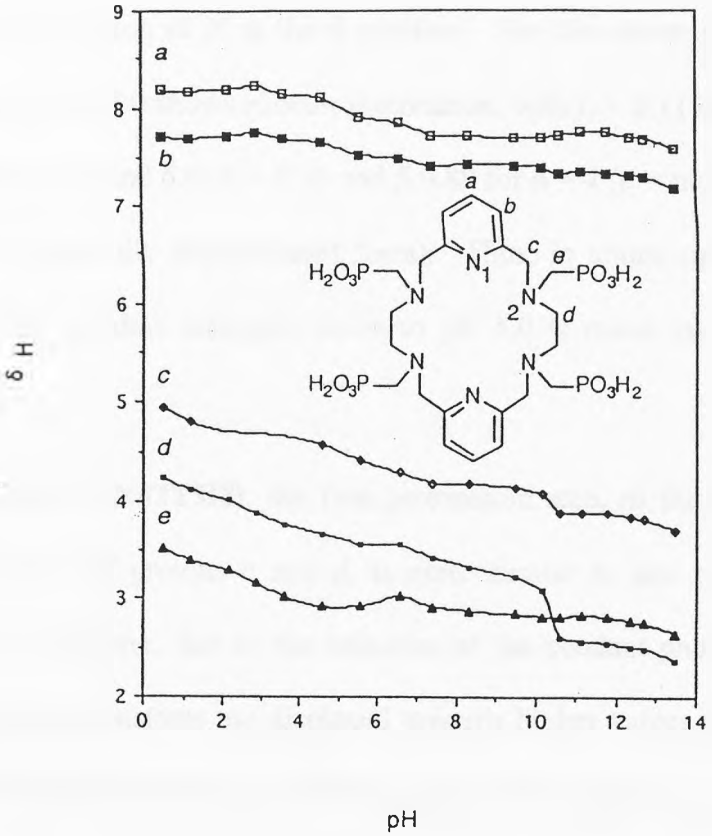


Figure 5: ^{1}H NMR chemical shifts of (**N6TPH8**) recorded as a function of the solution pH. Chemical shift assignments are shown.

Jackels and co-workers[25] reported a similar NMR protonation study on amine macrocycle **(18) (Scheme 11).** There findings are compared with those reported here for ligand (**N6TPH8**) using the interpretation procedure of Sudmeier and Reilley.[106] It can be concluded that the protonation shift of protons *d* reflect the protonation fraction at the four amine nitrogens N^2 (f_2), the protonation shift of *a* is proportional to the protonation fraction at the two pyridine nitrogen's at N^1 (f_1) while the difference of protonation shift of protons *d* and *e* is proportional to the protonation fraction at the phosphonate group (f_p). Using the protonation curves for amine macrocycle **(18)** of the literature,[25] the values $f_1 = 0.11$ and $f_2 = 0.44$ for the doubly protonated form are obtained. These are based on shielding constants $C_N = 1.12$ for protonation of an *N* atom at the *a* position and

C_N = 0.26 for protonation of N at the β position. For this amine macrocycle, the pH range between 8.5 and 7.0 shows another protonation, with f_1 = 0.11 and f_2 = 0.69 for n = 3, and between pH 7.0 and 5.0, f_1 = 0.21 and f_2 0.89 for n = 4 (n = number of equivalents of acid added to the fully unprotonated form). Thus, in amine macrocycle (**18**), the protonation of the pyridine nitrogens down to pH 5.0 is much lower than the amine nitrogens.

In the case of (**N6TPH8**), the first protonation step, in the range pH 11-9, as shown by the shifts of protons *c* and *d*, is quite similar to that observed for amine macrocycle (**18**). However, due to the influence of the pendant phosphonate arms, the first two protonation constants are displaced towards higher values (above 10) and the value of f_2 is even higher relative to f_1 when compared with the case of amine macrocycle (**18**). Thus, the amine nitrogens N^2 in (**N6TPH8**) are even more basic than those in amine macrocycle (**18**). The second protonation step, between pH 9 and 7 (n = 3) corresponds again to a predominant protonation at N^2, as shown by the *c* and *d* proton shifts. The third protonation step, between pH 7 and 4 (n = 4) shows that the fourth proton has a slight preference for N^1 versus N^2. Finally, between pH 4 and 1, N^1 is again negligibly protonated, while N^2 and the phosphonate oxygens are protonated steadily, as shown by the shifts of protons *c*, *d* and *e*, respectively.

In contrast to the insensitivity of the N^1 protonation of the pyridine nitrogen observed in amine macrocycle (**18**), the total protonation shift of protons a is 0.61 ppm and of protons b is 0.55 ppm in the range pH 0.5-13.5 of (**N6TPH8**). This supports a higher participation of protonation of pyridine nitrogens which is reflected in the large increase of f_1 observed in the change of n = 3 to n = 4. The proton shifts of the CH_2P

groups (protons *e*) are relatively unaffected by N^2 protonation between pH 9.5 to 12, possibly due to complexation of Na^+ ion by the phosphonate oxygen, as observed before for (**N4TPH8**).[107]

2.5.1.2 Phosphorus NMR study of N6TPH8

The ^{31}P NMR chemical shifts versus pH titration curve **(Figure. 6)** shows a large and a rather sharp upfield shift during the first protonation step of **(N6TPH8)** in the range pH 12-9.5 . This may be due to the complexation of Na^+ by the macrocycle, which has been observed for other tri- and tetra-aza macrocyclic methylenephosphonate systems using NaOD as a titrant.[107,108]

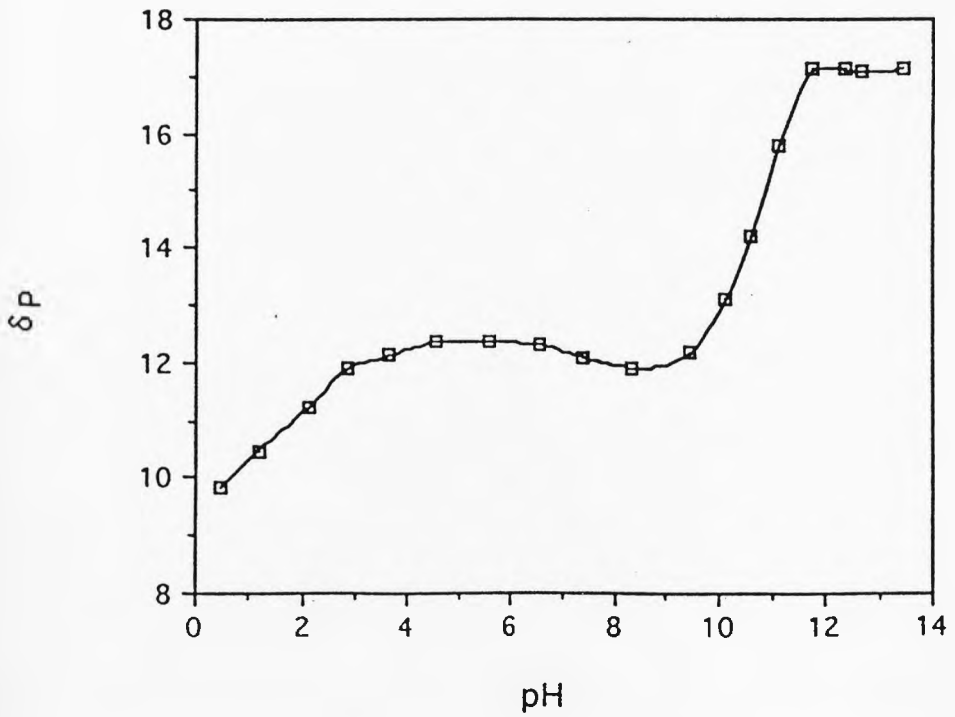
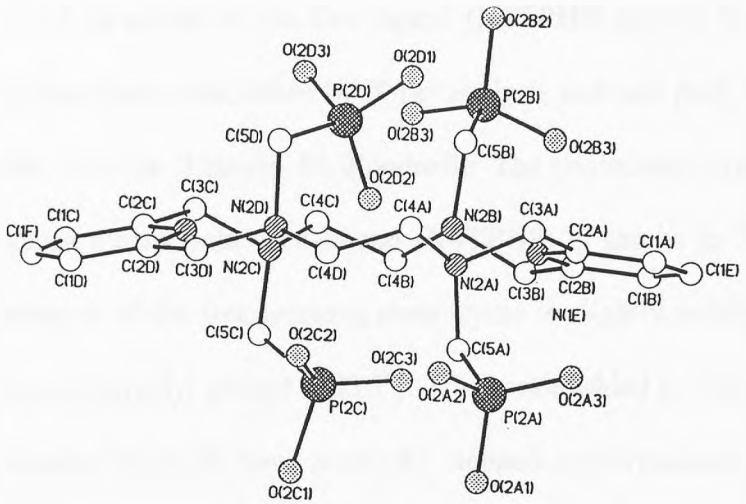


Figure 6: The ^{31}P NMR chemical shifts of **N6TPH8** recorded as a function of solution pH

The gradual increase of the ^{31}P shift from pH 8.3 to 6.0 indicates that the phosphonate oxygens are forming internal hydrogen bonds with the protonated ring amine nitrogens and there is evidence of this in the solid state **[Figure 7(a)].** The formation of this rather rigid structure is reflected in a considerable broadening of the ^{31}P signal observed below pH 6.5 indicating slowing down of the interconversion of the various possible hydrogen-bonded structures **[Figure 7(a)]**. Again, such a situation has been observed before for **(N4TPH8)** in solution and there is confirmation of intramolecular H-bonding in the crystal structure.[109] Finally the upfield shift of the ^{31}P resonance at a pH below 5.0 reflects protonation of the phosphonate oxygens, with gradual breaking down of the hydrogen bond.

(a)



(b)

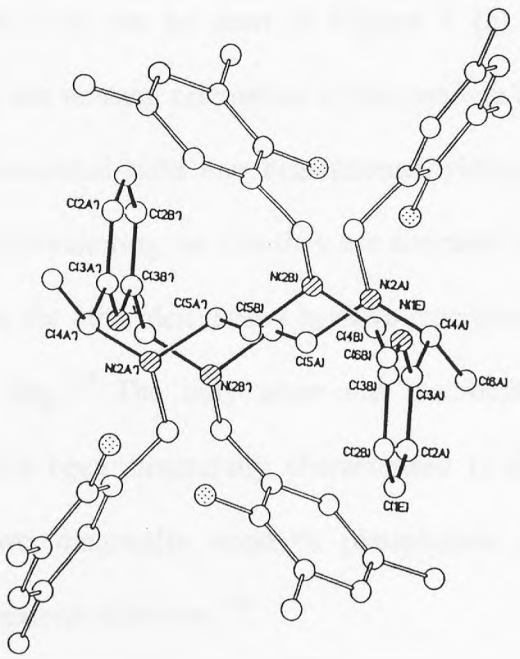


Figure 7: **(a)** The molecular structure of **(N6TPH8)** showing the unusual arrangement of the phosphonate pendant arms, and the conformation of the macrocycle which is preorganised for complexation. **(b)** Reported structure of tetramethyl-**N6H4** showing the step conformation of the macrocycle.[110]

2.5.2 Crystal structure of (N6TPH8) and its Lanthanum Complex [La(N6TPH5)]

The crystal structures of the free ligand (**N6TPH8**) and its lanthanum complex **[La(N6TPH5)]** have been established by X-ray analysis and was performed by Professor Mary McPartlin and Mr Thomas M.Woodroffe The molecular structure of the 18-membered hexaaza macrocyclic free ligand (**N6TPH8**) is shown in **Figure 7 (a)**. The overall conformation of the free hexaaza macrocycle is slightly twisted (dihedral angle between the dimethylpyridyl groups is 23.7°). This is not folded in contrast with a related hexaazamacrocycles which all have markedly stepped conformations. For example the pyridyl units, in the analogous tetramethyl-**N6H4** with 2-hydroxy-3,5-dimethyl-benzyl pendant arms were almost perpendicular to the best plane through the great ring the dihedral angle being 98.3° as can be seen in **Figure 7 (*b*)**.[110] The difference in conformation arises from the unusual orientation of the pendant arms in (**N6TPH8**), the phosphonate pendants associated with one bisaminomethylenepyridyl group lying on opposite sides of the macrocycle ring, so that they are alternate 'up and down' round the ring **Figure 7(a)**, whereas for other derivatised hexaaza macrocycles they occur in pairs 'above and below' the ring.[110] The only other aza macrocycle with four pendant phosphonate arms to have been structurally characterised is the tetraaza macrocycle (**N6TPH8**) in which two diagonally opposite phosphonate groups lie above the macrocycle ring and two extend sideways.[109]

The P-O bond lengths fall into two groups, one bond on each phosphonate group being significantly longer than the other two, indicating an anionic mono deprotonated PO_3H^- formulation. The shorter P-O lengths are in the range 1.48-1.52 Å (mean 1.50 Å) within the range observed for P-O bonds in aminophosphonates,[111,112] and the four longer

P-O bonds are in the range 1.57-1.59 Å and may be assumed to be protonated. From this evidence it may be deduced that the molecule exists in zwitterionic form with four protonated amine groups; the N-C bond lengths are in the range 1.49-1.52 (mean 1.51 Å) consistent, although at a low significance, with the characteristic slight lengthening observed for N-C bonds from protonated nitrogen atoms in other aminophosphonates.[108,112]

Three of four oxygen atoms assigned to the P (OH) groups make extremely short contacts with unprotonated phosphonate oxygen atoms of neighbouring molecules (2.50-2.57 Å) indicating very strong intermolecular H-bonding **(Figure 8)**, and the fourth is hydrogen bonded to a water molecule.

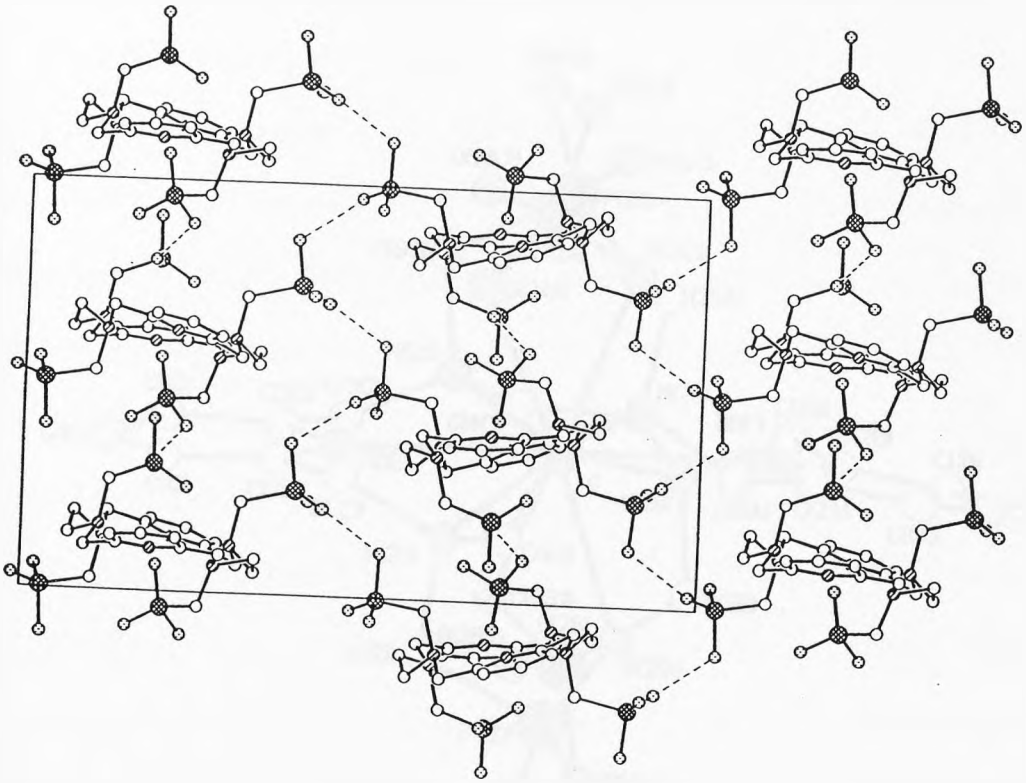


Figure 8: The two-dimensional polymer generated by hydrogen bonding between protonated and unprotonated phosphonate oxygen atoms in the solid-state structure of (**N6TPH8**) viewed down the b axis.

The X-ray structure analysis of **[La(N6TPH5)]** confirms the SSSS/RRRR conformation of the macrocycle indicated by the ^{1}H NMR studies; with both enantiomers being present in the crystal (**Figure 9**).

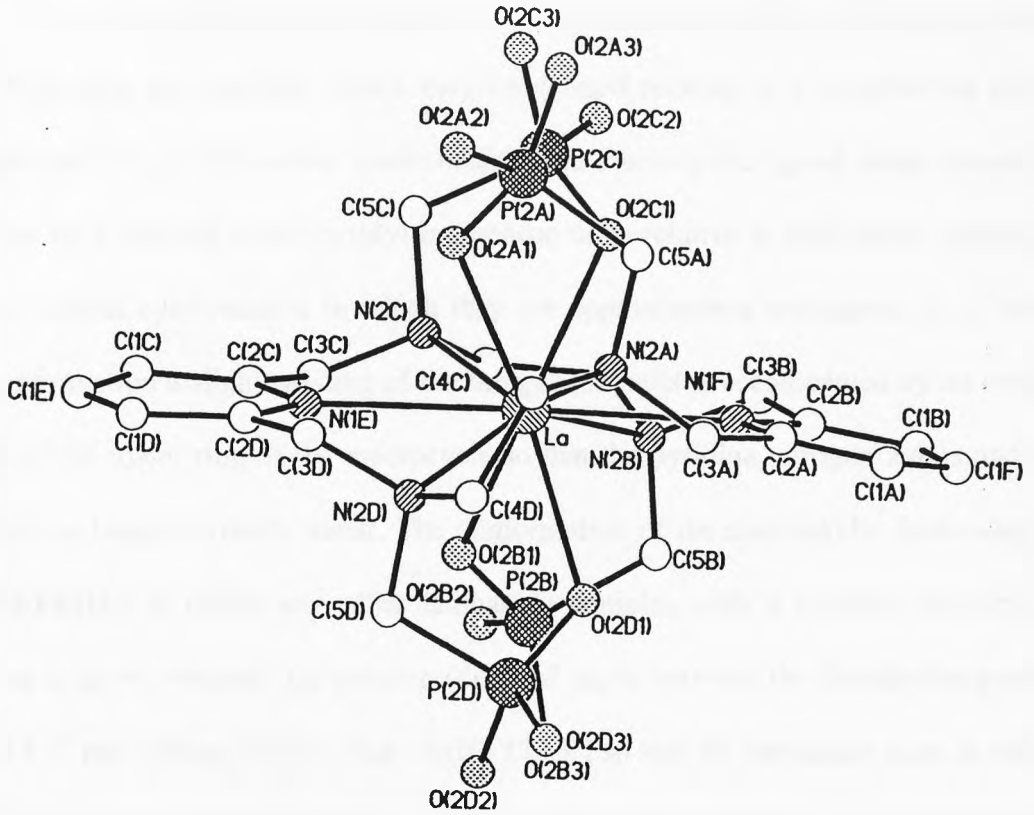


Figure 9: The molecular structure of the ten-co-ordinated hexaaza macrocyclic complex **[La (N6TPH5)]** showing the co-ordination of four pendant arms

The lanthanum ion has the irregular ten co-ordinate geometry derived from four oxygen atoms of the four phosphonate pendant arms and six nitrogen atoms of the 18-membered hexaaza macrocycle. The **[La (N6TPH5)]** complex is thus the first lanthanide macrocyclic complex with four co-ordinated pendant arms. For example, the gadolinium complex of **N6H4**, $[Gd(N6H4)(NO_3)]^+$, with the same 18-membered hexaaza macrocyclic framework, has only one of its four 2-hydroxy-3,5-dimethylbenzyl pendant arms co-ordinated to the metal ion and the other three pendant arms radiate out away from the metal centre.[110]

It has been observed previously that in hexaaza macrocyclic complexes two types of conformation are possible, which may be defined relative to a hypothetical planar arrangement.[113] In a 'twist-wrap' conformation, the macrocyclic ligand wraps round the metal ion by a twisting of the pyridyl bridgehead units relative to each other, eventually giving a helical conformation in which they are approximately orthogonal. In a 'twist-fold' conformation a slight twisting of the bridgehead units is accompanied by an overall folding of the major ring of the macrocycle so that the pyridine nitrogen atoms and the metal are no longer virtually linear. The conformation of the macrocyclic framework in **[La (N6TPH5)]** is unlike any other lanthanide complex with a hexaaza macrocyclic ligand as it shows virtually no twisting (dihedral angle between the dimethylenepyridyl units of 8.5^0 nor folding [N (lE)—La—N(lF) 173.3^o] so that the lanthanum atom is within 0.01 Å of the best plane through the six macrocycle nitrogen donors; this arrangement is in direct contrast to the macrocycle in the related complex $\mathbf{[Gd(N6H3)(NO_3)]^+}$, which shows a fold-dominated conformation with a N(lE)—Gd—N(lF) angle of only 146.3^o The bond lengths in the co-ordination sphere [La—N(pyridine) 2.694 and 2.731, La—N(amine) 2.780-2.824 Å; La—O 2.517-2.579 Å] are comparable to the ranges previously observed for ten-co-ordinated lanthanide complexes;[113] this appears to be the first example of this co-ordination number for a lanthanum hexaaza tetramine macrocycle. With one exception the shortest P—O bond lengths are those involving the donor atoms [1.492-1.506 Å]. The terminal bonds P(2A)—O(2A3) (1.504 Å) and P(2D)—O(2D3) (1.518 Å) may be assumed to be predominantly unprotonated P=O double bonds. Four protons may be assigned to the four longest bonds [range 1.558-1.587 Å] and it seems probable that the fifth is disordered over the rather shorter P(2B)—O(2B3) (1.526) and

P(2C)—O(2C2) bonds (1.534 Å). Very short intra- and inter-molecular distances are consistent with the hydrogen bonding pattern shown in **Figure 10**.

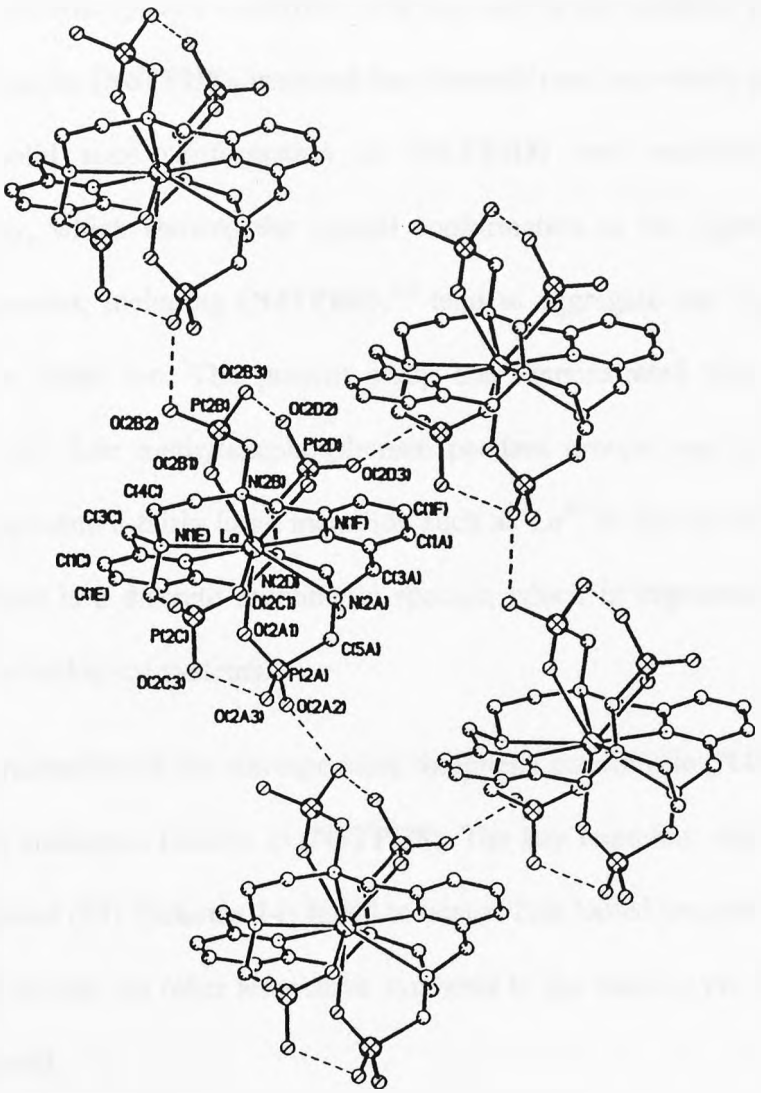


Figure 10: Part of the two-dimensional hydrogen-bonded network in the solid-state structure of **[La(N6TPH5)]**

2.6 Conclusions and Further Work

The synthesis of hexaazamacrocycle phosphonate (**N6TPH8**) has been achieved and its structure spectroscopically confirmed. The key step in the synthetic pathway to afford the target molecule, (**N6TPH8**), involved the Mannich reaction, which proceeded in high yield. The solid state conformation of (**N6TPH8**) was established using X-ray crystallography, which showed the overall conformation to be slightly twisted. Most aminophosphonates, including (**N4TPH8**),[114] tend to aggregate and oligomerize in the presence of a metal ion. The present study has demonstrated that the new ligand (**N6TPH8**), with four methylenephosphonate pendant groups, can provide ten donor atoms to encapsulate a fairly large metal ion such as La^{3+} in the macrocyclic ring. The complex formed is a discrete monomeric species, which is important for its potential applications in biological systems.

The preparation of the corresponding thiophene macrocycle (**N4S2TPH8**) did not proceed in an analogous fashion to (**N6TPH8**). The key reduction step from compound (**26**) to compound (**27**) (**Scheme 14**) failed to occur. This halted progress in this aspect of the work and to date, no other alternative synthesis to the macrocycle (**N4S2TPH8**) has been investigated.

Having achieved the target macrocycle (**N6TPH8**), further work remains to investigate the applicability of the metal complex of the macrocycle as a contrast agent. Gadolinium complexes have shown to be the best contrast agents and so the analogous gadolinium complex of the macrocycle (**N6TPH8**) would be a key target for future investigations.

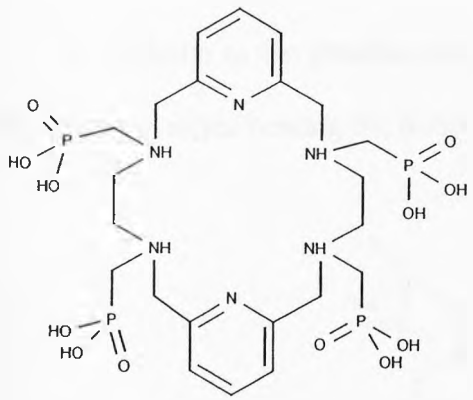
Chapter 3

Synthesis and Characterisation of α-Amino Phosphonic Acids Towards the Preparation of Novel Macrocycles

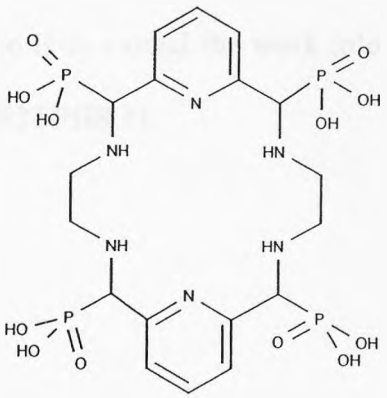
3.1 Introduction

As discussed previously, the overall aim was to develop a macrocycle with an embedded heterocyclic system bearing α-functionalised phosphonic acids (**N6TPH8_1**), **Figure 11**. This system is very analogous to the α-aminophosphonic acid macrocycle (**N6TPH8**) discussed in chapter 2.

Both systems are based on a 18-membered hexaazamacrocycle containing two pyridyl groups. Two 2,6-disubstituted pyridines are embedded in the ring which also bears four pendant phosphonic acid arms. The difference between these systems is that in (**N6TPH8**) the phosphonic acid groups are connected via methylene bridges to the four non-aromatic ring nitrogens, whereas the system proposed in this section of the work has the phosphonic groups directly attached to the macrocyclic carbons.



N6TPH8

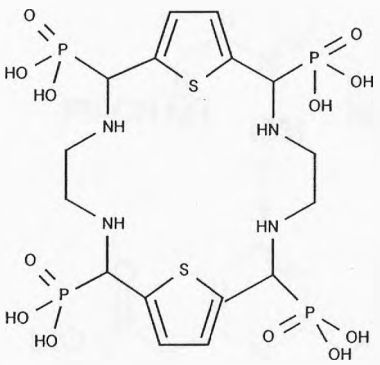


N6TPH8_1

Figure 11: Macrocycles with pyridine embedded functionalised phosphonic acid

(N6TPH8_1) is a macrocycle that is conformationally restrained in such a way that the phosphoryl groups will lead to better selectivity with respect to the lanthanides binding. Macrocycles of the **(N6TPH8)** type are well represented in the literature, there are several papers of **(N6TPH8)**-type macrocycles in which appended chains and rings exist. However, there are no examples with α-functionalised macrocycle of type **(N6TPH8_1)** and thus they have become more interesting targets. **(N6TPH8_1)**-type macrocycles have the advantage that various isomers exist which may give differences in selectivity towards lanthanide metals. However, the simple achiral preparative methodology will unfortunately lead to mixtures of stereoisomers.

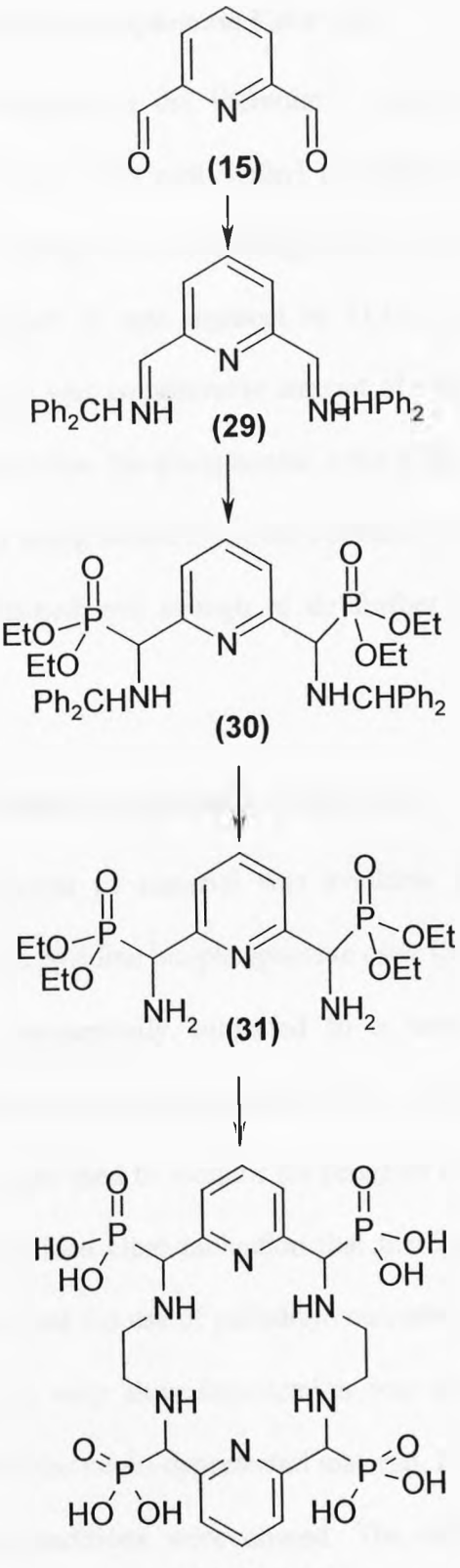
In addition to the pyridine macrocycles the intention is to extend the work into macrocyclic systems bearing the thiophene unit such as (**N4S2TPH8_1**).



N4S2TPH8_1

3.2 Proposed route to the (N6TPH8_1) Macrocycle

The synthetic route followed to (**N6TPH8_1**) is proposed in **Scheme 15**.



Scheme 15

3.2.1 Preparation of Pyridine Bis-phosphonate Ester (30)

Based on conditions reported in the literature[115] on an analogous reaction, pyridine bis-imino **(29)** was treated with neat diethyl phosphite at 150 °C for 2 hrs. Engel[115(a)] reported good yield using this methodology, however, when applied to this situation a poor yield was obtained. It was apparent by TLC analysis that no starting material remained, however there was considerable amount of base line material. After chromatographic purification pyridine bis-phosphonate ester **(30)** was obtained in 7% yield, with no other compound being eluted from the column. The amount of pyridine bis-phosphonate ester **(30)** obtained was enough to do further investigation into the synthetic pathway.

3.2.2 Hydrogenolysis of Pyridine Bis-phosphonate Ester (30)

Although a limited amount of material was available there was enough to investigate hydrogenolysis of the pyridine bis-phosphonate ester **(30)**. To carefully utilise the starting material it was sequentially subjected to a series of more vigorous hydrogenating conditions until complete deprotection of the diphenylmethyl group was observed. Both TLC and MS were used to monitor the progress of the deprotection. MS was particularly useful and provided clear indication that there was unreacted starting material. Initial conditions involved the use of palladium on carbon (10% w/w) and after 13h under hydrogen (1 atm); a very slow deprotection was occurring giving rise to production of a small amount of the mono-deprotected material. In an attempt to increase the rate of deprotection the conditions were altered. The catalyst was changed to palladium on alumina, however this did not provide significant amounts of the bis-deprotected product **(31).** Altering the conditions further using palladium hydroxide on

carbon (20%Pd)[116] at 50°C for 7h afforded the completely deprotected compound **(31).** It was clear that the latter reaction conditions provided rapid deprotection. However due to limited amount of compound **(30)** being available these conditions were not investigated further.

It is important to note that this is the first instance that the deprotection was observed on a bis phosphoryl-substituted heterocyclic system in the course of this work. The compound contains two stereogenic centres and it was clear from the NMR and HPLC that the diastereoisomers obtained were in roughly equal proportions. This is expected because the stereogenic centres are remote.

TLC analysis of the mixture of diastereoisomers showed a single spot, however, the two diastereoisomers were completely resolved by HPLC. No attempt was made at separating the diastereoisomers at preparative scale. Enough material was available at least for a single attempt at a macrocyclisation of compound **(31)**.

3.2.3 Attempted Preparation of (N6TPH8_1)

Previously the macrocyclic system of the hexaaza **(N6TPH8) (Scheme 11)** has been prepared by condensation of an aldehyde with ethylenediamine using barium template methodology. The resulting tetraimine was reduced to the desired amine using sodium borohydride. In the case of compound **(31)**, it should have been possible to alkylate compound **(31)** with 1,2-dichloroethane using barium template methodology to hydrolyse the resulting ester to give the **(N6TPH8_1)** macrocycle.

However, attempted cyclisation using the barium template procedure resulted in no macrocyclic products. Altering the base to potassium hydroxide did not enhance the

reaction. Given the limited material available it was not possible to investigate further the macrocyclisation conditions.

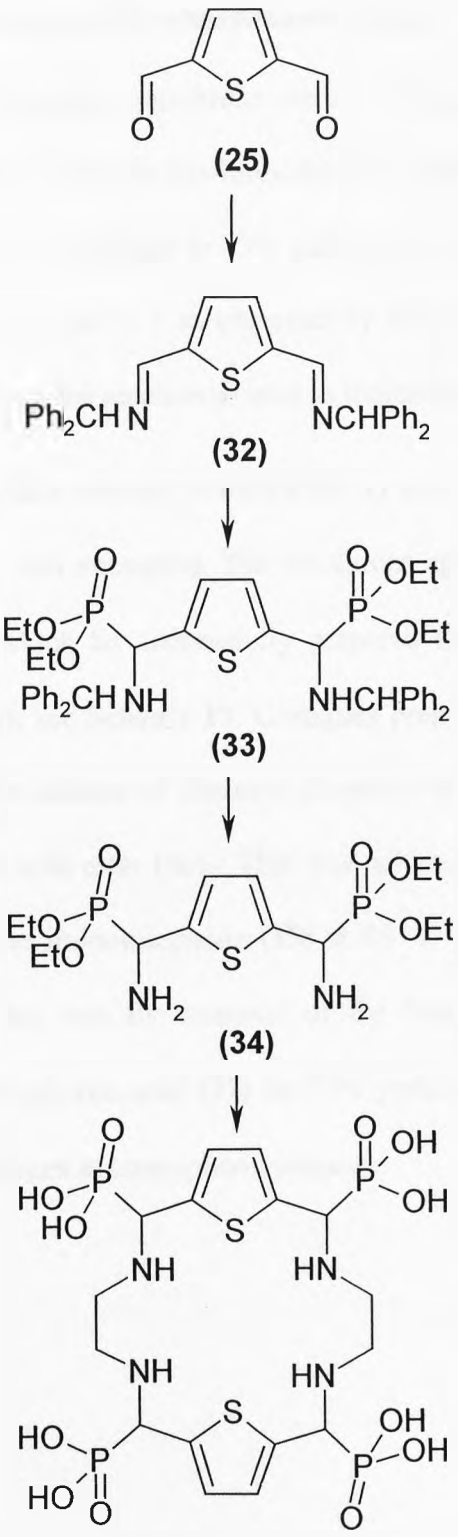
In order to investigate the macrocyclisation further it was necessary to prepare more of compound **(31)**. The reaction sequence was repeated however in this case the conversion of pyridine bis-imino **(29)** to pyridine bis-phosphonate ester **(30)** was more problematic and no product was isolated. This prevented any further work on the macrocylisation. A subsequent investigation on a different system (see section 3.3.1) indicated that the hydrophosphinylation is very sensitive and precise reaction conditions are required.

Given that every reaction towards the macrocycle **(N6TPH8_1)** was problematic, efforts were concentrated on an alternative system.

3.3 Alternative System

The macrocycle **(N4S2TPH8_1)** is analogous to the macrocycle **(N6TPH8_1)**, where the pyridine sub-units have been replaced by thiophene.

The proposed route to the thiophene macrocycle **(N4S2TPH8_1)** is illustrated in **Scheme 16**.



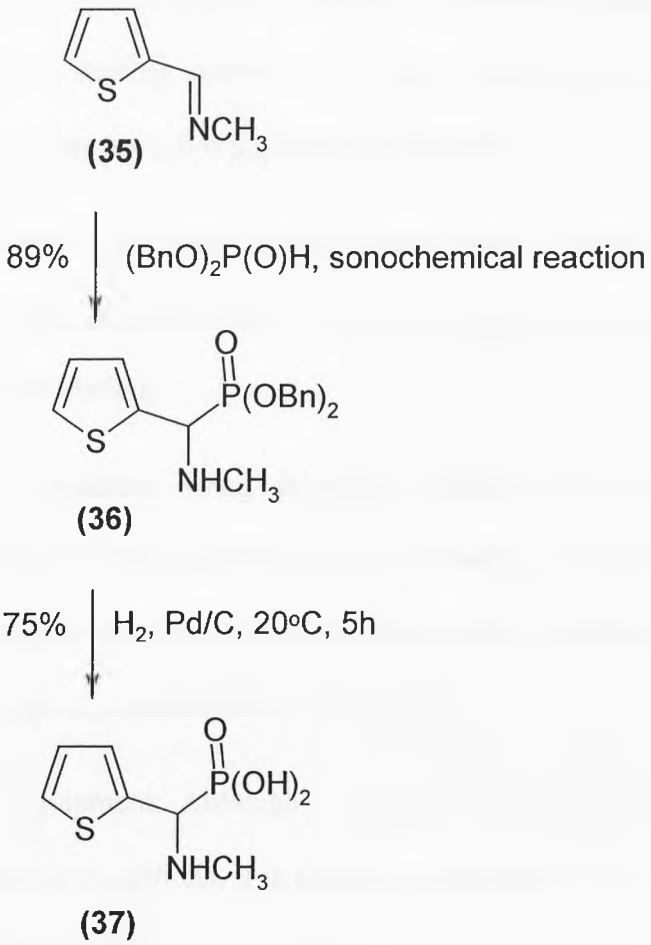
N4S2TPH8_1

Scheme 16

3.3.1 Preparation of Thiophene Bis-phosphonate Esters

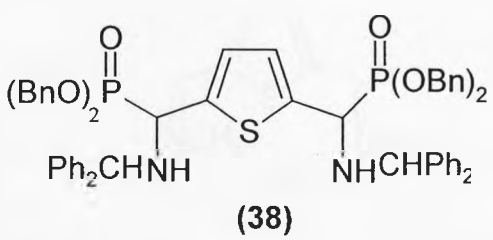
After a number of reaction conditions were investigated it was found that by heating neat diethyl phosphite with the bis-iminothiophene **(32)** at 150 °C the thiophene bis-phosphonate ester **(33)** was obtained in 43% yield (after column chromatography) as a mixture of diastereoisomers (*ca* 1: 1 as observed by HPLC). HPLC proved to be an excellent means of monitoring the reaction as well as indicating the purity of the product.

An alternative approach towards (**N4S2TPH8_1)** where the ethyl ester groups are replaced by benzyl groups was attempted. The conditions applied were similar to those used by Garrigues[117] in which he successfully prepared the N-methyl-substituted α-aminophosphonic acid **(37)**, see **Scheme 17**. Garrigues prepared compound **(37)** in two steps. The first step was the addition of dibenzyl phosphite to the iminothiophene **(35)** to give the aminophosphonic acid ester **(36)**. This was achieved in 89% yield by stirring dibenzyl phosphite with the iminothiophene **(35)** at 85 °C in toluene under ultrasonic irradiation. The second step was the removal of the benzyl groups to produce the corresponding α-aminophosphonic acid **(37)** in 75% yield using a 10% palladium on charcoal catalyst with hydrogen at atmospheric pressure.



Scheme 17

These conditions were applied, using thiophene bis-imino **(32)** **(Scheme 16)** as the starting material, in an attempt to prepare the bis-aminophosphonic acid benzyl esters **(38),**



(38)

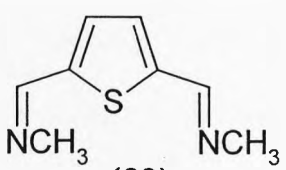
However in this latter case no observable reaction occurred. Another attempt was made by heating thiophene bis-imino **(32)** and dibenzyl phosphite in toluene to reflux, TLC analysis showed mainly starting material. It is unclear exactly why this reaction failed to proceed. However, there are a few possible explanations:

(i) Steric hindrance: In using thiophene bis-imino **(32)** the nitrogen is substituted with diphenylmethyl as such it is possible the reaction suffers from steric retardation;

(ii) Electronic impedance: using thiophene bis-imino **(32)** contains two conjugated imine bonds and the presence of a hetero atom near to the C=N double bond involves a bond delocalisation which stabilises the double bond; consequently no reaction is observed; and

(iii) Ultrasound equipment: Although Garrigues *et al* have produced good yields in precise conditions, it is unknown how sensitive the yield would be to alternative conditions/equipment.

To test the equipment the literature conditions should be repeated using iminothiophene **(35)** as starting material. Assuming that failure of the reaction was not equipment related, the other key reaction to undertake would be to react the thiophene bis methyl imino **(39)** under the conditions that were successful.



(39)

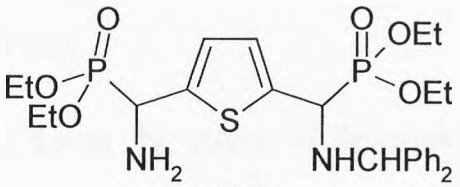
It does not appear that it is steric hindrance limiting the reactions as Garrigues *et al* showed the thiophene mono t-butyl imine reacts to give the corresponding aminophosphonic ester in 73% yield.

Inappropriate equipment can be partly ruled out since by simply heating the reaction mixture in toluene was shown to lead to reaction in the case of reported compound (**35**) albeit slowly in absence of sonication. In our case no significant product formation was observed even after extended heating. Hence, it appears that the bis-iminothiophene **(32)** is significantly less reactive towards the dibenzyl phosphite than compound **(36)**.

3.3.2 Hydrogenolysis of Thiophene Bis-phosphonate Ester (33)

The next step in the process involved the reductive deprotection of the diphenylmethyl groups. The conditions developed in the analogous pyridine system, employing a palladium hydroxide on carbon catalyst, were applied to thiophene bis-phosphonate ester **(33)**. However, in this case the protecting group was not removed.

Successful deprotection of one of the diphenylmethyl groups was achieved by addition of a catalytic amount of triflic acid. The product (**40**) was isolated by column chromatography and its identity confirmed by NMR and MS analysis.



(40)

Re-subjecting the mono deprotected compound to the above conditions did not afford the fully deprotected compound, however, all the starting material was consumed to give a complex mixture.

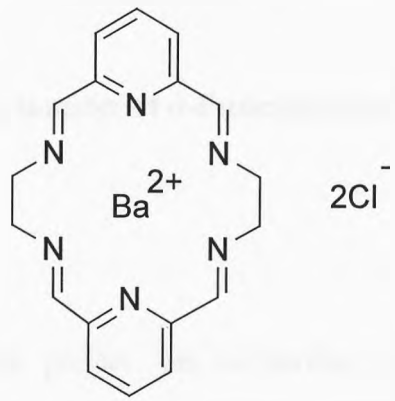
3.4 Conclusions and Further work

The synthesis of the target macrocycles **(N6TPH8_1)** and **(N4S2TPH8_1)** proved to be problematic. In the case of the pyridine system the synthetic route was achieved as far as the penultimate step at which point the key macrocyclisation step failed to occur. Further investigations were hindered as the two preceding steps both gave poor yields. In the case of the thiophene systems problems arose during the deprotection of the diphenylmethyl groups. Partial deprotection was obtained and this can be considered as an achievement as all previous attempts to remove this protecting group failed to occur (see section 4.5.4). However complete deprotection was not obtained and thus prevented progress with the proposed synthetic route, **(Scheme 16).**

There is another possible pathway to the target **(N6TPH8_1)** which involves macrocyclisation earlier in the pathway. This avoids potential problematic macrocylisation towards the latter portion of the synthetic sequence. An appropriate

precursor, the macrocycle Schiff base **(16) (Scheme 11),** has been developed for the preparation of **(N6TPH8)**.

As discussed during the course of the work, the preparation of the diethyl phosphonate ester from the bis-imino compound proceeded well as exemplified by conversion of compound **(32)** to **(33) (Scheme 16).** The conditions employed during the preparation of thiophene bis-phosphonate ester **(33)** can be employed for preparing macrocycles **(N6TPH8_1)** and **(N4S2TPH8_1)** using the synthetic pathway outlined in **Scheme 18**. In order to obtain the final desired products **(N6TPH8_1** and **N4S2TPH8_1),** demetallation and hydrolysis of the esters is required. One potential problem with this seemingly simple route is that the thiophene precursor imine macrocycle **(26)** is found to have poor solubility in a range of common solvents. However, the conditions required for preparation of diethyl phosphonate esters involve neat diethyl phosphite at high temperature where enough starting material is in solution for the reaction to proceed.



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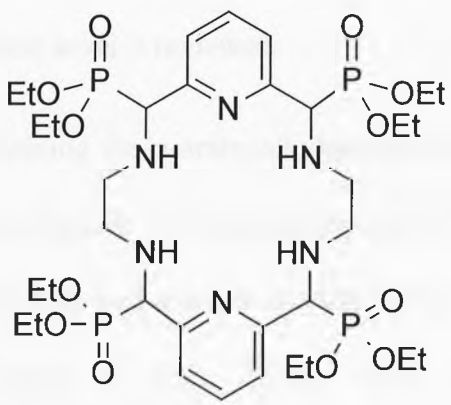
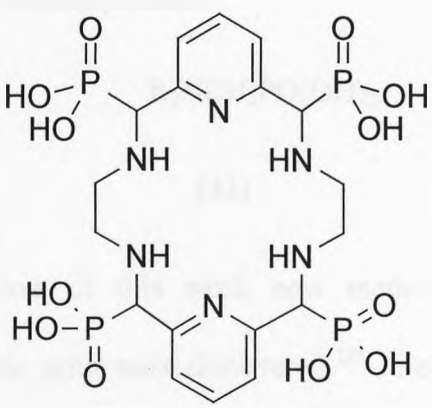


N6TP



N6TPH8_1

Scheme 18

Chapter 4

Synthesis and Characterisation of α-Functionalised Phosphinic Acids

4.1 Introduction

One of the aims of the project was to develop a synthesis of macrocyclic compounds involving heterocyclic skeleton systems containing α-aminoalkylphosphinic acid groups, (see chapter 1). The key intermediate in the synthesis of these macrocycles is the heterocycle bis[α-aminoalkylphosphinic] acid (**45**), **(Scheme 19)** thus the chemistry of α-aminoalkylphosphinic acids is reviewed.

Compounds containing the α-aminoalkylphosphinic acid functional group are of considerable importance because of their anti-bacterial,[118] herbicidal[74] and fungicidal activities.[119] Protonation studies of α-aminoalkylphosphinic acids **(41)** **(Figure 12)** have shown the nitrogen atom is very weakly basic compared to those of α-aminoalkylphosphonic acids **(42)** and α-aminocarboxylic acids **(43)** and that the phosphinic acid group is strongly acidic.[120]

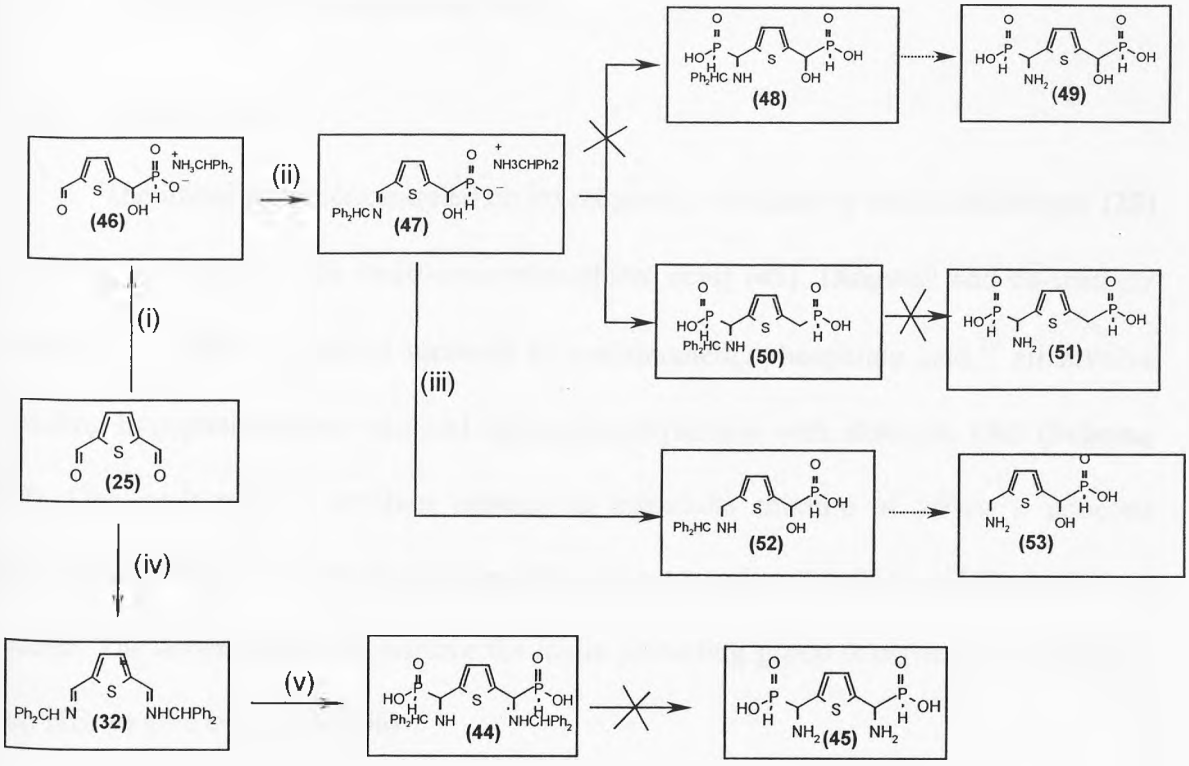
$R_2NCH_2P(H)(O)OH$ $R_2NCH_2PO(OH)_2$ $R_2NCH_2CO_2H$

(41) **(42)** **(43)**

During the course of this work new methods for the preparation of α-hydroxymethylphosphinic acids were discovered.[121] In contrast to the widely studied α-aminoalkylphosphinic acid derivatives, relatively few papers have reported on the

chemistry of α-hydroxylalkylphosphinic acids, although there is evidence that the α-hydroxyalkylphosphinate esters are biologically active and hence have pharmaceutical relevance.[122]

Many effective methods to prepare α-aminoalkylphosphinic acid have been developed,[79,123] but only a few synthetic routes to prepare α-hydroxyalkylphosphinic acids have been reported and these have involved prolonged heating of hypophosphorus acid with aldehydes or ketones,[124] or reaction of ketones with bis(trimethylsiloxy)phosphine.[125] In this study both types of α-functionalised phosphinate **(Scheme 19)** have successfully been prepared, of particular importance is the first isolation of the α-hydroxyalkylphosphinate compound **(46)** using mild reaction conditions, and the first characterisation by X-ray crystallography of this class of compound.[121]



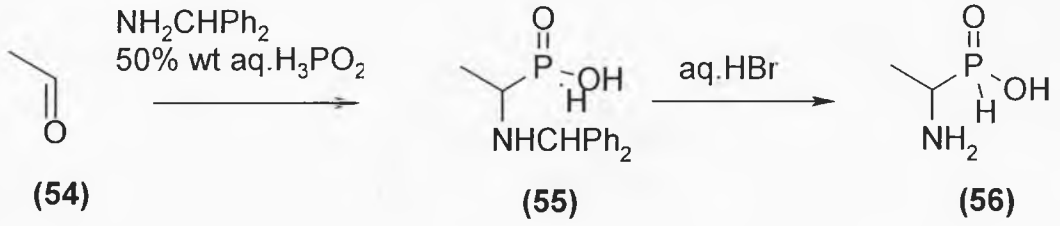
Scheme 19: (i) NH_2CHPh_2, 50% wt aq. H_3PO_2; (ii) NH_2CHPh_2, DMSO; (iii) $NaBH_4$, MeOH; (iv) NH_2CHPh_2, MeOH (v) H_3PO_2, 1,4-dioxane

The initial target was to develop a synthetic route to the thienyl bis[α-aminomethylphosphinic acid] system, **(45) (Scheme 19)**, and during this process new possible target compounds **(49)**, **(51)** and **(53)** arose which possess the desired chelating groups (NH_2/OH) and the ability to be extended to the target macrocycle.

4.2 α-Hydroxyalkylphosphinic Acid

4.2.1 Introduction

The initial work concentrated on investigating a method by which dialdehyde **(25)** could be converted to the bis[α-aminophosphinic acid] **(45)**. Dingwall and co-workers describe a number of general methods to α-aminomethylphosphinic acid,[79] all involve reacting hypophosphorous acid and diphenylmethylamine with aldehyde **(54) (Scheme 20)**. One such method involves heating an equimolar mixture of 50%w/w aqueous hypophosphorous acid and diphenylmethylamine to reflux to which aldehyde **(54)** is added. The debenzylation to remove the labile protecting group is carried out with 60% aq. HBr to give compound **(56)**.



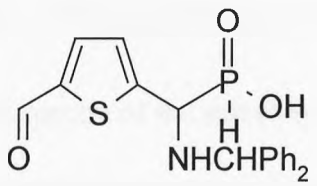
(54) **(55)** **(56)**

Scheme 20

These conditions were applied to 2,5-thiophenedialdehyde **(25)**, **(Scheme 19)**. However, this did not give the expected bis[α-aminomethylphosphinic acid] **(44)** but instead gave the α-hydroxymethylphosphinic acid **(46).** Literature investigation revealed no examples of α-hydroxymethylphosphinic acids in which the heterocyclic ring was substituted at the α position. In fact a combination of Scifinder and Beilstein database searching found only 18 literature examples of aromatic substitution α to the hydroxyphosphinic acid group.

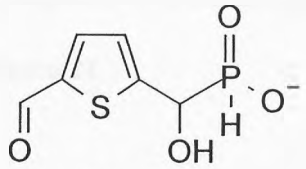
4.2.2 Discussion of α-Hydroxymethylphosphinic Acid (46)

In principle the addition of aqueous hypophosphorous acid, and diphenylmethylamine to the dialdehyde **(25)**, should lead to thienyl bis[α-aminomethylphosphinic acid] **(44) (Scheme 19),** as highlighted in the literature.[79] Initially 2,5-thiophenedialdehyde **(25)** was added to 2 equivalents of an equimolar mixture of diphenylmethylamine and aqueous hypophosphorus acid at 90°C, in water. However, the diadduct was not observed and one carbonyl group remained unreacted which was proven by an aldehydic ^{1}H NMR signal and a carbonyl stretch in the infrared spectrum. A likely possibility was that the product was the monoadduct, **(57)**. However, positive ion mass spectrometry (MS) did not support this, as there was no mass ion peak at 372, for the compound.



(57)

The mass spectrum did, however, show a peak at 184 and the base peak at 167. This information, together with a base peak in the negative ion mass spectrum at 205 which could be assigned to the anion **(58)** strongly suggest that the product was α-hydroxymethylphosphinic acid salt **(46).** The peak at 184 can thus be assigned to the $Ph_2CHNH_3^+$ ion and the base peak at 167 to the Ph_2CH^+ cation.



(58)

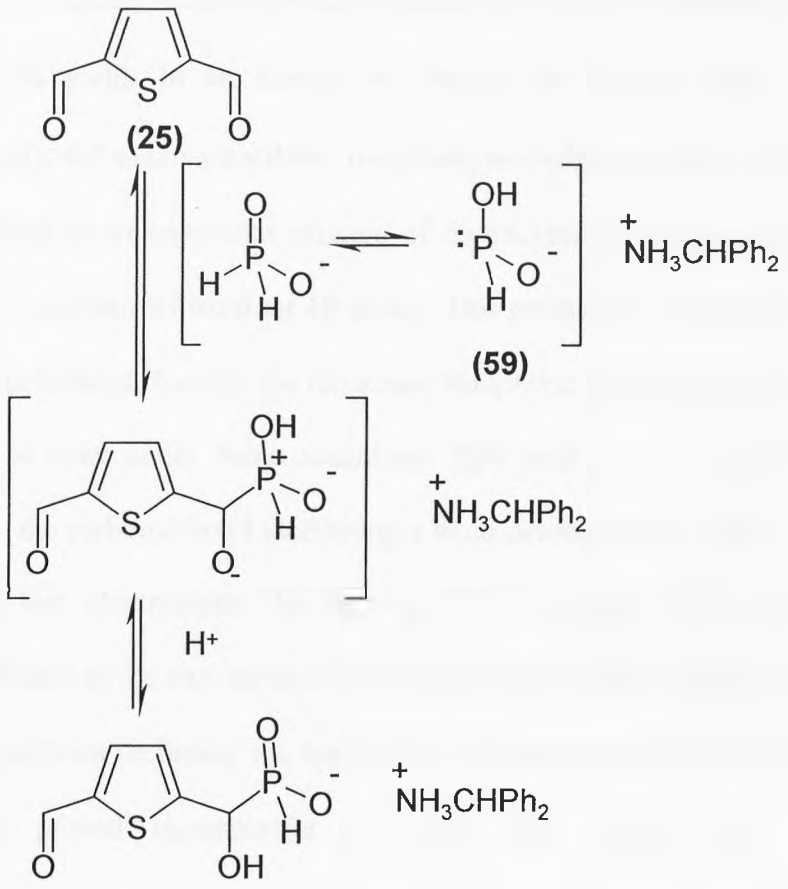
In addition to the MS data, a ^{1}H NMR experiment suggested the compound to be a salt. A pure sample of compound **(46)** was dissolved in d_6-DMSO and left standing overnight. The ^{1}H NMR spectrum of the resulting sample showed signals expected for compound **(46)** plus an additional signal which could be assigned to an imine proton. If compound **(46)** had been N-substituted then the self condensation reaction observed in the ^{1}H NMR sample would not have occurred. This suggests that compound **(46)** is a salt with $^{+}NH_3CHPh_2$ cation. The structure of compound **(46)** has been unambiguously confirmed by X-ray crystallography. This is discussed in a separate section below.

The ^{1}H, ^{13}C and ^{31}P NMR spectra of the salt **(46)** were also obtained in d_6-DMSO solution. First order analysis of the spectra was carried out.

In the ^{1}H NMR spectrum of α-hydroxymethyl phosphinic acid **(46)**, a *gem* coupling $J_{P\text{-}CH}$ 10 Hz with no observable vicinal coupling $J_{HP\text{-}CH}$ is seen. This is comparable with that observed by Dingwall[79] *et al* who reported that in some cases a $J_{HP\text{-}CH}$ coupling of 1.5-2 Hz was found. Also observed in the spectrum is a large doublet centred at δ 6.77 ppm with a coupling of J_{PH} of 552 Hz.

The ^{31}P NMR showed a sharp singlet at 19.4 ppm expected for α-hydroxymethyl phosphinic acid **(46)** however a concentrated d_6-DMSO sample showed two signals at 24.2 and 22.5 ppm expected for mixtures of the mono adduct and bis-adduct.

A mechanism can be proposed which accounts for this observation. This mechanism is summarised in **Scheme 21**



Scheme 21

A possible explanation to account for the differences observed in the current work to that published by Dingwall is as follows.[79] It is apparent that the equilibrium between the dialdehyde and the bis imine does not proceed sufficiently to ensure that hypophosphorous acid attack occurs on the imine. **Scheme 21** shows the likely mechanism where the carbonyl group is attacked by hypophosphorous acid, presumably through its nucleophilic tautomer **(59).** The addition of the phosphonate group to the

second carbonyl group does not occur as this work has clearly demonstrated since compound (**46**) is not electrophilic enough to be attacked by the nucleophilic phosphorus.

The α-hydroxymethylphosphinic acid **(46)** was obtained as a yellow crystalline solid in a consistent 30-34% yield. In an attempt to prepare the thienyl bis(α-hydroxymethylphosphinic acid), the mono-substituted α-hydroxymethylphosphinic acid **(46)** was added to 1 equivalent of an equimolar mixture of diphenylmethylamine and aqueous hypophosphorus acid and then refluxed for 48 hours. This produced no reaction and only starting material was isolated. Clearly the remaining thiophene carbonyl group is not electrophilic enough to react under these conditions. This may be due to the presence of the sulfur near to the carbonyl bond facilitating a bond delocalisation, which makes the carbonyl group less electrophilic. In the case of compound (**25**) this delocalisation is not as significant as the two carbonyl group share conjugation with the sulfur atom. A number of variations including the use of excess reagent, and increased temperature and time all proved unsuccessful in giving the thienyl bis(α-hydroxymethylphosphinic acid) **(44)**.

4.2.3 Crystal structure of α-Hydroxymethylphosphinic Acid (46)

The presence of the α-hydroxy group in compound **(46)** was confirmed by X-ray structure analysis of this diphenylmethylammonium salt. The arrangement of the ions in the solid, which are linked by a hydrogen bond between one of the phosphinate oxygen atoms and a proton on the ammonium cation [O(2)...H(1N) = 1.86Å] is shown in **Figure 12(a)**. The remaining two protons of the (diphenylmethyl)-ammonium counterion are also involved in hydrogen-bonding to the phosphinate oxygen atoms of the adjacent

symmetry-related anions [O…H(N) = 1.72-1.90 Å], resulting in a complicated spiral hydrogen-bonded chain of alternating cations and anions [**Figure 12(*b*)**]. Along this helix, adjacent anions are linked by hydrogen-bonding between the α-hydroxy group of one anion and a phosphinate oxygen of the next [H(1O)…O(3') = 1.98 Å] as can also be seen in **Figure 12(b)**.

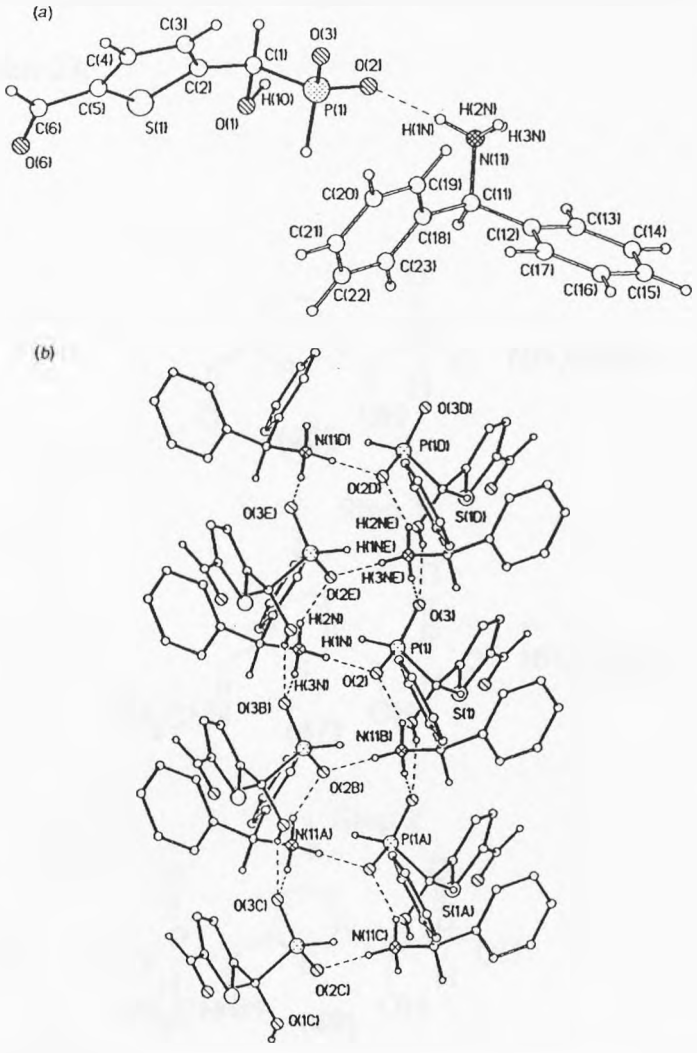
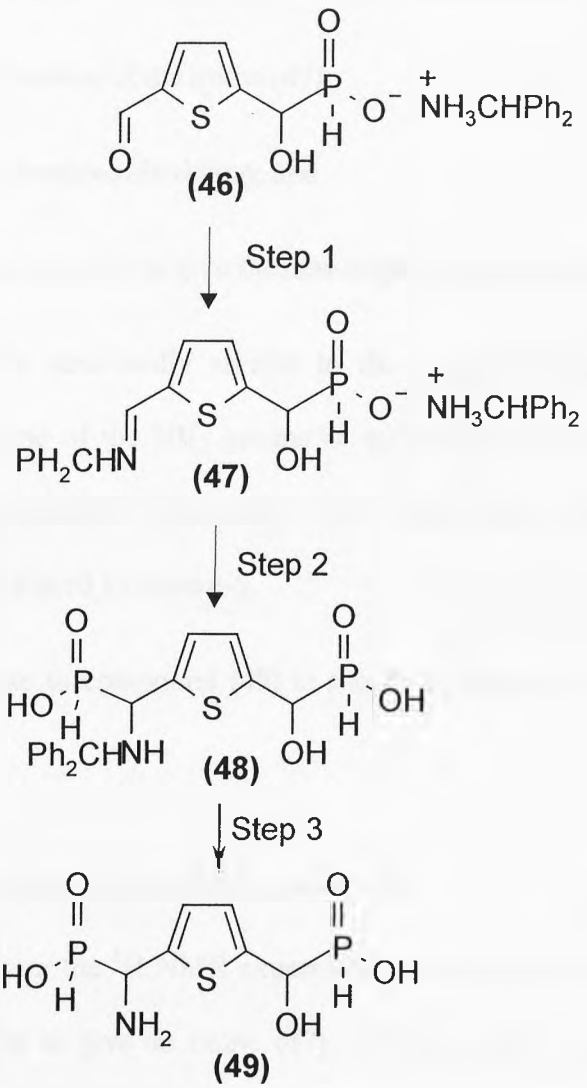


Figure 12 The structure of Compound (**46**): *(a)* the anion and cation linked by one of the H-bonds; *(b)* part of the helical H-bonded chain.

4.3 α-Hydroxy-α-Aminomethylphosphinic Acid (49) as a New Potential Target

An interesting observation was made during the ^{1}H NMR experiment using **(46)** in d_6-DMSO solution. Over the period of approximately 18 h the aldehydic signal in compound **(46)** was reduced in intensity and a new peak at δ 8.55 ppm appeared, which was tentatively assigned to an imine proton resonance. This suggested the diadduct **(47)** had been formed **(Scheme 22, Step 1).**

The proposed synthetic route to α-hydroxy-α-aminomethylphosphinic acid **(49)** is illustrated in **Scheme 22.**



Scheme 22

This observation led to the possibility of the diadduct **(45)** being synthetically accessible *via* a different approach. This led to the consideration of preparing the α-hydroxy-α-aminomethylphosphinic acid diadduct, compound **(49)**, **Scheme 22**.

The procedure proposed for synthesis of compound **(49)** was:

(i) formation of the imine **(47)**;

(ii) hydrophosphinylation; and

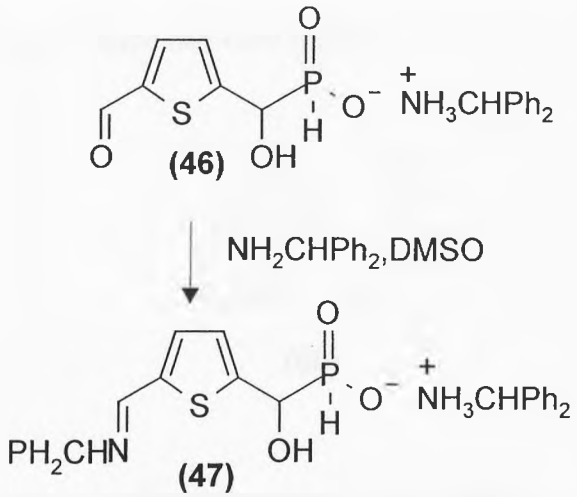
(iii) deprotection to give the new target, compound **(49)**.

The new target is structurally similar to the original target compound **(45)**, **Scheme 19** except that one of the NH_2 groups is replaced by an OH group. Being an isostere it would be potentially biologically active and able to be converted to a macrocycle such as ether linked 18-crown-6.

The proposed route to compound **(49)** is shown in **Scheme 22** and discussed in the following section.

4.3.1 Imino-α-Hydroxymethylphosphinic Acid (47)

As was evident from the ^1H NMR experiment described above, the salt **(46)** can undergo self condensation to give an imine **(47)**, **(Scheme 23)**. For this reason a new experiment was carried out in which an extra equivalent of diphenylmethylamine was added in DMSO at ambient temperature. This encouraged formation of the imine **(47)** which precipitated out of solution as a white solid in 80% yield.



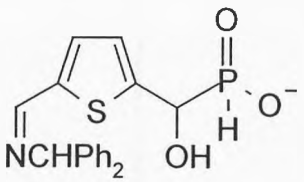
Scheme 23

It is unusual that condensation took place, in the absence of a dehydrating agent. It is also somewhat unusal the reaction was facile given that the carbonyl group is delocalised with the thiophene ring thus reducing its reactivity towards a nucleophile.

It was discovered during further investigation that imine **(47)** has very poor solubility in most common solvents, it is sparingly soluble both in methanol and DMSO. This led to consideration of using methanol as solvent for preparation of imine **(47)**. However, a slightly lower yield (65%) was obtained in methanol due to the imine **(47)** having greater solubility in methanol than in DMSO. An attempt was made to crystallise imine **(47)** from methanol but this failed to produce crystals suitable for X-ray analysis.

Imine **(47),** despite being a salt, is also not water soluble. The imine **(47)** was fully characterised and the major features of its MS, NMR and IR spectra are briefly discussed below. The significant feature in the negative ion mass spectrum of imine **(47)**

was a base peak at 370; this was assigned to the anionic portion of the molecule **(60)** indicating that the desired imine had been formed.



(60)

Infrared spectroscopy showed a strong broad band at *ca* 1675 cm^{-1} for ν (C=N) stretch in comparison with the precursor aldehyde which showed a band at 1666 cm^{-1} for the carbonyl stretch. The phosphoryl ν (P=O) band at *ca* 1149 cm^{-1}, the ν (P-H) band at 2334 cm^{-1} and the ν (P-O) band at 1050 cm^{-1} did not change significantly between aldehyde **(46)** and imine **(47)** as expected, as these portions of the structures are identical. The ^{1}H NMR of the imine **(47)** was compared with that of the precursor aldehyde **(46)**.

Figure 13 depicts the NMR spectra of these two compounds and includes label references explained in the discussion below.

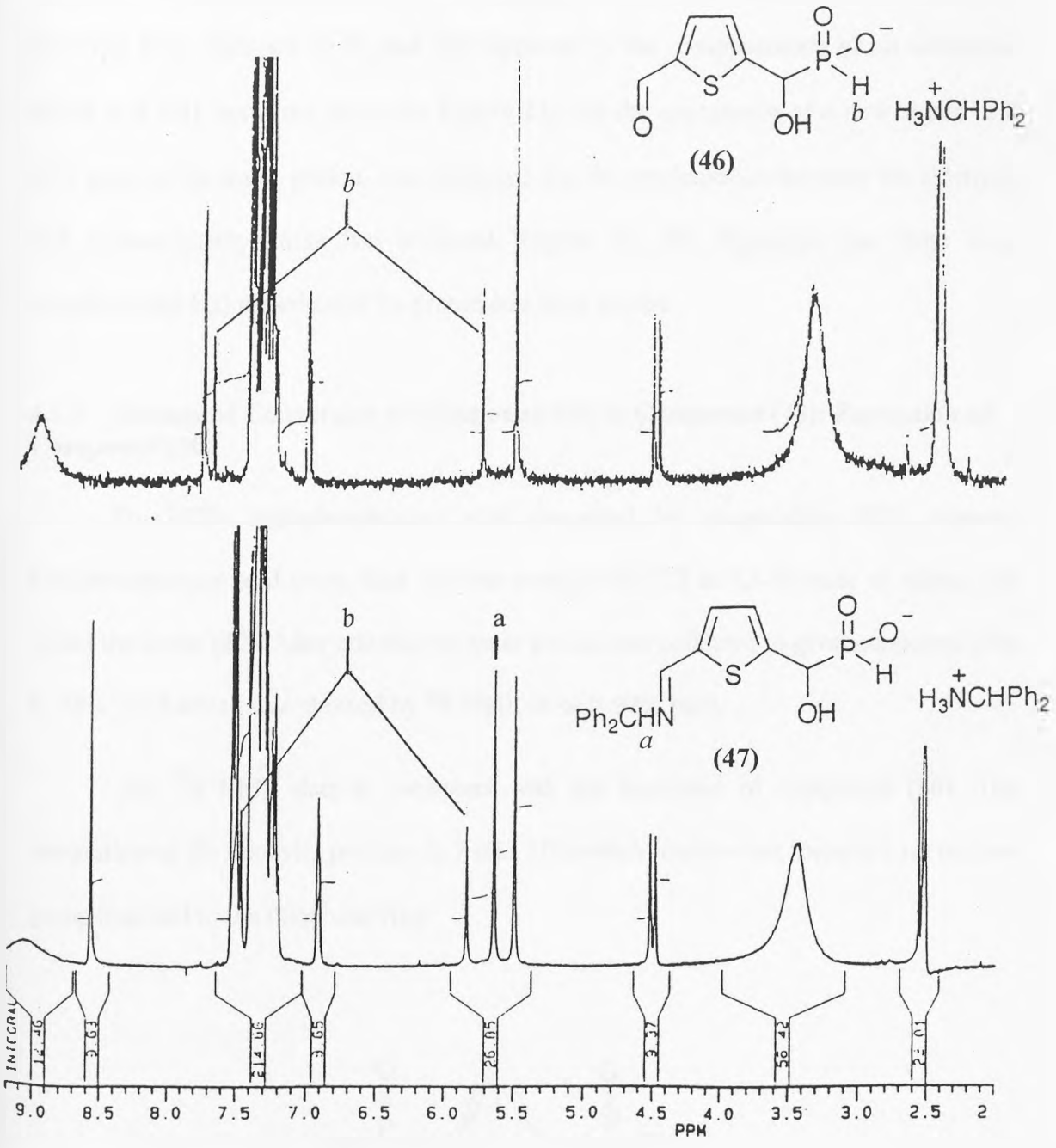


Figure 13: ^{1}H NMR spectra of compound **(46)** and **(47)**

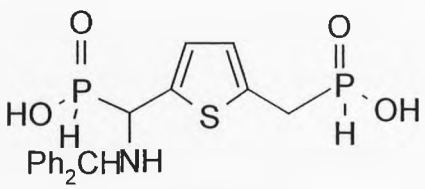
The signal due to the methine proton in $H_3N^+CHPh_2$ appears as a singlet and the chemical shift is similar in both imine **(47)** and aldehyde **(46)**. This is consistent with the fact that they are similar in structure in this portion of the molecule, i.e. both the imine

(47) and aldehyde **(46)** are salts. An additional signal in the spectrum of **(47)** at δ 5.62 ppm has been assigned to H_a and also apparent is the disappearance of an aldehydic signal at δ 9.81 ppm (not shown in **Figure 13**) and the appearance of a new signal at δ 8.55 ppm for the imine proton. This indicated that the condensation between the aldehyde and diphenylmethylamine had occurred. **Figure 13** also highlights the large $J_{P\text{-}CH}$ coupling (489 Hz) experienced by proton *b* in both spectra.

4.3.2 Attempted Conversion of Compound (47) to Compound (48): Formation of Compound (50)

To 100% hypophosphorous acid (prepared by evaporating 50% aqueous hypophosphorous acid using high vacuum pump at 50 °C) in 1,4-dioxane at reflux was added the imine **(47)**. After addition of water a solid was collected to give compound **(50)** in 28% yield which was showed by ^{1}H NMR to be > 97% pure.

The ^{1}H NMR data is consistent with the formation of compound **(50).** The integration of the benzylic position is 2 (Ha, Hb) which implies that there is a methylene group attached to the thiophene ring.

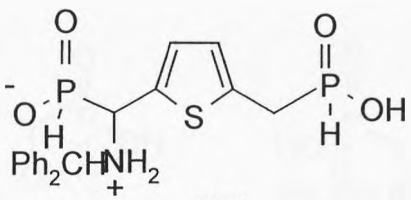


(50)

The two doublets at δ 6.91 ppm and δ 6.82 ppm showing extremely large splitting of 530, 510 Hz respectively are due to P-H coupling. Only one $CHPh_2$ signal is present

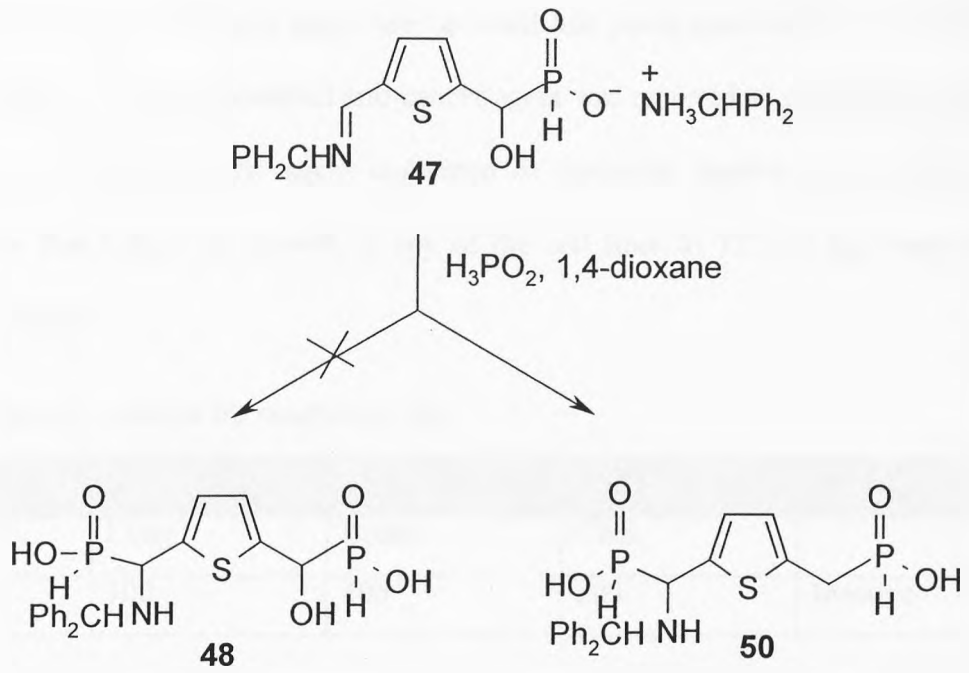
indicating that $H_3N^+CHPh_2$ counter ion is lost. As such compound **(50)** is a free acid and not a salt.

There are two phosphinic acid groups in **(50)** and either could be a proton donor to the amino group. It is likely that the phosphinic acid group in the α position has enhanced acidity and that the zwitterionic structure can be represented as **(61)**



(61)

Addition of imine (**47**) to neat hypophosphorous acid (3.0 eq) in boiling 1,4-dioxane causes addition of the phosphoryl group as expected, but unexpectedly the thiophene ring α- hydroxyl group is replaced with hydrogen. This is most likely a result of using neat hypophosphorous acid which protonates the hydroxyl group. Elimination of water then gives the stabilised benzylic cation which is reduced with hypophosphorous acid to give compound (**50**).



Scheme 24

It might be useful to consider why the benzylic like alcohol was not reductively removed in the conversion of compound **(25)** to **(46)** whereas removal of the hydroxyl group was observed in the conversion of compound **(47)** to **(50)**.

Two factors come into play as the reaction was performed in an aqueous environment, firstly the acidity of the solution would be much less in 50% aqueous hypophosphorus acid than in neat hypophosphorous acid and, secondly, if the benzylic cation was produced as an intermediate it would react with water around it to give benzyl alcohol.

The yield obtained for compound **(50)** was not optimised as enough material was made for further investigation.

4.3.2.1 The Results of the Anti-Cancer Screen

The primary anti-cancer assay used a 3-cell line panel consisting of lung, breast and CNS. Results for each potential anti-cancer agent was reported as percentage growth of the cells treated with the agent compared to untreated control cells **(Table 3)**. Compounds that reduce the growth of any of the cell lines to 32% or less were then further evaluated.

Table 3: Growth inibition for compound **(50)**

Concentration	Growth (%)			Activity
	Lung	Breast	CNS	
0.1mM	100	106	103	Inactive

4.3.2.2 Attempted Removal of the Protecting Group From Compound (50).

Although it is not our original target it would be interesting to deprotect the novel compound (**50**). The most common methodology for removing the diphenylmethyl group is aqueous hydrobromic acid,[79] however it has been shown during the course of our work that this is not the case for this class of compounds. Also attempted on compound (**50**) were the hydrogenolysis conditions using palladium black. However, hydrogenation with palladium black failed to cleave the diphenylmethyl group.

4.4 Investigation towards compound (53)

Having achieved the synthesis of compound (**47**) this gave an opportunity to prepare compound (**51**), as discussed above and also allowed the opportunity to prepare α-amino α-hydroxyphosphinic acid (**53**), **(Scheme 19).**

The work towards compound (**53**) was performed in parallel with investigation of converting compound (**47**) to compound (**51**).

The initial step from compound (**47**) to (**53**) involved the reduction of the imine (**47**) to the amine (**52**) this was first investigated using lithium aluminium hydride. However, this failed to produce the desired product. Alternative conditions were applied in which the reductive step was successfully carried out using sodium borohydride in methanol to give the required product in 46% yield after chromatography. Upon column chromatography two components were isolated the least polar component was recovered and identified as diphenylmethylamine which was originally the protected counter ion in the starting material. The more polar component was identified as the desired reduced material (**52**). Upon scale-up the yield increased to 86%. This was confirmed by ^{1}H NMR (D_2O) which clearly showed the loss of the imine signal at δ 8.55 ppm and appearance of a singlet at δ 3.64 ppm of integration 2 corresponding to the newly introduced methylene group.

Although the preparation of compound (**52**) was achieved it was decided not to spend time investigating the deprotection step, given the failure of analogous compound (**50**) to be deprotected. Exploration of the deprotection of compound (**52**) remains an area for future investigations.

4.5 Thienyl bis[α-aminomethylphosphinic acid] (45)

4.5.1 Introduction

The original target of this section was the synthesis of compound (**45**). However as noted in the previous section application of literature conditions of treating diphenylmethylamine and aqueous hypophosphorous acid with 2,5-thiophendialdehyde **(25)** did not provide the required protected precursor to compound **(45)**. As a result a different methodology was proposed one that involved preparing and isolating the thiophene bis imine **(32)** followed by hydrophosphinylation to give compound (**44**). This could be converted to the target compound (**45**) via the removal of the protecting group.

4.5.2 Thiophene Bis-imine formation (32)

The first requirement was to prepare and isolate the thiophene bis-imine **(32)** by condensing 2,5-thiophenedialdehyde **(25)** with diphenylmethylamine at reflux for 1 h in toluene using molecular sieves as dehydrating agent. This reaction has been also carried out in methanol. In both instances the product precipitated out of solution in 48-51% yield. Analysis of the product by TLC showed to be multi spots, however analysis of the product by ^{1}H NMR showed to be the required material and purity >97%. From this it can be inferred that multi spots on the TLC is presumably due to the imine **(32)** hydrolysing on the TLC plate. One interesting observation noted was that hydrolysing of the two imine bonds back to the starting material (dialdehyde) was not observed. This was proved by dissolving small amount of bis-imine in ethyl acetate and spotting the solution on the TLC plate and leaving the TLC plate standing for 20 min. After this period analysing of the TLC plate showed three spots, The two polar spots were assigned

to diphenylmethylamine and the monoadduct, and the least polar spot is due to the bis-imine. To improve the yield the condensation reaction was performed in toluene using a Dean Stark apparatus to drive the reaction forward and upon cooling the product precipitated out of solution in 80% yield and >97% pure by NMR. This material was successfully used in the subsequent step. The compound was fully analysed. The ^{1}H NMR of the bis-imine was simple because of the plane of symmetry, apart from the obvious aromatic region at δ 7.4 ppm due to the phenyl protons the other signal is a peak at δ 8.7 ppm assigned to the imine proton. The signal at δ 5.7 ppm is due to the benzylic proton and signal at 7.5 ppm is tentatively assigned to the thiophene protons.

4.5.3 Compound (44)

Treatment of compound **(32)** with 50% aqueous hypophosphorous acid did not give compound **(44)** as expected. TLC analysis of the reaction mixture showed the presence of multiple products. ^{1}H NMR analysis of the crude mixture showed hydrolysis products as indicated by the presence of aldehydic signals. To eliminate the problem of hydrolysis, compound **(32)** was treated with 100% hypophosphorous acid (prepared by evaporating 50% aqueous hypophosphorous acid at 50°C on high vacuum) in 1,4-dioxane. The compound **(44)** precipitated out of solution and was recovered by filtration as an off-white solid, in 72% yield. The negative ion mass spectrum shows a mass ion peak at 601 $[M-H]^-$ and a peak at 300 corresponding to doubly charged $[M-2H]^{2-}$. ^{1}H NMR showed good correlation with the required product as a *ca* 1:1 mixture of diastereoisomers as indicated by duplications of most of the key peaks in the ^{1}H NMR spectrum. Even though the product was a 1:1 mixture of diastereoisomers TLC indicated a single spot as such it was not possible to separate using chromatographic technique.

The compound showed limited solubility in range of organic solvents such as methanol, DMF, acetonitrile and toluene, which limits the scope of reaction it, can be applied in.

Attempts to grow crystals from methanol, methanol/glacial acetic acid and neat acetic acid failed to give crystal suitable for X-ray analysis.

4.5.4 Attempted Deprotection of Compound (44)

A range of deprotection conditions were used in order to effect the deprotection of compound **(44)**, these are listed in **Table 4**. In all cases either no reaction or degradation of starting material had occurred.

No reaction was observed even when harsh conditions were applied. Analysis of the reaction mixture by TLC showed multi spots and in no case was the deprotected product observed.

Table 4: Attempted deprotection conditions for compound **(44)**

Experiment	Conditions	Reaction Monitored
1	10% Pd/C, H_2, MeOH, 18h	By ^{1}H NMR no reaction
2	60% HBr/AcOH, reflux, 3h	Degradation of starting material by TLC (Toluene-CH_3OH, 60:40)
3	$CHCl_3$/cHCl, reflux 18h	TLC (Toluene-CH_3OH, 60:40) shows starting material
4	H_2O/cHCl (80:20), reflux, 18h	TLC shows starting material

5	Zn dust(12eq), AcOH, 22°C, 16h	TLC shows starting material
6	5% Pd/C , H_2, HCO_2NH_4, MeOH,	By ^1H NMR no reaction
7	Pd black, H_2, MeOH, 22°C, 52h	TLC shows starting material
8	10 Pd/C, 30 atms, H_2, 22°C, MeOH, 16h	TLC shows starting material

The poor solubility **(44)** hindered attempts at developing alternative deprotection strategy.

4.6 Alternative Protecting Group Strategy Towards Compound (45)

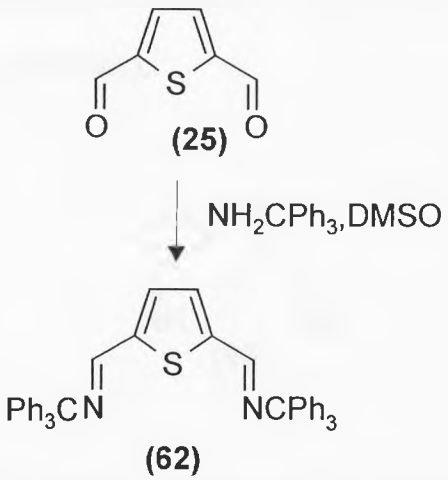
Given the inability to remove the diphenylmethyl protecting group from compound **(44)** an alternative strategy was investigated This involved a different protecting group namely the trityl or an absence of protecting group.

The reasons for selecting the trityl group are:

(i) trityl group is known to be easily deprotected under mild acidic conditions; and

(ii) trityl amine is commercially available.

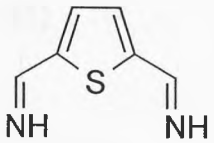
The condensation reaction between 2,5-thiophenedialdehyde **(25)** and trityl amine **(Scheme 25)** was carried out using similar methodology generated to prepare the thiophene bis-imine **(32)** as described in section 4.5.2.



Scheme 25

This reaction was forced to completion by azeotroping water using a Dean and Stark apparatus. Compound **(62)** precipitated out of solution and was isolated by filtration. Compound **(62)** was observed to be extremely insoluble in toluene, methanol, 1,4-dioxane, and chloroform. In fact the ^{1}H NMR could only be obtained in hot d_6-DMSO in which the compound is sparingly soluble. The ^{1}H NMR showed the uncrystallised material to be 97% pure and hence it was used without further purification. Having obtained compound **(62)** it was subjected to the method used in preparing compound **(44)**; however, under these conditions primarily starting material was recovered. The major contribution to this problem was the lack of solubility exhibited by compound **(62)** in conditions used for the hydrophosphinylation. No further experiments were performed in this area.

Another alternative strategy that was briefly explored was the direct formation of the unsubstituted bis-imine compound **(63)**.



(63)

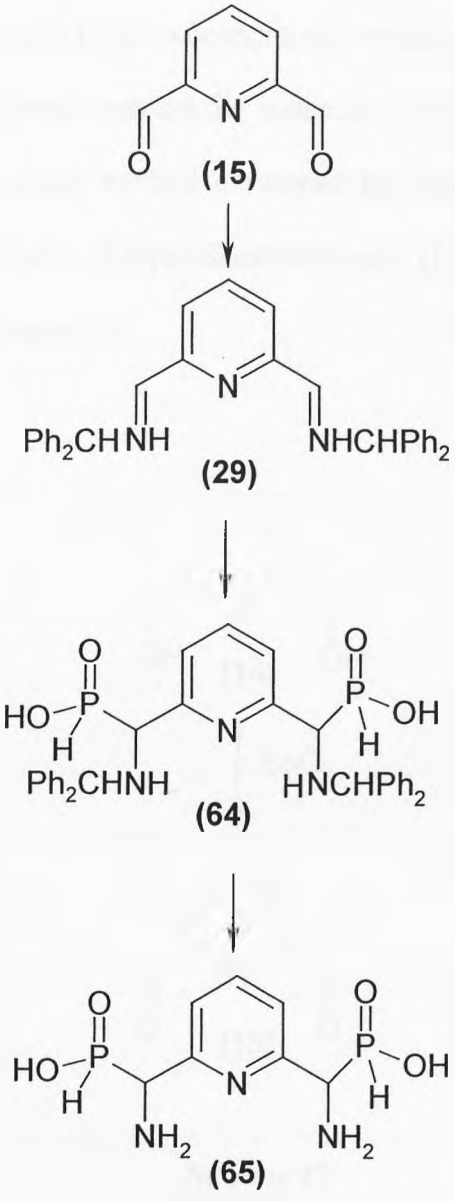
Two different procedures were investigated and one involved direct reaction of ammonia with 2,5-thiophenedialdehyde **(25)** and another involved the removal of the trityl group. In the former case a complex mixture was observed by TLC which has been attributed to the instability of the imine **(63)** and in the latter case there was no reaction. This is probably due to insolubility of compound **(62)**.

4.7 Pyridine system

4.7.1 Introduction

In parallel with the synthesis undertaken to prepare the thiophene system investigation of an analogous pyridine system was undertaken.

The proposed route is outlined in **Scheme 26**.



Scheme 26

The procedure proposed towards the synthesis of compound **(65)** was:

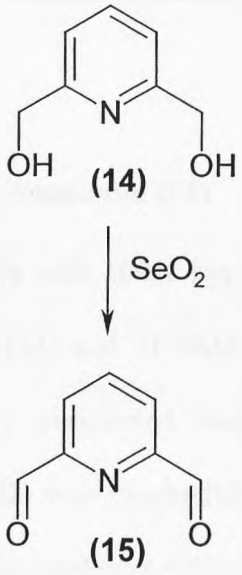
(i) formation of the imine **(29)**

(ii) hydrophosphinylation to compound **(64)**; and

(iii) deprotection to the new target compound **(65)**.

4.7.2 2,6-Pyridinedicarbaldehyde (15)

2,6-Pyridinedialdehyde **(15)** is commercially available from Aldrich, however its great expense (£56 per gram) restricts its usage in multi-step synthesis as starting material. Therefore a preferred method developed by Luning[100] was used involving oxidation of readily available 2,6-pyridinedimethanol **(14)** using selenium dioxide (oxidant) as depicted in **Scheme 27.**



Scheme 27

It was essential not to store the isolated 2,6-pyridinedialdehyde **(15)** as it is expected to be prone to oxidation. The isolated compound was >98% pure by ^{1}H NMR and was obtained in quantitative yield and was subsequently used without further purification. The IR spectrum showed a sharp signal at 1721 cm^{-1} expected for the C=O aldehyde stretch.

4.7.3 Pyridine Bis-imino (29)

Initial method employed for the synthesis of pyridine Schiff base **(29) Scheme 26**, was similar to that used for the preparation of thiophene Schiff base **(32)** depicted in **Scheme 19**. After work-up compound **(29)** was recrystallised from hot hexane as needle white crystals in 72% yield. The ^{1}H NMR clearly showed the loss of the aldehydic signal and the appearance of new signals at δ 5.5 ppm and δ 5.7 ppm corresponding to the HC=N and the diphenylmethylene protons respectively. However, in this case enough material was obtained by doing this reaction therefore yield towards compound **(29)** was not optimised.

4.7.4 Attempted Preparation of Compound (64)

Treatment of compound **(29)** with 100% hypophosphorous acid in 1,4-dioxane did not give compound **(64).** Both TLC and ^{1}H NMR analysis showed that mixtures of compounds had formed. This was unexpected because in the analogous thiophene systems **(Scheme 19)** compound **(32)** was successfully converted to compound **(44)** in good yield. A second preparation that employed 50% aqueous hypophosphorous acid was attempted. However, a similar complex mixture was obtained.

4.8 Conclusions and Further Work

In the course of this work a novel thiophene bearing α-hydroxymethylphosphinate substituent (compound (**46**)) was prepared. This compound arose during the reaction of 2,5-thiophenedialdehyde with an equimolar mixture of 50% aqueous hypophosphorous acid and Ph_2CHNH_2, rather than the expected thienyl bis[α-aminomethylphosphinic acid] (**44**). The discovery of compound (**46**) also led to the development of a series of associated compounds. One unusual reaction in the series involved the reduction of the α-hydroxyl group (compound (**47**) to compound (**50**)) in the presence of excess H_3PO_2. This reduced product (compound (**50**)) was submitted for screening in the anti-cancer programme conducted by the National Cancer Institute in Maryland, U.S.A, which was found to be inactive to lung, breast and CNS cell lines. Interestingly the α-hydroxyl group in compound (**47**) is stable to normal reduction conditions as shown by conversion of compound (**47**) to compound (**52**) using sodium borohydride.

Thienyl bis[α-aminomethylphosphinic acid] (**44**) was prepared from the 2,5-thiophenedialdehyde (**25**) in a two step process. The first step involved the preparation of the thiophene bis-imine (**32**) which was subsequently treated in step two with 100% hypophosphorous acid. Compound (**44**) proved to be resistant to a range of deprotection conditions and hence the target compound (**45**) was not achieved. Alternative approaches using a different protecting group or indeed no protecting group failed in the synthetic route. It remains for further investigations to discover the optimum deprotection conditions and once compound (**45**) has been achieved then macrocyclisation can be performed.

In the analogous pyridine series progress was not made beyond the pyridine bis imine step (**Scheme 26**) and the alternative α-hydroxy product pathway was not observed.

Chapter 5

EXPERIMENTAL

5.1 Reagents and General Analytical Techniques

The reagents and solvents were generally of GPR grade and used without further purification, unless otherwise stated.

High resolution FT-NMR spectra were recorded, at ambient temperature, on either:

(a) a Bruker AM 250 spectrometer; or

(b) a Bruker AM 400 spectrometer

FT-IR spectra were recorded as pressed potassium bromide discs for solid samples, or as a liquid film, with air as background on a FTS-40 spectrometer in the range 400-4000 cm^{-1}.

Mass spectroscopy was carried out on a MicroMass, Platform II, Single Quadruple spectrometer and recorded as positive and negative ion in methanol/formic acid mixture.

Melting points were recorded on a Gallenkamp melting point apparatus and were uncorrected.

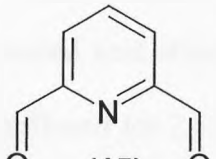
Analytical thin layer chromatography was carried out using precoated aluminium-backed silica plates (coated with Merck Kieselgel 60 GF_{254}). Plates were visualised under

ultraviolet light (254nm). Column chromatography was carried out on Merck Silica gel 60 (230-400 mesh).

High performance liquid chromatography (HPLC) was achieved on a Hewlett Packard 1100 instrument.

Elemental analyses were performed by the University of North London, Microanalysis Service using a Perkin-Elmer 240C elemental analyser.

5.2 Preparation of 2,6-Pyridinedialdehyde (15)

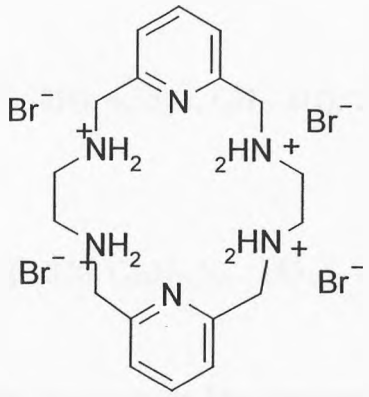


(15)

2,6-Pyridinedialdehyde **(15)** was prepared as described in the literature.[100] 2,6-pyridinedimethanol **(14)** (5 g, 36 mmol) and selenium dioxide (4 g, 36 mmol) were dissolved in 1,4-dioxane (100 cm^3) and refluxed for 2.5 h. After this period the solution was filtered to remove toxic grey selenium, and the filtrate was evaporated under water-pump pressure to give 2,6-pyridinedialdehyde (**15**) as an off-white solid (5.47 g), which was used without further purification. ^1H NMR analysis indicated >95% purity and was virtually identical to that in the literature.[100]

IR (cm^{-1}): Py-H 3086, aldehyde CH 2861, aldehyde C=O 1721

5.3 Preparation of Amine Hydrobromide (18)



(18)

To 2,6-pyridinedialdehyde (**15**) (5.47 g, 40 mmol) and $BaCl_2.2H_2O$ (4.94 g, 20 mmol) in methanol (150 cm^3) was added neat ethylenediamine (2.7 cm^3) dropwise. On complete addition, the mixture was refluxed for 2.5 h and then the solution was allowed to cool to ambient temperature, after which solid $NaBH_4$ (6.05 g, 160 mmol) was added in small portions over 40 min and the mixture stirred at room temperature for a further 1 h. The volatile organics were removed under reduced pressure to give a yellow-white solid which was extracted by trituration with dichloromethane (3×75 cm^3). The extracts were filtered and evaporation of the combined extracts to dryness under reduced pressure gave an orange mobile oil which was dissolved in methanol (100 cm^3). 48% Hydrobromic acid was added until the solution tested strongly acidic with universal pH paper. An off-white solid **(18)** precipitated during this addition, this solid was isolated by vacuum filtration and recrystallised from a minimum amount of hot water to give a white crystalline solid (4.49 g, 35%), m.p. 293 °C (dec.), (lit.[25] mp 291 °C (dec.).)

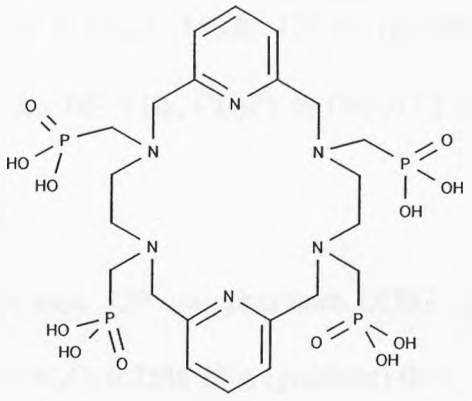
IR (cm^{-1}): N-H 3464

Found: C, 32.04; H, 4.81; N, 12.69. $C_{18}H_{30}N_6Br_4(H_2O)$ requires C, 32.24; H, 4.79; N, 12.58%.

^{1}H NMR (D_2O): δ 3.79 (s, CH_2, 8H), 4.55 (s, CH_2, 8H), 7.46 (d, *J* 7.8Hz, 4H) 7.90 (t, *J* 7.8Hz, 2H)

MS (LSIMS): m/z $[M\text{-}4Br^{-}\text{-}3H]^{+}$, 326; $C_{18}H_{26}N_6^{+}$, 163.

5.4 Preparation of Pyridine Macrocycle Phosphonate (N6TPH8)



N6TPH8

A solution of aqueous formaldehyde (9.96 g, 119 mmol, 37%) was added dropwise to a refluxing solution of amine hydrobromide **(18)** (5.5 g, 17.0 mmol), phosphorous acid (9.8 g, 119 mmol), 35% hydrochloric acid (17.7 g, 170 mmol) and deionised water (10 cm^3). The yellow-brown solution was refluxed for 24 h after the addition of the formaldehyde solution. Ethanol (200 cm^3) was added dropwise to the cooled solution with stirring until no further white solid precipitated. A white crystalline product (5.28 g, 44%) was obtained by recrystallisation of the crude product from boiling aqueous HCl and ethanol. However crystals isolated after this process proved unsuitable for X-ray analysis. Suitable crystals were obtained by recrystallising a small

sample from HCl and isopropanol. The product was dried at 80 °C for 24 h, m.p. 240 °C (decomp.)

IR (cm^{-1}):1598 C=N (py), 1158 (P-O) and 1074 (P-O).

Found: C, 37.6; H, 5.64; N, 11.9. $C_{22}H_{38}N_6O_{12}P_4$ requires C, 37.6; H, 5.45; N, 12.0%.

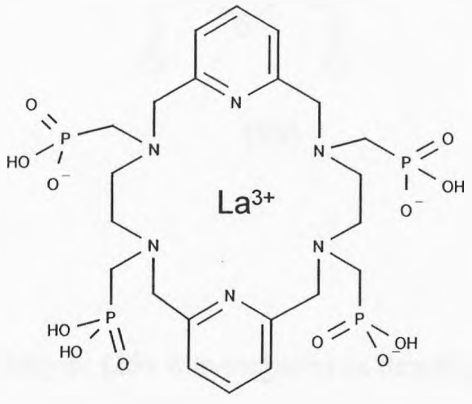
^1H NMR (250 MHz, D_2O): δ 3.3 (s, CH_2, 8H), 4.1 (s, CH_2, 8H), 4.9 (d, CH_2P, *J* 7.5Hz 8H), 7.6 (d, py (3,5 position) 4H) 8.1 (t, py (4-position), 2H)

^{13}C NMR (63 MHz, D_2O): δ 152.1, 143.8, 127.10 (pyridine) 63.0 (py-CH_2N), 54.8 (NCH_2CH_2N) and 52.0 (d, J_{CP} 143.0 Hz, CH_2P). δ_P (D_2O) 12.39.

LSIMS: *m/z* :703 $[M+H]^+$.

HPLC - R_t 1.64min, 100% area [20 cm spherisorb ODS2 column (5 μm; 4.6 mm i.d) mobile phase 50:50 CH_3CN:H_2O: 0.75% TFA (gradient) flow 1 cm^3/min].

5.5 Preparation of Lanthanide Complex La(N6TPH5)



[La(N6TPH5)]

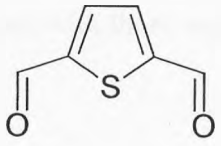
La_2O_3 (0.0261 g, 0.080 mmol) was added to a refluxing solution of (**N6TPH8**) (0.0755 g, 0.108 mmol) in water (15 cm^3). The mixture was refluxed for 5 h and was filtered hot to remove unreacted La_2O_3. The solvent was removed under reduced pressure to yield a white powder. The product was recrystallised from water-HCl at pH 2.5. The product was then dried at 90 °C for 30 h. Crystals obtained in this way were found to be suitable for X-ray analysis (0.062 g 68.5%), m.p. 252 °C (decomp.)

Found: C, 31.9; H, 4.22; N, 9.95. $C_{22}H_{35}LaN_6O_{12}P_4$ requires C, 31.5; H, 4.21; N, 10.0%.

^{13}C NMR (D_2O): δ 159.1, 140.4, 123.4 (pyridine), 66.0 (py-CH_2N), 57.4 (NCH_2CH_2N) and 56.5 (d, J_{CP} 125.9 Hz, CH_2P). ^{31}P NMR δ (D_2O) 22.92.

LSIMS: *m/z* : 839, $[M + H]^+$.

5.6 Preparation of 2,5-Thiophenedialdehyde (25)



(25)

Method A

2,5-Thiophenedialdehyde **(25)** was prepared as described in the literature.[104] To a solution of 2,5-dibromothiophene (20 g, 82 mmol) in dry ether (400 cm^3), was added *n*-butyllithium (100 cm^3), in ether (30 cm^3) dropwise at –65 °C over 35 min. After stirring the suspension for 1 h at –65 °C, DMF (18 cm^3, 256 mmol) in ether (10 cm^3) was added dropwise keeping the temperature of the mixture at –65 °C (±5). On complete addition the suspension was stirred for 2 h at –65 °C and then at ambient temperature for a further 12 h. The white suspension was transferred carefully to a mixture of 2 M hydrochloric acid and ether (1:1, 300 cm^3) at –10 °C. The combined organics were washed with water (50 cm^3) and saturated sodium bicarbonate (50 cm^3) and dried over $MgSO_4$. The organics were concentrated *in vacuo* to a 70 cm^3 solution. Brown crystals were formed, these were isolated by vacuum filtration and washed with ice cold ether (2×10 cm^3), and dried *in vacuo* at ambient temperature for 14h (3.9 g, 33%), m.p. 110-114°C, (lit.[105] mp 109-112°C).

IR (cm^{-1}): aldehyde C-H, 2875; aldehyde C=O, 1663; thiophene C-H, 3072; thiophene C=C, 1525.

^1H NMR ($CDCl_3$): δ 7.8 (s, 2H, thiophene, CH), 10 (s, 2H, CHO).

MS (EI): m/z 140$[M]^+$, 111$[M\text{-}COH]^+$, 83$[M\text{-}2COH]^+$.

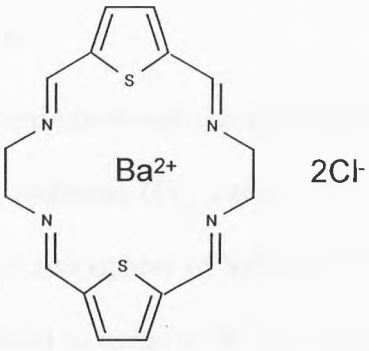
The spectroscopic data were consistent with those reported in the literature.[105]

Method B

2,5- Thiophenedialdehyde **(25)** was prepared as described in the literature.[105] To a solution of thiophene (2.5 g, 30 mmol), TMEDA (7.6 g, 131 mmol) in hexane (10 cm^3), was added *n*-butyllithium (41 cm^3) dropwise at 22 °C. On complete addition the suspension was stirred for 15 min at 40 °C and then cooled to ambient temperature. To the resulting white suspension was added THF (35 cm^3) and the mixture was cooled to −40 °C. After stirring the suspension for 5 min at −40 °C, DMF (18.2 cm^3, 256 mmol) was added dropwise keeping the temperature of the mixture at −40 °C. On complete addition the suspension was allowed to warm to ambient temperature and was stirred for a further 2 h. The white suspension was transferred carefully to a mixture of 30% hydrochloric acid (60 g) and water (500 cm^3) at −5 °C and this was stirred for a further 1h. Saturated sodium bicarbonate was added until pH 6 of the aqueous phase was achieved. The organic phase was separated and the aqueous phase extracted with ether (3×50 cm^3). The combined organic phases were washed with brine (150 cm^3) and dried over $MgSO_4$. The filtered organic solution containing the dialdehyde was concentrated *in vacuo* to 20 cm^3, this crystallised a brown solid, which was isolated by vacuum filtration and washed with ice cold ether (1×5 cm^3), and dried in vacuo at ambient temperature for 18h (0.91 g, 22%), m.p. 110-114 °C, (lit.[105] 109-112 °C).

^1H NMR ($CDCl_3$): δ 7.8 (s, 2H), 10 (s, 2H).

5.7 Preparation of Tetraiminethiophene Macrocycle (26)



(26)

A solution of ethylenediamine (1.4 cm^3, 21.4 mmol) in methanol (10 cm^3) was added dropwise to a suspension of 2,5-thiophenedialdehyde (3g, 21.4 mmol) and hydrated barium chloride ($BaCl_2.2H_2O$, 2.62 g, 10.7 mmol) in methanol (10 cm^3) at 10°C. On complete addition the solution was stirred for 15 min at 10 °C and then allowed to warm to ambient temperature. During this period crystallisation of a yellow solid from the pale brown solution had occurred, this solid was isolated by vacuum filtration and washed with cold methanol (3×100 cm^3), and dried in a vacuum oven at 45 °C for 14 h, (4.06 g, 71%).

IR (cm^{-1}): C=N, 1627.

^{1}H NMR (CF_3CO_2D): δ 3.8 (s, 8H), 8.0 (s,4H), 10.0 (s,4H).

5.8 Attempted Reduction of Tetraiminethiophene Macrocycle (26)

5.8.1 via Platinum (IV) Oxide

To the suspension of tetraiminethiophene macrocycle **(26)** (50 mg, 0.09 mmol) in methanol (5 cm^3) was added platinum (IV) oxide (7 mg, 20 mol%), and the above suspension was stirred under an atmosphere of hydrogen for 14 h. After this time a solid was isolated by filtration and dried *in vacuo* at 50 °C for 14 h (53 mg).

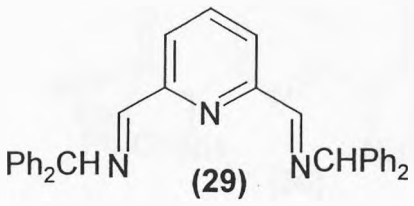
^{1}H NMR analysis showed only starting material.

5.8.2 via Platinum in Glacial Acetic Acid

To a solution of tetraiminethiophene macrocycle **(26)** (30 mg, 0.06 mmol) in glacial acetic acid (3 cm^3) was added platinum wet (30 mg) and the suspension was stirred under an atmosphere of hydrogen at ambient temperature for 7 days. The catalyst was then removed by filtration and the filtrate evaporated to dryness (23 mg).

^{1}H NMR analysis showed only starting material.

5.9 Preparation of Compound (29)



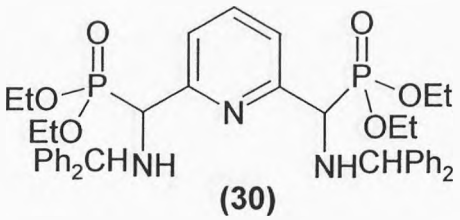
(29)

To a suspension of 2,6-pyridinedialdehyde (**15**) (1.13 g, 8.36 mmol), 3Å molecular sieves (0.57 g), in toluene (10 cm^3) at 70 °C, was added neat diphenylmethylamine (3.37 g, 18.4 mmol) dropwise. The suspension was stirred for 16 h at 70 °C and was then allowed to cool to ambient temperature and was filtered. The filtered molecular sieves were washed with toluene (10 cm^3) and the combined filtrates were evaporated under reduced pressure to a gum. Purification by flash chromatography (cyclohexane-EtOAc, 90:10) afforded a white crystalline solid, which was dried *in vacuo* at 40 °C for 24 h, (2.49 g, 72%).

IR (cm^{-1}): imine C=N 1632.

^1H NMR (d_6-DMSO): δ 5.7 (s, 2H, NCH); 7.3 (m, 20H, ArH); 7.8 (t, 1H, py-H); 8.3 (d, 2H, py-H); 8.5 (s, 2H, CHN).

5.10 Preparation of Compound (30)



(30)

Diethyl phosphite (4 g, 2.9 mmol) and pyridine bis imine **(29)** (1.4 g, 3.01 mmol) were heated for 2 h at 150-160 °C to give a red solution. The product was purified by flash chromatography (EtOAc) to give an off-white solid, which was dried *in vacuo* at 40 °C for 24 h, (0.15 g, 7%), which gave two peaks on HPLC.

HPLC - R_t 5.64min, 47 % area and 5.99 min, 51% area, [20 cm spherisorb ODS2 column (5 μm; 4.6 mm i.d) mobile phase 50:50 $CH_3CN:H_2O$: 0.75% TFA (isocratic) flow 1 cm^3/min],.

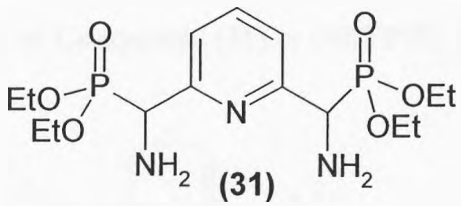
^1H NMR (400 MHz, $CDCl_3$) diastereoisomers δ 7.81, 7.58 (d, J_{HH} 7.8 Hz, py), 7.66, 7.49 (t, J_{HH} 7.8 Hz, py), 7.2 (m, PhH), 4.70, 4.68 (br s, $CHPh_2$), 4.18, 4.13(m, CHP), 4.09 (m, OCH_2), 1.2 (m, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) diastereoisomers δ 137.2, 132.8, 130.5, 156.3, 144.1, 142.7 (pyridine), 129.0, 128.9, 128.8, 128.6, 128.2, 127.7, 127.6, 127.5, 123.4 (phenyl), 65.3, 65.1($NCHPh_2$), 63.3, 63.2 (d, J_{POC} 50 Hz, $POCH_2$), 59.9, 59.2 (d, J_{PC} 153 Hz, py-CHP), 16.9, 16.8 (d, J_{POCC} 10 Hz, $POCH_2CH_3$).

^{31}P NMR (162 MHz, $CDCl_3$) diastereoisomers δ 22.6, 22.7.

LSIMS: *m/z* : 742, $[M + H]^+$.

5.11 Preparation of Compound (31)



(31)

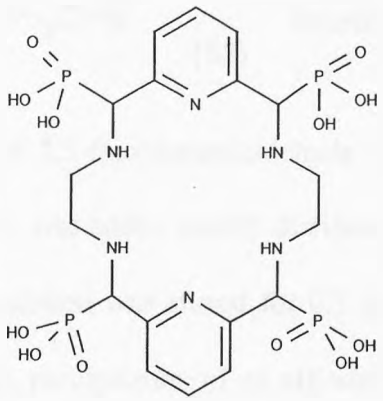
To the suspension of pyridine bis[α-aminophosphonous acid] (**30**) (0.14 g, 0.19 mmol) in ethanol (5 cm^3) was added palladium/carbon, (55 mg, 20 mol%) and the above suspension was stirred under an atmosphere of hydrogen for 13 h at ambient temperature. The suspension was filtered to remove the palladium catalyst. This was washed with ethanol (2 cm^3) and the combined filtrates were concentrated under reduced pressure to 5 cm^3. To this solution, palladium (10%wt on alumina powder, 58 mg) was added and the resulting suspension was stirred under an atmosphere of hydrogen for 2 h at ambient temperature. The suspension was filtered to remove the palladium catalyst and washed with ethanol (2 cm^3). The combined filtered solution was treated with palladium hydroxide on carbon (55 mg) and stirred under an atmosphere of hydrogen for 7 h at 50 °C. After this time the catalyst was filtered and washed with ethanol (2 cm^3), the combined filtrate was evaporated to a gum. The product was purified by flash chromatography (MeOH) to give an orange gum (21 mg, 27%).

^{1}H NMR (250 MHz, $CDCl_3$) diastereoisomers δ 7.68 (t, J_{HH} 8.1 Hz, py), 7.2 (m, $J_{HH.}$ py), 4.45, 4.43 (d, J_{PH} 18.6 Hz, CHP), 4.05 (m, OCH_2), 1.3 (m, CH_3).

^{13}C NMR (63 MHz, $CDCl_3$) diastereoisomers δ 154.5, 135.7, 121.05 (pyridine), 61.8 (m, $POCH_2$), 54.3 (d, J_{PC} 142 Hz, py-CHP), 15.4 (s, $POCH_2CH_3$).

LSIMS: *m/z* : 410, $[M + H]^+$.

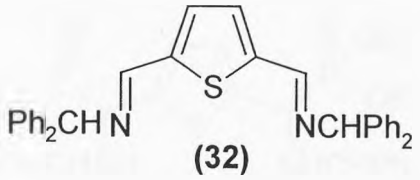
5.12 Attempted Conversion of Compound (31) to (N6TPH8_1)



N6TPH8_1

To pyridine bis[α-aminophosphonate ester] (**31**) (21 mg, 0.051 mmol), $BaCl_2.2H_2O$ (6.3 mg, 0.026 mmol) and potassium carbonate (28 mg, 0.20 mmol) in ethanol (0.5 cm^3) was added neat dibromoethane (4.5 µl, 0.051 mmol) dropwise. On complete addition, the mixture was refluxed for 2 h. To the suspension potassium hydroxide (0.1 g, 1.78 mmol) and further neat dibromoethane (4.5 µl, 0.051 mmol) were added and this was refluxed for 13 h. The mixture was filtered and evaporated to dryness. ^1H NMR analysis and MS showed starting material only.

5.13 Preparation of Compound (32)



(32)

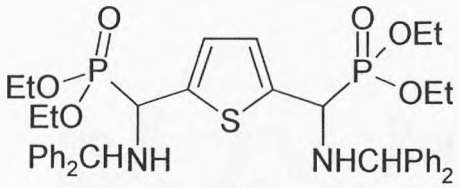
To the suspension of 2,5-thiophenedialdehyde (**25**) (2.97 g, 21.2 mmol) in methanol (30 cm^3) at 5-10 °C, was added freshly distilled diphenylmethylamine (7.77 g, 42.2 mmol) dropwise. The solution was stirred for 0.3 h at –5 °C and then allowed to warm to ambient temperature, precipitation of an off-white solid had occurred, this was isolated by vacuum filtration, washed with cold methanol (5 cm^3) to give compound (**32**).

To this crude solid in toluene (40 cm^3), 3Å molecular sieves (2 g), followed by neat diphenylmethylamine (2.1 g, 11.5 mmol) were added at ambient temperature and then stirred for 5 h. The solution was filtered to remove the molecular sieves and the toluene was evaporated under reduced pressure to leave a crude white solid. Crystallisation from hot cyclohexane (50 cm^3) afforded a snow white solid, which was isolated and dried *in vacuo* at 40 °C for 24 h, (5.1 g, 51%), m.p. 160-161 °C.

IR (cm^{-1}): imine C=N 1622.

^{1}H NMR (d_6-DMSO): δ 5.7 (s, 2H, NCH); 7.4 (m, 20H, ArH); 7.5 (s, 2H, thiophene CH); 8.7 (s, 2H, CHN)

5.14 Preparation of Compound (33)



(33)

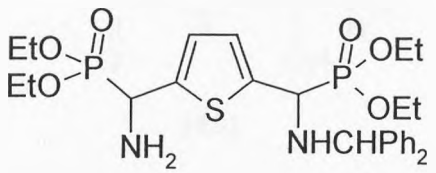
Diethyl phosphite (1.6 g, 11.7 mmol) and bis[imino]thiophene (**32**) (2.2 g, 4.68 mmol) were heated for 2 h at 150 °C to give a red liquid. The product was purified by flash chromatography (EtOAc-MeOH, 95:5) to yield a red gum (1.49 g, 43%).

^{1}H NMR (400 MHz, $CDCl_3$) diastereoisomers δ 7.3 (m, PhH), 6.95 (d, J_{HH} 6.1 Hz, thiophene, 4.90 (s, $CHPh_2$), 4.1(m, CHP), 4.2 (m, OCH_2), 1.36 (m, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) diastereoisomers δ 142.3, 140.6, 138.8, 138.7, 127.7, 127.5, 126.8, 126.5,126.3,126.2, 126.1,126.0 (thiophene & phenyl), 63.0($NCHPh_2$), 62.1 (d, J_{POC} 40 Hz, $POCH_2$), 52.6 (d, J_{PC} 161 Hz, CHP), 15.4 ($POCH_2CH_3$).

^{31}P NMR (162 MHz, $CDCl_3$) diastereoisomers δ 23.0.

5.15 Attempted Conversion of Compound (33) to Compound (34): Preparation of Compound (40)



(40)

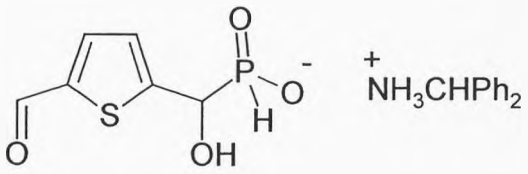
To a suspension of thiophene bis[α-aminophosphonous acid] (**33**) (0.4 g, 0.54 mmol) in methanol (10 cm^3) was added 20%wt palladium hydroxide (200 mg) and the above suspension was stirred under an atmosphere of hydrogen for 5 h at 50 °C. To the suspension trifluoromethanesulphonic acid (5 μl, 0.06 mmol) was added and the mixture was stirred under an atmosphere of hydrogen for 18 h at ambient temperature. The mixture was heated at 50 °C for 2 h and then left to stir at ambient temperature for 18 h. After this time the mixture was filtered to remove the palladium catalyst and the filtrate was evaporated under reduced pressure to a colourless oil. The product was purified by flash chromatography (EtOAc-MeOH, 90:10) to give a colourless oil (0.12 g, 39%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.3 – 6.8 (m, 12H, PhH and thiophene), 4.90 (s, 1H, $CHPh_2$), 4.48, 4.71(d, J_{PH} 18.8 Hz, 2H, CHP), 4.0 (m, 8H, OCH_2), 1.2 (m, 12H, CH_3).

^{13}C NMR (100 MHz, $CDCl_3$) poor solubility.

^{31}P NMR (162 MHz, $CDCl_3$) δ 22.4, 23.6.

5.16 Attempted Conversion of Compound (25) to Compound (44): Preparation of Compound (46)



(46)

To 50% aqueous hypophosphorus acid (3.77 g, 28.5 mmol) in water (20 cm^3) was added neat diphenylmethylamine (5.23 g, 28.5 mmol). During this addition a white precipitate of the ammonium salt was noted. On complete addition the white suspension was heated to 80 °C to give a clear solution. The solution was stirred for 10min and then solid 2,5-thiophenedialdehyde **(25)** (2.0 g, 14.2 mmol) was added over 10 min. The aqueous solution was refluxed for 1.5 h and then allowed to cool to ambient temperature. This solution was then carefully decanted (to leave residual oil at the bottom of the flask) to another flask, which was placed in the fridge for 48 h to give a yellow crystalline solid in a pale yellow solution. This solid was isolated by vacuum filtration and dried *in vacuo* at 40 °C for 48 h to afford a yellow crystalline solid (1.67 g, 30%) m.p. 159-161 °C.

IR (cm^{-1}): aldehyde C=O, 1666; P=O, 1149; P-H, 2334, O-H, 3221.

MS (Single Quadrupole, +ve ion): m/z 390 (M+1); 184 ($Ph_2CHNH_3^+$); 167 (Ph_2CH^+). MS (-ve ion): m/z 205 ($C_6H_6O_4SP$)

^1H NMR (d_6-DMSO, 250 MHz): δ 4.70 (d, 1H, J_{PH} 10Hz, PCH), 5.51 (s, 1H), 6.77 (d, 1H J_{PH} 552 Hz, PH), 7.10 (bm, 1H, thiophene CH), 7.35 (m, 10H, ArH), 7.64 (bm, 1H, thiophene CH), 9.81 (s, 1H, CHO), 9.37 (s, NH).

^{13}C NMR (63 MHz, $CDCl_3$) δ 183.6 (HCO), 147.2, 137.2, 132.4, 124.5(thiophene), 138.2, 128.6, 128.1, 127.1 (Ph), 69.1 (d, J_{PC} 107, CP),

56.9 ($CHPh_2$).

^{31}P NMR (101 MHz, $CDCl_3$) δ 19.35.

5.16.1 Reaction of 2,5- Thiophenedialdehyde (25) with Excess Diphenylmethylamine and 50% Aqueous Hypophosphorus Acid.

To 50% aqueous hypophosphorus acid (7.49 g, 56.7 mol) in water (45 cm^3) was added neat diphenylmethylamine (10 g, 56.8 mmol). During this addition a white precipitate of the ammonium salt was noted. On complete addition the white suspension was heated to 80 °C to give a clear solution. To this solution solid thiophene 2,5-dicarboxyaldehyde (**10**) (2.0 g, 14.2 mmol) was added over 10 min. The solution was refluxed for 2 h and then allowed to cool to ambient temperature overnight, the precipitated white solid was isolated by vacuum filtration, and washed with cold ethanol (2×20 cm^3), and dried *in vacuo* at 40 °C, (2.61 g, 65%).

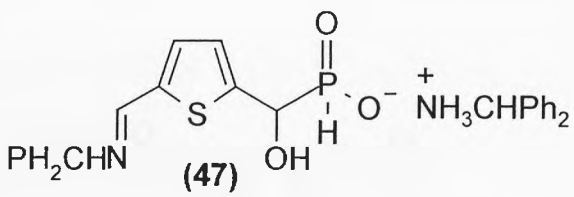
^1H NMR (d_6-DMSO): δ 5.8 (s, 1H, NCH); 7.4 (m, 10H, ArH); 7.7 (d, 1H, thiophene), 8.1 (d, 1H, thiophene); 8.8 (s, 1H, HC=N); 10.0 (s, 1H, CHO).

5.16.2 Reaction of α-Diphenylmethylamine-α-(5-formyl-2-thienyl)methylphosphonous acid (46) with Diphenylmethylamine and 50% Aqueous Hypophosphorus acid.

To 50% aqueous hypophosphorus acid (0.5 g, 3.78 mmol) in water (10 cm^3) was added neat diphenylmethylamine (0.25g, 1.42 mmol) at 80 °C. α-Diphenylmethylamine-α-(5-formyl-2- thienyl) methylphosphonous acid (**16**) was then added over 5 min. The resulting white suspension was refluxed for 48 h and then allowed to cool to ambient temperature. Water (8 cm^3) was removed under reduced pressure. The concentrated solution was placed in the fridge for 48 h. This gave an off-white crystalline solid which was isolated by vacuum filtration, and then washed with cold ethanol (2 cm^3) and dried *in vacuo* at 40-50 °C for 2h, (0.33 g).

^{1}H NMR was consistent with starting material.

5.17 Preparation of Compound (47)



(47)

To a suspension of α-diphenylmethylamine-α-(5-formyl-2-thienyl) methylphosphonous acid **(46)** (2.83 g, 7.28 mmol) in dimethylsulfoxide (15 cm^3) was added neat diphenylmethylamine (1.46 g, 8.00 mmol) at ambient temperature. After a period of 15 min a solution was obtained and after 40min stirring crystallisation of a white solid occurred. The white suspension was stirred for 1 h and then diluted with ethyl

acetate (15 cm^3). The white solid was isolated by vacuum filtration and then washed with ethyl acetate (2×7.5 cm^3), and dried *in vacuo* at 50 °C, (3.22 g, 80%), m.p. 185 °C.

IR (cm^{-1}): imine C=N, 1675.

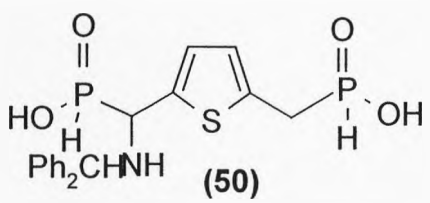
^1H NMR (d_6-DMSO, 250 MHz): δ 4.49 (1H, d, J_{PH} 12 Hz, PCH); 5.62, 5.47 (2H, s, NCH); 6.64 (1H, d, J_{PH} 489 Hz); 6.90 (1H, bd, thiophene CH); 7.25 (21H, m, ArH, thiophene CH); 8.55 (1H, s, HC=N), 8.87 (s, NH).

^{13}C NMR (d_6-DMSO, 100 MHz): δ 1854.8 (HCN), 150.0, 139.5, 131.4, 123.4 (thiophene), 139.2, 128.5, 128.1, 127.8, 127.1, 126.6 (Ph), 71.2 (d, J_{PC} 149, CP), 75.7, 56.9 ($CHPh_2$).

^{31}P NMR (d_6-DMSO, 101 MHz): δ 20.49

MS (Single, Quadrupole, -ve ion):m/z 370 $[M-H]^-$, 304 $[370-H_3PO_2]^-$, 65 $[H_2PO_2]^-$.

5.18 Attempted Conversion of Compound (47) to Compound (48): Preparation of Compound (50)



(50)

50% w/w aqueous hypophosphorus acid (0.5 g, 3.8 mmol) was evaporated under reduced pressure (0.01 mbar) at 50°C (oil bath temperature) to a more viscous liquid (0.4 g). This was heated to reflux in 1,4 dioxane (15 cm^3) and the thiophene 2,5 α-imine-

α-hydroxyphosphinate derivative (**47**) (1.0 g, 1.80 mmol, 1 eq) was added in three equal portions over 1.5 h. The resulting yellow solution was refluxed for 16 h (oil precipitated out from the solution). The 1,4-dioxane solution was decanted into another flask and water (5 cm^3) was added to the oil before placing it in an ultrasonic bath for 1 h. An orange solid precipitated out which was dried *in vacuo* at 35 °C for 48 h (0.14 g, 19%), m.p. 177-179 °C.

The filtrate on standing had precipitated out more solid. This solid was filtered under vacuum and dried *in vacuo* at 35 °C for 16 h (0.059 g, 9%).

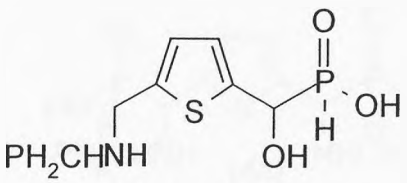
Total yield: (0.199 g, 28%).

^{1}H NMR (d_6-DMSO, 400 MHz): δ 7.46-7.19 (m, 11H, Ph & thiophene), 6.84 (s, 1H, thiophene), 6.91 (d, 2H, J_{PH} 530, PH), 6.82 (d, 2H, J_{PH} 510, PH), 5.05(s, 1H, $CHPh_2$), 3.78 (d,1H, $J_{P\text{-}CH}$ 16.5, CH), 3.26 (d, 1H, $J_{P\text{-}CH}$ 17.5,CH_2).

^{31}P NMR (d_6-DMSO, 101MHz): δ 27.76, 27.00.

^{13}C NMR (d_6-DMSO, 100 MHz): δ 146.6, 145.5, 141.5, 137.0, 132.5, 131.3, 131.1, 130.7 (thiophene & Ph), 67.4 ($CHPh_2$), 60.1 (d, J_{PC} 101, HCP), 36.2 (d, J_{PC} 88.2,H_2CP).

5.19 Preparation of Compound (52)

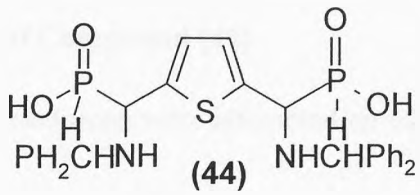


(52)

A suspension of compound (**47**) (0.5 g, 0.90 mmol) in methanol (15 cm^3) was cooled to ice bath temperature. Sodium borohydride (68 mg 1.80 mmol) was then added. The resulting suspension was allowed to warm to ambient temperature and was then stirred at this temperature for 18 h. Methanol was evaporated under reduced pressure to leave a crude yellow gum. The product was purified by flash chromatography (CH_3CN) to yield a pale yellow gum (0.29 g, 86%).

^1H NMR (D_20, 250 MHz): δ 3.64 (s, 2H, NCH_2); 4.60 (d, 1H, J_{PH} 12.5Hz, PCH); 4.72 (s, 1H, NCH); 6.60 (d, 1H, J_{PH} 525, PH), 6.58 (s, 1H, thiophene CH); 6.70 (bd, 1H, thiophene CH); 7.12 (m, 10H, ArH).

5.20 Preparation of Compound (44)



(44)

The commercially available 50% aqueous hypophosphorus acid (5 cm^3) was evaporated under reduced pressure (0.01 mbar) at 50 °C (oil bath temperature) to a viscous yellow oil. Nucleation was then affected by cooling the flask with dry card ice.

Crystalline hypophosphorus acid (0.29 g, 4.4 mmol) was dissolved in dry 1,4-dioxane (10 cm^3) and refluxed. To the refluxing solution thiophene bis imine **(32)** (0.5 g, 1.1mmol) in 1,4-dioxane (15 cm^3) was added dropwise over 1 h. The solution was refluxed for 1.5h. During this period crystallisation of a white solid had occurred. The reaction was cooled to ambient temperature and the white solid was isolated by vacuum filtration and then washed with cold methanol (2×5 cm^3) and dried *in vacuo* at 40 °C, (0.46 g, 72%), m.p. 173-175 °C.

^{1}H NMR (d_6-DMSO, 400 MHz): diastereoisomers δ 7.35 (m, 21H, Ph and thiophene), 6.95, 6.88 (s, 1H,thiophene), 6.92 (d, 1H, J_{PH} 546, PH), 5.07, 5.04 (s, 1H, $CHPh_2$), 3.89, 3.83 (d, 1H, J_{P-CH} 17.0, CH).

^{13}C NMR (d_6-DMSO, 100 MHz): diastereoisomers δ 146.6, 146.3, 145.3,145.1, 142.6, 142.0, 132.7, 132.5, 132.2, 131.4, 131.0 (Ph and thiophene), 67.5, 67.4 ($CHPh_2$), 60.3, 60.1 (d, J_{PC} 101, CP).

^{31}P NMR (d_6-DMSO, 101 MHz): diastereoisomers δ 27.26, 27.01.

MS (Single Quadrupole, -ve ion): m/z; 601 $[M-H]^-$, 418 $[M-Ph_2CHNH]^-$, 300 $[M/2]^-$

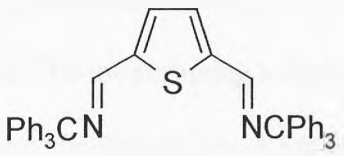
5.21 Attempted deprotection of Compound (44)

A series of various deprotection conditions were attempted an each of these are outlined below.

Experiment	Conditions	Reaction Monitored
1	Compound (**44**) (100 mg, 0.17 mmol) 10% Pd/C (50 mg) H_2, MeOH (2.5 cm^3), 18 h	By ^1H NMR no reaction
2	Compound (**44**) (100 mg, (0.17 mmol) cHBr (60% w/w, 1 g), AcOH (2 cm^3), reflux, 3 h	Degradation of starting material by TLC (Toluene-CH_3OH, 60:40)
3	Compound (**44**) (100 mg, 0.17 mmol) cHCl (0.2 g), $CHCl_3$ (2 cm^3), reflux, 18 h	TLC (Toluene-CH_3OH, 60:40) shows starting material
4	Compound (**44**) (100 mg, 0.17 mmol) cHCl (0.5 g) H_2O (2 cm^3), reflux, 18 h	TLC shows starting material
5	Compound (**44**) (100 mg, 0.17 mmol) Zn dust (260 mg, 3.98 mmol), AcOH (13 cm^3), 22 °C, 16 h	TLC shows starting material

6	Compound (**44**) (0.41 g, 0.68 mmol) 5% Pd/C (0.19 g, 3.01 mmol), H_2, MeOH (10 cm^3), HCO_2NH_4 (0.16 g, 2.54 mmol)	By ^1H NMR no reaction
7	Compound (**44**) (100 mg, (0.17 mmol) Pd black (50 mg) H_2, MeOH (5 cm^3), 22 ^oC, 52 h	TLC shows starting material
8	Compound (**44**) (10 mg, 0.02 mmol) 10% Pd/C (5 mg) H_2, MeOH (0.25 cm^3), 30 atms, H_2, 22^oC, 16 h	TLC shows starting material

5.22 Preparation of Compound (62)



(62)

To the suspension of 2,5-thiophenedialdehyde (**25**) (0.5 g, 3.57 mmol), in methanol (10 cm^3) at 22 °C, was added tritylamine (1.94 g, 7.48 mmol) in two portions. The suspension was stirred for 2 h at 22 °C. During this period a white precipitate had resulted. The suspension was diluted with further methanol (20 cm^3) and heated to reflux for 16 h. The resulting suspension was evaporated under reduced pressure to give a white solid. The white solid was diluted with toluene (10 cm^3) and the suspension was treated with further tritylamine (0.19 g, 0.72 mmol) and refluxed for 14 h. The suspension was cooled to ambient temperature and the white solid was isolated by vacuum filtration and washed with toluene (3×20 cm^3), and dried *in vacuo* at 45 °C for 20 h (1.59 g, 72%).

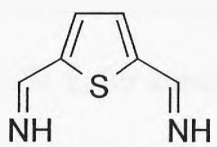
IR (cm^{-1}): imine C=N 1622.

^{1}H NMR (d_6-DMSO): δ 7.40 (m, 30H, ArH); 7.58 (s, 2H, thiophene CH); 8.07 (s, 2H, CHN)

5.23 Attempted Hydrophosphinylation of Compound (62)

Crystalline hypophosphorus acid (0.4 g, 6.1 mmol) was dissolved in dry 1,4-dioxane (10 cm^3) and refluxed. To the refluxing solution a suspension of compound **(62)** (0.94 g, 1.51 mmol) in 1,4-dioxane (20 cm^3) was added over 5 min. The resulting cloudy solution was refluxed for 1.5 h. During this period crystallisation of a white solid had occurred. The reaction was cooled to ambient temperature and the white solid was isolated by vacuum filtration and then washed with ethanol (3×5 cm^3) and dried *in vacuo* at 50 °C (0.73 g), m.p. 193-230 °C.

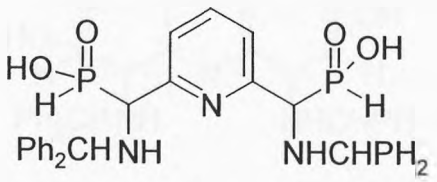
5.24 Attempted Preparation of Compound (63)



(63)

To the suspension of 2,5-thiophenedialdehyde (**25**) (0.1 g, 0.71 mmol), in methanol (2 cm^3) at 22°C, was added ammonia (7.0 M solution in methanol, 0.21 cm^3) dropwise. On complete addition the TLC (EtOAc) analysis of the resulting orange solution was found to be crude.

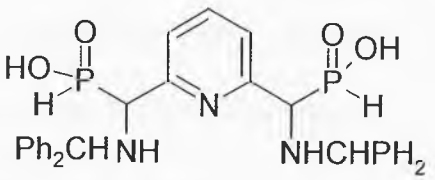
5.25 Attempted Preparation of Pyridine bis[α-Aminophosphinic Acid] (64) using 50% Hypophosphorus Acid



(64)

To 50% aqueous hypophosphorus acid (6.92 g, 52 mmol) in water (25 cm^3) was added neat diphenylmethylamine (9.60 g, 52 mmol). During this addition a white precipitate of the ammonium salt was noted. On complete addition the white suspension was heated to 80 °C to give a clear solution. The solution was stirred for 20 min and then solid 2,5-pyridinedialdehyde **(15)** (3.54 g, 26 mmol) was added over 10-15 min. The aqueous solution was refluxed for 3 h and then allowed to cool to ambient temperature. The resulting deep red solution was left standing in the fridge for 48 h. TLC analysis (toluene-CH_3OH, 60:40) indicated a mixture of compounds.

5.26 Attempted Preparation of Pyridine bis[α-Aminophosphinic Acid] (64) using 100% Hypophosphorus acid



(64)

The commercially available 50% aqueous hypophosphorus acid (5 cm^3) was evaporated under reduced pressure (0.01 mbar) at 50 °C (oil bath temperature) to a viscous yellow oil. Nucleation was then affected by cooling the flask with dry solid CO_2.

Crystalline hypophosphorus acid (0.32 g, 4.9 mmol) was dissolved in dry 1,4-dioxane (10 cm^3) and refluxed. To the refluxing solution bis[imino] pyridine **(29)** (0.14 g, 0.3 mmol) in 1,4-dioxane (20 cm^3) was added in two portions over 40 min. The resulting cloudy solution was refluxed for 1.5 h. The reaction mixture was evaporated to a semi-solid. A small sample was analysed by ^1H NMR (d_6-DMSO) and TLC (toluene-CH_3OH, 70:30) and was found to be a mixture with no observable product.

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Appendix: Publication List

Poster - Synthesis of Novel Thiophene Phosphinic Acid Derivatives and Crystal Structure of the First α-Hydroxyalkylphosphinic Acid Derivative

S.W. Annie Bligh, Mahesh J. Sanganee, Mary McPartlin and Thomas M. Woodroffe

GWICM, GlaxoWellcome, April 1996

G.W.I.C.M (GlaxoWellcome International Chemistry Meeting)

Publications - (1) A novel hexaaza macrocycle with methylenephosphonate pendant arms: a potential useful chelate for biomedical applications

S.W. Annie Bligh, Nick Choi, Carlos F.G.C. Geraldes, Stefan Knoke, Mary McPartlin, Mahesh J. Sanganee and Thomas M. Woodroffe,

J. Chem. Soc., Dalton Trans., 1997, 4119-4125

(2) Synthesis of novel α-functionalized phosphinic acid derivative of thiophen and the first crystal structure of an α-hydroxyalkylphosphinate

S.W. Annie Bligh, Carlos F.G.C. Geraldes, Mary McPartlin, Mahesh J. Sanganee and Thomas M. Woodroffe,

J. Chem. Soc. Chem. Commun., 1998, 2073