Complexation behaviour of Aza-phosphink acids

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Complexation Behaviour of Aza-Phosphinic Acids

by Eleanor Cole

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Declaration

The work for this thesis has been carried out in the Department of Chemistry at the University of Durham between October 1990 and October 1993. It is the work of the author unless otherwise stated. None of the work has been submitted for any other degree.

To my parents and Ian,

thank you for your support.

Three Rings for the Elven-kings, under the sky,
Seven for the Dwarf-lords in their halls of stone,
Nine for Mortal Men doomed to die,
One for the Dark Lord on his throne
In the land of Mordor where the Shadows lie.
One Ring to rule them all, One Ring to find them,
One Ring to bring them all and in the darkness bind them
In the Land of Mordor where the Shadows lie.

From Lord of The Rings
By J. R. R. Tolkien

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Prof. G. Ferguson and his group (University of Guelph, Canada) for the crystal structures of the Cu (II), Ni (II), Fe (III) and Ga (III) complexes with NOTPPh.

Prof. J. Howard and R. Copley (Durham) for the crystal structures of the Co (II), Zn (II) and In (III) complexes with NOTPPh, and for future work.

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Abstract

An alkylphosphinate is an attractive isostere for a carboxylate. The acid is more acidic than a carboxylic acid, is amenable to ^{31}P NMR analysis and is subject to easy structural modification by variation of the phosphorus alkyl or aryl substituent. Amino acid complexing agents incorporating carboxymethyl groups are ubiquitous, but the corresponding phosphinic acid analogues have been much less studied. On chelation of a metal ion to a ligand nitrogen and a phosphorus oxygen atom, a new stereogenic centre at phosphorus is created. In polydentate ligands diastereoisomeric complexes may form.

A new family of acyclic ligands with phosphinic acid binding groups have been synthesised. The protonation constants have been determined and used for the determination of the stability constants for a range of metal complexes.

A complexing agent based on a $9N_3$ macrocyclic skeleton incorporating pendant arm phosphinic acid donors, provides an octahedral site for metal complexation. The structures of seven complexes with a ligand of this type, have been determined by X-ray crystallography. They fall into two groups, those with a C_3 axis (Cu (II), Co (II), Zn (II) and Ni (II)) and those with an approximate C_3 axis (Ga (III), Fe (III) and In (III)).

Abbreviations

Ar	Aromatic
DMF	Dimethyl formamide
DOTA	1,4,7,10 Tetraazacyclododecane-N,N',N",N"'-tetraacetic acid
DOTP	1,4,7,10 Tetraazacyclododecane-N,N',N",N"'-tetramethylene phosphonic acid
DOTPPh	1,4,7,10 Tetraazacyclododecane-N,N',N",N"'-tetramethylene (phenylphosphinic) acid
DOTPMe	1,4,7,10 Tetraazacyclododecane-N,N',N",N"'-tetramethylene (methylphosphinic) acid
DPP	Diethylene-N-methylene(phenylphosphinic) acid
DTPA	Diethylenetriamine-N,N,N',N",N"-pentaacetic acid
DTPPPh	Diethylenetriamine-N,N,N',N",N"-penta(methylene(phenylphosphinic)) acid
EDDA	Ethylenediamine-N,N'-bisacetic acid
EDDM	Ethylenediamine-N,N'-bismethyl
EDDP	Ethylenediamine-N,N'-bismethylene phosphonic acid
EDDPi	Ethylenediamine-N,N'-bismethylene phosphinic acid
EDDPMe	Ethylenediamine-N,N'-bis(methylene(methylphosphinic)) acid
EDDPPh	Ethylenediamine-N,N'-bis(methylene(phenylphosphinic)) acid

EDTA	Ethylenediamine-N,N,N',N'-tetrakisacetic acid
EDTHE	Ethylenediamine-N,N,N',N'-tetrakis(hydroxyethylene)
EDTP	Ethylenediamine-N,N,N',N'-tetrakismethylenephosphonic acid
EDTPi	Ethylenediamine-N,N,N',N'-tetrakismethylene phosphinic acid
EDTPPh	Ethylenediamine-N,N,N',N'-tetrakis(methylene(phenylphosphinic)) acid
EDTPMe	Ethylenediamine-N,N,N',N'-tetrakis(methylene(methylphosphinic)) acid
en	Ethylenediamine
NOTA	1,4,7 Triazacyclononane-N,N',N"-triacetic acid
NOTP	1,4,7 Triazacyclononane-N,N',N"-trimethylene phosphonic acid
NOTPBz	1,4,7 Triazacyclononane-N,N',N"-tri(methylene(benzylphosphinic)) acid
NOTPMe	1,4,7 TriazacyclononaneN,N',N"-tri(methylene(methylphosphinic)) acid
NOTPPh	1,4,7 TriazacyclononaneN,N',N"-tri(methylene(phenylphosphinic)) acid
PDDPMe	Propylenediamine-N,N'-bis(methylene(methylphosphinic)) acid
PDDPPh	Propylenediamine-N,N'-bis(methylene(phenylphosphinic)) acid
THF	Tetrahydrofuran
TMDTA	Trimethylene-1,3-diamine-N,N,N',N'-tetraacetic acid
TMEDA	Tetramethyl Ethylenediamine

trm	Trimethylene-1,3-diamine
$9N_3$	1,4,7 Triazacyclononane
$12N_4$	1,4,7,10 Tetraazacyclododecane

Contents

Chapter 1

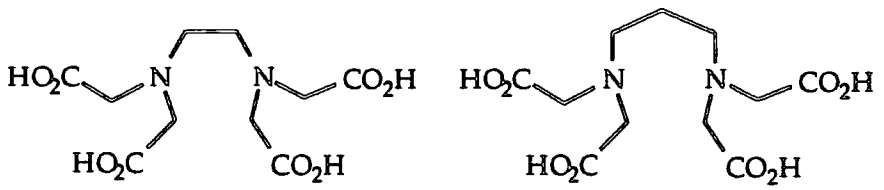
Factors Affecting the Synthesis and Complexation Behaviour of Polyaza-Phosphinic acid Ligands

1.1 Introduction

A considerable amount of work has been directed towards understanding the physical and chemical complexation properties of aminomethylenecarboxylic[1,2,3] and aminomethylenephosphonic acids. However relatively little has been done on the synthesis and characterisation of the related phosphinic acid derivatives.[4] Aminomethylenephosphinic acids have properties that are generally similar to carboxylic acids. They are less basic ligands and may form complexes that are more stable to dissociation at low pH, as is required for metal complexes used *in vivo*.

1.1.1 Aminomethylenecarboxylic Acids

The first examples in this large series of molecules are the naturally occurring amino acids. However, in general they are unsubstituted at the nitrogen atom. For complexation chemistry it is an advantage to have a ligand with several donor groups attached together. One of the first ligands of this sort was EDTA,[1] a hexadentate ligand that forms five-membered chelate rings with an N_2O_4 donor set. Since its initial synthesis in 1952 by Schwarzenbach, a wealth of information on its physical and complexation properties has been gathered.[5]



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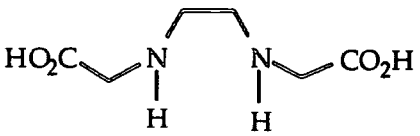

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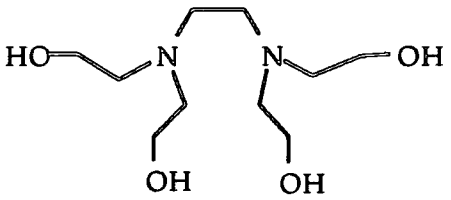

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1 Ethylenediamine-N,N,N',N'-tetrakis(acetic acid) [EDTA]

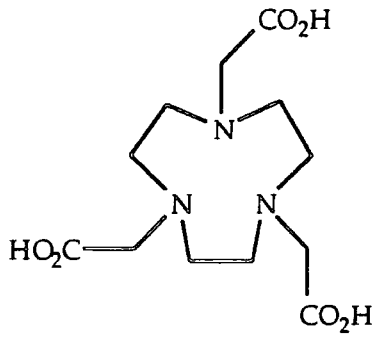
2 Trimethylene-1,3-diamine-N,N,N',N'-tetrakis(acetic acid) [TMDTA]

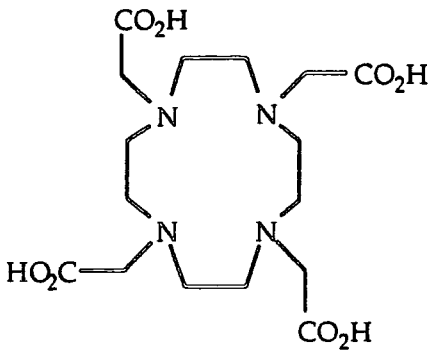
3 Ethylenediamine-N,N'-bis(acetic acid) [EDDA]

4 Ethylenediamine-N,N,N',N'-tetrakis(hydroxyethylene) [EDTHE]

Other ligands of this type followed and the effects of introducing six-membered ring chelates[6] (TMDTA), changing the type of donor oxygens from acids to alcohols (EDTHE) and altering the number of donor groups available[7] (EDDA) were studied.

More recently the use of macrocycles as the source of donor nitrogens has led to the synthesis of polydentate ligands based on a range of triaza and tetraaza rings. NOTA[2] and DOTA[3] are the smallest ring sizes to give hexadentate and octadentate ligands respectively.





5 6

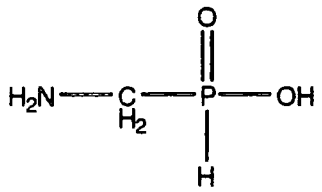
5 1,4,7 Triazacyclononane-N,N',N''-tris(acetic acid) [NOTA]

6 1,4,7,10 Tetraazacyclododecane-N,N',N'',N'''-tetrakis(acetic acid) [DOTA]

The physical and coordination chemistry of both has been intensively studied. It was found that NOTA had a remarkable ability to stabilise rare oxidation states of the first row transition metals,[8] eg Ni (III). The homologue DOTA displayed a selectivity for lithium over the other alkali metals,[9] and showed a strong binding affinity for calcium (log K H_2O, 298K: 17.2) and for the rare earths and lanthanides.

1.1.2 Aminomethylene Phosphinic acids

A lot of work has been done by Dingwall and coworkers[10,11] looking at α, β and γ phosphinic acid derivatives of amino acids.

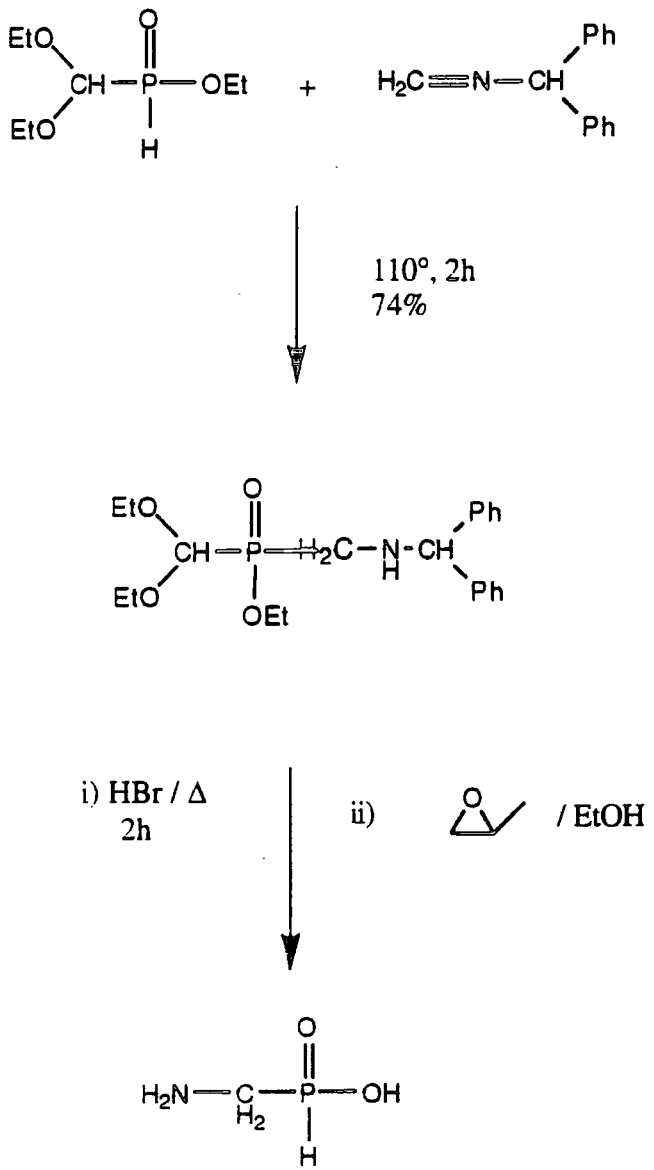


7

7 1-Aminomethylene-phosphinic acid

Their work was based on the C-substitued derivatives while the phosphorus and the amine groups were unsubstituted. Substitution at carbon gives the phosphinic acid analogues of the naturally occuring carboxylic based amino acids.

A general reaction scheme was developed that created a protected form of the phosphinic acid which could then be added to an imine to form the final aminomethylene phosphinic acid, (scheme 1.1).



Scheme 1.1

The pKa values for the phosphinic derivative can be seen to be lower than those for the other derivatives (table 1.1). It is the most acidic of the three ligands at both the nitrogen and oxygen sites. The phosphonic derivative has the effect of making the nitrogen atoms more basic. The phosphinic acid nitrogen can be seen to be the weakest base.

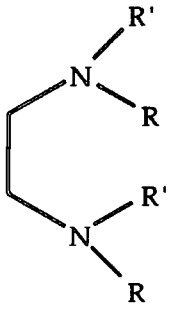
Acid	pK_1	pK_2	pK_3
$Me_2CHCH(NH_2)CO_2H$	9.36	2.28	-
$Me_2CHCH(NH_2)PO_2H_2$	7.79	1.19	-
$Me_2CHCH(NH_2)PO_3H_2$	10.46	5.68	1.23

Table 1.1 Comparision of the pKa values for analogous acids based on the amino acid, valine.

Data taken from ref 10.

1.1.3 Multidentate Aminomethylene Phosphinic acids

Early work was done by Martell[12] on ethylenediamine-N,N'-bis (methylenephosphinic) acid (EDDPi) 9 and ethylenediamine-N,N,N',N'-tetrakis(methylenephosphinic) acid (EDTPi) 8 in 1971.



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EDTPi

R = R' = $H_2C-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-H$

9

EDDPi

R = H

R' = $H_2C-\overset{\overset{O}{\|}}{\underset{\underset{OH}{|}}{P}}-H$

The protonation constants were determined by potentiometric titration followed by analysis. The EDDPi ligand displays two buffer regions and gives two pKa values, which are more acidic than those found for the EDDA analogue. The tetra substituted ligand EDTPi, has pKa values that appear very low compared to the EDTA and EDTPPh derivatives.

The fall in the pKa value for protonation at nitrogen could be attributed to the presence of electron withdrawing groups, lowering the basicity of the two nitrogens. The combined effect of four phosphinate groups of EDTPi is seen in the unusually low pKa values obtained.

Ligand	pK_1	pK_2
EDTPi [a]	6.87	2.43
EDTA [b]	10.77	6.11
EDDPi [a]	8.08	4.98
EDDA [b]	9.57	6.48

Table 1.2 Protonation constant for ethylenediamine based ligands.

a) Data taken from ref 12.

b) Data taken from ref 13.

Coordination studies with a range of first row transition metals were carried out. Values for the 1:1 ML stability constants were found to be lower than those for the corresponding carboxylic derivatives. Although no explanation was proposed this presumably reflects the weaker σ-donor ability of the less basic nitrogens.

1.1.4 Attachment to Small Rings

More recently Lukeš[14] has done work on aminomethylene phosphinic acid systems based on piperidine and piperazine. The synthesis were carried out by a Mannich reaction according to Maier.[15] The pKa values for the phosphinic acids are lower than those for the corresponding carboxylic acids[16] (table 1.3), i.e. they are more acidic.

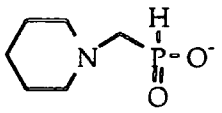
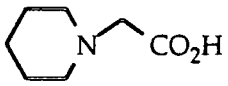
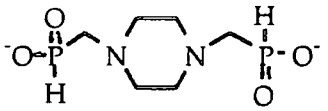
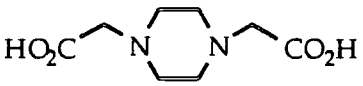
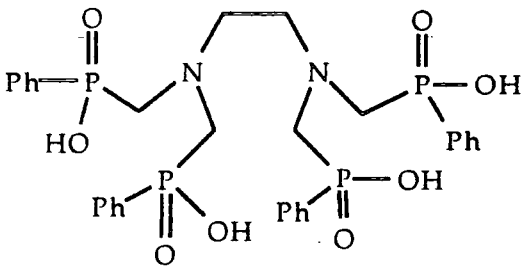
	pK_1	pK_2
	8.41	
	10.25	
	6.72	2.64
	8.70	4.46

Table 1.3 Protonation constants for acidic ligands based on small rings.

1.1.5 Substitution at Phosphorus



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10 Ethylenediamine-N,N,N',N'-tetra[methylene(phenylphosphinic)]acid [EDTPPh]

The systems commented on so far have all been unsubstituted at the phosphorus atom. Work, also by Lukeš,[17] in 1987 was carried out

on a phenyl substituted acid . A study of the protonation and stability constants was carried out by NMR and potentiometric titrations, and it was found that whilst the pKa values for the phenyl substituted phosphinic groups were lower than for the corresponding carboxylic derivatives, they were higher than those for the corresponding phosphonous acid analogues.

In summary all the examples so far have supported the idea that phosphinic acid groups are more acidic than carboxylic acid groups and that the electron withdrawing effect causes the nitrogens to be less basic. This is a feature that will be referred to with added examples in later chapters. The difference between the substituted and unsubstituted phosphinic acids could be due to the electron donating effect of the phenyl ring lowering the overall electron withdrawing effect of the phosphinate.

1.2 Complexation Effects

The complexes formed by ligands with phosphinic acid binding sites will be less basic so they should tolerate lower pH values before forming the protonated complex. This lowers the chances of them being protonated at physiological pH (pH = 7.4) and hence may reduce the possibility of acid catalysed dissociation of the complex. If this is the case it should enhance the kinetic stability of the complexes formed. At the same time, an enhanced sensitivity to base-catalysed hydrolysis may be expected.

1.2.1 Chelate Effect

The 'chelate effect' refers[1,18] to the extra thermodynamic stability of systems in which chelate rings are formed. The relative stability of nickel (II) complexes with ammonia and ethylenediamine[19] (table 1.4) illustrate this, as the electrostatic differences are small enough to be ignored.

$$Ni^{2+} + 6NH_3 \rightleftharpoons [Ni(NH_3)_6]^{2+} \quad \log \beta = 8.61$$

$$Ni^{2+} + 3en \rightleftharpoons [Ni(en)_3]^{2+} \quad \log \beta = 18.28$$

Table 1.4 Equilibrium constants for formation of nickel complexes

The increase in log β values can be considered to be due to a more negative enthalpy (ΔH) value or a large (more positive) entropy (ΔS) effect (Figure 1.1).

$$\Delta G^\circ = -RT\ln\beta = \Delta H^\circ - T\Delta S^\circ$$

Figure 1.1

The entropy contribution is favourable when one polydentate ligand replaces many monodentate ligands, however is unfavourable if several ligands try replacing one. The enthalpy change on complexation is affected primarily by two factors:

a) the change in ligand conformation necessary for binding,

b) the desolvation of both the ligand and the metal ion that has to occur before they can bind.

1.2.2 Macrocyclic Effect

The macrocyclic effect[20] is the thermodynamic advangate obtained when changing from a straight chain ligand to the ring-closed form. This shown by the different stabilities for metal complexes with diethylenetriamine[21] and triazacyclononane (table 1.5).

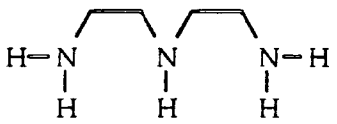
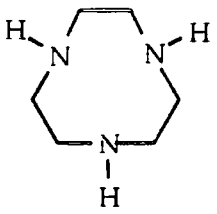
	log K_1		
	Ni (II)	Zn(II)	Pb(II)
	10.5	8.8	8.5
	16.2	11.6	11.0

Table 1.5 Effect of a macrocycle on stability constants of complexes.

This effect may be attributed both to a more favourable enthalpy[22] and entropy change in the cyclic case, in the same way as observed for the chelate effect.

1.2.3 Effect of Pendant arms on Macrocycles

	Cu	Co	Cd
$9N_3$ (log K_1)	15.5	11.2	9.5
NOTA (log K_1)	21.63	17.5	16.0
Δ log K	+6.13	+6.3	+6.5

Table 1.6 Stability Constants for $9N_3$ and NOTA complexes

a) Data taken from ref 24. b) Data taken from ref 25 and 26.

A variety of donor groups have been used as pendant arms to give ligands of higher denticity[23,24]. The effect of adding acetate groups to triazacyclononane on the overall 1:1 stability constant can be seen in table 1.6.

NOTA shows remarkable stability in its complexes with the smaller cations which is shown by the large log K_1 value for the Cu.NOTA complex. The addition of sidearms to the ring will affect both the entropy and the enthalpy of the system to give the increases in stability demonstrated.

The carboxylic groups are highly sterically efficient[25] when binding to a metal. That is the coordinating groups have an unhindered approach to the metal (figure 1.2). The phosphinic acid group can orientate itself in a similar way.

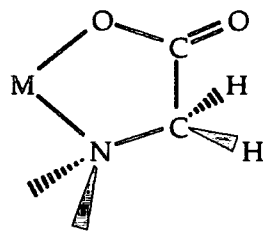


Figure 1.2

1.2.4 Macrocyclic Ligands

Macrocyclic ligands, can be found in many biological systems, controlling many important reactions, such as neurotransmitter release (Ca^{2+} dependent). Macrocyclic ligands are defined as a ring containing at least nine atoms with three donor atoms, acting as a polydentate ligand.[26]

Dissociation of the complex can be uncatalysed, acid or metal catalysed. The more thermodynamically stable the complex the less likely that uncatalysed dissociation will occur. If the protonation constants of the heteroatoms in the complex are low then protonation is less likely to occur in the system so reducing the chance of acid catalysed dissociation. This kinetic stability is manifested by the rate at which dissociation occurs. Irrespective of the magnitude of the binding constant, a small amount of dissociation of the complex, when in low concentrations, will always occur.

The conformational changes needed by a triazacyclononane derivative on binding are small, the ring is rigid and held in its regular [3 3 3] conformation when forming complexes. This is favourable as it minimises the enthalpy of formation for the complex although the desolvation of the cation can counteract this advantage. Macrocyclic ligands generally tend to have relatively small desolvation energies that lead to relatively favourable enthalpies of complexation, when compared to their acyclic analogues.

1.3 Ligand Design

A vast amount of knowledge on the effects of changing donor groups, chelate ring size and the degree of 'preorganisation' of the ligand on selectivity towards different cations has accumulated. Trends have been observed between different groups that allow attempts at ligand design to be undertaken with some confidence.

1.3.1 Donor Atom Selection (Hard and Soft Acid and Base classification)

Selection of donor atoms within a ligand can be a way to increase or decrease the binding strengths to certain cations. Pearson's[27] hard and soft acid and base classification can be used in an attempt to do this. The strongest bonds are going to be those formed between a soft acid and a soft base or hard acid and hard base, with weaker interactions occurring between mixed pairings.

Acids

Hard	Soft
H^+, Li^+, Na^+, K^+	Cu^+, Ag^+, Au^+,
Mg^{2+}, Ca^{2+}, Sr^{2+}, Ba^{2+},	Pd^{2+}, Cd^{2+}, Pt^{2+},
Al^{3+}, Ga^{3+}, In^{3+},	
Cr^{3+}, Co^{3+}, Fe^{3+},	

Borderline

Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, Zn^{2+}, Pb^{2+}

Bases

Hard	Soft
H_2O, OH^-, $CH_3CO_2^-$,	R_2S, RSH, H^-
ROH, RO^-, R_2O, NRH_2,	PR_3, RNC

Borderline

C_5H_5N, NO_2^-, N_2

Table 1.7 A classification of acids and bases according to the hard, soft, acid, base principle of Pearson.

This principle could be used if a ligand was wanted to selectively bind calcium, a hard cation. From table 1.7 it can be seen that acid, alcohol, ether or amine donor groups would be preferred. On the other hand, selectivity towards low oxidation state technetium[28], a large soft cation, is more likely to be enhanced by the use of soft donor atoms in donor groups like R_3P or RSH.

The borderline cations can be complexed by both hard and soft bases with selectivity being enhanced by the combination of donor groups used or size of the cavity.

1.3.2 Geometric Preference of Metals

The stability of a complex between a metal and a ligand can be increased by controlling the number of coordinating groups that a ligand has and the preferred geometry that the ligand will adopt.

The alkali metals can form complexes with coordination numbers between three and eight with a general preference for a coordination number of six. The preferred coordination number increases with increasing ionic size.

The first row transition metals tend to favour forming complexes with coordination numbers of four, five or six. Nickel II complexes tend to form regular structures of pseudo tetrahedral[28] for four coordinate systems or octahedral structures for six coordinate systems, whereas copper II complexes rarely form regular structures due to the distortions caused by the Jahn-Teller[29] effect. So this simple analysis suggest that copper complexes with the ligand NOTA would be favoured over those with DOTA as it is a relatively small cation that prefers coordination numbers between four and six.

Larger cations like europium and gadolinium would prefer to adopt an eight coordinate system, due to their larger ionic radii. Hence

the stability of the complex with DOTA would be expected to be greater than NOTA.

1.3.3 Chelate Ring size

The effect of chelate ring size[30] on the stability of a given complex depends on the size of the cation. In general five-membered chelate rings form more complexes with a wider range of cations than six-membered chelate rings, which tend to favour smaller cations, (table 1.8).

If a proton is considered as the smallest possible cation it can be seen (table 1.8) that it forms more stable complexes with the six-membered chelate than with the five-membered chelate ring. On the other hand, larger cations all tend to form more stable complexes with a five-membered chelate ring.

This leads to an observation that a larger chelate ring will tend to destabilise a complex with a larger cation to a greater extent than a complex with smaller cations.

Cation	en	trm	$\Delta \log K_1$
H	9.89	10.52	-0.63
Cu (II)	10.48	9.68	+0.8
Ni (II)	7.33	6.30	+1.03
Cd (II)	5.42	4.47	+0.95

Table 1.8 Log K_1 values for 1:1 complexes between the above ligands and cations.

Data taken from ref 13.

The lowest strain energy geometry has been calculated for the five- and six-membered rings[30,31] in metal complexes with chelates. The lowest energy conformation for the six-membered ring can be taken as being the same as for a cyclohexane ring in a chair conformation so the distances for an optimised chelate ring should be close to those as shown in figure 1.3. In an optional five-membered ring chelate the metal atom should be placed at the focus of the nitrogen lone pairs, figure 1.3 . This occurs for larger metal ions, at a greater M-N separation.

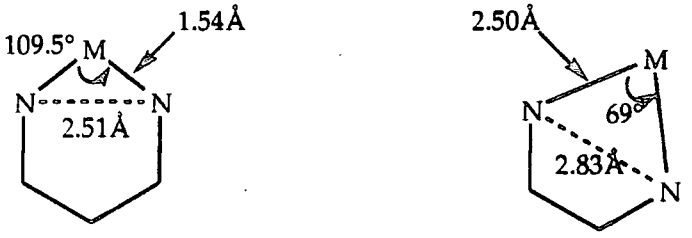


Figure 1.3 Showing lowest strain geometries for five and six-member chelate rings.

1.3.4 Stereochemistry of binding

Ligands need not possess a chiral centre however on binding to a metal the flexibility of the ligand is restricted and stereogenic centres may be created. The stereochemical consequences of metal ion complexation can manifest themselves in a variety of ways;

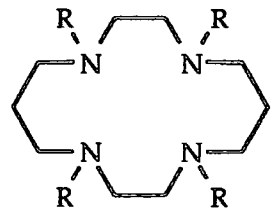
1 Selective binding with one conformer,

2 Formation of only one isomer,

3 Formation of a helical arrangment.

The actual effect of complexation on the chirality of a ligand is dependent on the structure of the ligand. The stereogenic centre could be at the metal atom itself or at a site on the ligand.

1.3.4.1 Selective Binding

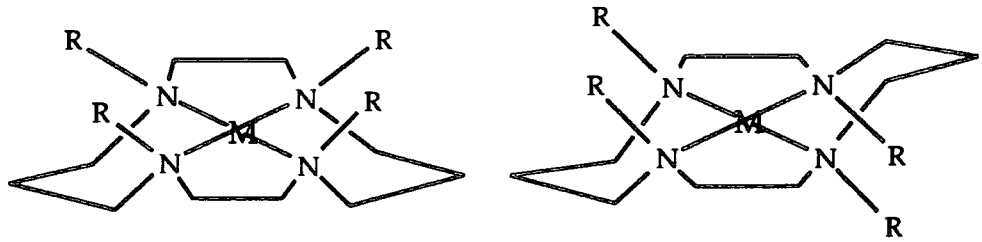


11 R=H 1,4,8,11-Tetraazacyclotetradecane [$14N_4$]

12 R=CH_3 N, N', N", N"'-Tetrakismethyl-1,4,8,11-tetraazacyclotetradecane [TMC]

The larger macrocyclic rings are relatively flexible and can exist in a variety of conformers.

The fourteen-membered cyclam ring has several low energy conformers that can be adopted in complex formation.[32]



Trans I (R,S,R,S) Trans III (R,S,S,R)

Figure 1.4 Conformers of $14N_4$ able to form complexes.

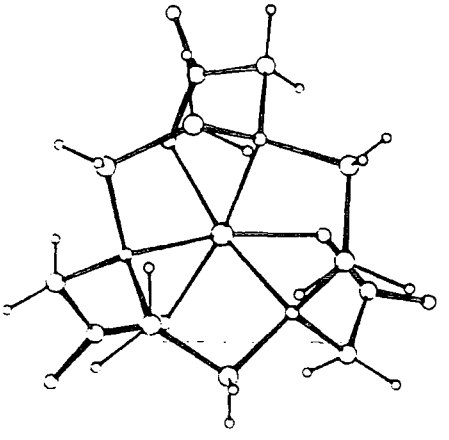
Conversion between the two forms is base catalysed, however TMC has four tertiary nitrogen centres and hence there is a high energy barrier for interconversion between the two structures. Complexes of TMC are of the trans I (R,S,R,S) type conformer, a single monodentate ligand is also often located above the plane of the ligand forming a square pyramidal structure.

1.3.4.2 Helical Induction

Complexes of NOTA have been studied by many people. The ligand itself is not chiral however when a complex is formed the ring becomes chiral. The carboxylic groups can then be seen to be orientated in a clockwise (type I) or anticlockwise (type II) direction in relation to the ring[33]. For a given metal only one of the two possible types appears to be found.

The X-ray structure of the Ni (II) NOTA.H_3O^+ complex shows a clockwise rotation giving a type I structure, whereas Fe (III) cations give a type II structure.

This has led to the tentative conclusion that a small M-N bond length will give a type I structure while a longer M-N bond length gives a type II structure.



Type I

Type II

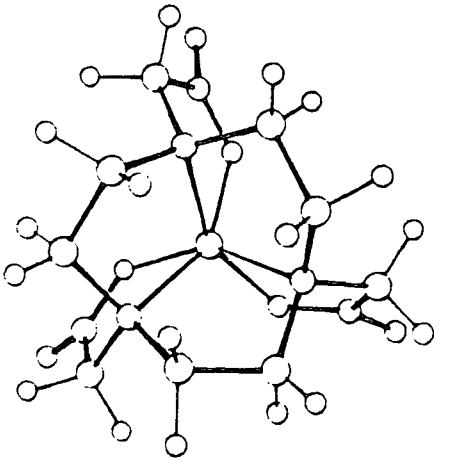


Figure 1.5 Structure of complexes with type I [Ni (II)] and II [Fe (III)] structures.

1.4 Applications

Two of the possible uses of such complexes (if they have appropriate stabilities) are;

a) in the treatment and therapy of cancer using γ, β+ or β- emitting isotopes as the cation and

b) as a way of supplying metal cations to plants that grow in soils deficient in them.

The first of these requires complexes that are very stable and unlikely to dissociate under any condition encountered *in vivo*.

The second however, requires that the complex be able to release the cation under the appropriate conditions. There is also a requirement that the complex is able to cross biological membranes to be more effectively absorbed by the plants. If it is possible to achieve this (e.g. using charge neutral, low molecular weight metal complexes) it could enable metal deficient soils to be used for cultivation which would be otherwise useless.

Biological membranes are composed of a double layer of fatty acids that align with their hydrophobic tails pointing in towards the centre of the double layer with their hydrophilic ends to the outside. Although the outside of the membrane is hydrophilic it is covered by clusters of water molecules. The overall effect is to render it impermeable to ions. Hence the desired complex would need to be neutral to pass through. The permeability[34] is measured in terms of permeability coefficient, defined as;

"The permeability coefficients of small molecules are correlated with their solubility in a non-polar solvent relative to their solubility in water."

The presence of alkyl or aromatic substituents that are oriented to the surface of the complex would increase the chances of a higher coefficent.

1.4.1 General Use Complexing Reagents

For a complexing ligand to be useful for titrimetric analysis it has to meet certain requirements[28]:

i) the complexation reaction must fit a stoichiometric equation,

ii) the complex must be formed rapidly,

iii) there must be a way to identify when equivalence has been reached,

iv) must be possible to prepare and maintain a solution of the titrant of known concentration.

Pentaethylenehexamine has been used for cases were the metal ions favours bonds with nitrogen donors. However it is a highly basic ligand and is susceptible to protonation reducing the stability of its complexes.

EDTA[28] is the complexing agent most commonly used for analytical purposes. It fulfils the above requirements, forming highly stable 1:1 anionic complexes. A range of indicators[35] have been developed for use with it, for example murexide being used in calcium EDTA titrations.

1.4.2 Selectivity

Valinomycin is a naturally occurring ionophore[36] that was found to form remarkably selective complexes with potassium ions. Pederson[37] started looking at possible synthetic ionophores in the cyclic

polyethers and found that they exhibited an unusual affinity for the cations of the alkali metals.

1.4.2.1 Crown Ethers

Polyether	'Cavity' size	Alkali metal	Ionic radii
12-crown-4	1.2	Li^+	0.73
15-crown-5	1.8	Na^+	1.02
18-crown-6	2.8	K^+	1.38
21-crown-7	3.8	Rb^+	1.49
		Cs^+	1.70

Table 1.9 Shows the cavity size of some simple crown ethers and the ionic radii for the alkali metals. (All radii are given in Å.)

It can be seen (table 1.9) that sodium should be the best fit for the 15-crown-5 ether and form the most stable complex. However caesium is the best fit with the largest of the rings, while 18-crown-6 will form the most stable complexes with potassium, figure 1.6.

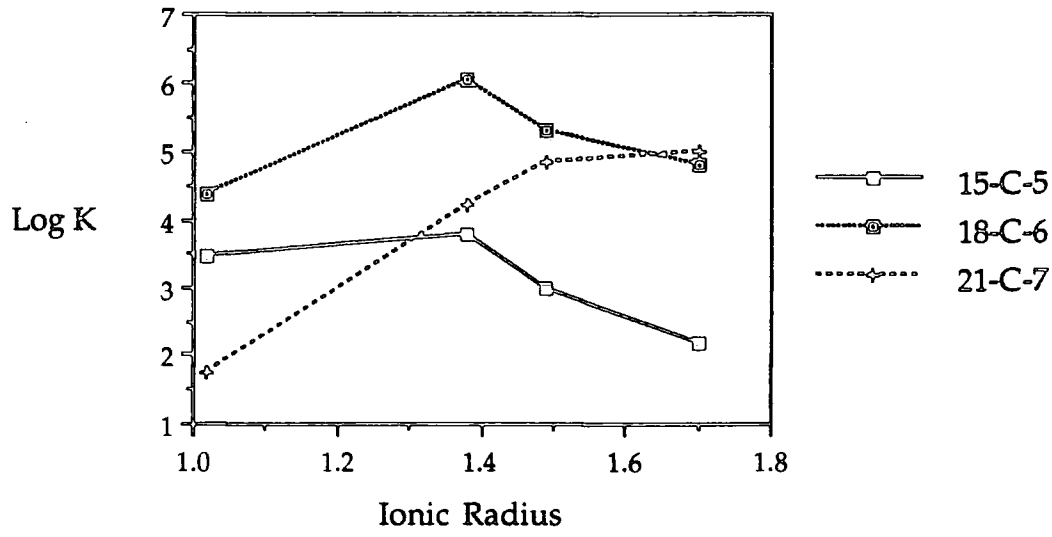
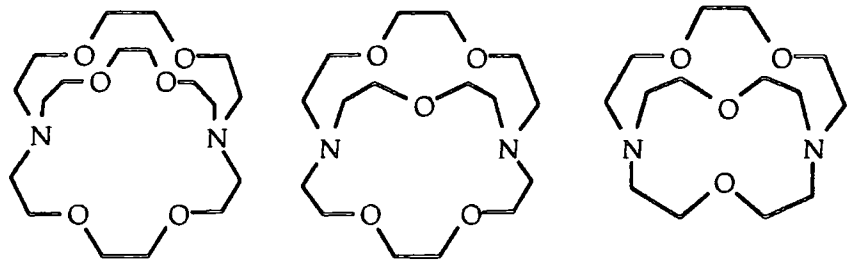


Figure 1.6 Plot of ionic radius against Log K for 15-crown-5, 18-crown-6 and 21-crown-7.

[Data taken from ref 38.]

1.4.2 2 Cryptates



222 221 211

13 **14** **15**

Cation to form most stable complex:

K^+ Na^+ Li^+

Selectivity can be enhanced by fitting the size of the cation to the size of the cavity available. This was demonstrated by the different stabilities of alkali metals with 222, 221 and 211 cryptate[39]. The size of the cavity governs which of the cations will be the best fit, that is has

the most favourable bonding distances between cation and donor groups.

It has been shown that the selectivity of the cryptand decreases as the size of the cavity increases.

1.4.2.3 Effect of Preorganisation

The amount of change in conformation that a ligand has to undergo before it can form complexes will lower the overall stability of a complex. If this is minimised by having a ligand that is fixed in a conformation ready for binding, increases in the complex stabilites can be seen.

Figure 1.7 Structure of 18-Crown-6 Before and After Complexation with KSCN (not included).

Crown ethers show (figure 1.7) very little preoganisation for binding and have to undergo considerable changes in conformation before complexation can occur[40,41]. However spherands have relatively rigid structures with three donor oxygens orientated to bond to a cation with little reorientation,[42] figure 1.8.

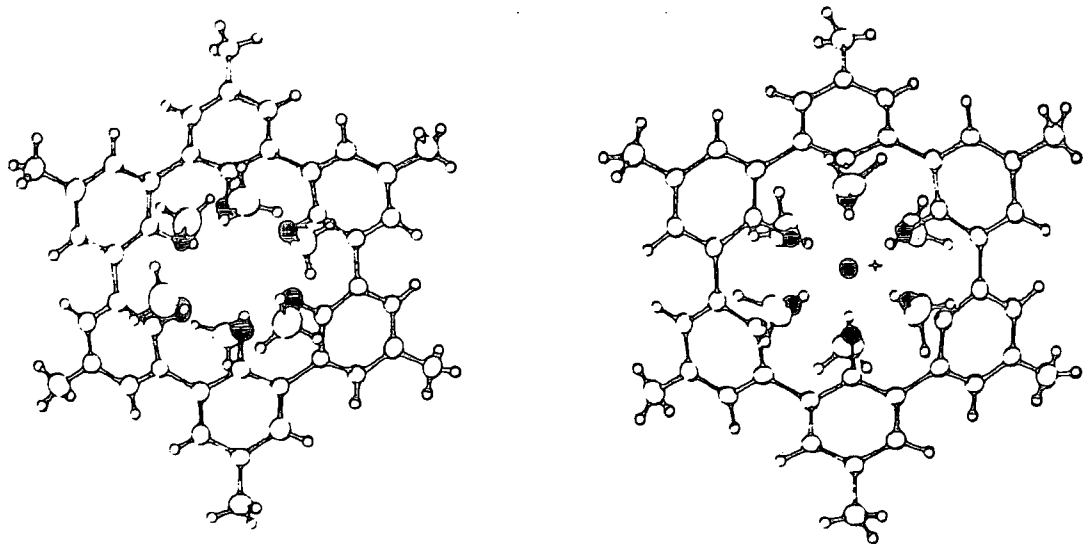
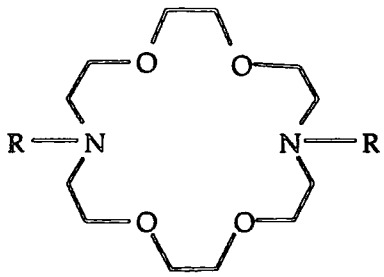


Figure 1.8 Structure of spherand before and after complexation with lithium.

1.4.2.4 Effect of Pendant Side-Arms

The addition of side arms to crown ethers has to be via one of the carbon atoms in the ring. The addition of an ether or ester side-arm to 15-crown-5 showed no apparent aid to binding.[43] If a nitrogen atom is substituted for an oxygen atom and the pendant arm added to that a centre of inversion is created. In this case a marked effect on complexation strengths has been observed.

Selectivity can also be enhanced by the use of side-arms. Different donor groups will also change the selecivity of a ligand. It can be seen that the ligand $18N_2O_4$ does display selectivity between cations.[44] Complexation of the ligand with the ether binding groups display no selectivity between calcium and sodium cations, whereas with ester binding groups the ligand shows an increased selectivity for the calcium cation.



16 R=CH_2CH_2OMe

17 R=CH_2CO_2Et

18 R=CH_2CONH_2

19 R=$CH_2CONHMe$

20 R=$CH_2CONHCH_2CO_2Et$

It can be seen (table 1.10) that all three derivatives with amide groups have higher stabilities with calcium than either sodium or potasium. The increased stability for 20 with the second ester group suggest that this is contributing to the binding of the calcium.

ligand	Na^+	K^+	Ca^{2+}
18 [a]	<2	<2	5.65
19 [b]	2.48	2.36	4.99
20 [b]	2.36	2.45	5.97

Table 1.10 Stability constants for complexation of **18-20** with cations.

a) Data taken from ref 45.

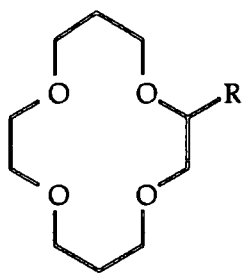
b) Data taken from ref 46.

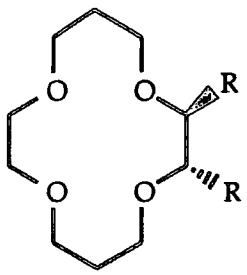
1.4.2.5. Lithium Selectivity

Finding a stable binding agent for lithium has been very important for both electronic and biological applications.[47] Lithium is a small relatively hard cation that has a preference for hard donor atoms. It will form stable six membered chelate rings where other larger

cations could not, this allows a chance of creating a selective ligand for lithium that would form weaker complexes with other alkali metals.

The increased selectivity of 14-crown-4 over 12-crown-4 for lithium, is due to the formation of two six membered chelate rings. The use of a disubstituted ligand prevents the formation of 2:1 complexes ensuring that it is the 1:1 complexes are formed. This increases the stability of the lithium complex with respect to the sodium or potassium complexes.





21 R=CH_2OCH_2Ph 22 R=CH_2OCH_2Ph

23 R=CH_2CO_2Me 24 R=CH_2CO_2Me

25 R=CH_2CONMe_2 26 R=CH_2CONMe_2

It was found that all the above ligands showed some selectivity towards lithium over sodium and potassium. However the diamide (**26**) gave the highest selectivity for lithium over sodium of all the ligands[48]. The response of an electrode incorporating **26**, in the concentration range required for biological use, was better than that of the electrode currently used.

1.4.3 Applications of Complex stability

If complexes of appropriate stability can be formed, a range of *in vitro* and *in vivo* uses exist. If stable complexes can be formed that remain complexed and clear the body without building up dangerous

concentrations in vital organs, this would allow the introduction of metal isotopes for diagnostic and therapeutic purposes that if uncomplexed are potentially harmful. Further adaptation of the ligands by attachment of side arms may aid localisation in tumours or organs for imaging.[49]

1.4.3.1 Isotopes of Interest

There are two fields of work involving the use of stable complexes in biological systems:

i) binding Gd^{3+} to act as a paramagnetic contrast reagent,[50] in magnetic resonance imaging.

ii) binding radioactive isotopes for use in cancer diagnosis and therapy.[51]

The ligands used to bind the radioisotopes depend on the cation used and follow the same ligand design features as discussed above. It is also important that complexation of the isotope is relatively rapid, for those isotopes with short half lives.

1.4.3.2 Resistance to Dissociation

Initially EDTA and DTPA were studied as ligands for *in vivo.* use. Further substituents could be added to a carbon on the amine chain of the ligand, to allow localisation at specific sites. However the complexes formed with these ligands were anionic and under physiological conditions attracted protons and cations present in serum.[52,53] Protonation may lead to decomplexation and cation exchange would lead to release of harmful ions. Macrocyclic ligands generally form complexes that have slower rates of disociation under these conditions and the use of alternate binding groups (e.g.

phosphinic versus carboxylic acids) could lower the pH at which protonation occurred.

1.4.3.3 Complexation of γ -emitters

There are two ions that are of interest as γ-emitters, gallium III (^{67}Ga : γ, $t_{1/2}$ 3.25 days) and indium III , (^{111}In : γ, $t_{1/2}$ 2.81 days).γ-Emitters are used to locate and image tumors in single photon emission computerised tomography (SPECT imaging). They can be considered together for complexation purposes, notwithstanding the size difference, as they both require a ligand with three anionic groups to form a neutral complex in which both ions are six coordinate.

Several groups have worked on ligands for this role. NOTA[54] has been found to be most favourable out of the triazacycloalkanetriacetates with ring sizes between nine and twelve. Acyclic[55] ligands based on ethylenediamine have also been studied and appears to remain intact in *in vivo* studies.

1.4.3.4 Complexation of β-emitters

β-emitters are of use in the treatment of tumors. Yttrium-90 (β^-, $t_{1/2}$ 64 hours, Emax 2.25MeV) has properties that make it the most suitable choice. It also requires a ligand with three anionic groups to form a neutral complex, however it prefers an eight coordinate binding site.

It has been concluded that a ligand based on DOTA would have the required characteristics[56,57]. A series of related ligands have been synthesised[58] with side-arm groups that allow binding to an antibody for tumor localisation.

1.4.3.5 Complexation of Paramagnetic Contrast Reagents

Gadolinium is the favoured paramagnetic contrast reagent but the free ion is quite toxic if released in the body. Its ligand requirements are similar to those for yttrium. DTPA[52] is used as a complexing agent for MRI imaging although the complex is not as stable *in vivo* as that with DOTA. It was found that complexes of macrocyclic ligands were considerably more stable. A range of ligands based on the $12N_4$[59] skeleton with acetic acid and phosphinic acid groups have been synthesised and are undergoing biological testing.

1.4.4 Scope of this work

The work in this thesis can be divided into three sections. Initially the synthesis and study of aminomethylenephosphinic acid ligands and their complex formation with a variety of metal ions. It was proposed at the outset to examine the effects of ;

i) changing the amine used, cyclic or acyclic,

ii) changing the substituent on the phosphorus atom,

iii) complexation with a range of metal atoms. (Chapters 2 and 3).

In the second part of the thesis an attempt is made to control the geometric arrangement of the complexes formed by incoorporating a rigid unit into the ligand. Molecular models of the first ligand indicated that a square planar arrangement was preferred, so a modification of the ligand was required, (Chapter 4).

The final section was an attempt to modify the phosphinic acid ligands by substituting one of the oxygens for a sulphur, thus creating a phosphinothiolic acid. This would give ligands that favoured complexation with soft cations, (Chapter 5).

The experimental procedures followed in the above sections are given in chapter 6. This also includes details of methods for determination of protonation and stability constants.

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Chapter 2

Acyclic Polydentate Aza-Phosphinic Acid Ligands

A study of aza-phosphinic acid ligands allows an informative comparison of their protonation and metal complex stability constants with those of the related ligands with carboxylic acid donor groups.

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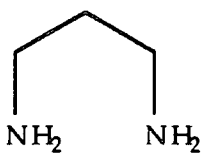
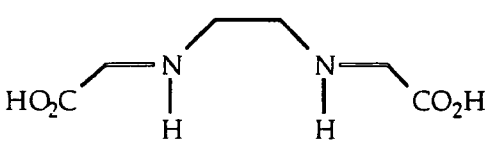


28

27 Ethylenediamine [en]

28 Trimethylene-1,3-Diamine [trm]

The free amines ethylenediamine and trimethylene-1,3-diamine (en and trm) and their carboxymethyl derivatives (EDDA, EDTA and the homologue DTPA) have been extensively studied.[1] The stable complexes formed by these ligands allow them to be used practically to scavenge cations in biological systems[2] and in analytical work[3].



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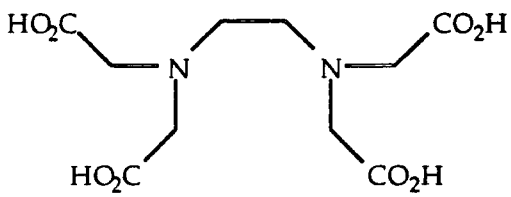
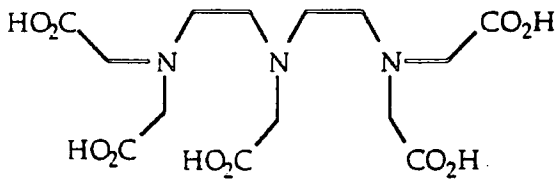


30

29 Ethylenediamine-N,N'-diacetic acid [EDDA]

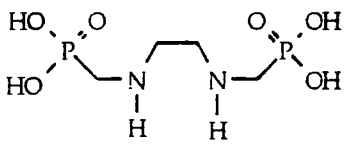
30 Ethylenediamine-N,N,N',N'-tetraacetic acid [EDTA]

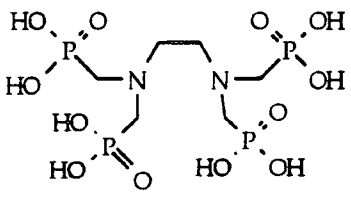


31

31 Diethylenetriamine-N,N,N',N'',N''-pentaacetic acid [DTPA]

The analogous phosphonic acid derivatives have been made by Martell[4,5] The oxygens of the phosphonic acid derivatives are more acidic than the corresponding carboxylates and the electron withdrawing effect the $PO(OH)_2$ group has on the proximate nitrogens is greater than that of the phosphinic acid groups, increasing their acidity.

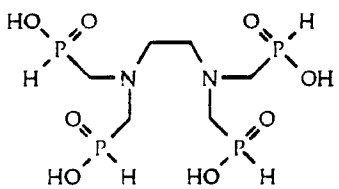


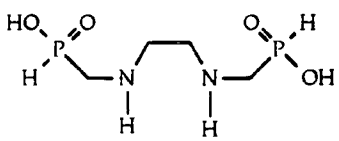


32 33

32 Ethylenediamine-N,N'-di(methylenephosphonic) acid [EDDP]

33 Ethylenediamine-N,N,N',N'-tetra(methylenephosphonic) acid [EDTP]





34 35

34 Ethylenediamine-N,N,N',N'-tetra(methylenephosphinic) acid [EDTPi]

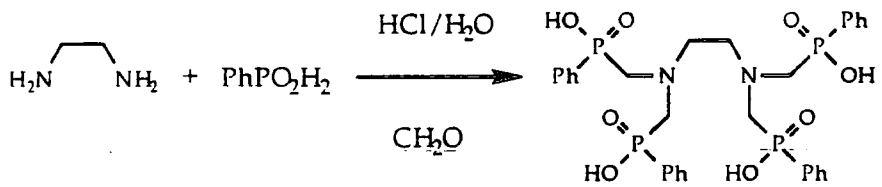
35 Ethylenediamine-N,N'-di(methylenephosphinic) acid [EDDPi]

The di and tetra ethylenediamine phosphinic acids[6] have also been made. The pKa values for the tetrasubstituted ligand, 34, appeared to be remarkably low, so the substituted phosphinic acids were made to see if this was a characteristic of this whole class of ligands.

2.1 Synthesis

The synthesis of these ligands was undertaken by two routes. The 'aqueous route' was used to form the phenyl phosphinic acid derivative: it could also be termed the direct route. The second route involved use of the appropriate dialkoxy-phosphine as the source of phosphorus. It is a more flexible method, but it involves two steps.

2.1.1 Aqueous Route



Scheme 2.1

This was not found to be a very general reaction and could only be used to form fully substituted ligands with the phenyl substituent at phosphorus[7]. The ethylenediamine could be replaced by diethylenetriamine without changing the conditions to yield a penta-substituted product. The reaction yield was around 50% and some of the phosphinic acid starting material was always remaining at the end

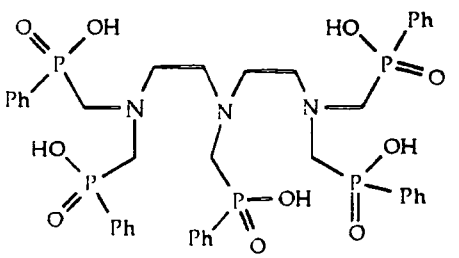
of the reaction. This crude reaction mixture could be purified by dissolving the residue in base and then adding acid gradually until precipitation started. After standing at pH 3-4 for 16 hours a precipitate of the acid formed that could be obtained by filtering.

2.1.1.1 Ethylenediamine-N,N,N',N'-Tetrakis(Methylene(Phenylphosphinic)) acid (EDTPPh)

The actual reaction shown in scheme 2.1 was done by Lukeš and Pech[8]. It was used as a standard to which to compare our work. Their procedure was found to work with a 50-60% yield to give a material with a comparable melting point.

2.1.1.2 Diethylenetriamine-N,N,N',N",N"-penta(methylene(phenylphosphinic))acid (DTPPPh)

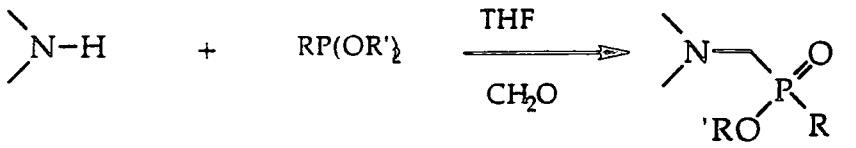
The reaction of diethylenetriamine in scheme 2.1 was found to work well. The penta-substituted compound was obtained in a slightly reduced yield however the sample was microanalytically pure and could be used directly for potentiometric studies. It is a novel octadentate ligand that may be compared to DTPA[9].



36

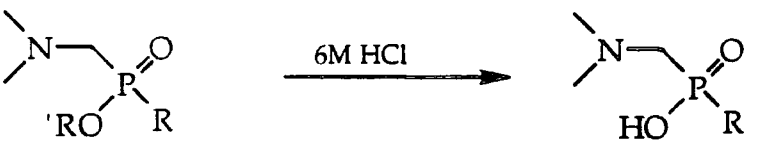
Diethylenetriamine N,N,N',N",N"-penta(methylene(phenylphosphinic))acid [DTPPh]

2.1.2. Dry Route



Scheme 2.2

The reaction shown in scheme 2.2 was used as a general route for the formation of phosphinic acid derivatives. The substituent on the phosphorus could be altered by using the appropriate phosphine. This route was highly sensitive to moisture, so a soxhlet extraction apparatus was used with 3Å molecular sieves under an atmosphere of dry nitrogen. The intermediate ester was purified by column chromatography on alumina eluting with dichloromethane/methanol solutions.



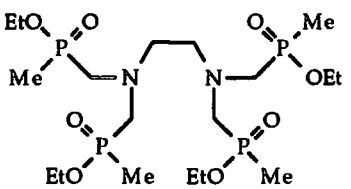
Scheme 2.3

The hydrolysis shown in scheme 2.3 worked cleanly to give the acid with a yield of greater than 95%. The acid was difficult to purify further, although this was a function of the substituent at phosphorus. The methyl derivatives are highly soluble in aqueous solutions

making recrystallisation difficult. Those with a phenyl derivative are less soluble in water and were easier to recrystallise.

2.1.2.1 Ethylenediamine-N,N,N',N'-Tetra(Methylene(Methylphosphinic)) acid Attempted Preparation (EDTPMe)

The first reaction tried was to form an analogue of EDTPPh with methyl phosphinic acid derivatives, EDTPMe. However it was found that a mixture of two esters was obtained which proved inseparable by column chromatography. It could be seen by ^1H NMR that the bridged tetrahydro imidazole (38) was formed as well as the desired tetra-substituted product (37).



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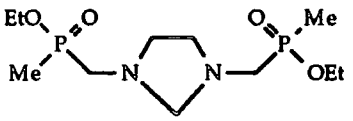


38

37 Tetraethyl ethylenediamine-N,N,N',N'-tetrakis(methylene(methylphosphinate))

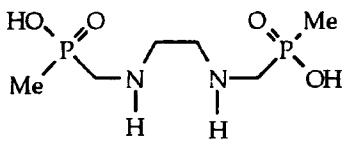
38 Diethyl 1,3-tetrahydroimidazole N,N'-bis(methylene(methylphosphinate))

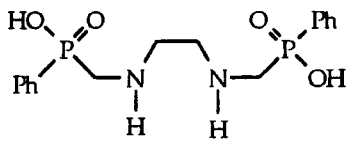
If this mixture was hydrolysed under the conditions of scheme 2.3 a mixture of the tetra and di acids were obtained. During hydrolysis, the aminal, 38, was also hydrolysed (liberating the equivalent of formaldehyde) thereby generating the analogue of EDDA. Purification of this mixture by use of ion exchange chromatography was attempted and although it was possible to obtain a mixture of the tetra and di acids with ammonium as the counterion, it was not possible to obtain a homogeneous sample of the tetra acid from the column.

2.1.2.2 Diphosphinic acid Ligands based on 1,2-Ethylenediamine

It was found that if the soxhlet containing the molecular sieves was removed, the reaction gave only the tetrahydroimidazole product and with an increased yield. This reaction was found to work irrespective of the phosphine used. The carbon between the two nitrogens is well known[10] to be easily removed by acid hydrolysis.

It is possible to selectively hydrolyse the ester groups but leave the methylene bridge intact by a basic hydrolysis at room temperature. The fully hydrolysed products were symmetrical tetradentate ligands with a N_2O_2 donor group and this simple, new synthetic route allows a wide range of structurally similar ligands to be prepared.





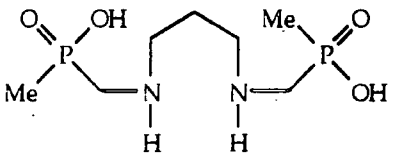
39 **40**

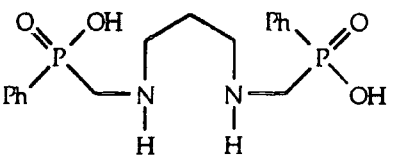
39 Ethylenediamine N,N'-di(methylene(methylphosphinic)) acid [EDDPMe]

40 Ethylenediamine N,N'-di(methylene(phenylphosphinic)) acid [EDDPPh]

2.1.2.3 Diphosphinic acid Ligands Derived from 1,3-Propylenediamine

The synthesis of ligands based on 1,3-propylenediamine was basically the same as that for the diacids, **39** and **40**, based on 1,2-ethylenediamine. The six-membered ring aminal formed during the reaction and was removed under the acidic hydrolysis conditions, to yield a tetradentate ligand.





41 42

41 Propylenediamine N,N'-di(methylene(methylphosphinic)) acid [PDDPMe]

42 Propylenediamine N,N'-di(methylene(phenylphosphinic)) acid [PDDPPh]

PDDPMe and PDDPPh provide the same binding group as EDDA, EDDPPh and EDDPMe so direct comparisons can be made. The use of propylenediamine gives a six-membered (N-M-N) chelate ring when the cation binds to the nitrogens. This possibly could introduce an increased selectivity towards smaller cations since they prefer such six-membered rings compared to large cations that are destabilised by them (see Chapter 1 p 14-15).

2.2 Protonation Constants

The protonation constants for the phosphinic acid ligand, EDTPi, seem very low when compared to those of the carboxylic and phosphinic acid donor groups (table 2.1). All the phosphorus based ligands have lower protonation constants than their carboxylic analogues.

The first proton added to an aminomethylene acidic ligand will position itself on nitrogen. When the system has a reasonable amount of flexibility the conformation of the ligand at its different protonation states may change to give the lowest energy conformation, eg. minimising electrostatic repulsions.

Ligand	pK_1	pK_2	pK_3	pK_4
EDTA [a]	10.77	6.11	2.68	2.0
DTPA [a]	10.45	8.53	4.28	2.65
EDTPi [b]	6.87	2.34	<2	<2
EDTPPh [c]	8.24	3.97	2.5	1.0
EDTPPh [d]	8.07	4.08	2.62	<2
DTPPPh [d]	9.32	5.06	3.4	2.57

Table 2.1 Protonation constants for phenyl phosphinic acids and the carboxylic analogues.

a) Data taken from ref 11.

b) Data taken from ref 6.

c) Data taken from ref 8.

d) This work.

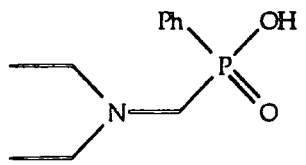
2.2.1 Techniques

Two techniques were used to determine the protonation constants of the ligands studies in this chapter. Values between 2 and 10 were evaluated by potentiometric titrations followed by iterative least-squares analysis using the programmes 'Scogs' and 'Superquad'[12]. Higher values were determined by ^{31}P NMR titrations then plotting the ^{31}P shift against the pH.

The potentiometric titrations were carried out in a cell at 25°C and at an ionic strength of 0.1M tetramethylammonium nitrate. The base was tetramethylammonium hydroxide (0.05M) which was calibrated by a titration against a standard solution of hydrochloric acid (0.02M). The additions were controlled by a computer which allowed the volume added and time between the additions to be adjusted.

2.2.2 High pH phenomena

Initially the pH region investigated was that above 10, as the second pKa appeared to be rather low for a protonation on a nitrogen. It was found that in the range pH 7 to pH 13 δ_p increased with increasing pH. It was found that beyond pH 13 δ_p decreases quite steeply.



43

43 Diethylamine N-methylene(phenylphosphinic) acid [DPP]

It was originally thought that there may be a deprotonatation from N occurring at elevated pH. However, ligand **43** was synthesised and studied. DPP has only one nitrogen and one oxygen. Two pKa values were expected, the first around 9 for protonation at nitrogen while the second, for oxygen was expected to be below 2. These were both crudely identified by NMR titrations. However, as the pH was raised above 13 the ^{31}P shift was seen to fall again (figure 2.1) as had been observed with EDTPPh, DTPPPh NOTPPh and DOTPMe (see chapter 3).

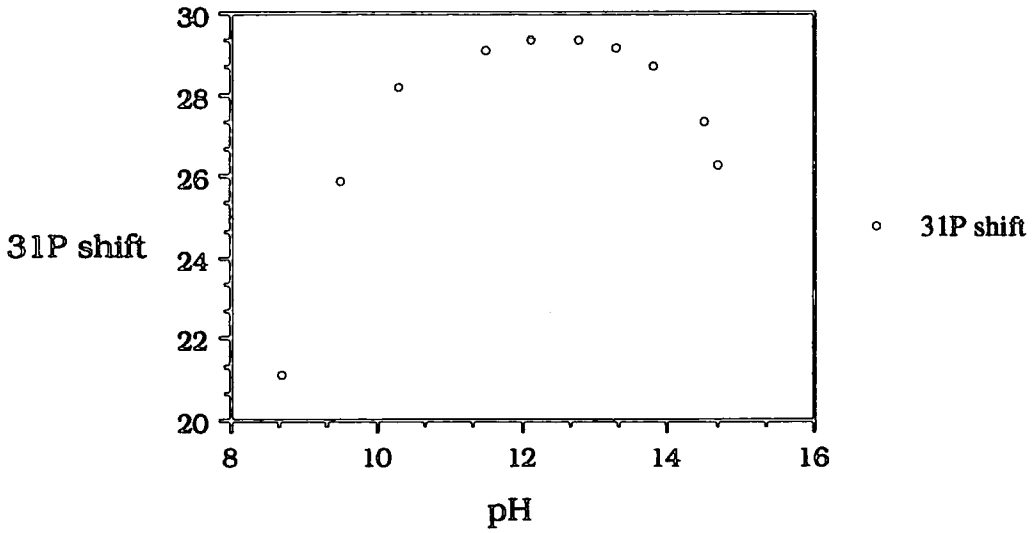


Figure 2.1 Plot of pH versus ^{31}P shift for DPP.

A possible cause for this effect was the variation in ionic strength of the solution needed to give the changes in pH. At pH > 13 the ionic strength becomes impossible to maintain at 0.1 as this is the concentration of base needed to give the pH without any acid present. As the ligand being added is acidic the ionic strength has to be greater than 0.1 to give the desired pH values.

Two sets of solutions were made up using EDTPPh at several pH values above 13. One set was at minimal ionic strength while the other had tetramethylammonium nitrate added to create a saturated solution. The ^{31}P NMR of these two sets of solutions were run. The solutions at higher ionic strength could be seen to be at lower ^{31}P shifts than those at lower ionic strength. This confirmed that it was an ionic strength effect that was causing the drop in pH values in this region.

2.2.3 DTPPPh vs DTPA

The expected trend with the phosphinic donor groups having lower protonation constant was observed (table 2.2). The DTPPPh is a novel octadentate ligand with an N_3O_5 donor set, like DTPA.

Ligand	pK_1	pK_2	pK_3	pK_4
DTPA [a]	10.45	8.53	4.28	2.65
DTPPPh [b]	9.32	5.06	3.4	2.57

Table 2.2 Protonation constant of two diethylenetriamine based ligands with different binding groups.

a) Data taken from ref 11.

b) This work.

2.2.4 Disubstituted systems

Ligand	pK_1	pK_2
en [a]	9.89	7.08
trm [a]	10.52	8.74
EDDA [a]	9.57	6.48
EDDPi [b]	8.08	4.98
EDDPMe [c]	8.35	5.33
EDDPPh [c]	8.63	4.34
PDDPMe [c]	8.91	7.00

Table 2.3 Nitrogen protonation constants for a range of ligands.

a) Data taken from ref 11.

b) Data taken from ref 6.

c) This work

The protonation constants in table 2.3 show that the phosphinic acid derivatives are all more acidic than either the carboxylic analogues or the free amine. This is as expected, with the phosphinic acid oxygen atoms having protonation constants lower than 2. The values shown in the table are the constants for protonation on the nitrogen atoms.[6]

The protonation constants for the unsubstituted phosphinic acid (PHO_2H) are only slightly lower than those for the substituted ligands, suggesting little effect of the phosphorus substituent on the pKa value.

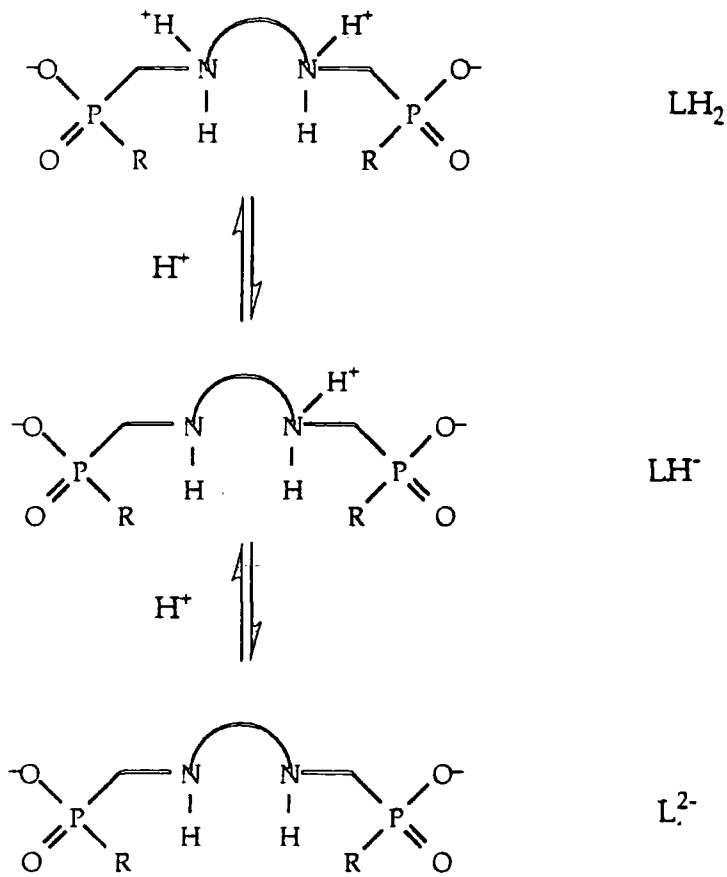


Figure 2.2 Protonation constants for the disubstituted ligands.

2.2.4.1 Effect of different substituents at the Phosphorus centre

ligand	pK_1	pK_2
EDDPMe	8.35	5.33
EDDPPh	8.63	4.34

Table 2.4 Effect of changing the substituent at phosphorus

The table above (table 2.4) shows the effect of changing the substituent at phosphorus on the ligand protonation constants. The difference in the two phosphinic acid protonation constants is small. This is due to the slightly greater electron withdrawing effect of a phenyl compared to a methyl group, so it is a slightly weaker base. The second protonation constant for the phenyl substituted acid is lower. This could be due to a steric effect, involving the phenyl rings, preventing formation of an unstrained conformation.

2.2.4.2 Efffect of different size Chelate ring formation

ligand	pK_1	pK_2
en [a]	9.89	7.08
trm [a]	10.52	8.74
EDDPMe [b]	8.35	5.33
PDDPMe [b]	8.91	7.00

Table 2.5 Effect of five- and six-membered rings on protonation constants.

a) Data taken from ref 11.

b) This work.

The protonation constants for trm and PDDPMe are higher than for en and EDDPMe. All the protonation constants quoted in the above table are for protonations on nitrogen. When en and EDDPMe protonate a bifurcated hydrogen bond generates a five-membered ring, figure 2.3. While with trm and PDDPMe a six-membered ring chelate with the proton is defined. If the proton is regarded as a small cation then the ideas of bite angles apply[13] and it can be seem that the proton will fit best into the six membered. Hence this proton will be harder to remove and have a higher pKa value, than with the five membered ring.

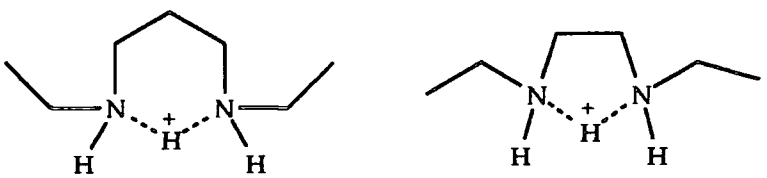


Figure 2.3 Chelation of singly protonated ligands.

In the zwitterion, both nitrogens are protonated and both of the acids are deprotonated. A different conformation to the singly protonated form is expected, since the protonated nitrogens will move as far apart as is possible to minimise the electrostatic repulsion between the two positive charge centres (figure 2.4). Hence the second pKa for the propylene diamine ligands is higher, as electrostatic repulsion is less than with the ethylenediamine ligands.

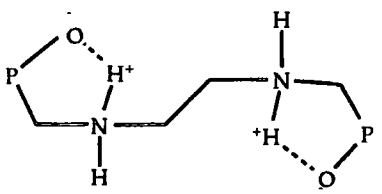


Figure 2.4 Possible solution configuration of zwitterion.

2.3 Stability Constants for Metal Complex Formation

These were determined and analysed in a similar way to the protonation constants of the pure ligands. The thermostatted cell is filled with a 1:1 ratio of the cation and ligand solutions, and the ionic strength was maintained at a constant value with tetramethylammonium nitrate (0.1M). The mixture was left stirring for fifteen minutes before the titration was started.

The first constant quoted, unless otherwise stated, is the log K_{LM} value. Protonation of the 1:1 complex was usually observed and the corresponding log K_{LMH} values are given. Some of the cations (eg. Mg^{2+} and Zn^{2+}) are prone to form MOH species, and could be seen to form LM(OH) complexes.

$$L^{n-} + M^{2+} \underset{K_{LM}}{\rightleftharpoons} [LM]^{(n-2)-} \overset{H^+}{\underset{K_{LMH}}{\rightleftharpoons}} [LMH]^{(n-3)-}$$

$$L^{n-} + M(OH)^{+} \underset{K_{LMOH}}{\rightleftharpoons} [LM(OH)]^{(n-1)-}$$

Figure 2.5 Complexation equilibrium.

2.3.1 Complexes with DTPPPh

The stability constant for the nickel with the phosphinic acid based ligand is much lower than that for the carboxylic derivative, whereas the stability constants with copper were both very high.[14] The constant with DTPPPh was too high to be calculated by the method we

were using. Both of the β_{MLH} values for the calcium complexes are quite high.

Cation	DTPA [a]	DTPPPh [b]
$\log \beta_{MLH}$ Ca^{2+}	16.84	18.25
$\log K_{ML}$ Ni^{2+}	20.17	10.55
$\log K_{ML}$ Cu^{2+}	21.38	Not determinable

Table 2.6 Stability constants for the octadentate ligands based on diethylenetriamine.

a) Data taken from ref 11.

b) This work.

With calcium a relatively high stability constant was expected as the ligand is potentially octadentate which is a favoured coordination number for calcium.[15]

$$H_2L^{3-} + Ca^{2+} + 2OH^- \longrightarrow LCa^{3-} + 2H_2O$$

Figure 2.6 Complexation reaction with first row transition metals.

Although the phosphinic acid, DTPPPh is more acidic than DTPA it was expected to follow similar complexation reactions. The complexes that are formed in a 1:1 solution between the ligands and calcium are much weaker that those with the first row transition metals. The log K_{LM} value could not be determined for the DTPPPh complex. This could be due to a different mechanism of complexation occurring, figure 2.7.

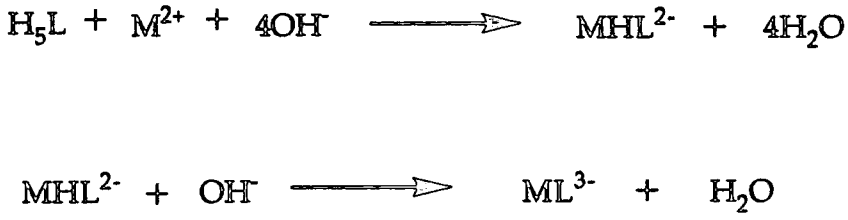


Figure 2.7 Possible reaction for complexation of calcium

The form of the ligand used in the titrations is highly acidic as it is in its fully protonated form. So it is possible that the reaction in figure 2.7 is occurring, hence the number obtained is a sum of $K_{LH/M}$ and $K_{LMH/LM}$.

2.3.2 Disubstituted Systems

Ligand	Ca^{2+}	Mg^{2+}	Ni^{2+}	Cu^{2+}
EDDPPh	2.92	-	8.14	6.56
EDDPMe	3.85	3.96	8.35	8.03
PDDPMe	3.4	7.40	-	7.93
o-phen diPMe [a]	-	-	5.40	4.12

Table 2.7 Showing log values of the stability constants for the phosphinic acid based ligands.

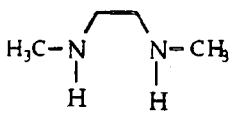
a) See chapter 4 for further discussion

Table 2.7 shows all the stability constants that have been obtained for the disubstituted ligands. The effects of the ligands with the different cations is discussed in following sections, while the ligand o-phen diPMe is discussed in detail in chapter 4. In general it appears that calcium is not bound strongly by any of these ligands. Binding to

nickel seems to be the strongest of those studied, while the complexes with copper are all weaker than those with nickel. The order of copper, nickel stabilities seen here is unusual[16] It is opposite to that predicted by the classical Irving-Williams series[17]

The magnesium is a small, hard cation. The complexes have greatly different stability constants, with the ligand that forms a six-member chelate ring apparently forming the much stronger complex.

2.3.2.1 Nickel Complexes



44 Ethylenediamine N,N' dimethyl [EDDM]

Ligand	log K_{ML}
en [a]	7.35
EDDM [a]	6.89
EDDA [a]	13.5
EDTA [a]	18.52
EDDPMe [b]	8.35
EDDPPh [b]	8.14

Table 2.8 Stability constants for 1:1 nickel complexes with ligands based on ethylenediamine.

a) Taken from Martell and Smith, "Critical Stability Constants", Vol 2.

b) This work.

The stability constants, for 1:1 complex formation, for a range of nickel complexes are collated in table 2.8 . It was expected that EDDPPh

and EDDPMe would have similar binding constants to those of EDDA. However the ligands EDDPPh and EDDPMe appear to have stability constants which are similar to those of the nickel amine complexes. This suggests that although two nitrogens and two oxygens are available for binding, the two nitrogen atoms dominate the binding and interaction with the phosphinate oxygen is relatively weak and does not contribute much to the overall binding constants. It appears that the change of substituent at phosphorus has little effect on the stability constants.The complex between EDDPPh and Ni does not give a log K_{MLH} value, however it does give a log K_{MLOH} of -0.59. This suggests that the protonation constant for the complex is high and outside the range of the technique.

2.3.2.2 Calcium Complexes

ligand	Log K_{ML}
EDTA [a]	11
EDDPPh [b]	2.92
EDDPMe [b]	3.85
PDDPMe [b]	3.4

Table 2.9 Comparison of stability contants for complex with calcium.

a) Data taken from ref 11.

b) This work.

Calcium is a relatively large cation (ionic radius 1.12Å) and prefers an eight coordinate binding site, with hard donors[15]. It appears that only weak binding through the nitrogens is being seen, with little if any binding of the phosphinic acid groups. Even though calcium is a

larger cation there appears to be no preference for a five- over a six-membered chelate ring.

The electron donating abilities of the methyl substituent on the phosphorus makes it more acidic than the phenyl substituted form. This does appear to have an effect on the binding constants of the two ligands, with the more acidic EDDPMe forming a more stable complex than EDDPPh. The observation of this effect does indicate that some binding through the phosphinic acid groups may be occurring.

2.3.2.3 Magnesium Complexes

Using the data processing package 'Superquad' it is possible to distinguish between the two pathways in figure 2.8. The value found as log β_3 is 12.83, this is not a log K_{ML}. The constant β_1 gives a log K_{MLOH} value of 5.46, which when subtracted from β_3 gives the log K_{ML} constant, 7.37.

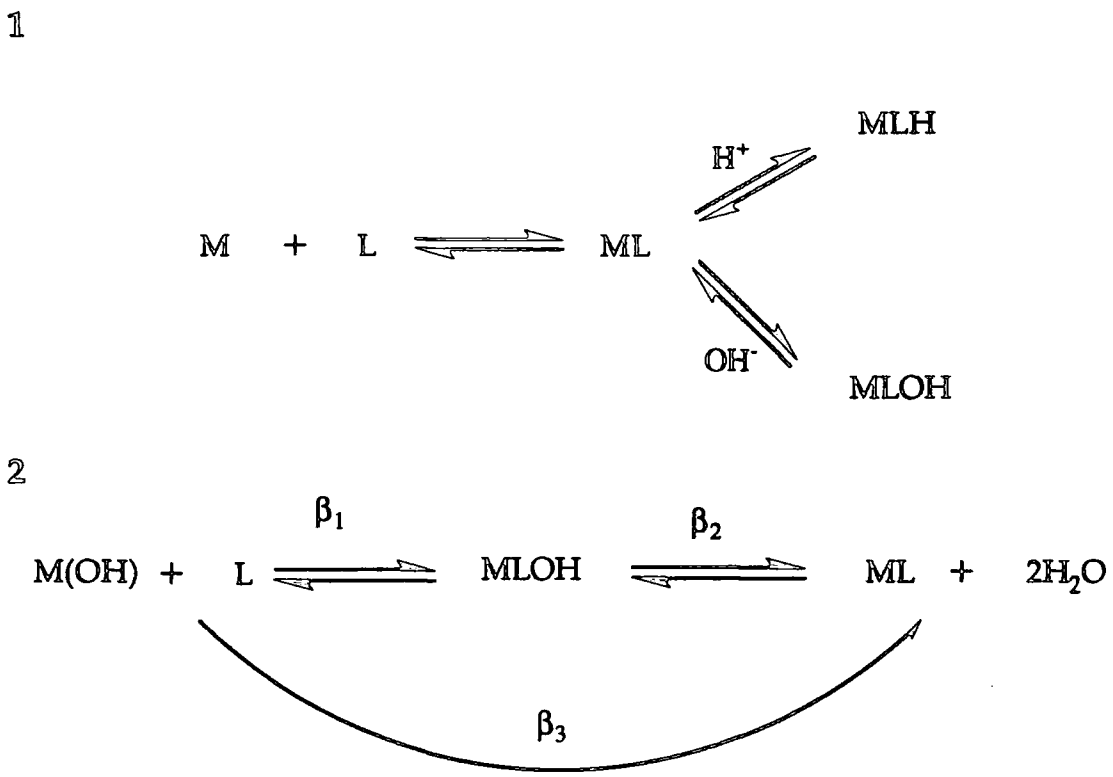


Figure 2.8 Schematic complexation pathways of magnesium with PDDPMe

Magnesium is a small cation (ionic radius 0.72Å, for a four coordinate complex) which is expected to show a preference for forming six-membered chelate rings and this effect is observed. The similarity between the stability constants with EDDA and EDDPMe suggests that they are binding in a similar manner involving the nitrogen and oxygen atoms. The remarkable increase in stability that is seen with PDDPMe must be due to the formation of the six-membered chelate ring. It also suggests that the oxygen atoms must be involved in binding to the magnesium. The binding constant with PDDPMe is only slightly lower than for the Mg EDTA complex[18] which has two extra donor oxygens that are used, in the six coordinate complex.

Ligand	Log K_{ML}	Log K_{MLOH}
en [a]	0.37	
EDDA [a]	3.9	-
EDDPMe [b]	3.96	-
PDDPMe [b]	7.40	5.46
EDTA [a]	9.12	-

Table 2.10 Stability constants for complex with magnesium for a range of ligands.

a) Data taken from ref 11

b) This work.

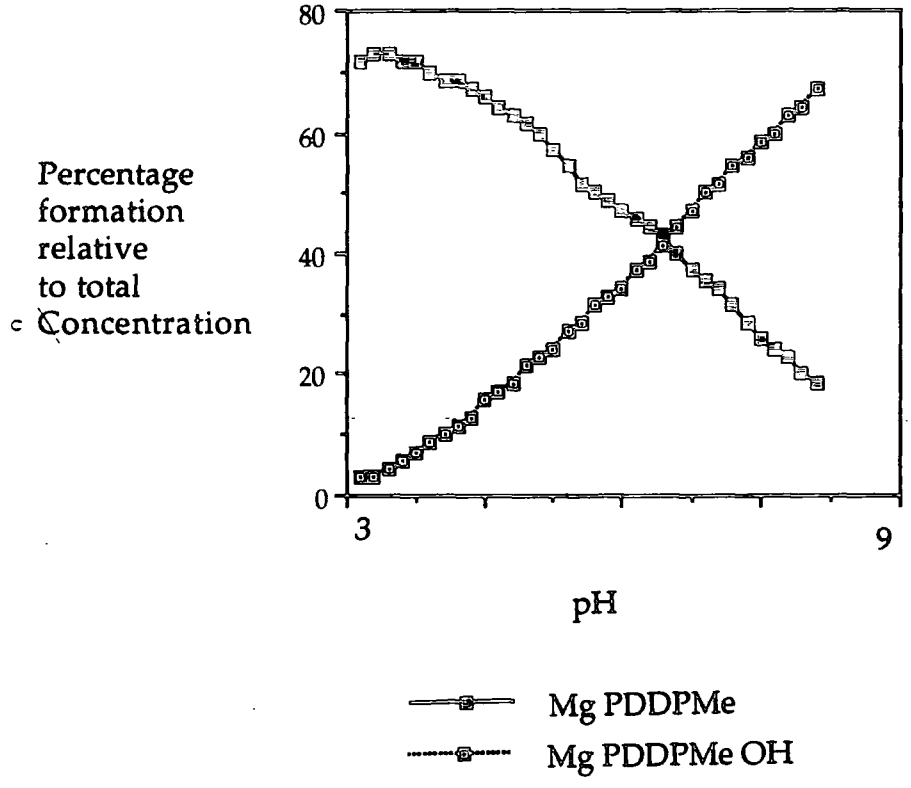


Figure 2.9 Partial species distribution plot for the 1:1 magnesium PDDPMe complex.

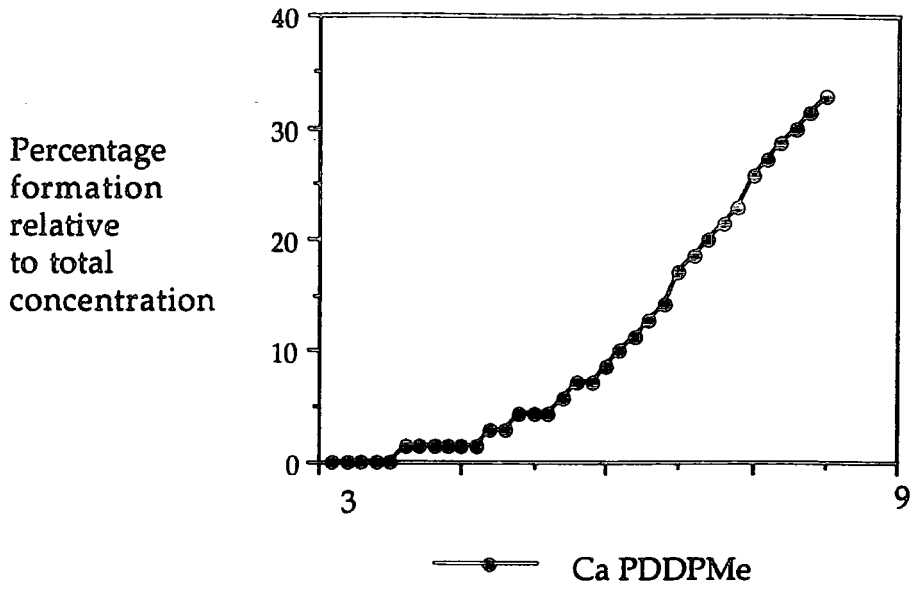


Figure 2.10 Partial species distribution plot for the 1:1 calcium PDDPMe complex.

The second constant found for the magnesium complex is not the Log K_{MLH} that is usually found, it is a Log K_{MLOH} constant. The species distribution plot for the magnesium complex (figure 2.9) shows the formation of the complex followed by formation of the MLOH species as the concentration of base increases. This can be compared to a species distribution plot found for formation of the 1:1 Ca complex, figure 2.10.

2.3.2.4 Copper Complexes

The 1:1 complexes formed between EDDPPh, PDDPMe and EDDPMe and copper are relatively weak. Table 2.9 shows that the 1:1 complex between the amines and copper have similar stability constants to the disubstituted ligands. This observation shows that the nitrogens are binding to the copper, but the oxygens are not contributing to the overall binding of the complex. It is likely that not

all the potential binding sites are being used, this is seen in the copper complex of EDTA, where both of the nitrogens bind but only two of the oxygens are involved.[19,20]

ligand	log K_{ML}
en [a]	10.54
trm [a]	9.75
EDDPPh [b]	6.56
EDDPMe [b]	8.03
PDDPMe [b]	7.93
EDTA [a]	18.52
EDDA [a]	16.2

Table 2.11 Stability constants for complexes with copper II.

a) Data taken from ref 11.

b) This work.

2.3.3 Visible Photospectroscopy of Disubstituted Ligands With Copper

Ligand	λ_{max} nm(H_2O, pH 7)	ε
EDDPMe	725	42
EDDPPh	710	40
PDDPMe	780	10
PDDPPh	774	20
o-phen diPMe [a]	727	75

Table 2.12 λ_{max} (nm) and extinction coefficients ($dm^3mol^{-1}cm^{-1}$) for the 1:1 complexes of copper with the ligands.

a) See Chapter 4.

The uv/visible spectra of the ligands show that all the ligands form complexes with copper. The three ligands that form five-membered chelate rings involving the two nitrogen atoms have similar λ_{max} values. The propylenediamine based ligands may bind in a slightly different manner as the λ_{max} values are a little higher than for the others. This difference could be due to the different complex geometries, since in all cases the extinction coefficients are similar.

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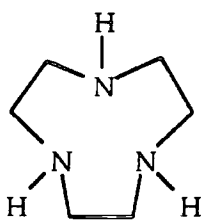
Chapter 3

Polyazaphosphinate Complexes: Solid-State and Solution Structural Studies

The ligands in the following chapter are all based on 1,4,7 triazacyclononane ($9N_3$). The synthesis and measurements of protonation constants and complexing properties have been undertaken and compared to those of the triacetate analogue.



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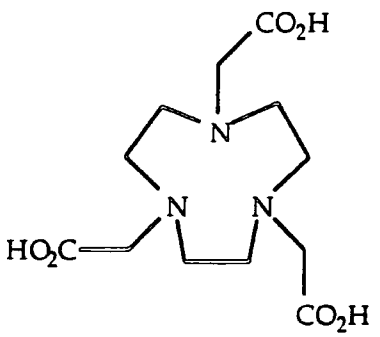


46

45 1,4,7-Triazacyclononane [$9N_3$]

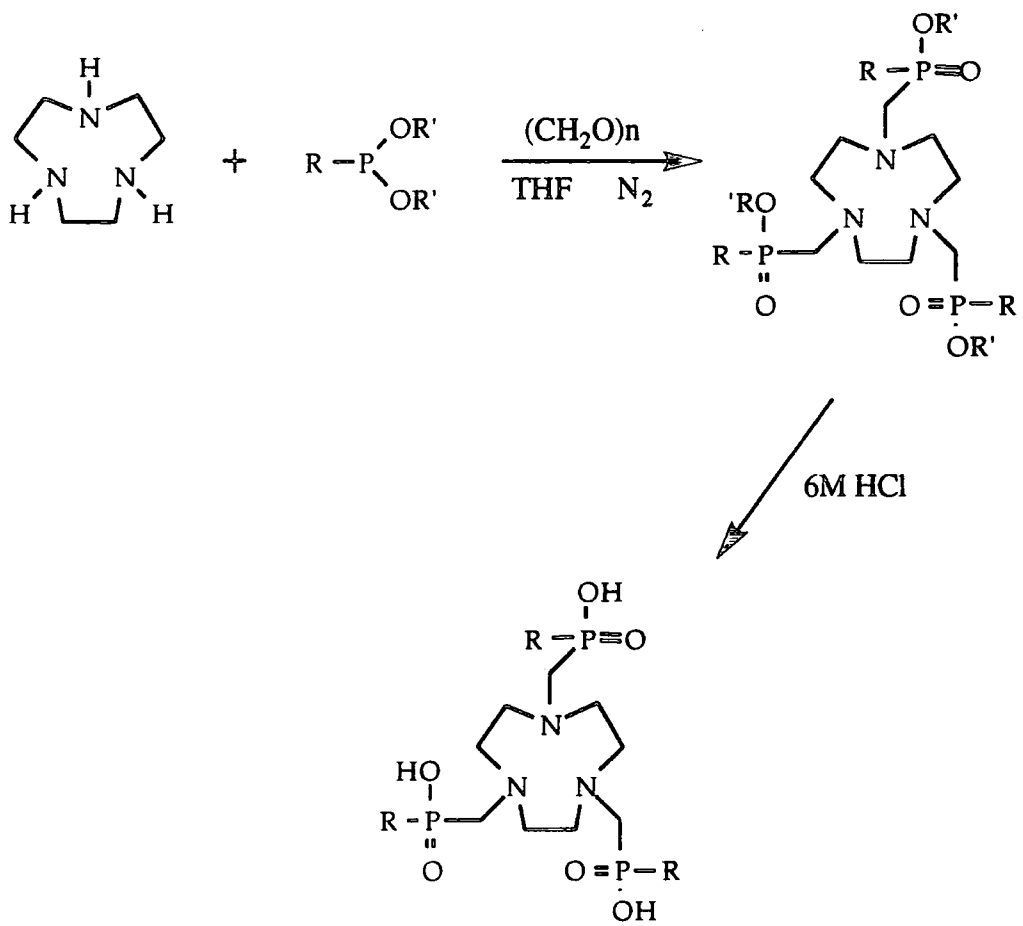
46 1,4,7-Triazacyclononane-N,N',N''-triacetic acid [NOTA]

3.1 Synthesis

The route shown in scheme 3.1 could be used to obtain pure samples of each of the acids. The esters are synthesised under dry conditions and can be purified by column chromatography, on alumina. Hydrolysis under acidic conditions (6M HCl, 110°C) yields the acids, in excellent yield.

3.1.1 P-Methyl Substitution (NOTPMe)

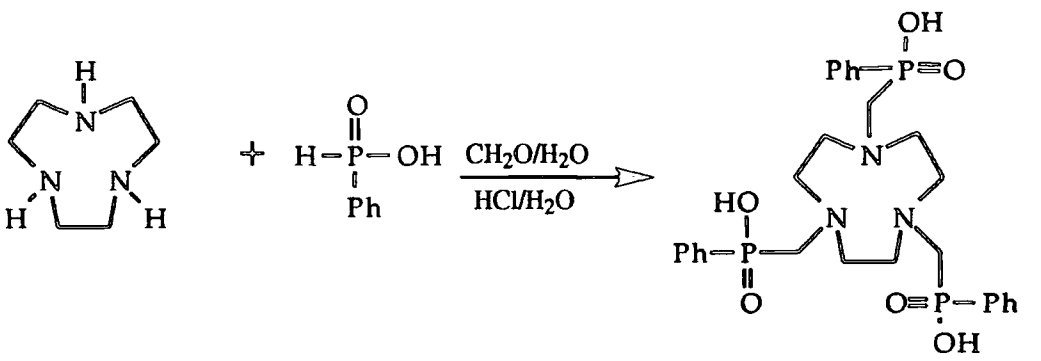
The phosphine $MeP(OEt)_2$ used to synthesise the ester was obtained from Aldrich and could be used without further purification, although ^{31}P and ^{1}H NMR spectra of the sample were obtained to confirm its purity. Purification of the triethyl ester had to be carried out by column chromatography as purification of the acid proved to be difficult by crystallisation.



	47	R=Me R'=Et	50	R=Me	NOTPMe
Scheme 3.1	48	R=Ph R'=Me	51	R=Ph	NOTPPh
	49	R=Bz R'=Et	52	R=Bz	NOTPBz

3.1.2 P-Phenyl Substitution (NOTPPh)

There were two routes that could be used to synthesise this acid. The reaction scheme 3.1 gave a pure sample of the triester that could be hydrolysed to give a pure sample of the acid.

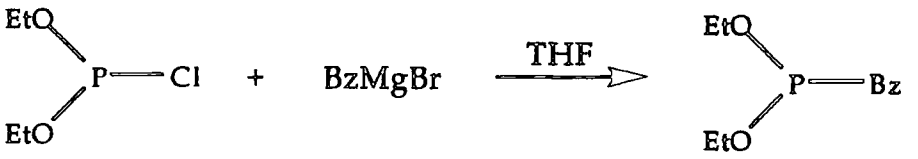


Scheme 3.2

An alternative route is shown in scheme 3.2. This gave an impure sample of the acid. Purification of this sample was attempted by a variety of methods (selective crystallisation in water and alcohols) without success. However this crude material could be used to form complexes. The amount of acid present could be estimated from the ^{31}P NMR spectrum and this was used when calculating the amount of metal to be added. The complexes crystallise without contamination from the impurities present in solution.

3.1.3 P-Benzyl Substitution (NOTPBz)

This derivative was made by the reaction shown in scheme 3.1. The phosphine in this case had to be made rather than purchased, (scheme 3.3). Purification by distillation under reduced pressure gave a sample of phosphine that could then be used, directly.



Scheme 3.3

Again, the macrocyclic triphosphinate ester had to be purified before hydrolysis to the acid, as with the other derivatives, as at the acid stage purification was difficult.

3.2 Protonation Constants

The protonation constants in the pH range 3 to 10 were determined by potentiometric titrations followed by 'Superquad'[1] data analysis, as discussed in chapter 2. The ionic strength was maintained constant at 0.1M using tetramethylammonium nitrate solution, at 25°C.

3.2.1 NMR Titrations

The first pKa value (pK_1, for nitrogen protonation "in" the ring) is too high to determine by potentiometric titration methods, but can be found by ^{31}P NMR titrations. Tetramethylammonium hydroxide was used to adjust the pH of the solutions, the tetramethylammonium ion was used as a large non-complexing cation. The ^{31}P NMR spectra of solutions of the ligands at different, but known, pH values give singlets with different shifts. These can then be plotted and the pKa obtained (+/- 0.15).

When preparing solutions of ligands based on 1,4,7-triazacyclononane and 1,4,7,10-tetraazacyclododecane it was found

necessary to leave them for 72 hours to allow the equilibrium to be established. During this time the addition of more base was often required. The pH values of all the solutions were taken before and after the spectra were recorded to eliminate any error due to drifting.

$$pD = pH \text{ meter reading} + 0.4$$

Figure 3.1 Convertion to pD using a standard electrode.

The titrations could be carried out in either D_2O or H_2O. The pD of these solutions was measured using a standard electrode[2] calibrated for H_2O solutions and converted to a pD using the equation in figure 3.1.

3.2.2 $9N_3$ Derivatives

Ligand	pK_1	pK_2	pK_3
NOTP [a]	11.79	8.65	7.09
NOTA [b]	11.7	5.7	3.2
NOTPPh [c]	12.2	6.66	3.86
NOTPMe [c]	12.1	7.76	3.75

Table 3.1 Protonation constants for selection of $9N_3$ based ligands.

a) Further values 5.38, 2.53, <2.

Data taken from ref 3.

b) Data taken from ref 4.

c) This work

The pKa values shown in the table above do not seem to follow the expected trend of phosphinic acids being more acidic than their carboxylic derivatives. However it is quite possible that while pK_3 for NOTA is an

oxygen protonation, for NOTPPh and NOTPMe, the third ring nitrogen is being protonated. The phosphinate oxygens are not protonated in the pH range, in accord with their higher acidity. Notwithstanding this effect, the higher nitrogen protonation constants (pK_1 and pK_2) are somewhat surprising given that in acyclic amino-phospinates, the effect of the phosphinate group is to lower the nitrogen basicity.

The first three protonation constants for NOTP with phosphonic acid binding groups are higher than those for the other derivatives. The nitrogen atoms are more basic with the phosphonic donor groups.

3.2.3 1,4,7,10-Tetraazacyclododecane based Ligands

Ligand	pK_1	pK_2	pK_3	pK_4
DOTP [a]	12.11	11.52	8.46	7.28
DOTA [b]	12.09	9.68	4.55	4.31
DOTPPh [c]	11.7	7.44	6.23	2.28
DOTPMe [c]	11.3	8.12	3.66	(2.1)

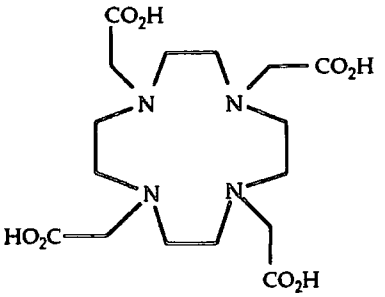
Table 3.2 Protonation constants for some DOTA analogues.

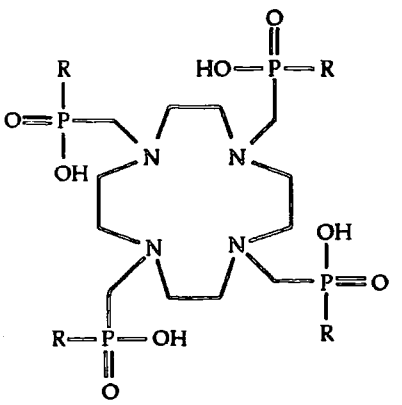
a) Following values: 5.73, 4.88, < 2, < 1. (I=1M, KNO_3) Data taken from ref 5.

b) Data taken from ref 6.

c) This work

It can be seen that the protonation constants of the phosphinic acid derivatives are lower than the carboxylic analogues. This is expected, and fits the trend seen with the acyclic ligands. However the third pKa value of DOTPPh is rather high while the fourth pKa values is lower than that of the others. Presumably the diprotonated ring in DOTPPh is adopting a different conformation (due to unfavourable steric interactions between P-phenyl groups) that exposes the third nitrogen of the ring to a proton.





53 54 R=Me 55 R=Ph 56 R=OH

53 1,4,7,10-Tetraazacyclododecane-N,N',N",N'"-tetrakis(acetic acid) [DOTA]

54 1,4,7,10-Tetraazacyclododecane-N,N',N",N'"-tetrakis(methylene(methylphosphinic)) acid [DOTPMe]

55 1,4,7,10-Tetraazacyclododecane-N,N',N",N'"-tetrakis(methylene(phenylphosphinic)) acid [DOTPPh]

56 1,4,7,10-Tetraazacyclododecane-N,N',N",N'"-tetrakis(methylene(phosphonic)) acid [DOTP]

A differing set of pKa values for DOTP were published by Kaden and coworkers[7] in 1990. They used conditions different to those of the Russian group,[5] (I = 0.1M, tetramethylammonium nitrate) and obtained the following values; 13.7, 12.2, 9.28, 8.09, 5.22. The first two values are very high and were obtained from ^{1}H NMR titration data.

3.2.4 NMR Titration Results for 1,4,7-Triazacyclononane based Ligands

A plot of δ_p vs pH revealed the highest pKa values for removal of the last proton from the ligand. The high value would be expected if the proton was acting as a small cation and partially binding to the three ring nitrogens.

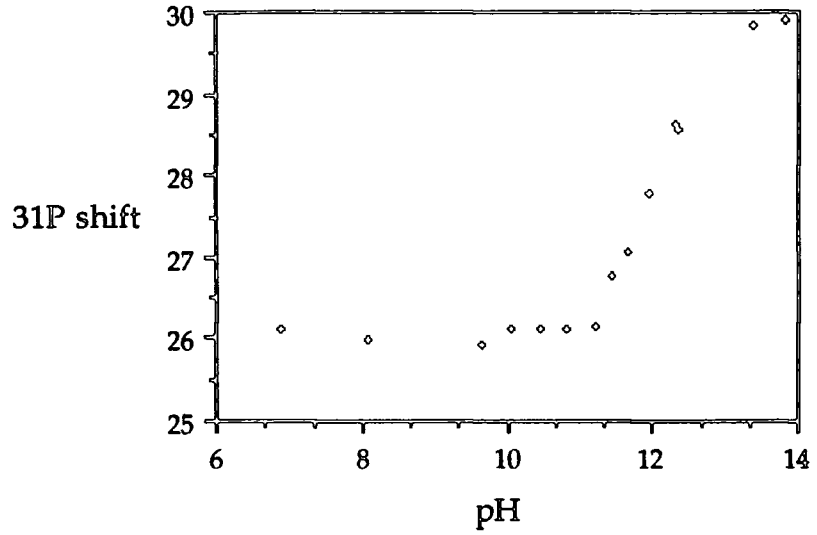


Figure 3.2 Showing the highest pKa value for the ligand NOTPPh as 12.2. (293K, I=0.1)

3.2.5 NMR Titration Results for 1,4,7,10-Tetraazacyclododecane based Ligands

The high first pKa for a $12N_4$ ring is not unexpected as the positive charge may be delocalised over each of the four nitrogens. This was found to be the case for DOTPPh, the plot of δ_p vs pH (figure 3.3) also shows the second and hints at a third pKa value for the ligand DOTPPh, these occur too close together to be separated by NMR techniques although they were distinguishable by potentiometric titrations.

These plots were repeated using sodium hydroxide as the base and sodium nitrate to maintain the ionic strength. When sodium is used as the cation, it is expected that the pKa values will all be lowered because sodium is competing with the proton for binding to the ligand heteroatoms. Hence if there is a pKa value above 12.5 it will be found. The final plot showed that there was not a higher value, but it did confirm the lower pKa values already obtained.

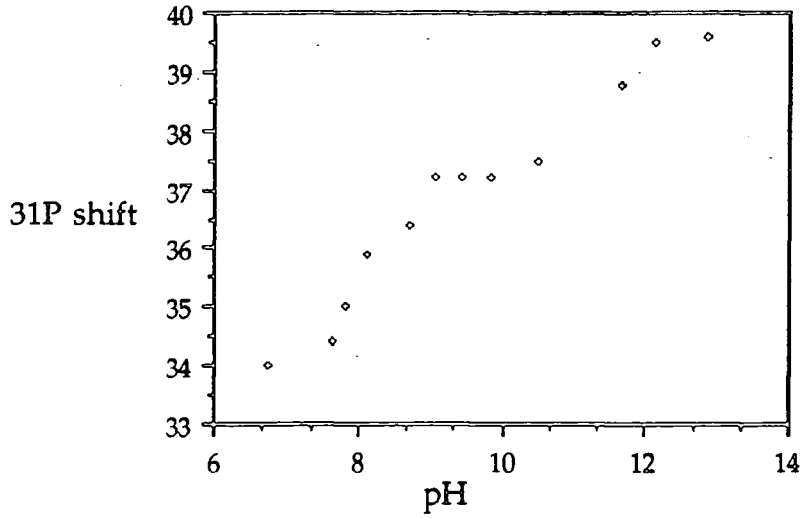


Figure 3.3 Showing two highest pKa values for the ligand DOTPPh.

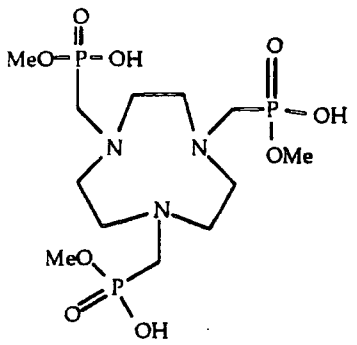
(293K, I=0.1)

3.3 Stability Constants

The ML, MLH and MLH_2 constants for the formation of complexes were determined by potentiometric titrations, as for the protonation constants. In each case an equivalent concentration of the metal was added to each solution before the titration was started. The direct method of potentiometric titrations used to determine the stability constants of the complexes does not work when equlibrium is very slow to be reached and for very stable complexes. Martell[8] found stability constants for NOTA complexes with Fe III , Ga III and In III of 28.3, 30.98 and 26.2. Spectrophotometry was used for the gallium and iron complexes while ligand competition experiments were needed to establish the indium constant.

3.3.1 Complexes with 1,4,7 Triazacyclononane based Ligands

The magnesium complexes of NOTPPh and NOTPMe are more stable than those of NOTA, perhaps due to the phosphinate oxygen being a stronger σ-donor group than a carboxylic oxygen for the polarising charge dense cation.



57

57 TriMethyl-1,4,7-triazacyclononane-N,N',N''-tris(methylenephosphonic) acid [NOTPM]

It can be seen from table 3.3 that there is no pattern in the stability constants for complexes with pendant arm ligands based on 1,4,7-triazacyclononane. The values for magnesium and calcium are similar for NOTA and NOTPM complexes. However the NOTA complexes are more stable by several orders of magnitude. The ligand NOTP appears to show a significant selectivity for magnesium over calcium.

The two phosphinic ligands both behaved in different ways. NOTPPh had two similar values for the stability constants with calcium and magnesium, although they were higher than those previously seen. However NOTPMe was again seen to show a high selectivity towards complexes with magnesium.

Ligand	Ca 2+	Mg 2+
NOTPPh a	11.48(25)	11.32
NOTPMe a	5.66	11.12
NOTA [b]	8.92(1)	9.69(3)
NOTP [c]	6.4	11.0
NOTPM [d]	5.1	6.2

Table 3.3 Calcium and Magnesium log binding 1:1 constants with a selection of $9N_3$ based ligands.

a) This Work

b) Data taken from ref 4.

c) Data taken from ref 3.

d) Data taken from ref 9.

3.3.1.1 Complexes formed by 1,4,7-Triazacyclononane-N,N',N''-Tris(methylene(methylphosphinic)) acid

	Ca^{2+}	Mg^{2+}
Log K_{ML}	5.66	11.12
Log K_{MLH}	-	7.29

Table 3.4 Stability constants for NOTPMe complexes

The same trend can be seen with the methyl substituted phosphinic acid as is displayed by the phosphonic analogue. The anionic oxygens attached to the phosphorus atoms are apparently better σ-donors for charge dense ions and hence increases the ability of the ligand to bind magnesium.

The best model to fit the magnesium titration data gives the constants for formation of the 1:1 complex and of the protonated form.

The model including MLOH (which has been found with other phosphinate ligands) as one of the products, was found not to fit and gave a species distribution plot that was not chemically reasonable. The data for the calcium complex gave only the Log K_{ML} constant. The selectivity for magnesium over calcium seen here has previously been observed in the NOTP system[3].

3.3.1.2 Complexes formed by 1,4,7-Triazacyclononane-N,N',N''-Tris(methylene(phenylphosphinic)) acid

	Ca^{2+}	Mg^{2+}
Log K_{ML}	11.48	11.32
Log K_{MLH}	6.68	7.18
Log K_{MLH2}	3.69	5.0

Table 3.5 Stability constants for NOTPPh complexes.

The stability constants for the two complexes can be seen to be very similar, table 3.5, that is no selectivity is displayed by NOTPPh between the dicationic ions of calcium and magnesium. The main difference that can be seen is in the protonation of the two complexes. It appears that the magnesium complex is harder to successively protonate than the calcium complex.

3.3.2 Complexes with 1,4,7,10-Tetraazacyclononane based Ligands

The ligands in table 3.6 are all able to form eight coordinate complexes. It can be seen that with DOTA and DOTP stronger complexes are formed with calcium than magnesium. DOTA shows the greatest stability with a selectivity for calcium over magnesium of five orders of

magnitude. DOTP follows the same pattern but both of the complexes are weaker.

Ligand	Ca^{2+}	Mg^{2+}
DOTA [a](Log K_{ML})	17.23(1)	11.92(1)
Log K_{MLH}	8.68	3.92
Log K_{MLH2}	3.11	-
DOTP [b](Log K_{ML})	10.3	7.3
Log K_{MLH}	7.7	6.0
Log K_{MLH2}	4.7	3.2
DOTPMe [c](Log K_{ML})	11.96	13.01
Log K_{MLH}	6.92	8.02
Log K_{MLH2}	4.75	-
DOTPPh [c] (Log K_{ML})	8.72	not
Log K_{MLH}	7.15	determinable
Log K_{MLH2}	3.26	

Table 3.6 Stability constants for 1:1 complexes between alkali earth metals and ligands based on $12N_4$

a) Data taken from ref 6.

b) I = 1.0 M, KNO_3: Data taken from ref 5.

c) This work

At the outset it was expected that the phosphinic ligands would follow the same pattern with values around those of the phosphonics. DOTPMe forms relatively strong complexes with both cations giving similar stability constants with that of magnesium being slightly higher. In comparison, the DOTPPh complex with calcium is relatively weak,

while the stability constant for the magnesium complex could not be determined. This could be due to a steric effect of the phenyl substituents or slow formation of the complexation equilibrium.

3.4 Complex Structures

It has only been possible to grow crystals of the complexes between $9N_3PPh_3$ and the first row transition metals, iron to zinc, and of gallium and indium. This study has raised several interesting points;

i) the structure adopted appears to be dependent on the charge on the molecule, (anionic versus neutral complexes)

ii) the hydronium ion is the counterion to the anionic charge of the complex with a divalent cation, despite the presence of sodium in the solution,

iii) the presence of only one pair of enantiomers, [ie one diastereoisomer (RRR/SSS) in 50:50 ratio form selectively]

iv) the presence of five waters of crystallisation within the unit cell, in each case.

Before considering the complex structures in detail, some general considerations related to the structures will be discussed:

3.4.1 Formation of Chiral Centre on Complexation

Figure 3.4 shows the chelate ring that forms when a complex is formed. In the free ligand there is no chiral centre at phosphorus, however when a complex is formed the configuration at the phosphorus atom becomes either R or S. The phosphorus substituent will either be pointing in a forward or backward direction. For any one molecule of complex, it was found that the phosphorus atoms were of the same

configuration. That is the pair of enantiomers that are seen are either (R,R,R) or (S,S,S). For the diamagnetic complexes, it was also apparent from their ^{31}P NMR spectra that only one diastereoisomer was present in solution The diastereiomers (R,R,S) or (S,S,R) are not seen in the crystal structures. This is probably due to the steric effect of the large phenyl rings, once one of the phosphorus-oxygen-metal has formed, the other two will twist in the same direction.

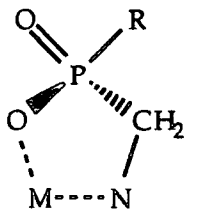


Figure 3.4 Chelate ring with stereogenic centre at phosphorus

3.4.2 Jahn-Teller Effect

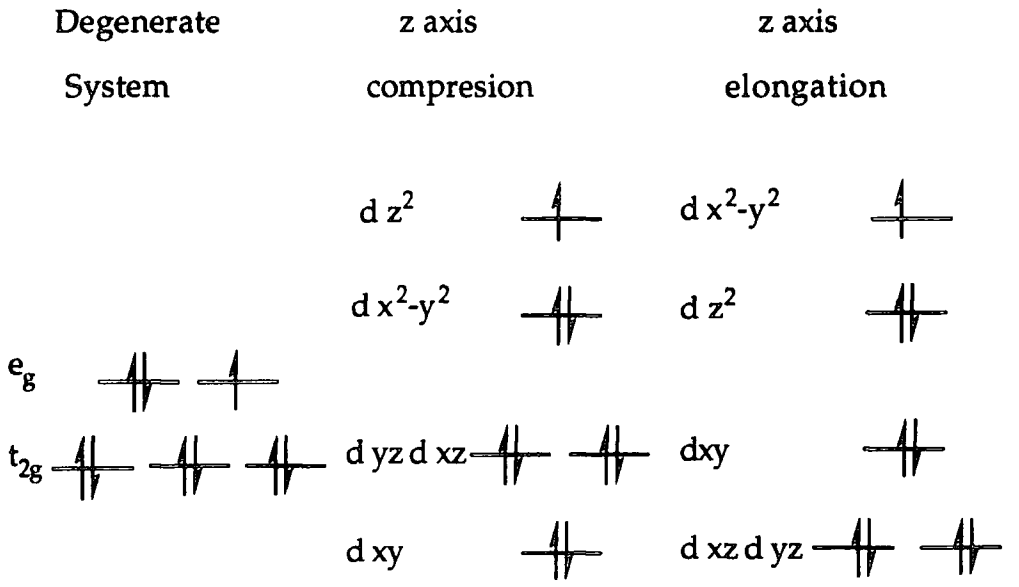


Figure 3.5 Showing the orbital arrangement for a d^9 electronic configuration and the possible distortions to stabilise the system.

The Jahn-Teller effect may be summarised as follows:

"If degenerate orbitals are unsymmetrically occupied then loss of degeneracy will occur to lower the energy and increase stability of the system."

The Jahn-Teller effect does not dictate what sort of distortion will be seen, only that some distortion will occur. It allows the observed phenomenon to be explained, according to the type of structure. This is most frequently seen in copper (II) complexes with the d^9 electronic configuration. However it can also be seen in d^1, d^2 and d^7 systems, for example titanium (III) with a d^1 electronic configuration.

For copper (II) complexes this means that the observed structures are usually distorted octahedra or are square planar with two axial sites filled by ligands positioned at a greatly increased distance. Exceptions to this are known where the ligand can induce copper to adopt a more symmetrical environment[10,11].

Lingafelter and coworkers in 1970 found[12] an early example of this and since then crystallographic evidence for several other examples have been found including $[Cu(en)_3]^{2+}$[10] and $Cu(phen)_3(NO_3)_2$ complexes. These examples have always had the same donor atoms, either all nitrogen atoms or all oxygen atoms. The lack of a room temperature distortion has been termed the "Dynamic Jahn-Teller" effect[13]. It is seen when the energy levels of the system are sufficiently close together to allow transitions to occur between the electronic structures and hence no overall distortion is seen. If the temperature of the system is lowered it is usually possible to *freeze-out* this effect so that a distortion can be seen.

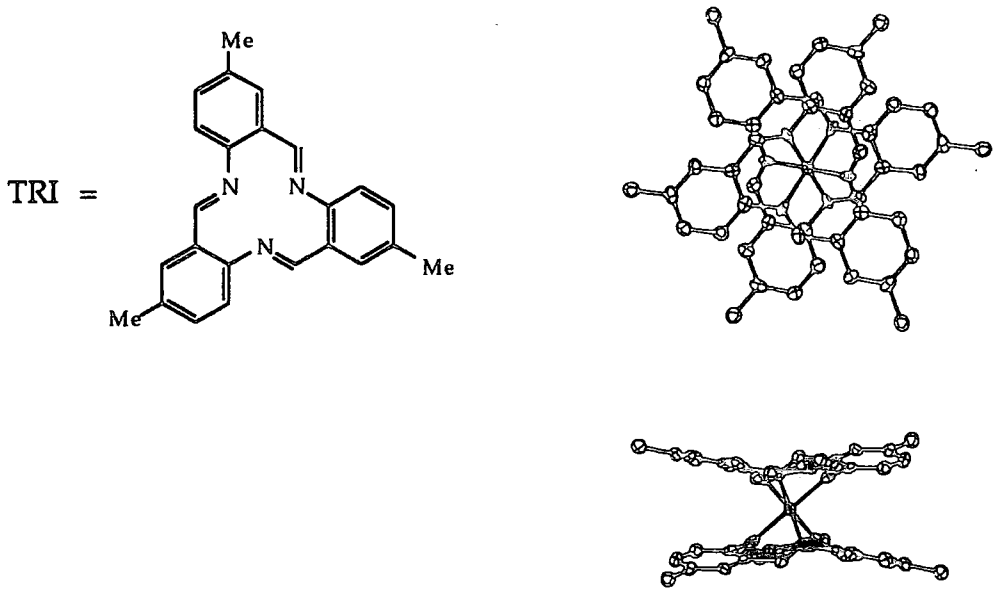


Figure 3.6 Structure of TRI and $Cu(TRI)_2$ Complex Taken from ref 11

3.4.3 Twist Angles

The twist angle of the complex is defined in the diagram below. Where $\theta = 0°$ the structure is a trigonal prism and when $\theta = 30°$ then it is a regular octahedral structure. It is rare to obtain the extreme cases and slightly distorted forms are more common. When $\theta > 20°$ it is termed 'pseudo octahedral' consequently $\theta < 20°$ is termed 'pseudo trigonal prismatic'.

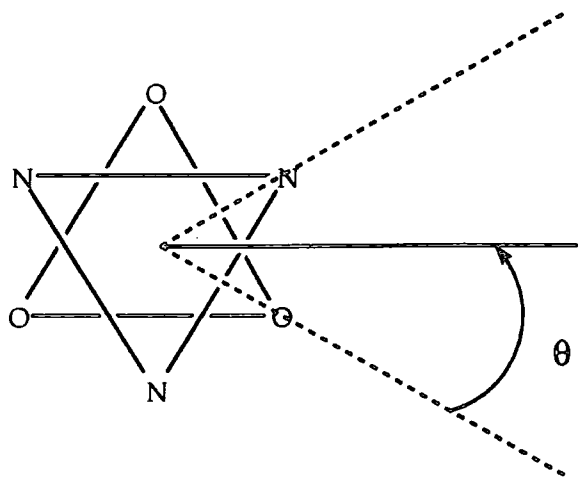


Figure 3.7 Defining the angle refered to as the twist angle.

Cation	$9N_3[CH_2PPhO_2]^-_3$	$9N_3[CH_2CO_2]^-_3$
Co II	25.3	-
Cu II	25.6	13.3 [a]
Ni II	25.45	22.5 [a]
Zn II	25.4	-
Fe III°	24.45	12.6 [a]
Ga III°	26.0	23.8 [b]
In III°	23.56	10.4*[c]

Table 3.7 Variation of twist angle (θ) for phosphinate and carboxylate $9N_3$ structures.

* Value for ligand with methyl substitution at the N-C-P carbon.

° Average of three values.

a) Data taken from ref 14.

b) Data taken from ref 15.

c) Data taken from ref 16.

The angles shown in table 3.7, for the P-Phenyl complexes are all very similar, having a distorted octahedral structure. The complexes with Ga III and In III could be considered to possess the geometry preferred by the ligand as they both have d^{10} electronic configurations with no ligand field effects present to perturb the complex geometry. However the other metals do have orbitals available for interaction with the ligand yet no change in conformation due to a preferred electronic configuration was seen.

For the copper II NOTPPh complex the octahedral form is adopted and is slightly favoured by electronic considerations. It is likely that this structure is associated with the preferred rigid confirmation adopted

by the ligand. On the other hand in the carboxylic acid analogue, NOTA, the strain on the ligand overrides this slight preference and a nearer prismatic structure[14] is adopted.

The gallium, indium and zinc complexes all have a d^{10} electronic configuration and are not affected by ligand field stabilisation energies. The structures seen are entirely due to ligand effects. So it could be concluded that the preference of the ligand for a pseudo octahedral structure is the effect that dominates in all cases.[17] This could partially be due to a steric effect with the phenyl rings orientating themselves in a minimum energy conformation, as far away from each other as possible.

If the system for describing macrocyclic structures put forward by Hancock and coworkers[18] is adopted, a type I structure (clockwise rotation) refers to twist angles of less than 15° while type II (anticlockwise rotation) refers to twist angles greater than 15°. This suggests that all the structures of NOTPPh complexes are of the type I category.

3.4.4 Bond Lengths

It can be seen for the data in table 3.8 that the metal-nitrogen bonds are all longer than the metal-oxygen bonds, consistent with the preference of a charged metal for an anionic donor.

In the $P\bar{3}$ structures (eg for copper II) the difference between the oxygen and nitrogen bonds is less than 0.147 Å suggesting that the metal sits well down on to the three nitrogens. The ionic radii of the cations are similar and the differences in bond lengths are small and could arise simply from crystal packing effects.

For the $P\bar{1}$ structures, the metal oxygen bonds are shorter by at least 0.208 Å, suggesting that the metal is sitting further above the N_3 plane in the cavity and closer to the oxygen atoms. This could be explained by the

cations with the greater charge being attracted more strongly to the anionic oxygens.

Cation	M-N	M-O	(M-N)-(M-O)	Ionic Radius Å
Co II	2.165(3)	2.103(2)	0.062	0.75
Cu II	2.134(3)	2.103(2)	0.031	0.73
Ni II	2.104(3)	2.083(3)	0.017	0.69
Zn II	2.219(1)	2.072(1)	0.147	0.74
Fe III*	2.205(3)	1.932(2)	0.273	0.65
Ga III*	2.135(6)	1.912(4)	0.223	0.62
In III*	2.303(1)	2.0947(9)	0.208	0.8

Table 3.8 Showing metal-nitrogen and metal-oxygen bond lengths (Å) from the crystal structures, and ionic radii for the six coordinate ion.

* Indicates a value that is the average of three.

Ionic radii taken from ref 36.

	1	2	3	4	5	6	7
Formula	$C_{27}H_{44}CuN_3O_{11}P_3$	$C_{27}H_{44}CoN_3O_{11}P_3$	$C_{27}H_{44}ZnN_3O_{11}P_3$	$C_{27}H_{44}NiN_3O_{11}P_3$	$C_{27}H_{43}GaN_3O_{11}P_3$	$C_{27}H_{43}FeN_3O_{11}P_3$	$C_{27}H_{43}InN_3O_{11}P_3$
fw	743.10	738.5	744.93	738.3	748.28	734.4	793.37
Colour	Blue	Pink	Colourless	Sea-blue	Colourless	Yellow	Colourless
Crystal System	Trigonal	Trigonal	Trigonal	Trigonal	Triclinic	Triclinic	Triclinic
a,Å	14.399(3)	14.428(1)	14.412(2)	14.356(1)	11.883(3)	11.941(7)	12.061(3)
b,Å	14.399(3)	14.428(1)	14.412(2)	14.356(1)	12.468(4)	12.427(8)	12.261(2)
c,Å	9.023(17)	8.911(5)	8.937(3)	9.042(6)	11.842(5)	11.967(9)	12.128(4)
α,deg	90	90	90	90	99.39(3)	98.525(6)	96.69(2)
β,deg	90	90	90	90	98.47(3)	99.522(6)	101.24(2)
γ,deg	120	120	120	120	79.97(2)	79.155(2)	77.72(2)
V,Å^3	1620.0(4)	1605.0(7)	1607.5(6)	1613.9(2)	1691.7(1.0)	1707.7(2)	1713.5(7)
Z	2	2	2	2	2	2	2
D_C,gcm^{-3}	1.522	1.528	1.539	1.519	1.47	1.43	1.538
space group	P-3	P-3 (147)	P-3(147)	P-3	P-1	P-1	P-1
T,K	294	120	120	294	294	294	150
R	4.0	4.15	3.13	4.0	5.10	3.8	1.99

3.4.5 Comparisons with Carboxylic Analogues

It can be seen that the solid state structures of the complexes formed with NOTPPh are all very similar. The cationic complexes have an extra proton to neutralise the overall charge of the crystal. They all have a C_3 axis of symmetry, for the cationic complexes it is a true axis whereas for the neutral complexes there is a slight distortion from C_3 symmetry. The carboxylic complexes with the same range of cations are very different from each other.

3.4.5.1 Cobalt II Complex

The carboxylic complex formed with cobalt (II) has been reported and characterised by Weiss and coworkers[14] however crystallographic studies have not been undertaken. For the NOTPPh complex, a susceptibility to oxidation was seen, however this was not at a rate that caused problems with obtaining the crystal structure. The crystals of the Cobalt III NOTPPh complex were a dark blue/purple colour and could be deliberately formed by oxidation of the complex solution.

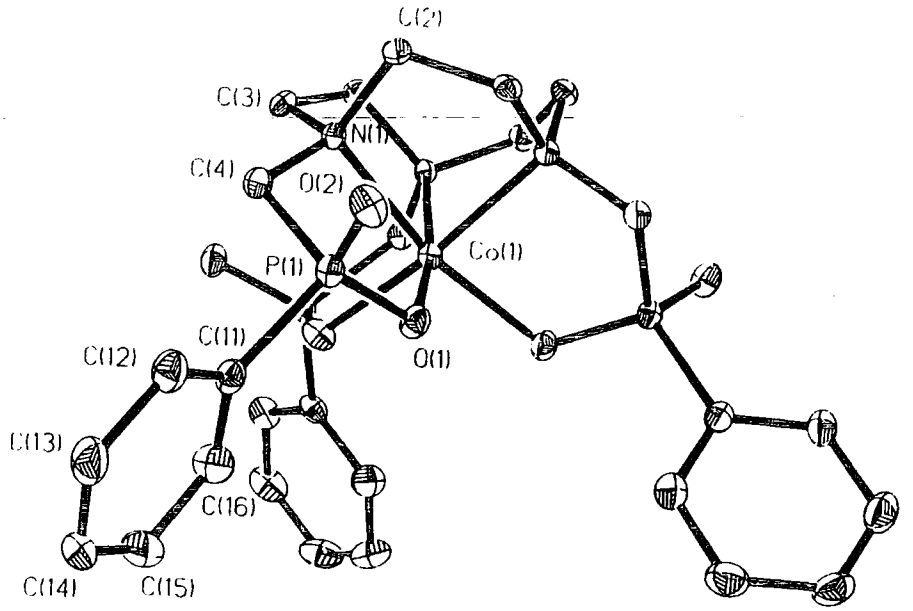


Figure 3.8 Structure of the Co (II) NOTPPh complex, view perpendicular to C_3 axis.

3.4.5.2 Copper II complex

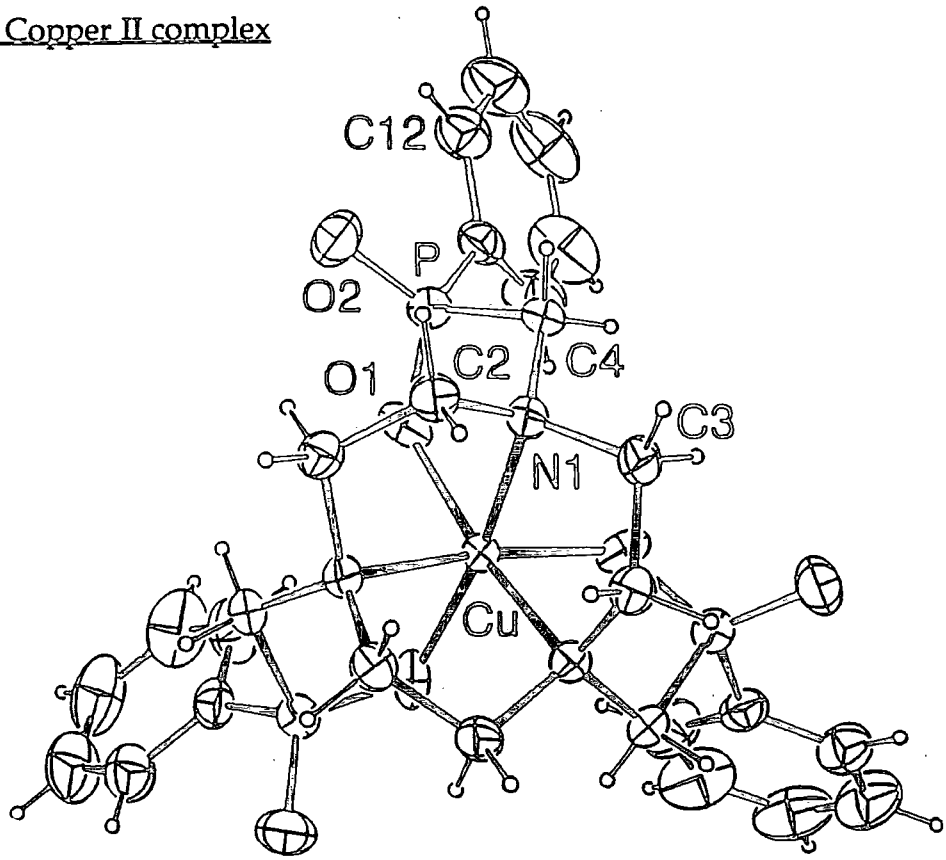


Figure 3.9 Structure of the Cu (II) NOTPPh Complex viewed down the C_3 axis.

The three fold axis that is seen in the copper structure indicates that a dynamic Jahn-Teller effect is observed. Unlike in previous examples, the donor set contains three oxygen atoms and three nitrogen atoms. The original crystal structure was obtained at 298K. A second data set at 123K was collected to determine whether the distortions could be seen at this temperature. No such effect was seen, with the structure which was still in the $P\bar{3}$ space group and no elongation of the thermal ellipsoids for the N and O donor atoms was observed.

The Electron Paramagnetic Resonance Spectra have been run at 298K and 8.6K. At 298K, the observed spectrum confirmed the high symmetry of the complex by showing only one g value. At 8.6K the EPR

spectrum gave 2 g values. This is indicative of a loss of C_3 symmetry and the onset of a Jahn-Teller distortion.

Complex	'Low temperature'	'High temperature'
$Cu(phen)_3(NO_3)_2$ [a]	g 2.273 g 2.062	g 2.134
$CuNOTPPh(H_3O)$ [b]	g 2.58 g 2.16	g 2.22

Table 3.9 g-values at varying temperatures for copper complexes displaying the dynamic Jahn-Teller Effect.

a) Low temperature 73K, High temperature 403K Data taken from ref 19.

b) Low temperature 8K, High temperature 298K. This work.

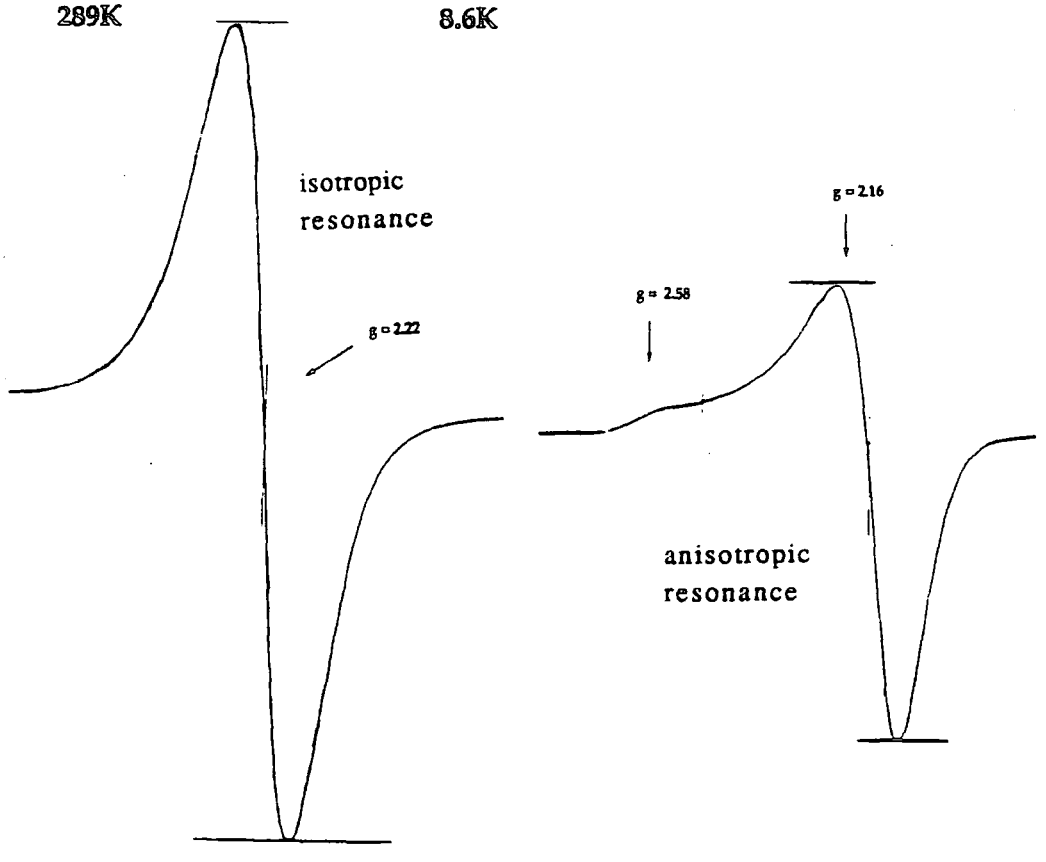
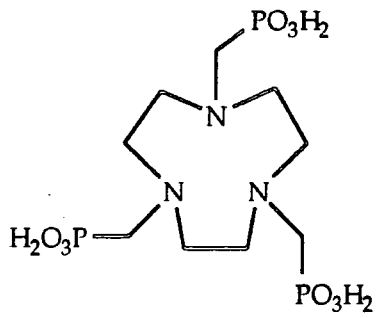


Figure 3.10 ERP spectra of the Cu II NOTPPh complex at 298 and 8 K.

This can explained in terms of energy levels. At room temperature the energy levels of the two states are close enough to have equal

occupancy. At 8K, the energy of the system is too low to allow the interchange between the levels to give the average symmetry so the lowest energy form is adopted with a Jahn-Teller disortion being seen.



58

58 N,N',N''-Tris(dihydroxyphosphorylmethyl)-1,4,7-triazacyclononane [NOTP]

If a comparison of the structures of the copper complexes with NOTA, NOTP and NOTPPh is undertaken several important differences can be seen. The N_3O_3 donor groups, for the complex between copper and NOTA[14] are not fully utilised as one of the oxygens does not bind to copper, and a five coordinate complex is observed figure 3.11.

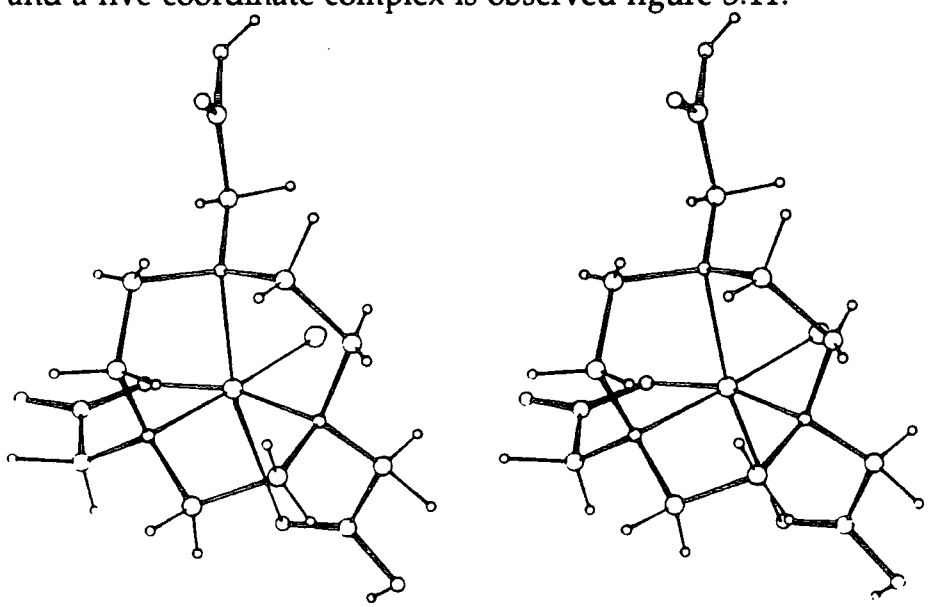


Figure 3.11 Structure of Cu(II) NOTA Showing the Non-complexed Pendant Arm

The complex with NOTP also behaves in this manner using only five of the six possible donor atoms[20]. It has one oxygen atom that is unfolded, out of the cavity, giving a structure reminiscent of a 'ladle'. The NOTPPh ligand gives the third possible structure with all six donor atoms being used to give a pseudo octahedral structure.

The copper II NOTP complex has bond lengths and a twist angle (23.7°) which are very similar to that of the NOTPPh complex. It could be suggested that two possible factors control the geometry of these complexes;

1) The strong electron donating properties of the P-O$^-$ groups.

2) The interactions between the other substituents at the phosphorus, either the large steric hindrance due to the phenyl rings or the dipolar interactions of the P-O-H and P=O bonds.

3.4.5.3 Nickel II Complex

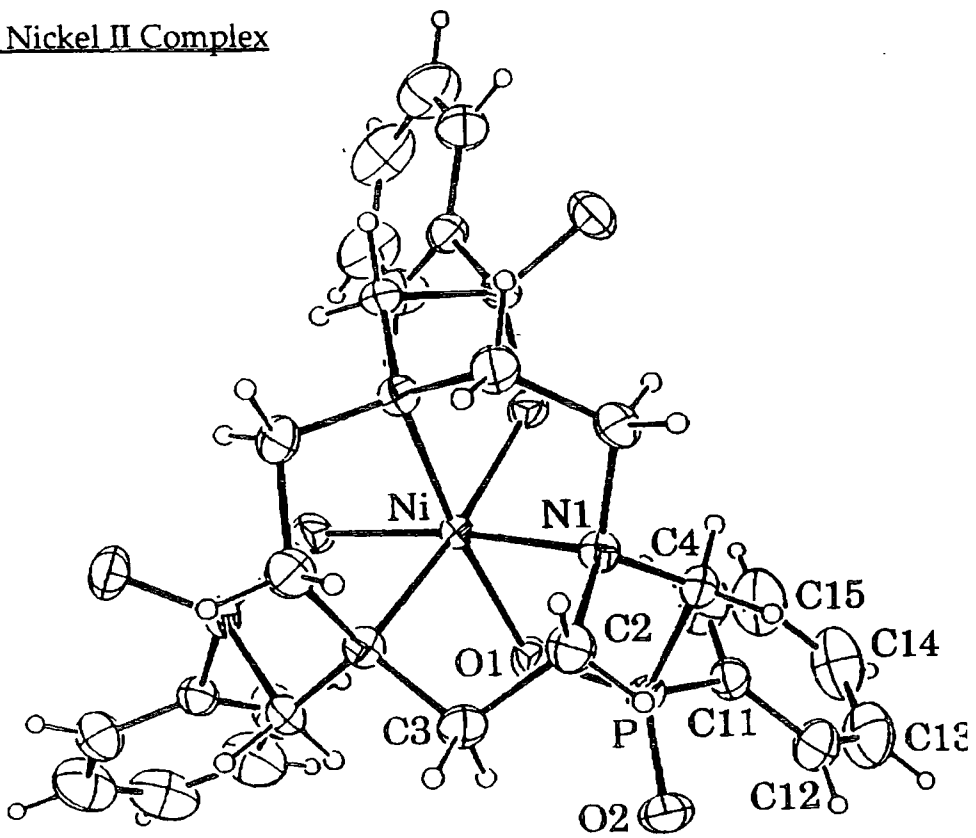


Figure 3.12 Structure of the Ni (II) NOTPPh Complex Viewed Along the C_3 axis.

Both the Nickel II and III [21] complexes with NOTA have been crystallised and studied. With NOTPPh it was not possible to oxidise the nickel to the III oxidation state, even after several weeks in nitric acid or hydrogen peroxide. This stability could be due to steric hindrance from the phenyl rings preventing approach of a reagent to carry out the oxidation. The twist angles for the complexes with NOTA and NOTPPh are very similar[21].

3.4.5.4 Zinc II Complex

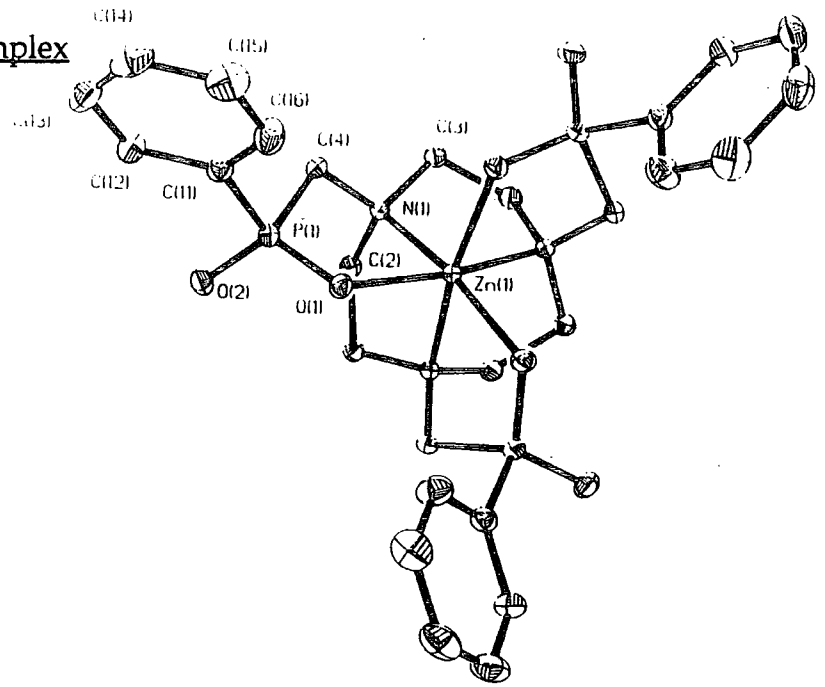
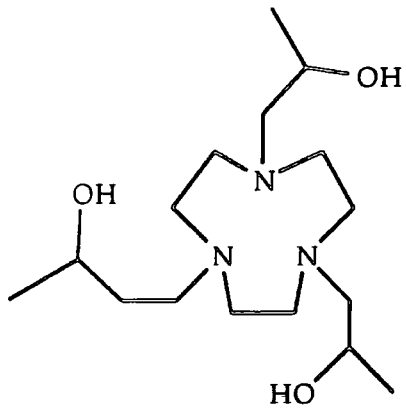


Figure 3.13 Structure of the Zn (II) NOTPPh complex, viewed along the C_3 axis.

The carboxylic acid $9N_3$ complex with zinc has not been studied by X-ray crystallography. A dimer between zinc and vanadium complexes with NOTP2A has been crystallised and studied by Peacock and coworkers[22].

The bond lengths from zinc to the binding groups, oxygen and nitrogen, are very similar. This was proposed to be due to the lack of potential for ($p\pi$-$d\pi$) orbital overlap between the metal and the oxygen

atoms. The corresponding vanadium complexes have a greater difference between the bond lengths with the bond to oxygen being 0.3Å shorter. However the NOTPPh complex has a difference in M-O and M-N bond lengths of 0.19Å, and no pπ-dπ orbital overlap is possible.



59

59 N,N',N''-Tris(2S)-2-hydroxypropyl-1,4,7-triazacyclononane [NOTP2A]

3.4.5.5 Iron III Complex

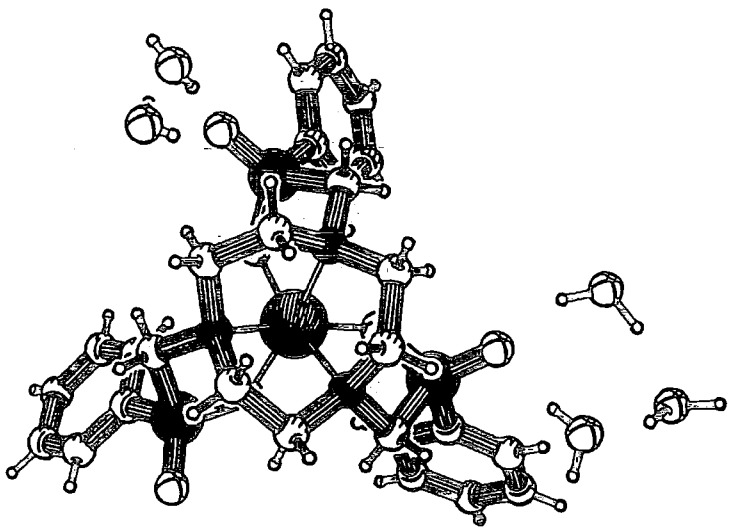
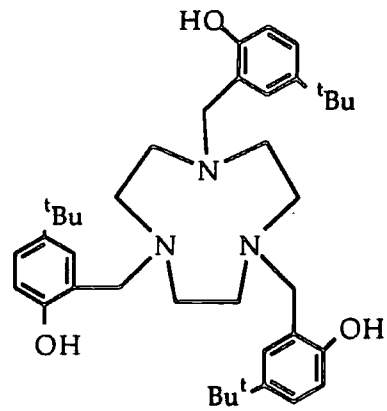


Figure 3.14 Structure of the Fe (III) NOTPPh complex showing the position of the five waters of crystallisation, viewed along the C_3 axis.

The NOTA complex with iron III has a small twist angle and is verging on having a distorted trigonal bipyramidal structure[14]. This is also seen with other iron complexes especially the catechol derivatives studied by Raymond[23], where a true trigonal bipyramidal structure with a twist angle of 0° is observed. This was proposed to be due to the weak pπ-dπ orbital overlap that can occur between the iron and oxygen donor atoms, so stabilising the trigonal bipryamidal structure.



60

60 N,N',N''-Tris(5-*tert*-butyl-2-hydroxybenzyl)-1,4,7-triazacyclononane [NOT5B2HB]

Complex	M-N	M-O
Fe III NOTPPh [a]	2.205(3)	1.932(2)
Fe III NOTP [b]	2.206(2)	1.945(2)
Fe III NOTA [c]	2.181(3)	1.962(2)
Fe III NOT5B2HB (aver. of 3) [d]	2.187	1.952
Fe III catechol deriv. [e]	n/a	2.015

Table 3.10 Iron to Oxygen and Nitrogen bond lengths for a range of hexadentate ligands.

a) This work. b) Data taken from ref 24. c) Data taken from ref 8.

d) Data taken from ref 25. e) Data taken from ref 23.

From the similarities in bond lengths between the ligands on table 3.7, it could be suggested that the Fe III NOTPPh complex is undergoing a similar type of pπ-dπ orbital overlap. However, in this case it is not causing the change in structure and the distorted octahedron is still observed. It is possible that the steric preferences of the ligand are greater so the "ligand preferred" structure is found.

3.4.5.6 Gallium III Complex

The neutral complexes formed with gallium between NOTA and NOTPPh are very similar.[15] They are both type I structures with twist angles >15° giving distorted octahedral structures. There are no electronic effects that can influence the structures adopted, so both display the structure favoured by the ligand.

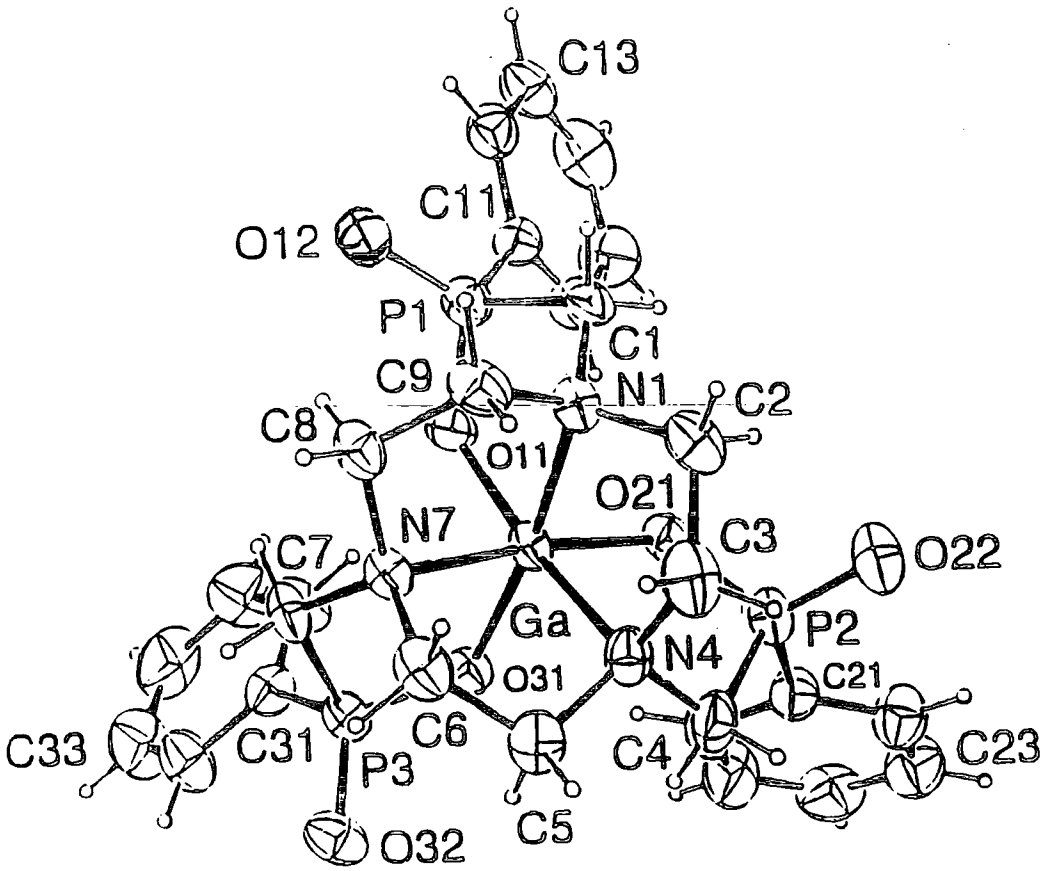
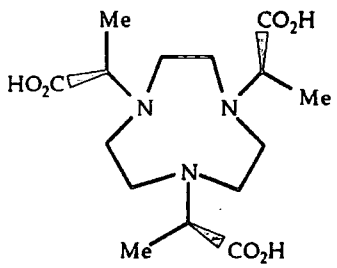


Figure 3.15 Structure of the Ga (III) NOTPPh complex, viewed along the C_3 axis.

3.4.5.7 Indium III Complex

The analogous structure with NOTA has not been obtained although the structure of the monohydrochloride complex[15], is known. This is a seven coordinate structure, with the chloride ion filling the seventh site on the cation. The overall structure is a distorted pentagonal bipyramid.



61

61 (*R*)-1,4,7-Tri(2'-methylcarboxymethyl)-triazacyclononane [NOTAMe]

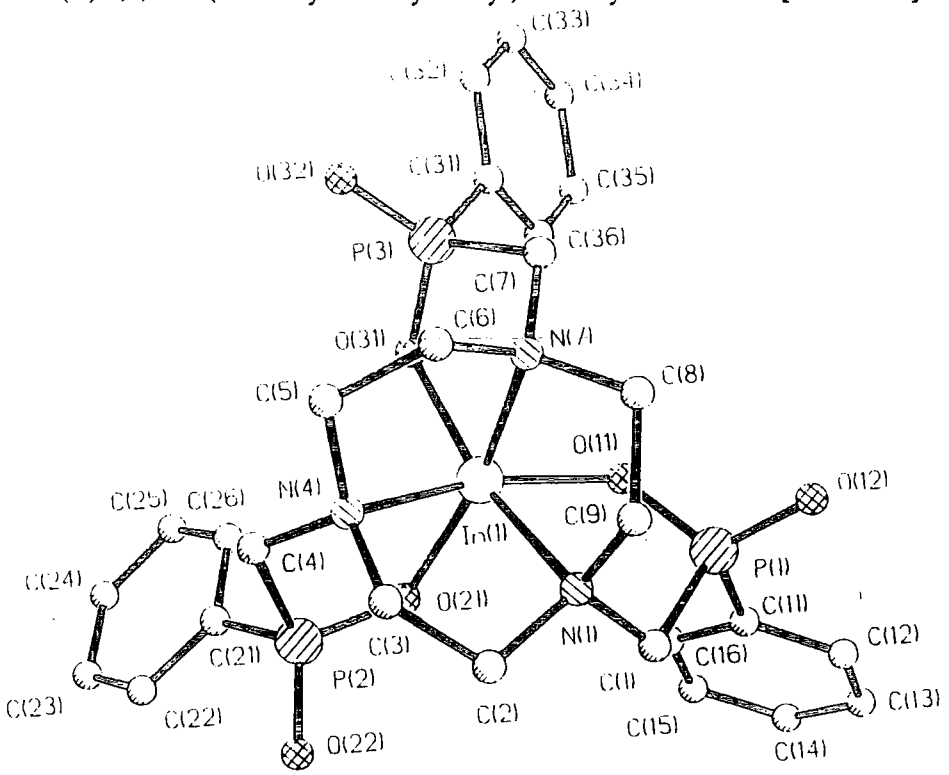


Figure 3.16 Structure of the In (III) NOTPPh complex, viewed along the C_3 axis.

The complex between NOTAMe and In III is six coordinate[16] using just the N_3O_3 donor set of the ligand. The structures of the two complexes are rather different. The In NOTAMe complex has a distorted trigonal prismatic geometry, similar to FeIII NOTA[14]. In contrast, the In NOTPPh complex possesses a distorted octahedral structure. However, the bond lengths in both complexes are similar, with the indium-nitrogen bond being longer than the indium-oxygen bond as expected, table 3.11.

Ligand	M-N	M-O
NOTAMe [a]	2.259(4)	2.096(4)
NOTPPh [b]	2.303(1)	2.0947(9)

Table 3.11 Indium-Donor bond lengths.

a) Data taken from ref 16

b) This work.

3.5 Spectroscopic studies of Complexes

3.5.1 Spectrophotometry

Cation	NOTPPh [a]	NOTA [b]
Ni II	610, 790	557, 805
Co II	521	500, 650
Co III	565	511
Cr III	437, 627	388, 512

Table 3.12 Comparison of UV/Visible spectrophotometric data, λ_{max}(nm).

a) This work b) Data taken form ref 14.

For the phenyl substitituted ligand it has been possible to form a wide range of complexes and these have also been studied by uv/visible spectrophotometry. Samples were run at 20°C in methanol at known concentrations.

3.5.1.1 Nickel and Chromium Complexes

The absorbances that are seen generally occur at a higher wavelength with the phosphinic acid complex, apart from the highest absorbance of the nickel NOTA complex. The complexes with NOTA, therefore, have a stronger inherent ligand-field.

3.5.1.2 Copper

The complexes between copper and each of the P-Me, P-Ph and P-Bz ligands were synthesised and their uv/visible spectra obtained. The concentrations of the solutions were all approximately 0.01 molar, exact concentrations were known, so that the extinction coeficients (ε) could be determined.

Substituent at phosphorous	λ_{max} (H_2O pH 3.5) nm	ε
Me	710	
Ph	700	82
Bz	720	

Table 3.13 UV/Visible Spectrophotometry of the copper complexes with three phosphinate ligands.

Under the same conditions free copper nitrate has a λ_{max} at 760nm. The change of λ_{max} between the cation in solution and the cation/ligand mixture supports the idea that complexation is occuring. The copper is

fitting into an octahedral site with binding to three nitrogens and three oxygens.

The copper complex with the carboxylic analogue has been observed to undergo protonation at a lower pH, pKa = 2.77[4]. However the spectra of the copper complex with the phenyl substituted phosphinic acid have been studied in the range 2 to 9 and no change in λ_{max} was observed. This suggests that the phenylphosphinic derivative is more resistant to protonation than the carboxylic analogue, and has a pKa < 2.0. The occurrence of the H_3O^+ cation in the crystal structures of the divalent cations accords with the difficulty of protonating the phosphinate oxygen.

3.5.2 Gallium Complexes

3.5.2.1 Gallium NMR

The two comon stable isotopes of gallium both have a nuclear spin of 3/2 consequently it is possible to carry out ^1H, ^{13}C, ^{31}P and ^{69}Ga or ^{71}Ga NMR studies.

	I	% present	relative receptivity*
^{69}Ga	3/2	60.4	237
^{71}Ga	3/2	39.6	319

Table 3.14 Showing the natually occuring isotopes of gallium and their NMR properties.

* relative to ^{13}C

The ^{69}Ga spectra show a singlet of varying line width, in which the observed linewidth ($\omega_{1/2}$) may be related to the symmetry or the stability of the complex. Solutions of the complexes were made up in 6M HNO_3 and the ^{69}Ga NMR spectra was run within an hour of being made up and

then at monthly intervals up to six months. These studies were undertaken with the three ligands based on $9N_3$ the results being shown in table 3.15.

Substituent at Phosphorus	δ_{Ga} [a]	ω 1/2 (Hz)
Me	139.0	200
Ph	133.0	560
Bz	130.3	1220
NOTA [b]	171	210

Table 3.15 Results of gallium with the phosphinate ligands.

a) Samples were referenced externally to a sample of $Ga(NO_3)_3$ in 6M HNO_3.

b) Data taken from ref 15.

The methyl and phenyl derivatives showed no change over the six month time interval. The benzyl derivative behaved in a different way, after one month an additional peak at 0 ppm was seen as well as that due to the complex. The resonance at 0.0 ppm was due to free gallium in the solution. After two months most of the gallium was in this state with little of the complex remaining, showing that this complex was less stable than the other two.

The linewidth of the gallium resonance is proportional to the interaction of the electric-field gradient at the nucleus with the quadrupole moment. In complexes of high symmetry (eg $Ga(OH)_4^-$, $Ga(OH_2)_6^{3+}$ and C_3-symmetric complexes). the electric-field gradient at the nucleus is small and relatively sharp lines may be obtained. Slight deviations from highly symmetrical solution structures are manifested by an increased linewidth (assuming no other exchange processes are occurring which may affect the natural linewidth). Thus the complexes of

gallium (III) with NOTA and NOTPMe conserve C_3 symmetry in solution, while P-Ph and P-Bz analogues deviate increasingly from this symmetry.

3.5.2.2 Full Assignment of the Ga NOTPPh Complex

Using a range of 1 and 2 D. NMR methods it has been possible to fully assign the solution state structure of the gallium complex with the phenyl phosphinic acid ligand.

a) 1-D NMR Studies

In the ^{31}P NMR spectrum (293K, D_2O), a singlet is seen at 27.4ppm. In solution the complex exhibits a 3-fold axis. In the ^{1}H NMR spectrum run under the same conditions rather a complicated coupling pattern is seen. The integrals fit to the number of protons expected and suggest that the protons in each of the CH_2 groups round the ring and in the N-CH_2-P group are chemical shift nonequivalent.

In the ^{13}C NMR spectrum, all carbons were seen, however the two N-C-C-N ring carbon atoms were nonequivalent. The peak at 57.6 ppm was a doublet, this was due to P-C-N-C coupling where there is a torsion angle of approximately 180°. The other ring carbon has a P-C-N-C torsion angle of approximately 90° and only a singlet is seen, ie $J_{PC} < 1$ Hz.

b) 2-D NMR Studies

COSY

The aromatic protons were assigned by considerations of the appropriate coupling patterns and constants. The methylene protons were assigned by considering the coupling patterns, constants and observing

the carbon they were attached to. Application of the Karplus equation was required to assign axial and equatorial protons, figure3.17.

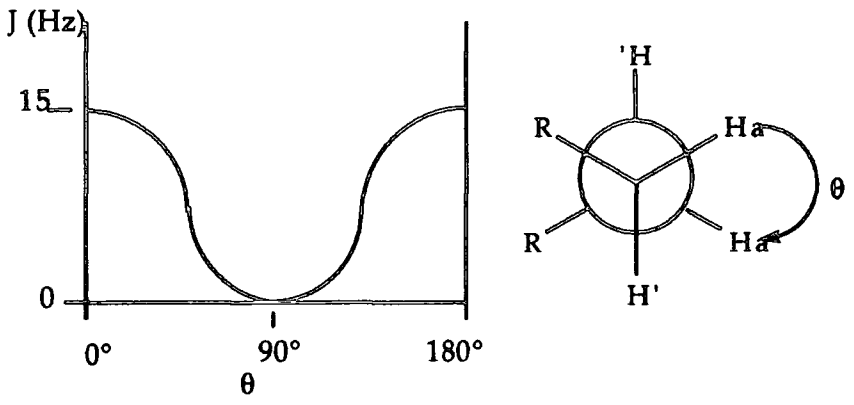


Figure 3.17 Plot of angle versus coupling constant from the simple Karplus Equation and definition of the angle

It could be seen (figures 3.18 and 3.19) that the two NCH_2CH_2N equatorial protons H_a and H_a' had a θ of 90°, hence would not be expected to couple to each other. This meant it was possible to distinguish the equatorial protons, with only two couplings from the axial protons which possess three.

Figure 3.18 COSY spectra of Ga III NOTPPh showing protons in the region (3-4 ppm).

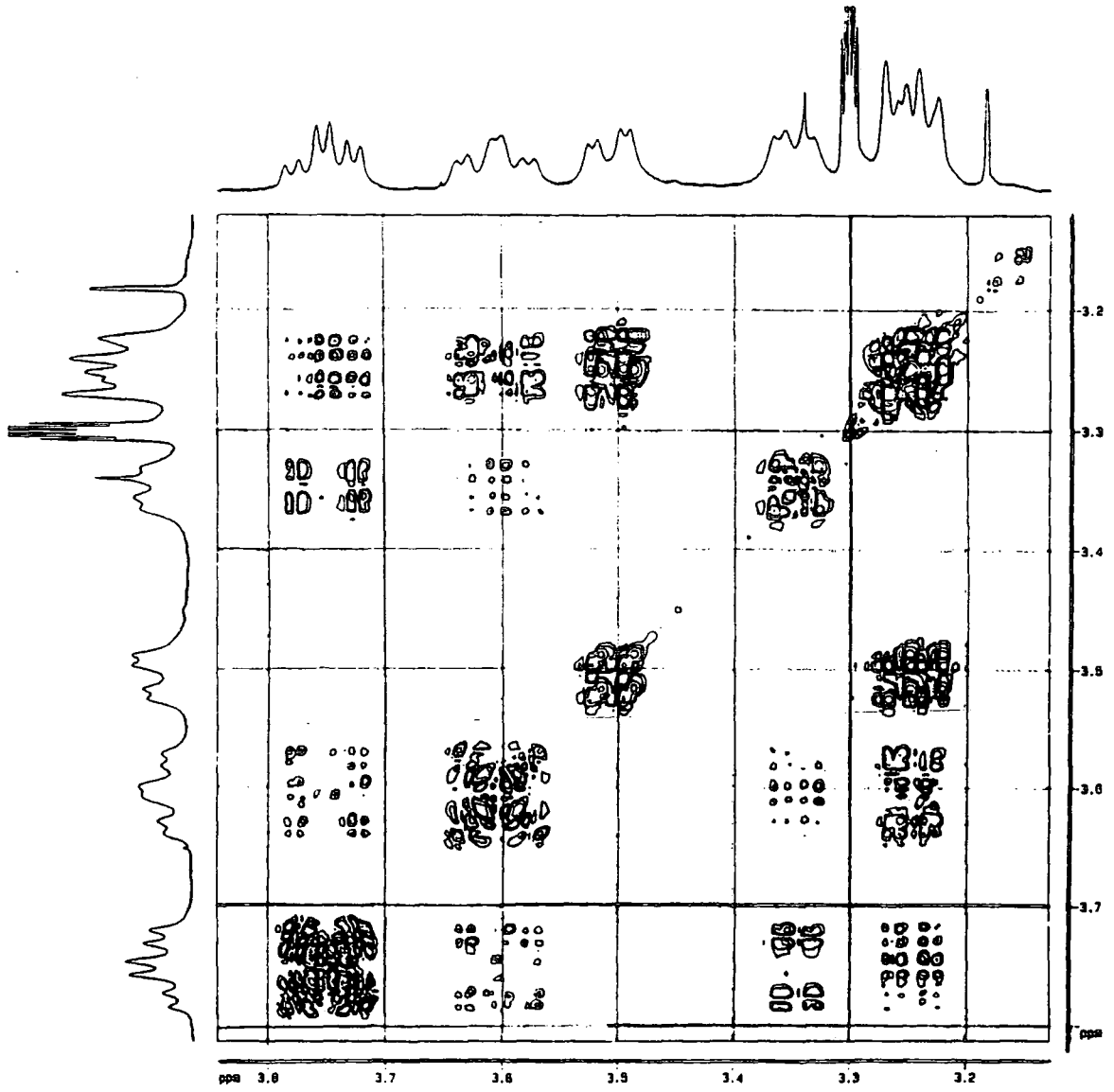
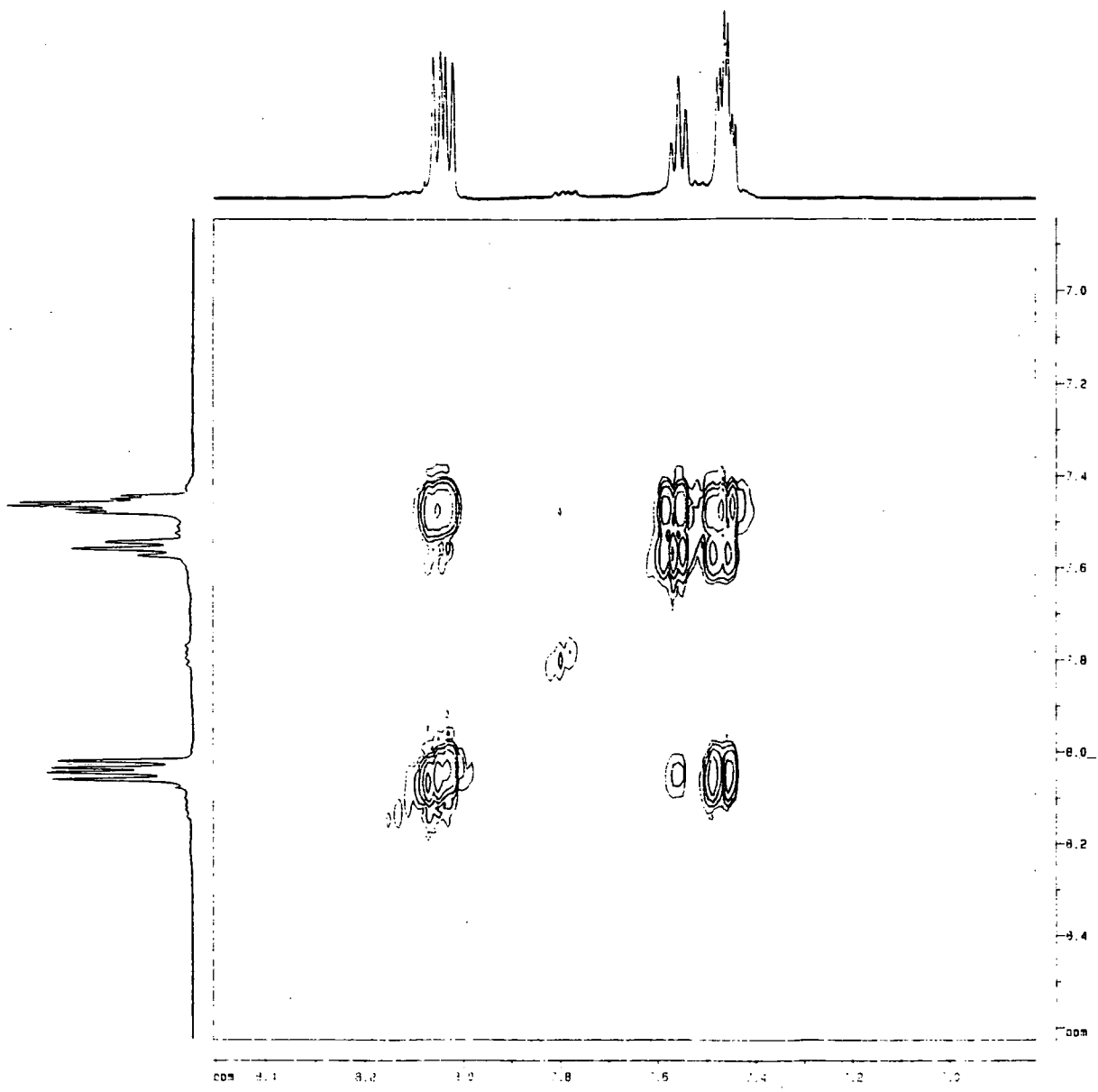


Figure 3.19 COSY spectra of Ga III NOTPPh showing protons in the region (7-8.4 ppm).



Heteronuclear Correlation

Having already established that the two ring carbons were non-equivalent and having distinguished each type of proton (axial, equatorial or C(1) diastereotopic,) it was possible to relate the solution structure to that obtained from the solid state crystal structure.

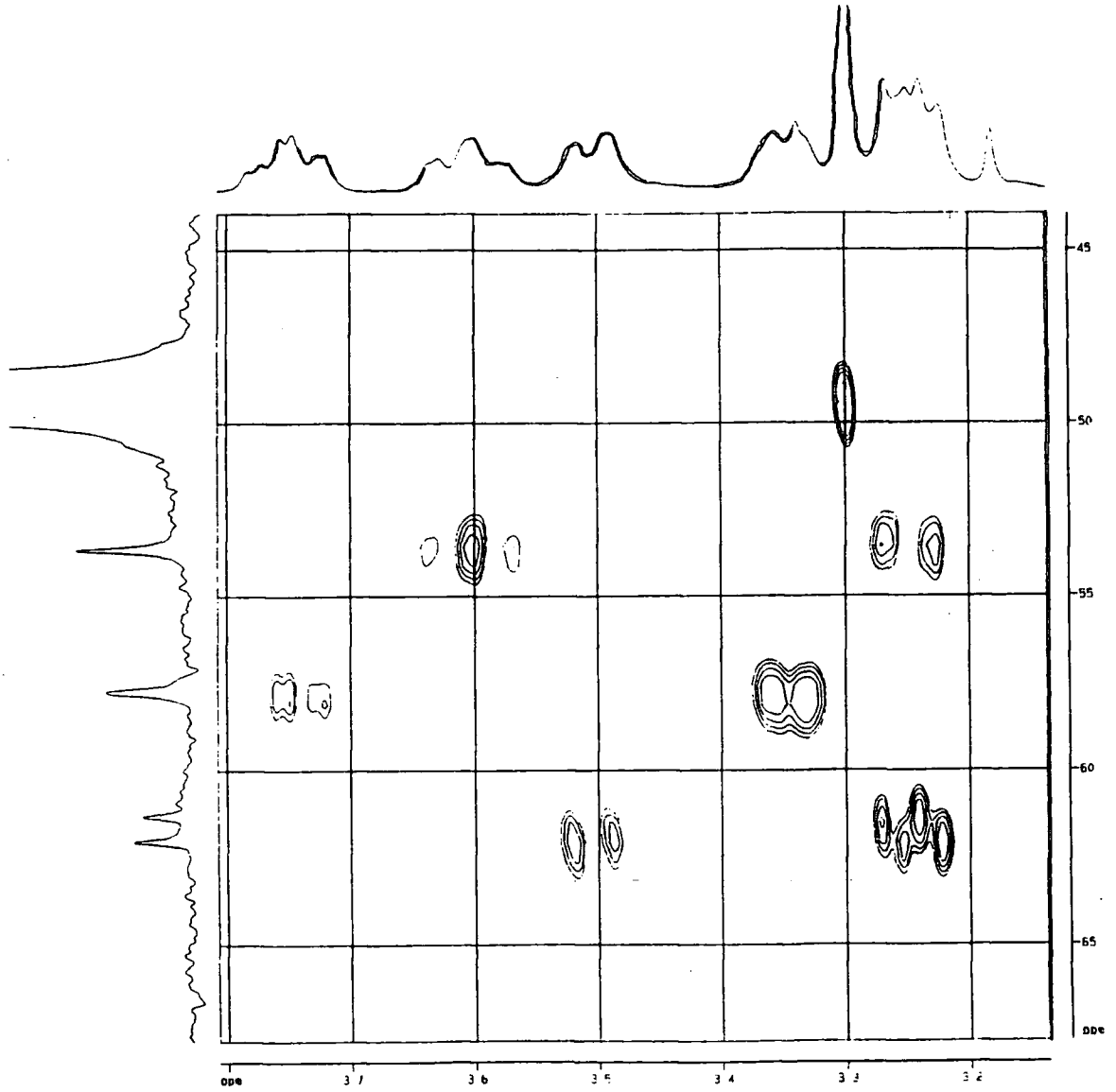


Figure 3.20 Heteronuclear Correlation between ^{1}H and ^{13}C for Ga III NOTPPh complex.

Figure 3.21 ^{1}H-^{1}H NOE spectra for all the protons of the Ga III NOTPPh complex.

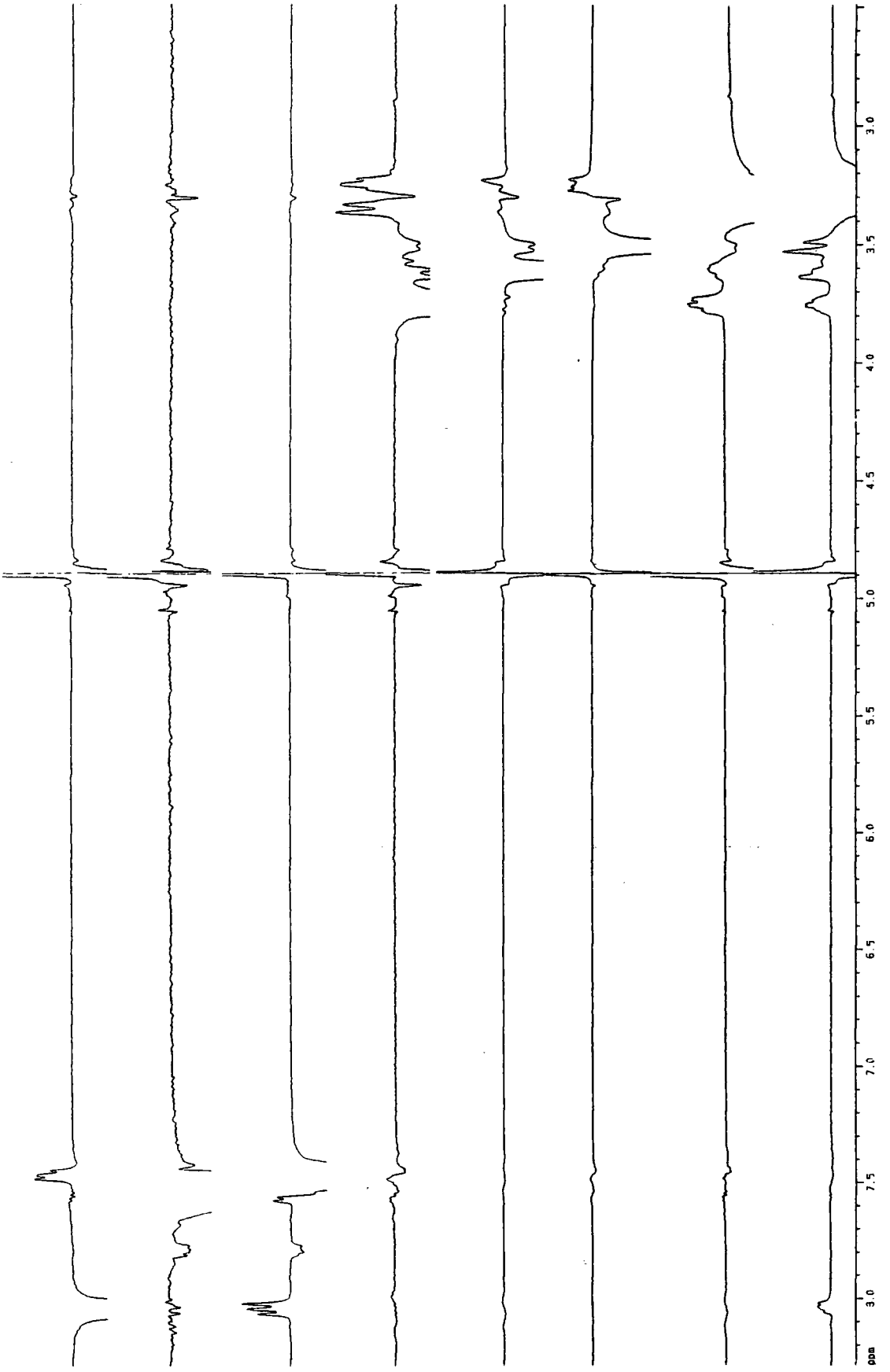
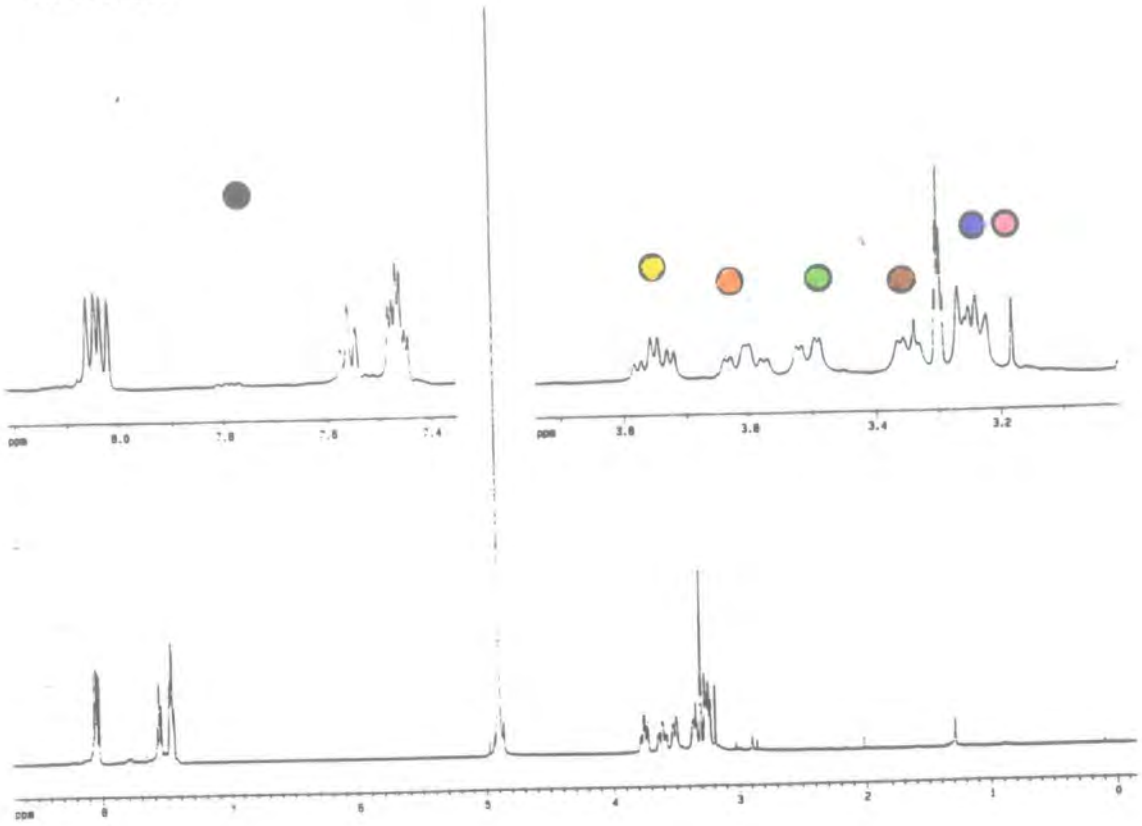
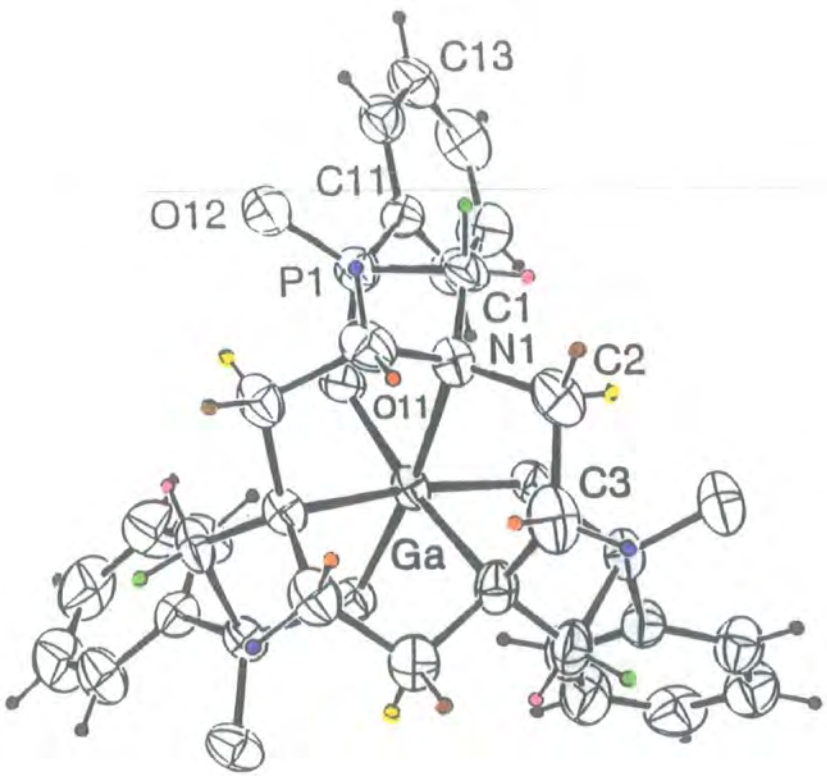


Figure 3.22 Assignment of solution state ^{1}H NMR to the solid state crystal structure.

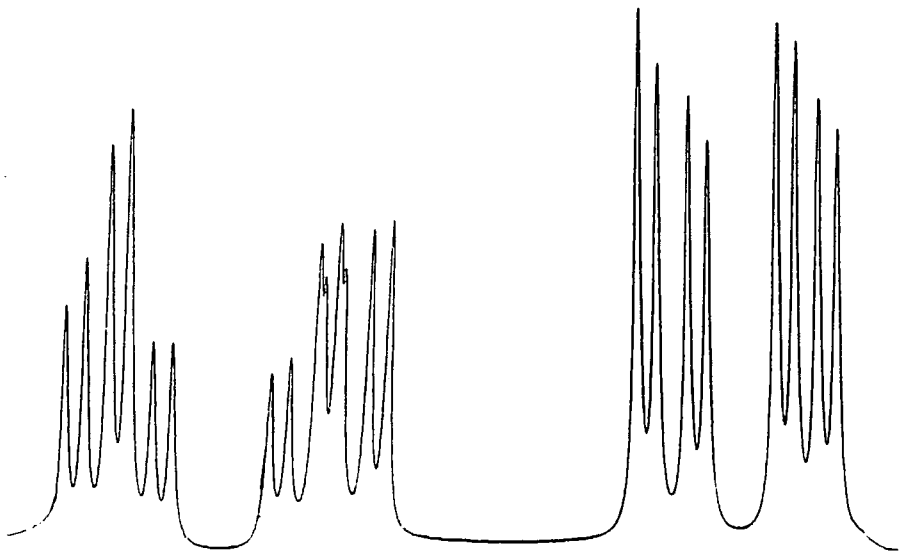




NOE Experiments

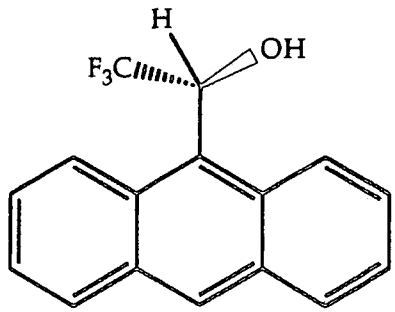
The diastereotopic hydrogens at C(1) were distinguished by nOe experiments. The low frequency doublet of doublets showed a strong nOe with the ortho phenyl hydrogen, figure 3.21.

In addition using a simulation package it was possible to simulate the coupling pattern of the ring protons without the interference from the NCH_2P protons. The classical coupling of an AA'BB' system is shown below;



3.5.2.3 Resolution of Enantiomers

It was noted in the crystal structure that only one of the two possible pairs of diastereoisomers was formed. After trying a range of chiral solvating agents[26] in several different solvents, it was possible to resolve the two enantiomers to give two separate ^{31}P NMR signals ($\Delta\delta P$ 0.19ppm) using Pirkle's reagent[27] (62) in C_6D_6.



62

62 2,2,2-Trifluro-1-(9-anthryl) ethanol

The next step was to attempt separation using a chiral HPLC column. A Daicel Chiralpak OT(+) column eluting with methanol at reduced temperature, approximately 5°C, gave preparative resolution of the two enantiomers.

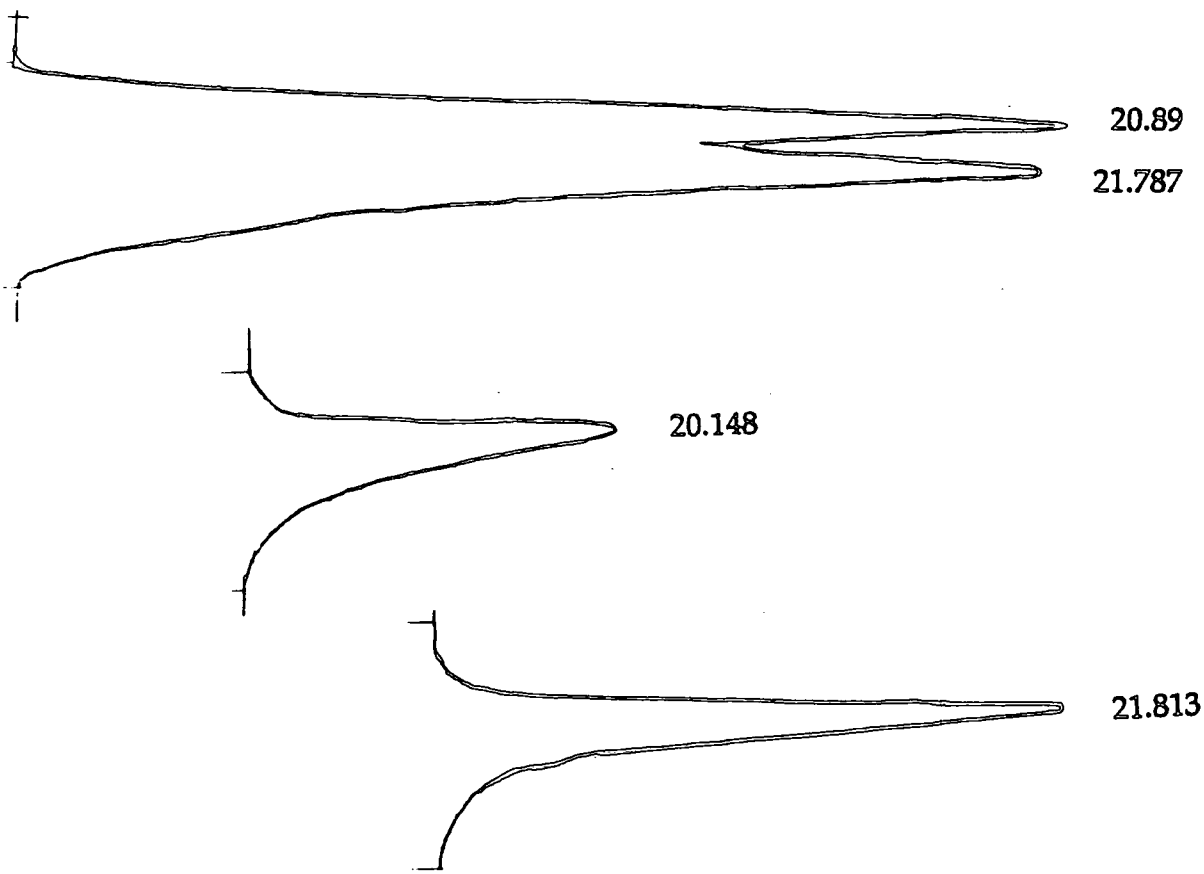


Figure 3.23 HPLC Traces showing separation of the enantiomers.

The observed optical rotations, in methanol at 25°C, showed opposite signs confirming that they were the two separate enantiomers. As the concentrations of these were known, the specific rotations could be calculated.

$$\underline{1}: [\alpha]_D^{20} = + 85.7$$

$$\underline{2}: [\alpha]_D^{20} = - 87.5$$

(0.015 mmolar, MeOH)

(Error + or - 2.5)

3.5.3 Cobalt III Complexes

A solution of the cobalt II complex that had formed initially with NOTPPh was pink. Aerial oxidation of this solution to a purple cobalt III solution was found to occur naturally after several months. Formation of the oxidised complex was accelerated by the addition of hydrogen peroxide to the cobalt II solution. The transition was observed to occur within a few weeks.

3.5.3.1 Proof of oxidation

The electronic spectra of the Co III complex can be seen to be rather different from that of the Co III NOTA complex studied by Weiss[14] and Yoshitake[28] and their groups. This indicated that we are seeing the cobalt changing oxidation state rather than the formation of a species with an oxygen metal double bond. The change in the relative conductivity reading, also supports the suggested change from the anionic cobalt II complex to the neutral cobalt III complex.

	Co II	Co III
λ_{max} (nm) (MeOH)	521	565
conductivity*(mho cm^{-1})	297	96
NMR (d_4 MeOH)	Not possible	^{1}H, ^{31}P and ^{13}C obtained

Table 3.16 Comparison of data obtained for the Co II and Co III complexes with NOTPPh.

* Measured in dry methanol (80),

Related values: Cu II NOTPPh complex 303, and Ga III NOTPPh complex 98.

Cobalt II has a d^7 electronic configuration, hence irrespective of whether it is a high or low spin complex there will always be an unpaired electron making it paramagnetic. Whereas cobalt III has a d^6 electronic configuration which in a low spin complex will be diamagnetic so allowing NMR studies to be undertaken.

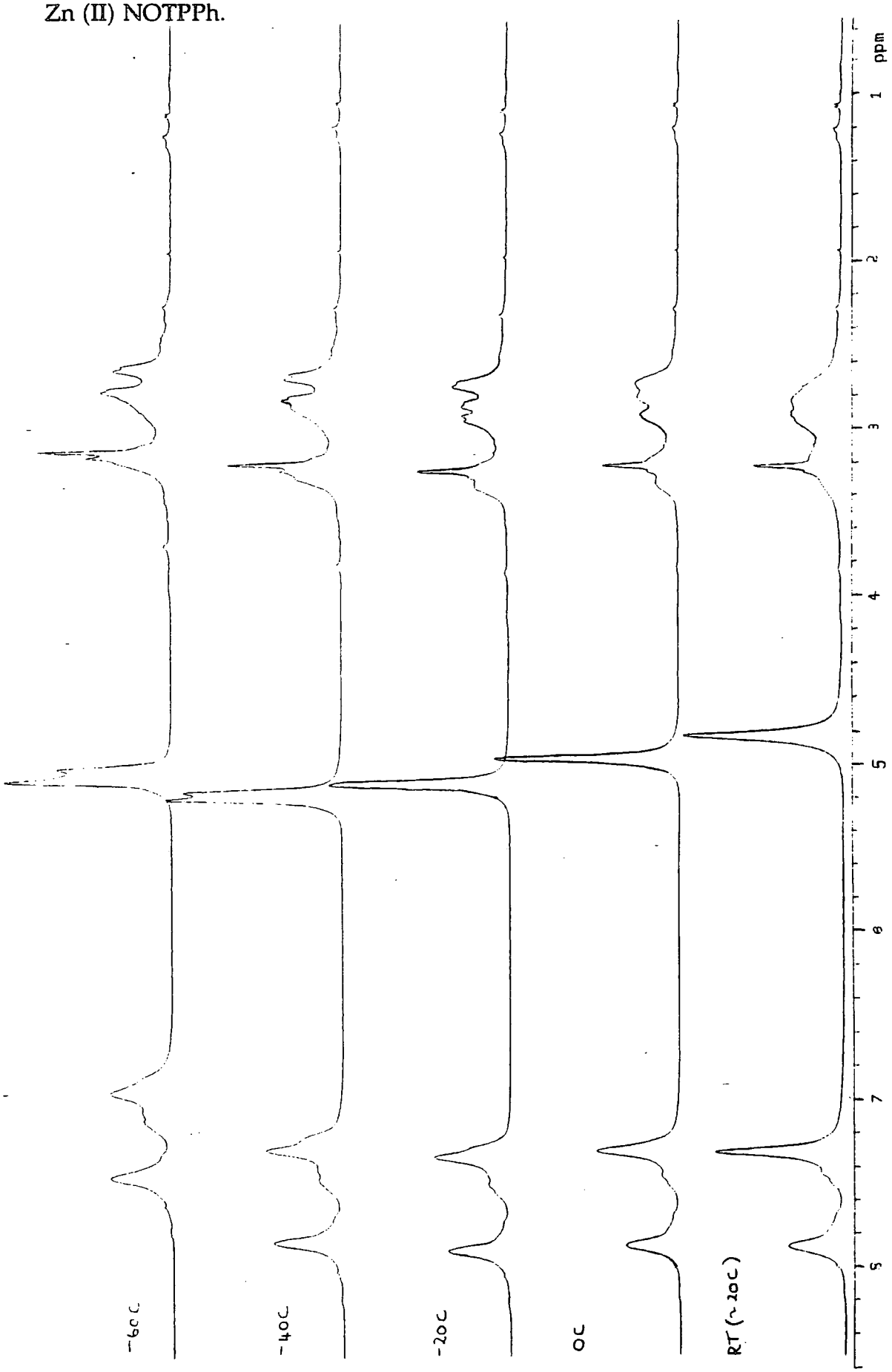
3.5.3.2 NMR

The ^{1}H, ^{31}P and ^{13}C spectra were run and could be seen to be very similar to those obtained for the Ga III complex. The phosphorus singlet was shifted to higher frequency (58.8ppm compared to the Ga complex 27.4ppm). The proton coupling patterns were the same with very little change in shift values.

3.5.4 Zinc Complex: NMR Studies

The ^{1}H NMR of the zinc complex with the phenyl phosphinic acid ligand was different to that of the Ga III complex. The protons from the $9N_3$ ring and the NCH_2P group were not distinguishable (293K, d_4 methanol) and appeared as a broad multiplet between 2.6 and 3.4 ppm. A

Figure 3.24 Results of variable temperature experiment carried out on Zn (II) NOTPPh.



variable temperature experiment was run between room temperature (20°C) and -60°C. Resolution of separate resonances was gradually seen at -20°C although resolution was lost as the temperature was further reduced.

A similar effect has been reported by Desreux[29] and Aime[30] with lanthanide III complexes of DOTA. From the NMR studies undertaken by Aime the observed change is due to a concerted movement of the methylene groups in the side arm and not a movement of the $12N_4$ ring as has been originally suggested. This dynamic process leads to an interchange between the two enantiomeric forms of the complex.

3.6 Biodistribution Studies

3.6.1 General

Radionuclide	t 1/2	E_{photon} keV, (%)	Source
^{111}In	2.83 d	171 (88) 247 (94)	Cyclotron
^{67}Ga	3.25 d	184 (24)	Cyclotron
^{68}Ga	1.20 h	511 (178)	Generator

Table 3.17 Imaging radioisotopes for use in radioimmunoscintigraphy that can be bound by $9N_3$ based ligands.

Much work has been carried out by different groups[31,32,33,34,] on forming stable complexes of the radioactive nuclei of gallium and indium.[35] It has been shown that the ligands NOTPPh and NOTPBz bind

with both of these cations. The NOTPPh complexes appear to be stronger, however both were examined in the studies.

3.6.2 Results from Experiments with Gallium Complexes

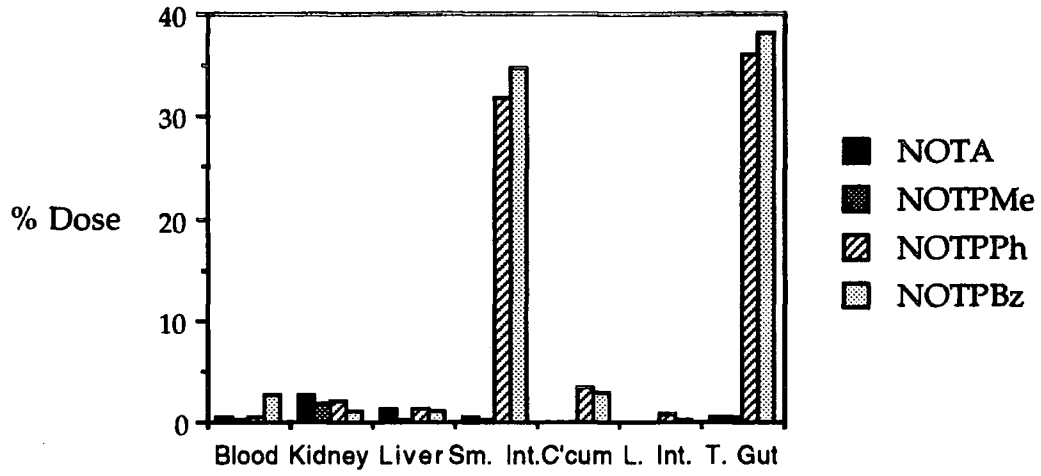


Figure 3.25 Plot of distribution of Ga complex after 1 hour.

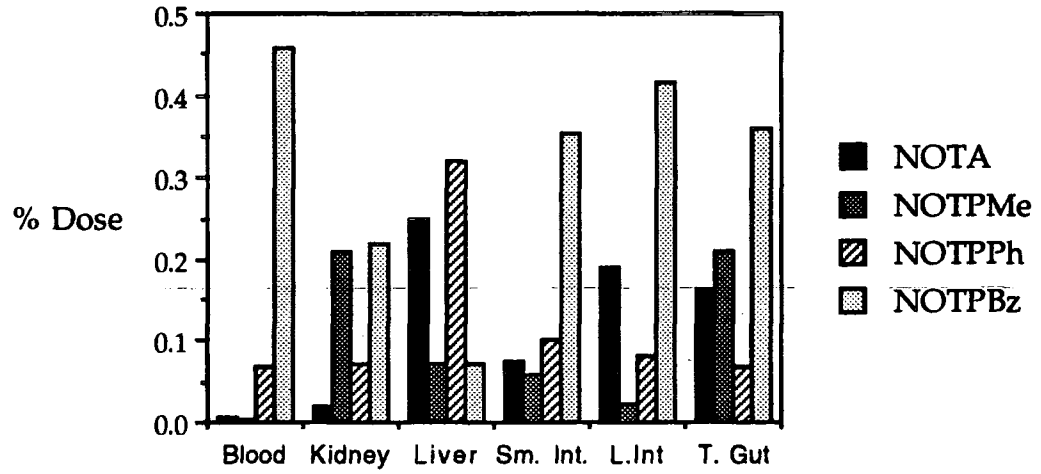


Figure 3.26 Plot of distribution of Ga complex after 24 hours.

Sm. Int.	Small Intestine
C'cum	Caecum
L. Int.	Large Intestine
T. Gut	Total Gut

Figures 3.25, 3.26 and 3.27 show the percentage of the dose of the complex given to be found in certain organs at set times. If the values of the total dose present in the gut are compared, it can be seen that the gallium complexes with NOTPPh and NOTPBz clear the mice by a different route, ie via the biliary system (liver-gall bladder-intestine-caecum), in contrast to those with NOTA and NOTPMe, which clear via the kidneys. The NOTPPh and NOTPBz complexes can be seen to behave in a similar mannar with respect to build up in other organs, this says that they remain intact *in vivo*.[33]

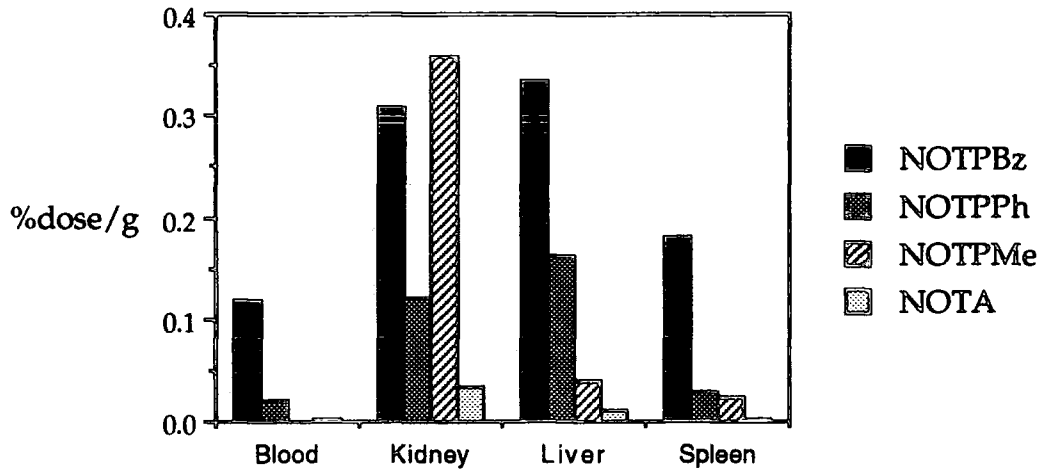
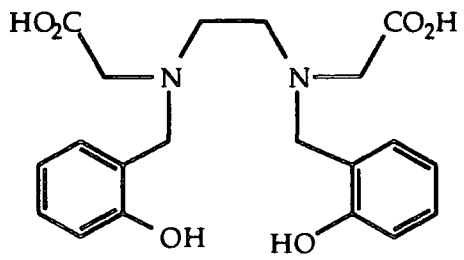


Figure 3.27 Plot of distribution of Ga complex after 24 hours.



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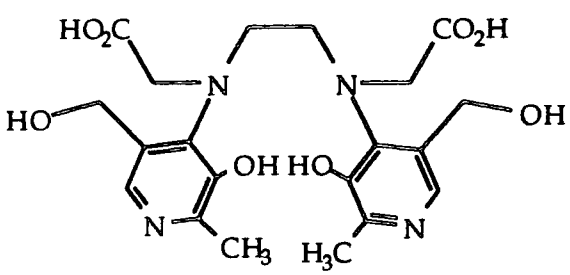


64

63 PLED

64 HBED

The main route for clearance of radiolabelled gallium complexes observed previously by Martell and coworkers[31] with a ^{68}Ga PLED complex was via the kidneys. There appeared to be no build up in tissues with time although data was not reported for after 1 hour. Evidence was also obtained that the ^{68}Ga HBED complex was cleared by both the kidneys and the intestines with little preference.

A stable complex of gallium could be used in two different applications. The ^{68}Ga complex could be used for positron emision tomography (PET), while the ^{67}Ga complex could be of use for *in vivo* single photon emission computerised tomography (SPECT imaging).

3.6.3 In Data

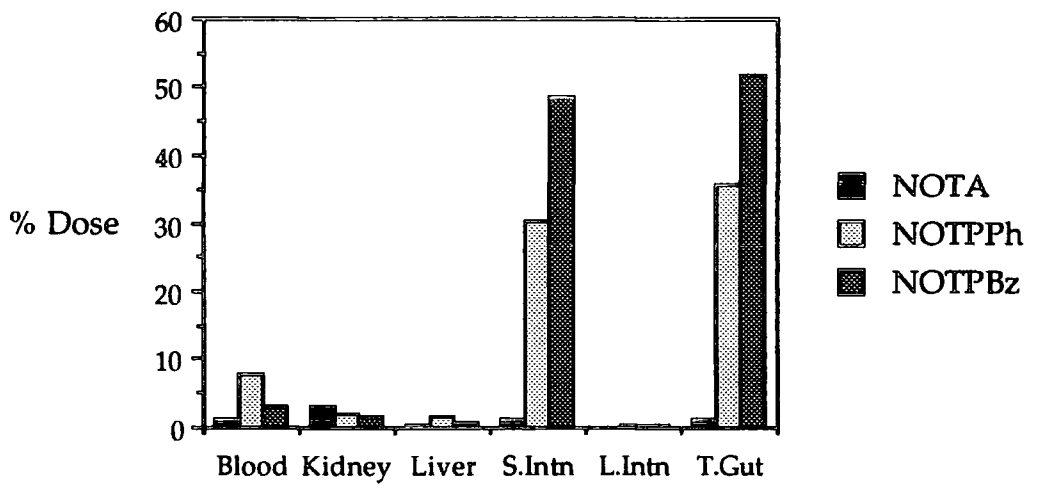


Figure 3.28 Distribution of ^{111}In complex after 1 hour.

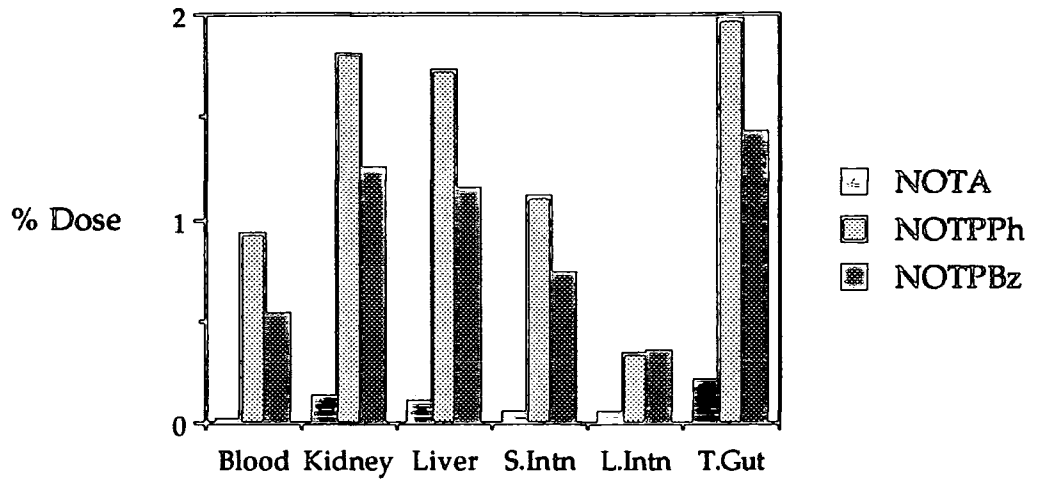


Figure 3.29 Distribution of ^{111}In complex after 24 hours.

The indium complexes of NOTPPh and NOTPBz can be seen to have a high percentage dose in the gut. After one hour the total excreted via the kidneys of the NOTA complex is 80% whereas only 28% of the NOTPPh complex is excreted via the kidneys with 36% being excreted via the gut. Unlike the gallium complexes, there is clear evidence of indium build up (in the liver/kidneys) with the two phosphinate complexes studied, when comparing the 24 hour data versus the NOTA complex. This is most likely to be due to premature dissociation of ^{111}In *in vivo* and suggests that these phosphinate complexes are not stable for *in vivo* applications.

A stable complex of ^{111}In could be used in single photon emission computed tomography (SPECT). The PLED indium complex studied by Martell and coworkers[31] cleared via the kidneys, apparently within three hours as results at longer times were not given. The ^{111}In HBED complex[32] showed results that suggested it cleared mainly via the intestines.

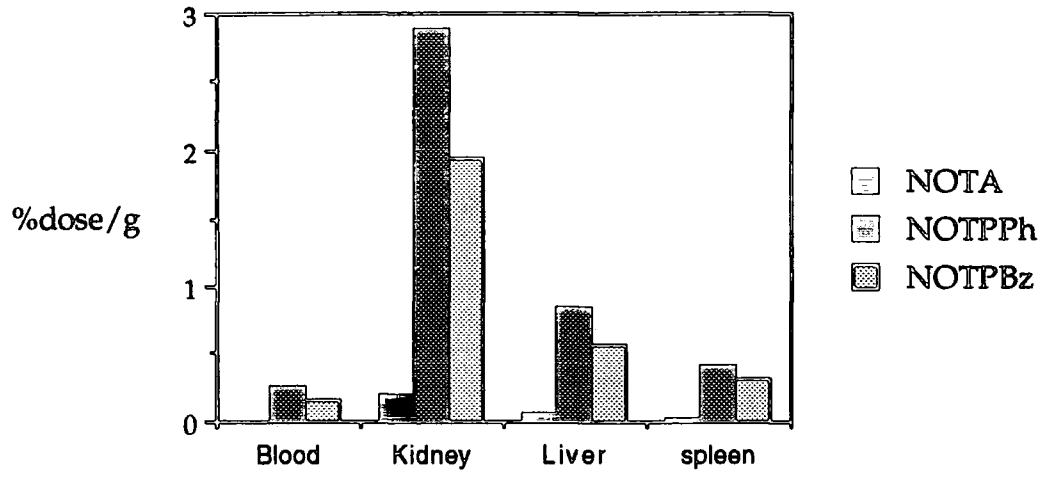
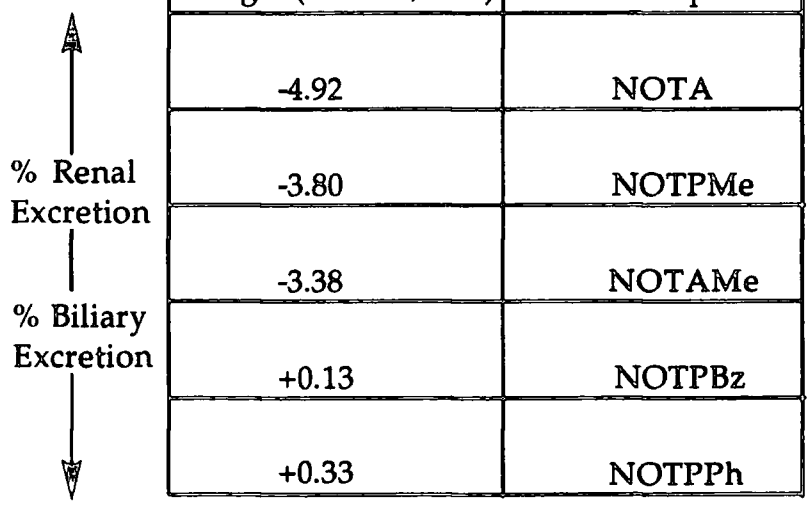


Figure 3.30 Distribution of ^{111}In complex after 24 hours.

3.6.4 Conclusion

The different behaviour of the NOTPPh and NOTPBz ligands can be related to the relative complex lipophilicity. Figure 3.31 shows the correlation between the partition coefficient and the method of excretion for the indium complexes. This should equally well apply to the gallium complexes.



Log P (octanol/PBS)	In Complex
-4.92	NOTA
-3.80	NOTPMe
-3.38	NOTAMe
+0.13	NOTPBz
+0.33	NOTPPh

Figure 3.31 Correlation of complex lipophilicity with excretion pathway.

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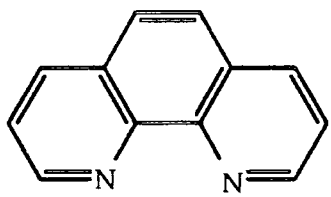
Chapter 4

Phosphinic Acid donors Attached to a Rigid Skeleton.

4.1 Introduction

Following on from the work on phosphinic acid ligands based on amines with flexible skeletons, an investigation of a ligand with a rigid skeleton was undertaken. 1,10-Phenanthroline was used as the rigid unit to which to attach the appropriate side arms. The synthesis of the target ligand involved known reactions to create a bromide that would undergo an Arbuzov reaction, giving the phosphinate ester, scheme 4.1.



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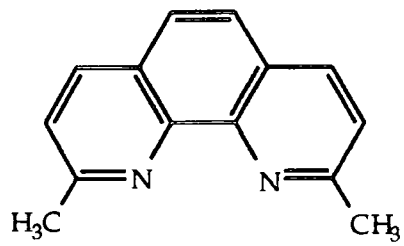

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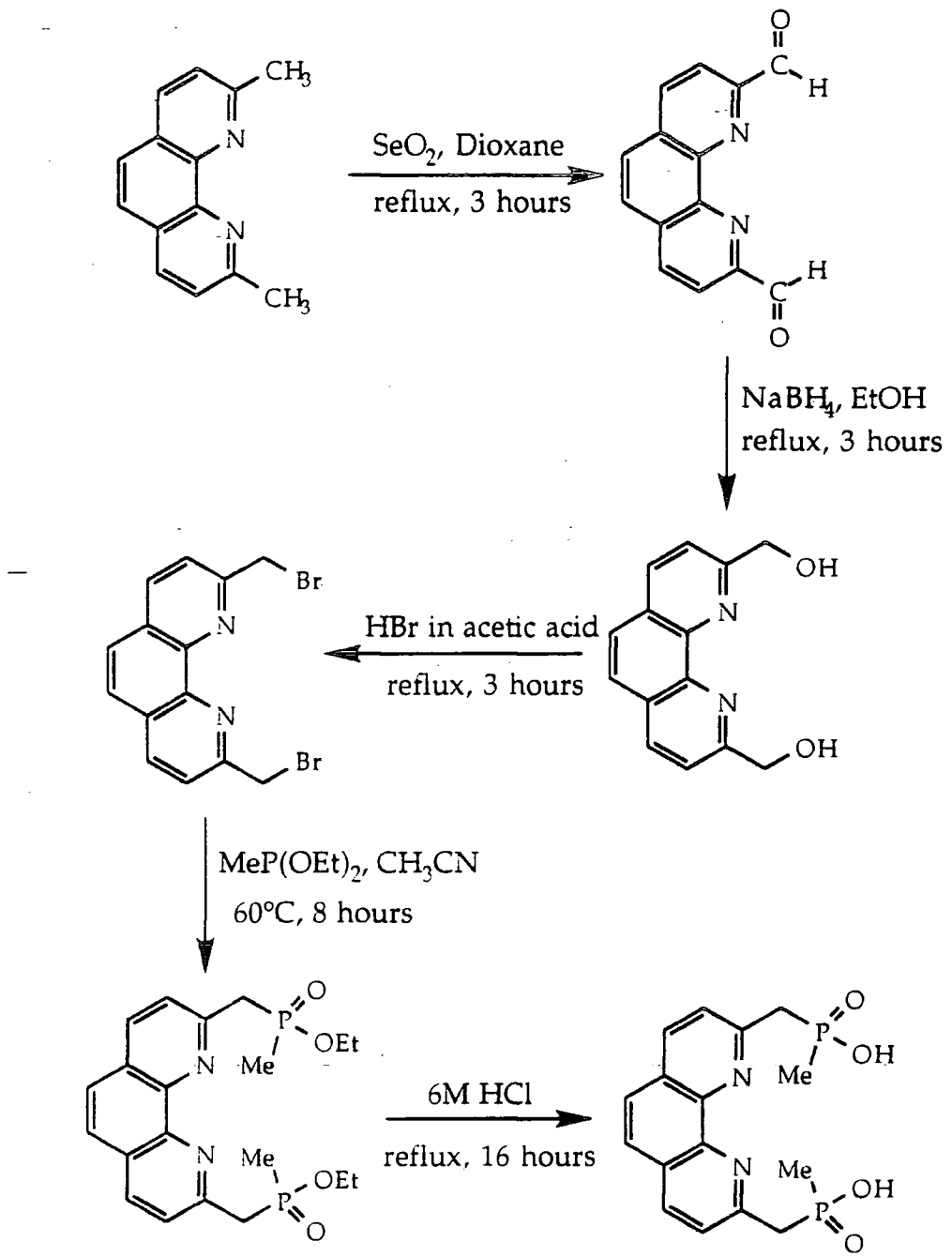
65 1,10-Phenanthroline (o-phen)

66 2,9-Dimethyl-1,10-Phenanthroline (o-phen diMe)

It has been seen (chapter 2) that the acyclic phosphinic acid ligands apparently bind through nitrogen only to copper and through nitrogen with a small donation from the oxygens to nickel. The complexation of these and other cations with these ligands provides a useful comparision of properties.

4.1.1 Synthesis



67 68

Scheme 4.1

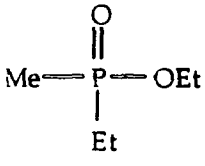
67 Diethyl-1,10-phenanthroline-2,9-di(methylene(methylphosphinate))

68 1,10-Phenanthroline-2,9-di(methylene(methylphosphinic)) acid [o-phen diPMe]

The first three steps of this synthesis could be taken from work done by Reiss and coworkers[1]. The first two steps worked as described in the literature, with yields of 60-70%. A hot filtration in step one was needed in order to achieve a good yield.

Formation of the dibromide gave problems by the published method, which involved refluxing with aqueous HBr, so an anhydrous method was tried. If the reagent was changed to hydrogen bromide in acetic acid, the reaction was found to give the desired product, although with a poorer yield, 40%. An advantage of this method was that the product was formed in an anhydrous state, which was required as reaction with a sensitive phosphine was to be carried out in the subsequent step.

There was ample precedent for step four as it involved doing an Arbuzov reaction on a reactive halide[2]. The problem was identifying the exact conditions needed for the reaction to proceed in a reasonable yield. Initially the neat reaction between the bromide and the phosphine was attempted over a range of temperatures. The main identifiable product from these reactions was the rearranged phosphinate, 69.



69

It was eventually found that dry acetonitrile was the solvent needed for the reaction to give the phosphinate ester, 68. Purification by column chromatography was necessary at this stage to give the pure ester, before it was hydrolysed to the diacid, as with the previous ligands. This

sample was analytically pure and could be used directly for potentiometric titrations.

4.1.2 Protonation Constants

The determination of protonation constants was undertaken as described in chapter two.

ligand	pK_a
o-phen [a]	4.93
o-phen diMe [a]	5.85
o-phen diPMe [b]	5.96

Table 4.1 Protonation constants for phen based ligands.

a) Data taken from ref 3.

b) This work.

The protonation constants for the three ligands given are all for protonation of one of the two nitrogen centres, figure 4.1. Whilst it appears that the methylene phosphinic acid groups have a similar electron donating effect as the methyl groups, on the phenanthroline nitrogens do, it is more likely that the increase in pKa is due to a steric effect. Deprotonation of LH^+ for the 2,9-disubstituted derivatives being sterically inhibited compared to the parent 1,10-phenanthroline. The phosphinic acid groups in o-phen diPMe protonate below 2 so are not detected by this method.

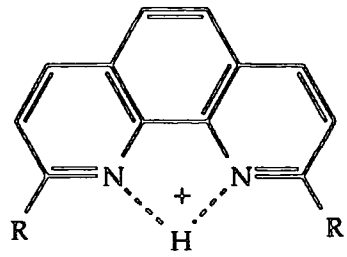


Figure 4.1 Protonation of the two nitrogens in 1,10-phenanthroline based ligands.

In the monoprotonated ligand, there will be a bifurcated hydrogen bond and the second protonation is only going to occur under very acidic conditions, due to charge repulsions. This explains why there are two nitrogens present but only one nitrogen protonation constant is observed. As these structures are rigid, rotation is prevented and there is no way that the nitrogens can move away from each other to allow a second proton to easily approach, as is possible in the acyclic ligands.

4.1.3 Stability Constants for Metal Complexation

The method of determination was as described in chapter two.

	Zn	Ni	Cu
o-phen [a]	6.4	8.6	7.4
o-phen diMe [a]	4.1	5.0	5.2
o-phen dmpMe [b]	8.86	5.39	4.11
Ionic Radii [c]	0.60	0.57	0.55

Table 4.2 Comparison of stability constants including ionic radii (Å).

a) Data taken from ref 3.

b) This work.

c) Values for M^{2+} with four coordinating ligands.

The complex of o-phen diPMe with copper shows no increase in the binding constant due to the presence of the phosphinic donor oxygens. The binding appears therefore to be due to the nitrogens, which is weakened due to the presence of the substituents.

4.1.3.1 Copper and Nickel Complexes

The complex formed between o-phen diPMe and nickel is slightly stronger than the one with copper. This suggests that nickel may be forming weak bonds to the σ-donor oxygens atoms. The stability of the zinc complex in comparison with the other two is of great interest and will be discussed in detail in the next section.

The difference in binding can not really be related to the differences in the size of the cation as the ionic radii for the four coordination state cations are all very similar. If this is combined with the evidence in chapter two is seems reasonable to suggest that copper does not form bonds to phosphinic acid groups, while nickel does so poorly. This is in contradiction to the Irving Williams series[4] which says that copper would be more likely to form stronger complexes than nickel. A similar effect is observed by Irving and Mellor[5,6] in the work that they undertook on the 1:1 complexes of first row transition metals and o-phen.

4.1.3.2 Zinc Stability

The stability constant for the o-phen diPMe zinc complex is higher than any of the complexes where there are only nitrogen donors available, table 4.3. This shows that the oxygens must be making a significant contribution to the binding of the ligand. The o-phen diPMe ligand is showing a selectivity for zinc over nickel and copper of $10^{3.5}$. This could be the first step towards a zinc selective ligand, if it could be improved.

Ligand	log K_{ML} (H_2O, 298K)
en [a]	5.7
o-phen [a]	6.4
o-phen diMe [a]	4.1
o-phen dmpMe [b]	8.86
EDDA [a]	11.20

Table 4.3 Stability constants for complexes 1:1 with Zinc (I=0.1).

a) Data taken from ref. 3.

b) This work.

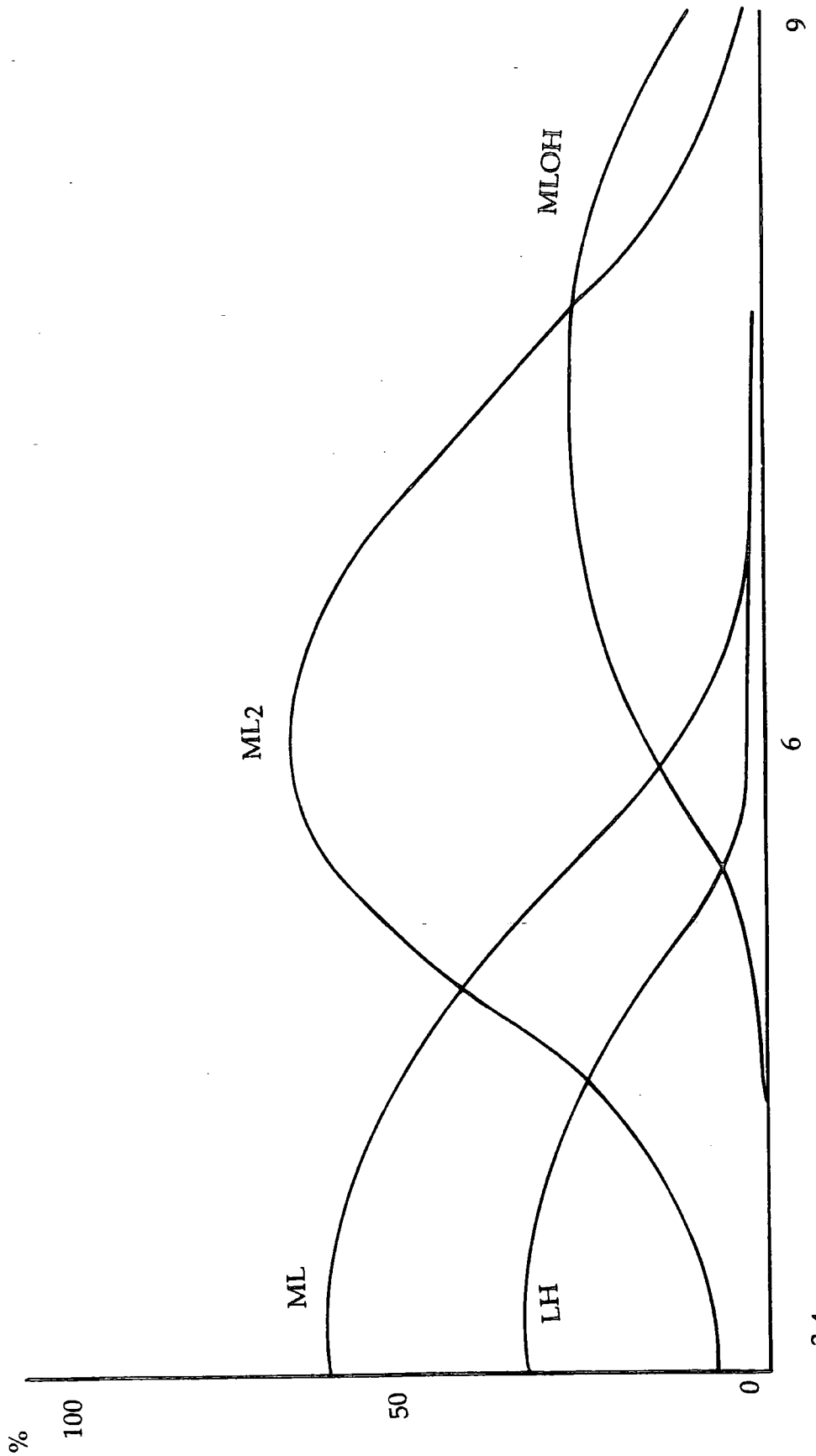
The titrations were carried out following the same method as used previously, however it was found that the zinc standard solution was less concentrated than the ligand solution. This led to the presence of excess ligand in the solution which resulted in the competitive formation of the 2:1 L:M complex. The stability constants for both these complexes have been determined.

Species being formed	Log K value
ML	8.86
ML_2	4.67
MLOH	2.78

Table 4.4 Stability constants determined for Zinc o-phen diPMe complexes. (n.b. the sign of the MLOH constant in the data analysis implies formation from M(OH) and L directly, and not from ML and OH^-)

The 1:1 complex between the ligand and metal does not undergo protonation to give an MLH constant as often seen. The second

Figure 4.2 Species distribution plot for zinc complexes with o-phen diPMe.



constant obtained is due to the formation of the complex MLOH, this is seen to be formed as the pH of the solution increases. A distribution plot of the different species versus pH is shown in figure 4.2. This MLOH complex is formed from the reaction of a Zn(OH) species with the ligand and protonates (at lower pH) to give the ML complex (see Chapter 2 for a full discussion).

4.1.4 In Summary

In summary it can be seen that in the complexes of o-phen diPMe with copper and nickel where it was hoped to make use of the full, 'N_2O_2', donor set to give a tetrahedral complex, there is only binding to the nitrogens. With zinc it appears that complexation with the oxygens as well as with the nitrogens occurs, to form considerably stronger complexes than with o-phen or o-phen diMe.

4.2 Creation of a Tetrahedral Binding Site

The structural feature that controls the conformation of o-phen diPMe is the rigid phenanthroline unit. This keeps the two nitrogens in a fixed position but exerts no control over the orientation of the phosphinc oxygens. This means that the ligand may be capable of forming either a tetrahedral or a square planar structure depending on the cation. However if a ligand could be made which only forms one structure, then an enhanced stability constant for a cation that prefers that structure may be observed.

If the phenanthroline unit is used again as the source of the nitrogens with phenyl ring substituents in the 2 and 9 positions a tetrahedrally ligating molecule may be observed.

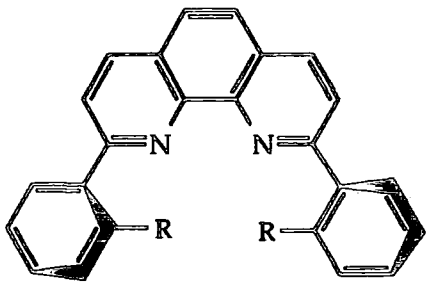


Figure 4.3 Showing orientation of the phenyl rings with respect to the phenanthroline unit, 65, in a putative tetrahedral complex.

The introdution of the phenyl rings at this site is achieved by nucleophilic attack, which preferentially occurs at the 2,9 positions. The phenyl ring used needs to be functionalised in the ortho position to allow further interconversion of the donors. Much work has been done by Sauvage[7] and coworkers on addition of phenyl rings with para subtituents however little work has been reported with the substituents in the ortho position. However the groups present must not affect or be affected by the formation of the lithiated species used, so acids protected as amides or protected alcohols could be used.

4.2.1 Addition of "Aromatic ortho Amide"

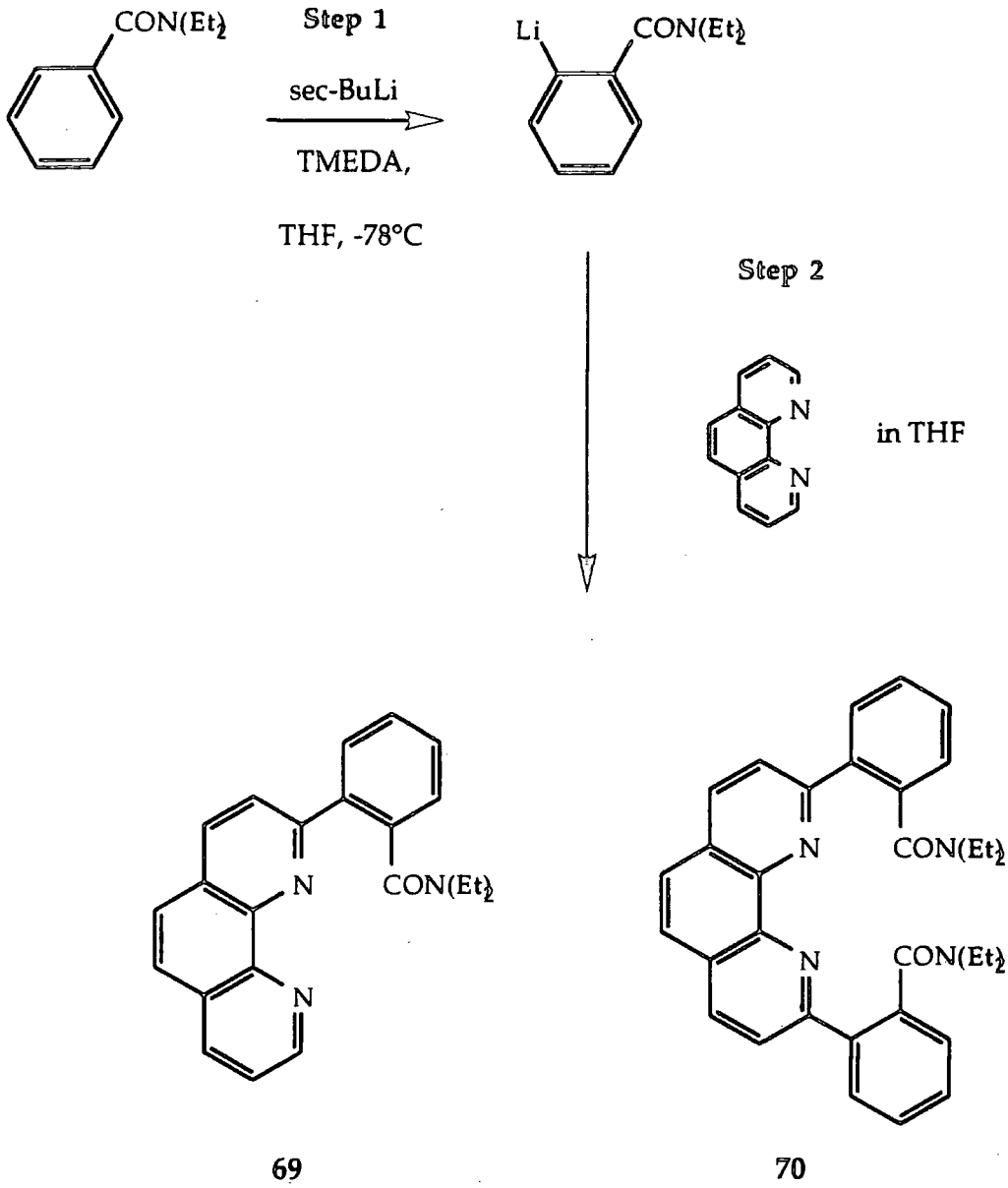
An acid functionality, that is protected as an amide should be stable to lithiation conditions. Deprotection by reaction with potasium tert-butoxide[8] would provide the desired acid. Further interconversion of the acid functional group by reduction to an alcohol and then to a bromide would provide a molecule suseptible to an Arbuzov reation to create a phosphinate ester.

The first step in scheme 4.2 is taken from a report by Beak and coworkers[9,10]. Initially the lithiate was formed and quenched with D_2O to

allow the amount of conversion to be assessed. A maximium yield of 80% was obtained so this was used when calculating the amount of o-phen added in the second step. The work-up involved quenching the remaining lithiate with water and then rearomatising the two rings by stirring with MnO_2.

The product of scheme 4.2, was always the monosubstituted form and never the disubstituted species, although the ratio of reactants was calculated to be in excess of the 2:1 needed to give the di product. When further reaction of the monoamide were attempted a mixture of products was obtained, including products derived from attack of the lithiated species on the amide carbonyl, to give a ArC(O)Ph species with a ^{13}C NMR peak 196.4ppm[11].

The monosubstituted amide was bright orange and could be purifued by column chromatography on silica gel.



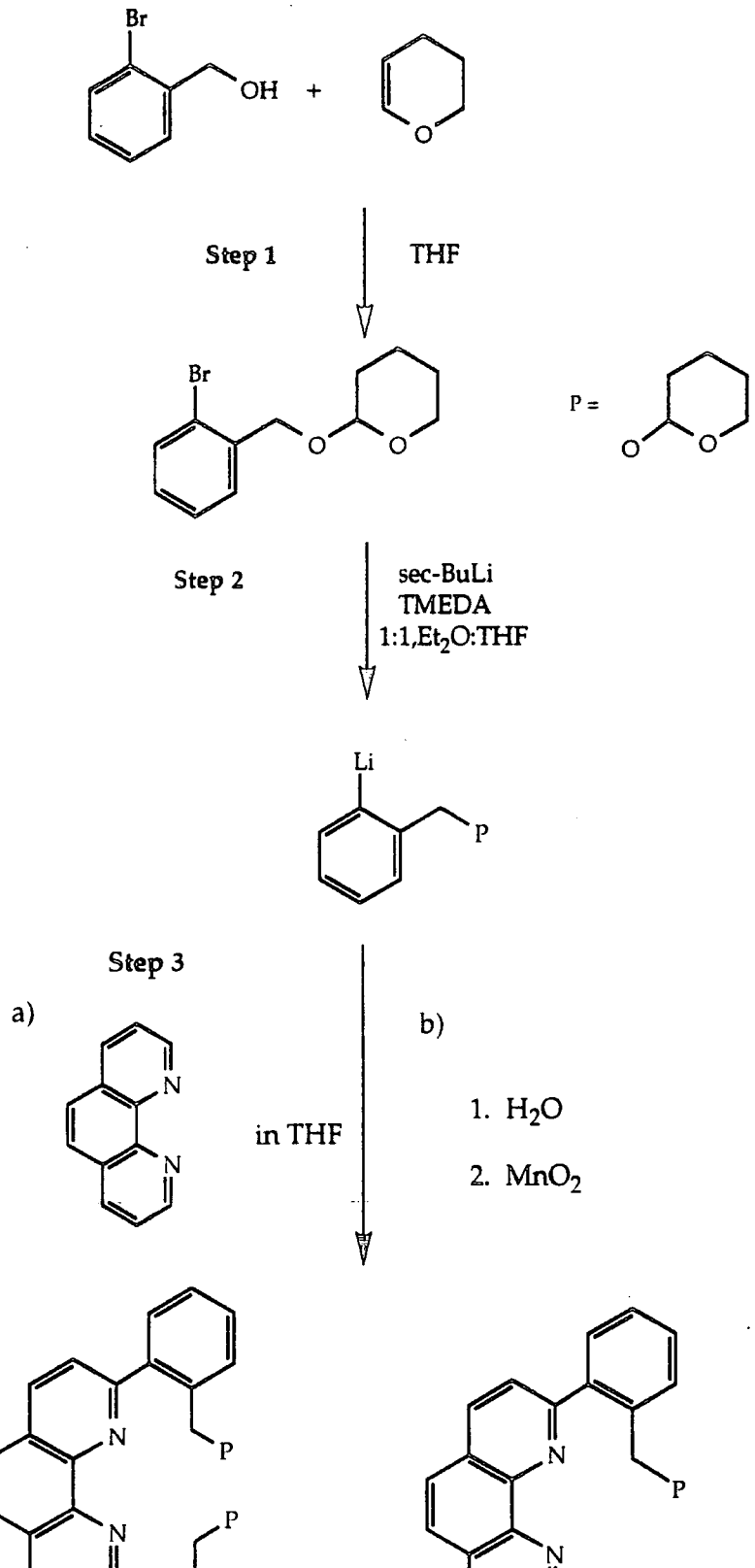
69 70

Scheme 4.2

69 2-(N,N diethyl 2' toluamide)-1,10-phenanthroline

70 2,9-bis(N,N diethyl 2' toluamide)-1,10-phenanthroline

4.2.2 Addition of Aromatic ortho Protected Alcohol



71

Scheme 4.3

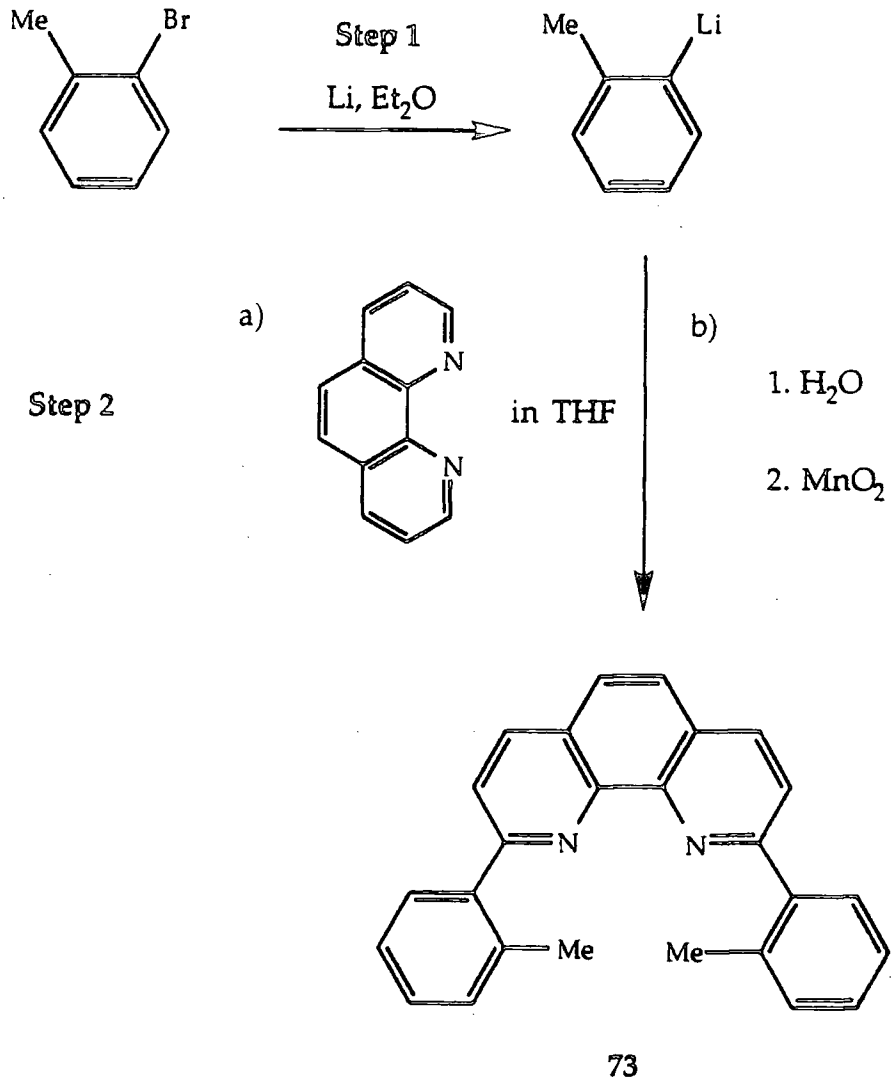
72

The use of a protected alcohol[12] as the ortho functionality is an alternative strategy that allows the subsequent deprotection of the alcohol before conversion to the bromide and then to the phosphinic acid. The protection[13] and deprotection[14] of the alcohol can be done by a standard reaction (eg. aqueous HCl/MeOH). The pyran derivative was chosen as it is known to tolerate the conditions of the lithiation reaction.[15]

The lithiation step was tried and quenched with D_2O, as before and the yield found to be 75%. The ratio of o-phen to the lithiate was 1:2.2 to encourage formation of the disubstituted product. However only the monosubstituted product was obtained with reclaimed alcohol. Even when the monosubstituted form was added to the reaction instead of o-phen no further substitution was seen.

4.2.3 Addition of ortho Toluene

The use of methyl as the ortho functional group should allow several possible methods of further functionalistion. It also requires a change in method to form the lithiate. If toluene was used and the lithiation carried out with sec-BuLi the methyl group would be the site of lithiation instead of the ortho aromatic site.[16,17] The use of elemental lithium is a more selective reagent and will replace the bromide, to give the desired lithiate. The quenching reaction gave a yield of 85% and this was used to calculate the ratios of reagents in step 2.



73

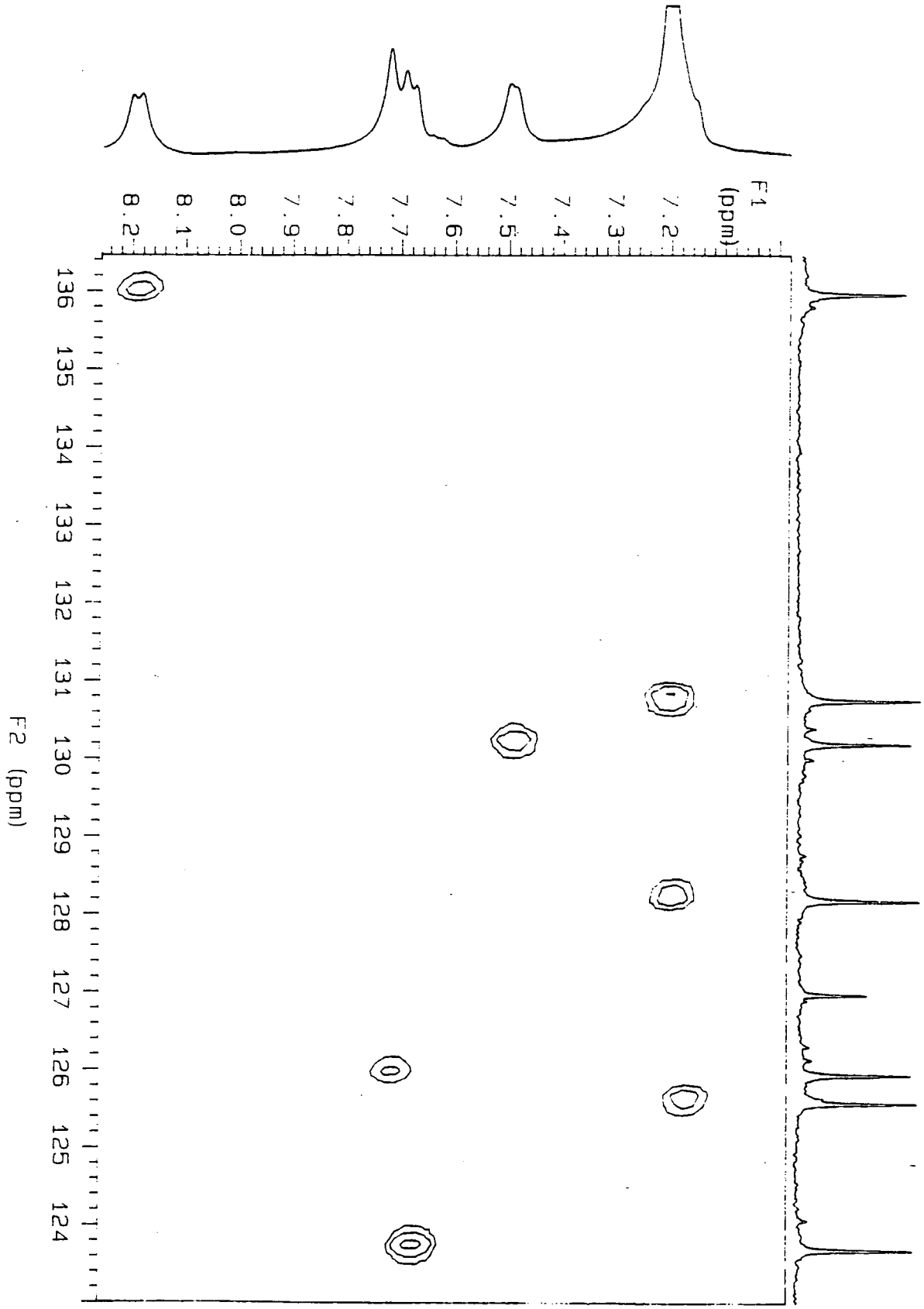
Scheme 4.4

73 1,10-Phenanthroline-2,9-di(2'toluene) [o-phen tol][18,19]

The hydrolysis of any remaining lithiate by water is followed by rearomatisation of the o-phen rings using MnO_2, figure 4.5. The residue of the reaction could be recrystallised from cyclohexane and was found to be the desired disubstituted product.

The presence of a plane of symmetry in the molecule meant that there were only twelve aromatic carbons seen in the ^{13}C NMR spectrum. Assignment of these was possible with the help of a Hetcor spectrum, figure 4.3, correlating the ^{1}H and ^{13}C spectra.

Figure 4.4 Hetcor Spectrum for 73.



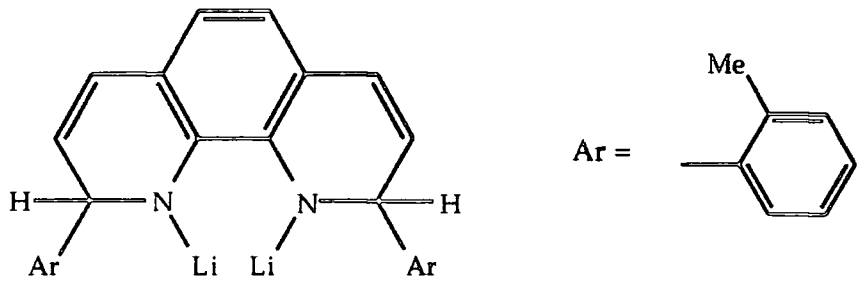
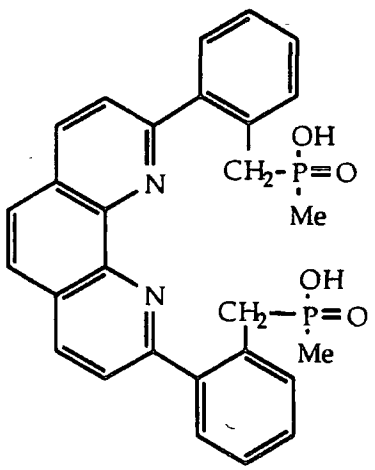


Figure 4.5 Intermediate in step 2 before rearomatization.

4.3 Functionalisation

Once a unit with aromatic groups in place is achieved, the rigid phenanthroline system should force them into a perpendicular arrangement. At this point functionalisation of the methyl groups became necessary to allow the creation of the phosphinic acid binding groups. The previous groups working with this type of compound did not appear to have carried out any further functionalisation of the methyl groups to the desired product, 74.



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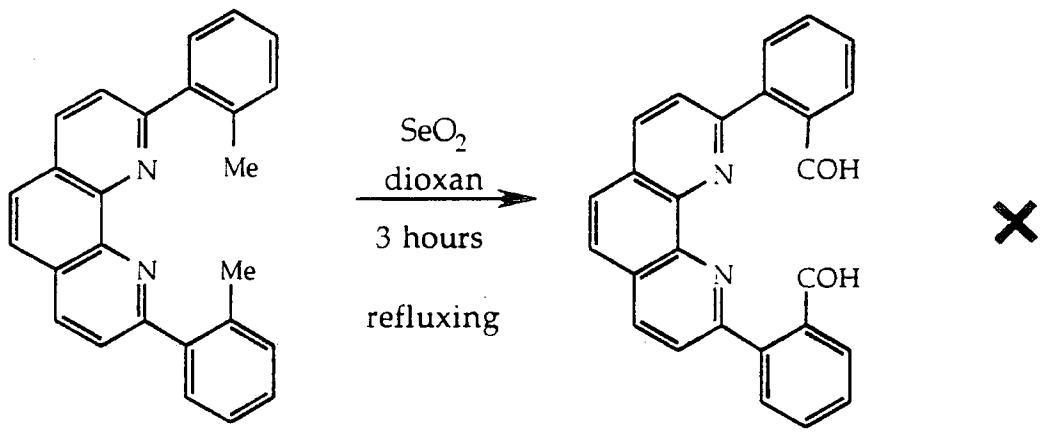
The functionalisation of an aromatic methyl can be carried out in several ways. Oxidation would give an acid or aldehyde which could subsequently be converted to a halide, or direct bromination should be possible. Once the bromide is obtained then an Arbuzov reaction as in 4.1.1 can be carried out.

4.3.1 Selenium Dioxide Oxidation

Oxidation of the methyl groups with selenium dioxide was attempted[1]. The putative route to the phosphinic acid group was that described in scheme 4.1. However this oxidation reaction failed (even after refluxing for extended lengths of time), and the starting material was always recovered. The methyl hydrogens are insufficiently acidic for this reaction to occur.



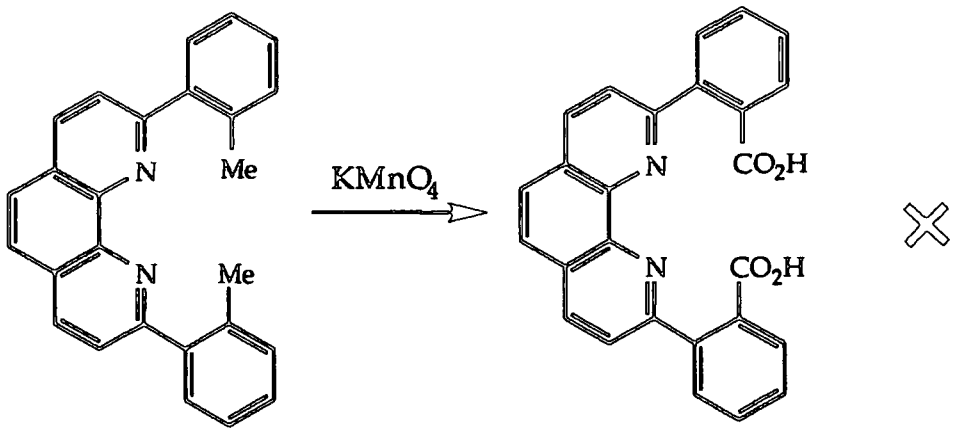
75

Scheme 4.5

4.3.2 Potassium Permanganate Oxidation

The oxidation of the methyl groups to carboxylic acid groups can be carried out using potasium permanganate in aqueous solution.[20] The reaction apparently behaved in the expected manner, and a purple

solution change to give a clear solution with a brown precipitate of MnO_2 being formed.



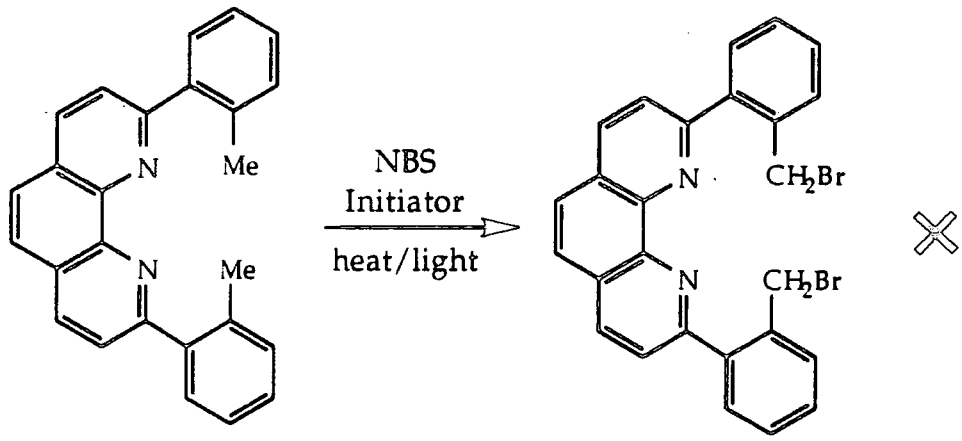
76

Scheme 4.6

Several methods of isolating the product were tried but if the pH became too low effervecence could be seen and a mass spectrum of the product indicated that decarboxylation had occurred. Formation of the lithium complex followed by passing the crude mixture through a cation exchange column gave a solid that could be analysed. The NMR spectra that were obtained showed that the methyl groups had been lost, however the aromatic region also showed signs of being disrupted. No clean sample of the diacid was ever obtained.

4.3.3 Bromination

If direct conversion of the methyl groups to bromomethyl groups were possible, then formation of the phosphinate groups would only need one further step. There are several factors that can be varied in order to induce radical bromination reactions to work including; changing the initiator and altering the method of initiation.



77

Scheme 4.7

The reactions were carried out in dry carbon tetrachloride and all the reagents used were recrystallised by standard methods[21]. Initially AIBN was used as the initiator with a light source that also provided heat to reflux the mixture. Some reaction was seen however the ^{1}H NMR spectra indicated a mixture of methylene and methyl peaks. Further reactions were tried using a range of peroxide initiators that gave no reaction.

Improvement of the route to give a sample of the pure bromide was not achieved. Irrespective of the ratio of reaactants used a mixture of the product and unreacted starting material was always obtained.

4.4 Conclusion

Some progress has been made towards finding a ligand with an enforced tetrahedral binding site. This work has shown that a simple synthetic route to such a ligand is viable and some very promising zinc selectivity has already been achieved with a relatively non-rigid bis(phosphinate).

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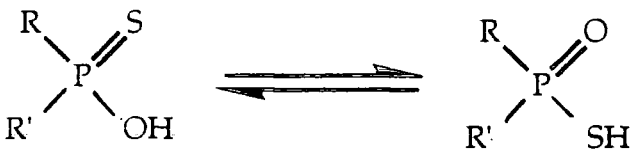
Chapter 5

Phosphinothiolic and Phosphinothionic Acids

5.1 Introduction

If it were possible to replace one oxygen atom of the phosphinic acid moiety with a sulphur atom a new series of ligands could be formed. These would have a N_2S_2 donor set, containing two soft donors This would give two possible forms, depending on the location of the proton. An equilibrium exists between the two forms which favours the P=S species[1] (figure 5.1).

Phosphinothionic acid Phosphinothiolic acid



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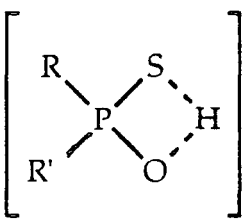


Figure 5.1 The equilibrium between the two forms.

5.1.1 Effect on Protonation Constants

If the protonation constants for a series of acids are considered,[1] (table 5.1) it can be seen that replacing the oxygen atoms with sulphur atoms decreases the protonation constants obtained. It is possible that they would form complexes that were resilient to acid-catalysed dissociation.

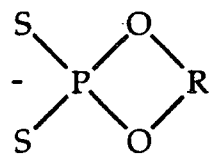
Ligand	pKa
$Et_2P(O)OH$	3.29
$Et_2P(O)SH$	2.54
$Et_2P(S)SH$	1.71

Table 5.1 Protonation constant for the acids.

Data taken from ref. 1

5.1.2 Effect on Stability Constants

Sulphur is know to act as a 'soft' donor and forms its strongest complexes with soft cations (table 5.2). The dithiophosphate system, **78**, below is used as an example of this;



78

Metal	Ni	Co	Ag
Log β	4-8	3-6	14-16

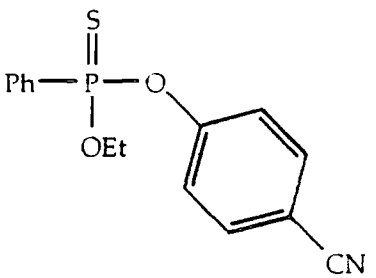
Table 5.2 Stability constants for complexes with **78.**

Data taken from ref 2.

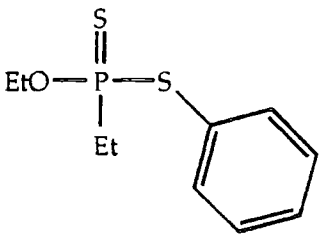
Values are given for 1:1 metal ligand complexes and a range is quoted due to the different R groups that are possible. Nickel Ii and cobalt II are both relatively hard cations and form relatively strong complexes with the phosphinic acid ligands in chapters 2 and 3. When a soft donor is used the complexes they form are much weaker. The complexes formed between silver and the soft donor groups are much stronger and demonstrate the soft-soft preference.

5.1.3 Uses to Date

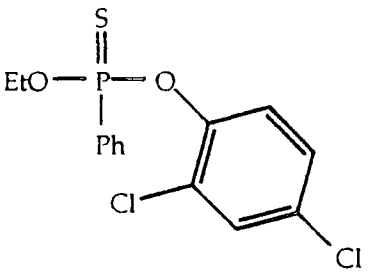
Both the mixed thio and dithioic acids are known to be biologically active. It is the phosphonic analogues that are used as insecticides, herbicides and fungicides. Hägele and coworkers[3] have carried out work using amino methylene phosphinic acids as herbicides and fungicides.



Cyanofenfos



Fonophos



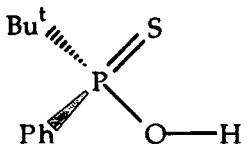
Acaricide

Figure 5.2 A range of the uses of sulpur substituted phosphorus acids.

5.1.3.1 Chiral Shift Reagents

In 1978 M. J. P. Harger[4] reported the use of optically active phosphinothionic acids as chemical shift reagents to be used in proton magnetic resonance studies.

More recently several groups have been developing P-SR bonds as ways of inserting known chirallity to the molecule as SR^- can act as a good leaving group. Enantiopure phosphorus molecules of a known absolute configuration have been used as chiral solvating agents for chiral analytes. For example, chiral solvating agent 79, (figure 5.3)) has been used to determine the enantiomeric purity of a series of chiral phosphinic esters[5], 80.



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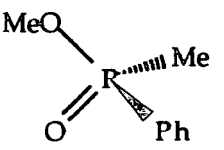


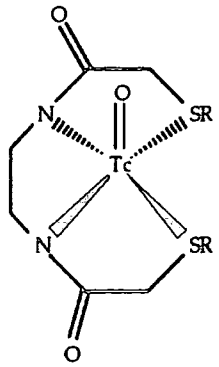
80

Figure 5.3 Use of a chiral phosphinthionic acid.

5.1.4 A New Possible Application

Technetium in its lower oxidation states (I and III) is a large soft cation. The element exists in many isotopic forms, one of which is a β emitter (^{99m}Tc, Emax = 140keV, t 1/2 6 hours).[6] Complexes of ^{99m}Tc are used as diagnostic radiopharmaceuticals provided that the complex is stable *in vivo* [7].

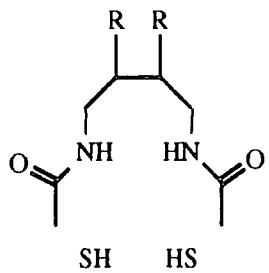
Initial work using a N_2S_2 donor set was carried out in 1979 by Davison and coworkers.[8] A crystal structure was obtained of a complex with technetium V in a square-based pyramidal arrangement, figure 5.4.



R = H

Figure 5.4 Position of Tc=O sitting above N_2S_2 plane.

E. Deutsch and coworkers[9] have studied variants of this ligand using N,N'-Bis(mercaptoacyl)butane-1,4-diamine (figure 5.5). The complex that was formed with Tc also had a $(TcO)^{3+}$ core. The substituents on the alkyl backbone allowed variation of the lipophilicity of the complex for biodistribution studies.



R = H, Ar or aliphatic

Figure 5.5 Skeleton of ligand with N_2S_2 donor set.

5.2 General Synthesis

Species containing P-S bonds have been known for 150 years since Berzelius discovered di(phosphorus pentasulphide) in 1843. There are a range of other phosphorus sulphides now known. The structures are based on phosphorus cages with added sulphur atoms. Di(phosphorus

pentasulphide) is of an intermediate reacitvity and hence is useful as a source of P-S bonds[10,11] (figure 5.6).

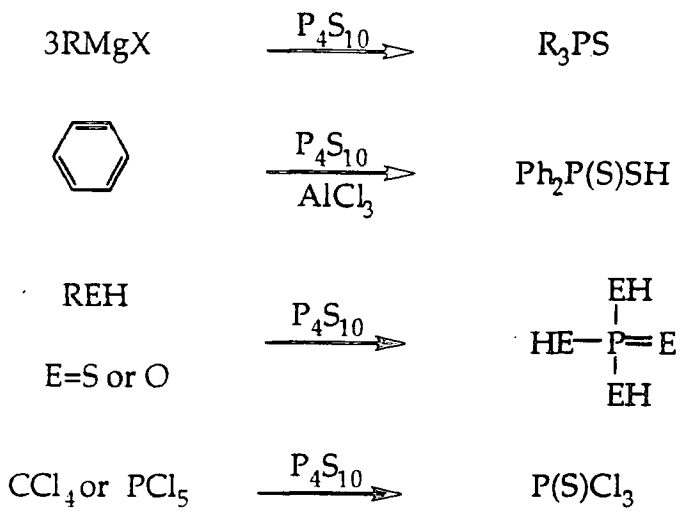


Figure 5.6 Introduction of P=S bonds with P_4S_{10}.

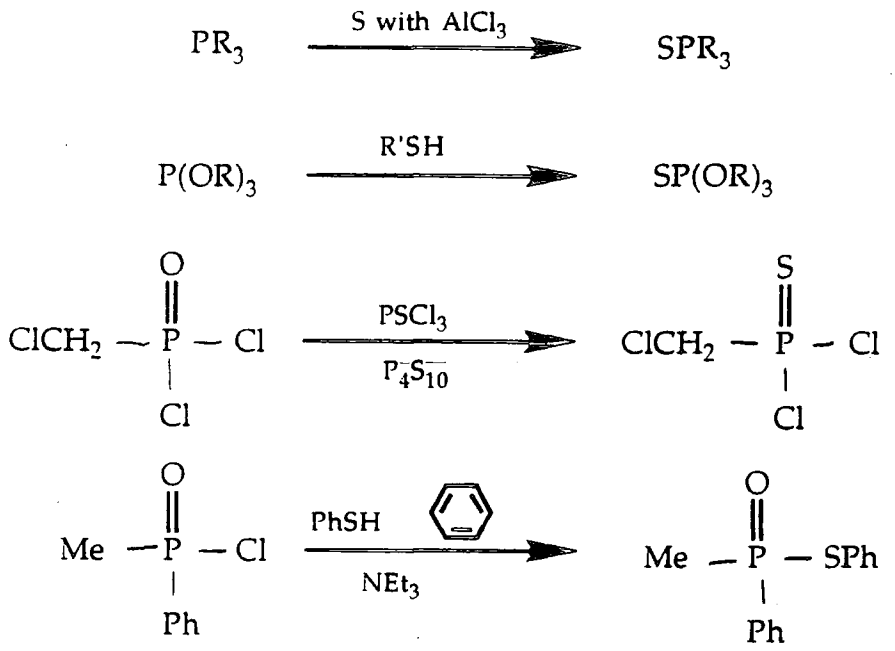


Figure 5.7 Formation of P=S bonds with an already substituted phosphorus centre.

These methods break down the cage structure of di(phosphorus pentasulphide) and add to it. It is not always possible to create the structure you want starting from this point. Several methods for adding sulphur to a phosphorus (III or V) compound that is already partially functionalised are given, figure 5.7. These reactions include a mixture of direct addition, reaction to add a group containing sulphur and exchange.[12]

There are many reactions that will provide phosphine sulphides.[13,14] It could also be possible that if the amount of reagent added was precisely controlled this could be a route to thiophosphinic acids, figure 5.8.

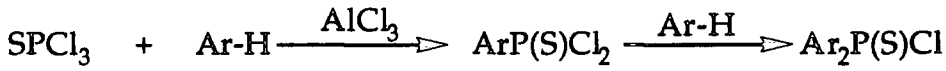
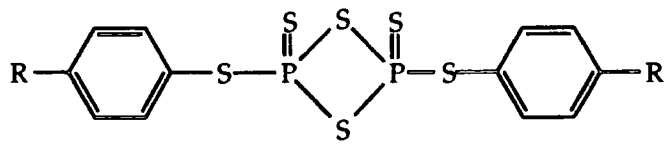


Figure 5.8 Possible route to a thiophosphinic acid.

Lawesson's reagent[15,16] and its derivatives, eg 81, are also available as milder reagents for converting P=O systems into P=S systems. The advantage of these reagents is their increased solubility that allows lower reaction temperatures to be used.



81 R = H 82 R = OCH_3

5.3 Routes to Thiophosphinates

The system studied initially was relatively complex, consisting of a secondary or tertiary amine and a phosphorus that already had two P-C bonds in place. There were three routes that were possible starting with a system of this sort.

5.3.1 Direct addition

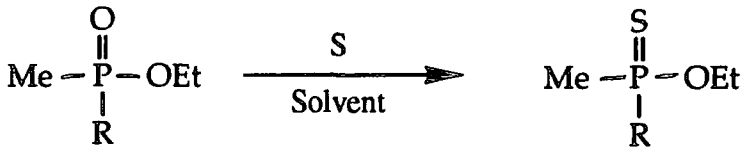
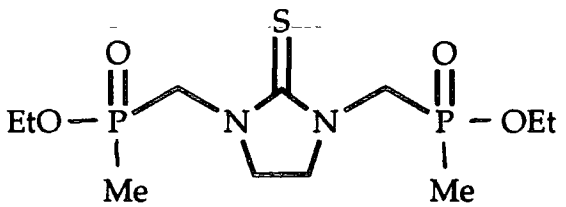


Figure 5.9 Direct addition of sulphur to a phosphinate ester.

It was hoped that it might be possible to carry out the substitution of an oxygen for a sulphur directly (figure 5.9) This was attempted using elemental sulphur, P_4S_{10} and one of the Lawesson's derivatives under a variety of conditions but to no avail.



83

83 Dimethyl-1,3-(2-sulphoxide)-tetrahydroimidazoleN,N'dimethylene(methylphosphinate)

The reaction of diethyltetrahydroimidazoleN,N'di(methylene (methylphosphinate) with elemental sulphur in pyridine initially gave an interesting result. A mass spectrum of the crude product showed a

gain in weight of 32, corresponding to replacement of two oxygen atoms by sulphur atoms. However NMR analysis proved this to be a false assumption as the ^{31}P shift had scarcely changed. The proton NMR showed that the NCH_2N multiplet had disappeared. The ^{13}C NMR spectrum solved the problem as not only had the signal due to NCH_2N carbon disappeared but also a new signal appeared at 183ppm. The addition of sulphur to the 2 position had been achieved giving the thiourea, 83.

5.3.2 Reduction/Oxidation Methods

The addition of elemental sulphur to P III species[1] will result in a P V species containing a P-S double bond. Hence reduction of the phosphinate ester to a phosphine followed by sulphur oxidation (figure 5.11) should give a secondary phosphine sulphide.

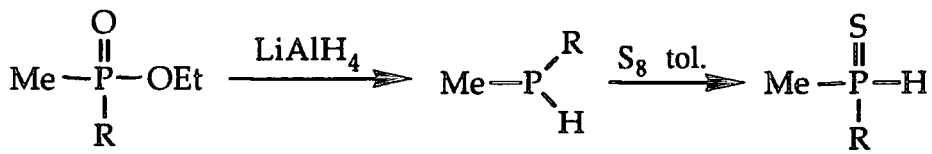


Figure 5.10 Reduction/Oxidation to form secondary phosphine sulphide.

The reduction of a phosphinate ester has been reported using either lithium aluminium hydride[17] (figure 5.10) or dibutylaluminium hydride[18]. Both reactions were followed by oxidation of some sort.

Further oxidation to the phosphinothionic acid should be possible by reaction with sulphuryl chloride followed by quenching in water (figure 5.11). This would give the phosphinothionic acid form, which is equivalent to the desired product.

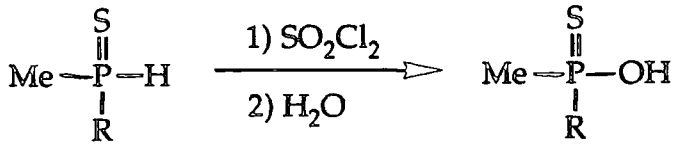


Figure 5.11

It is possible with this reaction to add an excess of sulphur and obtain the dithiophosphinic acids, which in concentrated solution is known to form dimers. However even considering this, no product which could be explained was obtained.

5.3.3 Strategies to Form Thiophosphinic Acids

There were two ways to view this and overcome the possible problem due to the N-H groups;

a) create the phosphinothiolic group before adding to the amine skeleton. (Conversion-Addition)

b) use an amine with protected nitrogens. (Addition-Conversion)

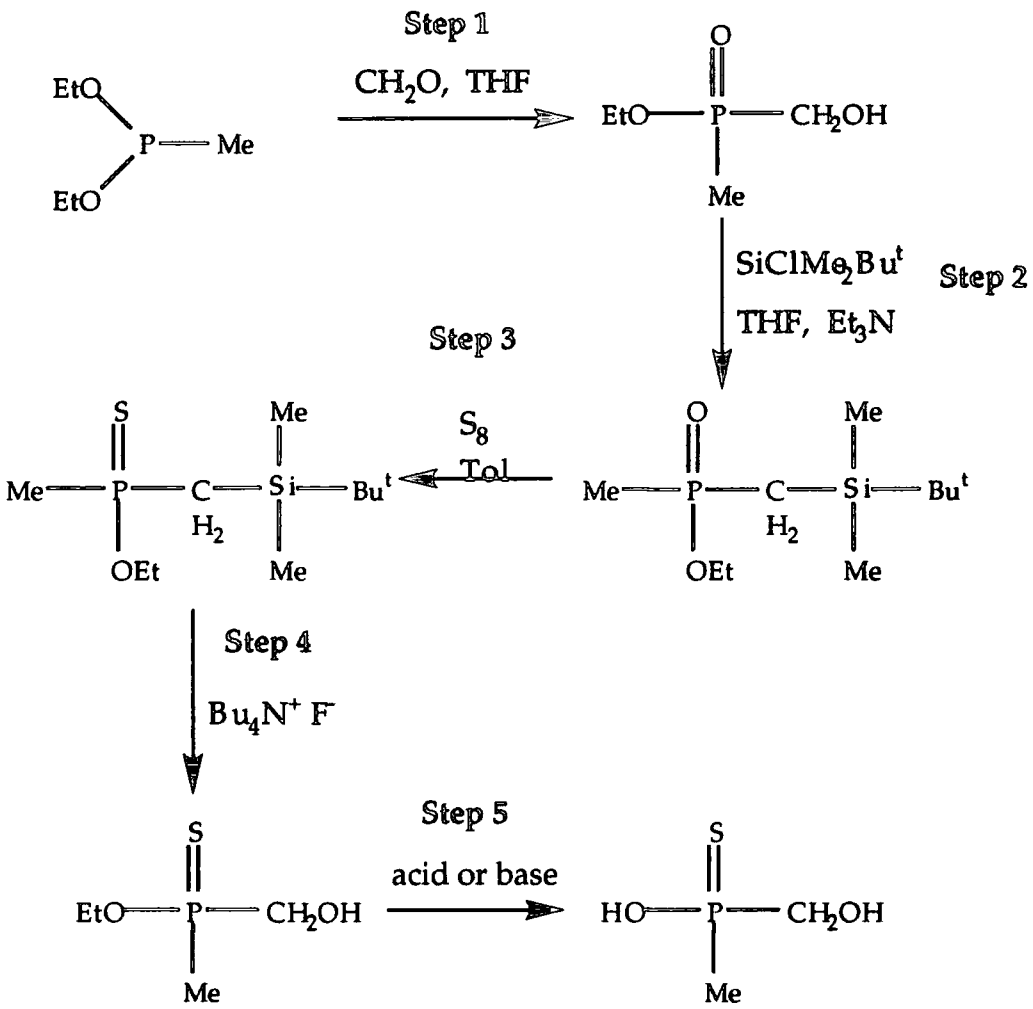
Both of these have been attempted. The first involved chemistry on ethyl(hydroxymethylene(methylphosphinate)) involving protection of the alcohol group, addition of sulphur and then deprotection. The second route required reacting a 1,3-ditosylated amine with the mesylate of ethyl(hydroxymethylene(methylphosphinate)) followed by conversion of P=O into P=S.

5.3.3.1 Conversion-Addition

It was found that if the alcohol protected form of ethyl[(hydroxymethyl)(methylene(methylphosphinate))] was used a P=S could be created under relatively mild conditions (scheme 5.1, step 3). After monitoring the reaction by ^{31}P NMR, reaction conditions of 4 hours

at 20°C with P_4S_{10} were found to work well with minimum decomposition of the starting material.

The protection and deprotection steps are shown below (scheme 5.1). The silyl ether of the alcohol was the easiest to form and remove[19] so this was used (steps 2 and 4). A problem was found with this route. It is known that silyl groups can be used to deprotect phosphinic esters and it was found that when deprotecting the alcohol the ester group was also removed (steps 4 and 5), giving the undesired acid.



Scheme 5.1

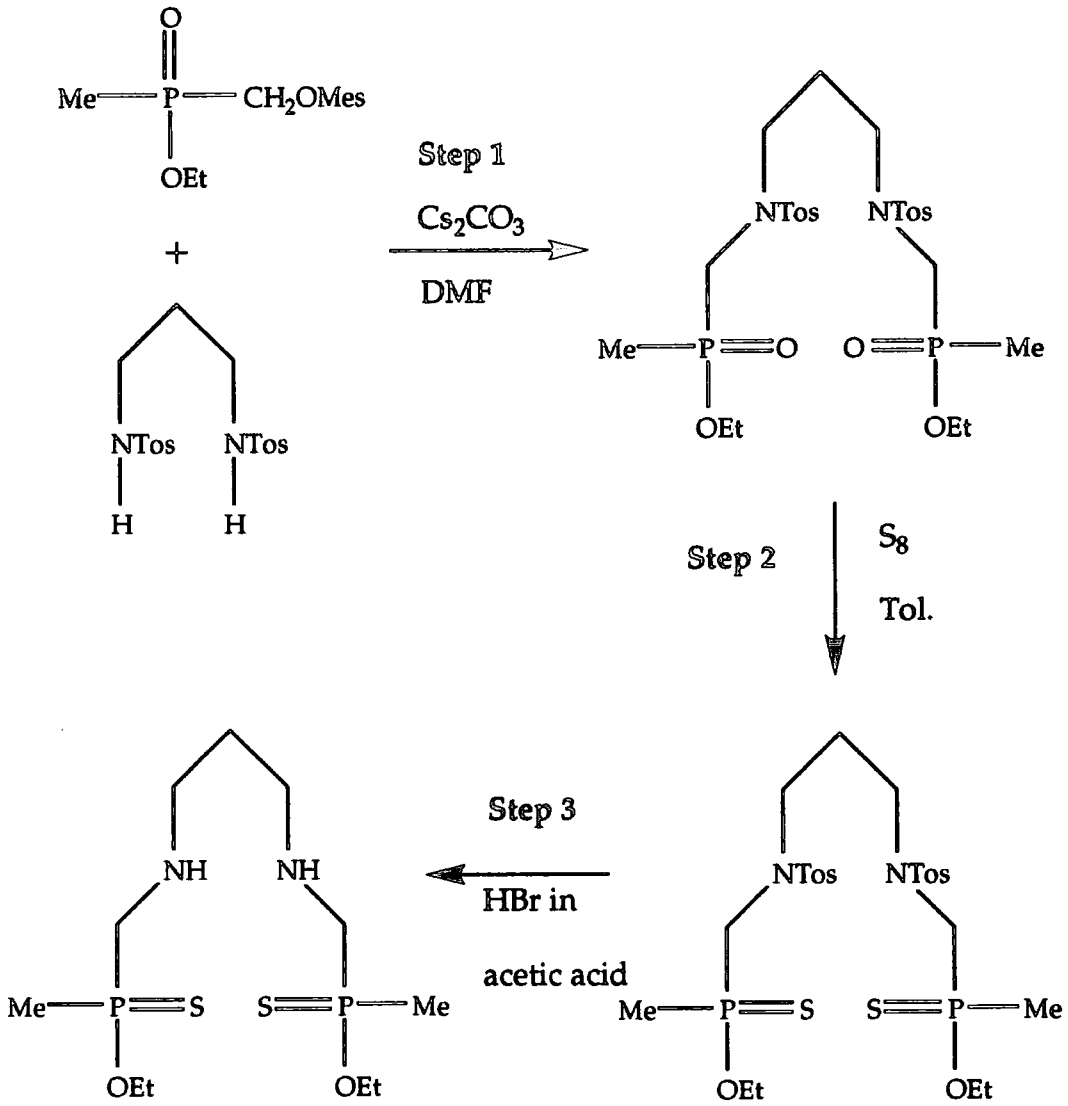
5.3.3.2 Addition-Conversion

Having noted that it was possible to convert P=O to P=S when the hydroxyl group is protected, an attempt to create a phosphinic ester attached to a protected nitrogen was made, scheme 5.2. The first step of this sequence works in DMF with caesium carbonate, although the yield is rather poor. The second step was attempted and there is some evidence from ^{31}P NMR to suggest that this does occur, although it was done on a very small scale and no further characterisation was then possible. The final step is a known reaction to remove the tosyl groups. The remaining question is would the rest of the molecule remain intact under the relevant conditions.

5.4 Conclusion

Although this work has not actually produced any of the final products several of the steps along each path have been completed.

There are several possible reasons for the problems with this chemistry. Initially reactions were done on a small scale (<50mg of reactant) and much of the literature related to these sorts of compounds does state low yields even when large scale (>10g of reactant) reactions are carried out.


Me
P
CH2OMes
OEt
+
NTos
NTos
H
H
Step 1
Cs2CO3
DMF
NTos
NTos
Me
P
O
O
P
Me
OEt
OEt
Step 2
S8
Tol.
NTos
NTos
Me
P
S
S
P
Me
OEt
OEt
Step 3
HBr in
acetic acid
NH
NH
Me
P
S
S
P
Me
OEt
OEt

Scheme 5.2

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Chapter 6

Experimental

6.1 Introduction

All reactions were carried out under nitrogen in apparatus that had been oven dried and cooled under nitrogen. Merck grade three molecular sieves were used, which were activated before use by heating while under vacuum. Silica refers to Merck Kieslgel and Alumina refers to Merck Alumina activity II - III that was soaked in ethyl acetate for 24 hours prior to use. Mass spectra were obtained on a VG 7070 E spectrometer using DCI or FAB ionisation modes from methanol solutions. Infra-red spectra were obtained on a Perkin-Elmer 577 spectrometer using NaCl discs with the samples as oils or mulls with Nujol. ^{31}P nmr were obtained with a Bruker AC 250 spectrometer (101 MHz) and chemical shifts are given to higher frequency of H_3PO_4/H_2O (external reference). ^{1}H and ^{13}C nmr were obtained with a Bruker AC 250 and a Bruker 500 and Varians at 400 and 200 MHz, (all referenced to TMS.)

6.2 Synthesis

6.2.1 ROUTE 1

1*Diethylamine N Methylene Phenylphosphinic acid* **[43]**

Diethylamine (2g, 0.027 moles) and Phenylphosphinic acid (3.8g, 0.027 moles) were dissolved in a flask with water (6 cm^3) and concentrated hydrochloric acid (4 cm^3). This was heated with stirring until all the solid had dissolved and once the mixture was boiling formaldehyde solution (3

cm^3 of 37-41%) was added. The solution was heated at 120°C for 2 hours. The product remained in solution on cooling and did not precipitate on adjustment of pH (1 to 8). The water was then removed under reduced pressure. There remained a dark yellow oil (5g, 81%) of desired product and hydroxymethylene phenylphosphinic acid.

δp (D_2O, pD= 10) 24.2 ppm

δH (D_2O, pD= 10) 0.86 (6H, t, CH_3, ^2J = 7.5 Hz) 2.9 (4H, m, CH_2) 3.03 (2H, d, NCH_2P, ^2J = 13.0 Hz)

M/e (DCI) 228 (M^+ +1)

2 *Ethylenediamine Tetra(methylene(phenylphosphinic))acid* [10]

The synthesis from reference[1] was followed without alteration to give the desired product.

3 *Diethylenetriamine Penta(methylene(phenylphosphinic))acid* [36]

Following the same method as used for 1 diethylenetriamine (4.1g 0.04 mole), phenylphosphinic acid (28.4g 0.2 moles), water (65 cm^3) and concentrated hydrochloric acid (45 cm^3) were added. After dissolving the solid the formaldehyde solution (40 cm^3 37-41%) was added. After boiling under reflux for 24 hours an orange oil had formed at the bottom of the flask. This was dissolved in sodium hydroxide solution (15 cm^3, 5%) and precipitated out by addition of hydrochloric acid (20cm^3, 10%) to pH 5.5, giving an off white solid (19.6g, 56.7%) melting point 246-8°C.

δ_P (NaOD, pD=14) 29.3 (4P,s) 27.6 (1P,s)

δ_H (NaOD, pD=14) 2.67 (10H d, N CH_2 P, ^2J = 8.8 Hz) 7.3 (10H, m, Aromatic) 7.5 (15H, m, Aromatic)

δ_C (NaOD, pD=14) 55.52 (s, NCH_2CH_2N) 56.4 (d, N CH_2 P, ^1J = 113 Hz) 127.99, (ortho Aromatic,) 130.95 (meta Aromatic) 130.8 (para Aromatic)

Elemental analysis; Found: C, 49.02%; H, 5.78%; N, 4.23% ; P, 16.6% ; Cl, 4.35% $C_{39}H_{48}N_3O_{10}P_5.HCl.2H_2O$ requires: C, 49.5%; H, 5.61%; N, 4.44%; P, 16.4%; Cl, 4.10%.

4 1,4,7 Triazacyclononane N, N' N" tri(methylene(phenylphosphinic)) acid [51]

Using the same method as above with 1,4,7 triazacyclononane (0.96g, 7.4 mmoles), phenylphosphinic acid (3.23g, 23 mmoles), water (9 cm^3) and concentrated hydrochloric acid (6 cm^3). This mixture was boiled under reflux for 24 hours . No precipitate formed during this time. All solvent was removed under reduced pressure to leave a white foam which would not recrystallise from dilute acid on lowering of the pH (crude mass 4.22g). ^{31}P NMR analysis revealed two major products in molar ratio 6 : 4 of which one was $PhP(CH_2OH)O_2H$.

δ_P (D_2O pD=0.5) 29.6 (4P, s, $Ph(CH_2OH)PO_2H$) 26.2 (6P, s, $RPhPO_2H$)

M/e (DCI) 592 (M^+ +1)

6.2.2 ROUTE 2

All reagents for these reactions were dried prior to usage as these reactions are sensitive to the presence of water.

5Tetraethyl ethylenediamine tetrakis (methylene(methylphosphinate)) [37]

The ethylenediamine (0.24g, 4 mmoles) was placed into the flask with THF (40 cm^3) and diethoxymethylphosphine (2g, 16 mmoles). This was heated to reflux with a Soxhlet filled with molecular sieves (3Å). Once this was boiling under reflux paraformaldehyde (0.6g 0.02 moles) was added. After heating for 18 hours the reaction was stopped and the solvent removed under reduced pressure. This also removed any volatile reactants remaining to leave a clear colourless oil which was purified by

column chromatography on alumina using dichloromethane with increasing amounts (0-5%) of methanol (0.76, 35%). Thin layer chromatographic analysis (Al_2O_3, 10% MeOH-CH_2Cl_2) gave a pale yellow oil, R_f = 0.54.

δ_P ($CDCl_3$) 51.1 (s)

δ_H ($CDCl_3$) 1.33, (t, $POCH_2CH_3$,) 1.53 (d, PCH_3, ^2J=14.0 Hz) 2.91 (d, PCH_2N, ^2J=10.1 Hz) 2.96 (s, NCH_2) 4.1 (m, $POCH_2$) *3.6 (br, NCH_2N)

δ_C ($CDCl_3$) 12.3 (d, PCH_3 ^1J=93.6) 16.0 (d, OCH_2, ^3J=12.2 Hz) 53.75 (d, PCH_2N, ^1J=116.3 Hz) 53.65 (d,OCH_2, ^1J= 19.0 Hz) 60.0 (m, NCH_2) *79.0, (t, NCH_2N, ^3J= 12.6 Hz)

M/e (DCI) 541 (M^+ +1) *M/e (DCI) 313 (M^+ +1)

* Due to a tetrahydroimidazole ring formed as a minor product during the reaction.

6 ***Pentaethyl diethylenetriamine pentakis (methylene (methylphosphinate))***

Following the procedure for 5 but using diethylenetriamine (0.4g, 3.9 mmoles) diethoxymethylphosphine (2.6g, 0.02 moles) and paraformaldehyde (0.85g, 0.028 moles). A clear light yellow oil was isolated (0.82g, 30%), R_f = 0.48 (2.5% methanol in dichloromethane on alumina). However this was a mixture of the desired product and of the bridged form that proved to be inseparable.

δ_H ($CDCl_3$) 1.28, 1.35 (superimposed doublet of triplets $POCH_2CH_3$) 1.52 (^2J=8.8Hz) 1.57, (^2J=9.0Hz) 2.9 (m, NCH_2 & NCH_2P) *3.5 (br, NCH_2N) 4.1 (m, $POCH_2$)

δ_P ($CDCl_3$) 51.7 (4P,s) 52.2 (1P,s)

δ_C ($CDCl_3$) 12.55 and 12.7, (d, PCH_3 ^1J=93Hz) 16.55 (d, OCH_2CH_3 ^3J= 6 Hz) 53.25 and 54.25 (d, amine, ^3J=8 Hz) 54.1 (d, NCH_2P, ^1J=115 Hz) 60.15 and 60.25, (d, $POCH_2$, ^2J=7 Hz) *78.05, (d, NCH_2N, ^3J=10 Hz)

* Due to the presence of the bridged species.

7 Trimethyl 1, 4, 7 Triazacyclononane N, N' N", tris(methylene (phenylphosphinate)) [48]

Using the same method as for 5 with 1,4,7 triazacyclononane (0.3g, 2.4 mmoles), phenyldimethoxyphosphine (1.8g, 12 mmoles), THF (40 cm^3) and paraformaldehyde (0.45g). The mixture was boiled under reflux for 16 hours at 80°C before removing the solvent and purifying using column chromatography on alumina to give a clear pale yellow oil (0.52g, 34.4%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.58.

δ_P ($CDCl_3$) 40.7 (s)

δ_H ($CDCl_3$) 2.7 (m, ring) 2.98, (d, PCH_2N, ^2J = 7Hz) 3.65 (d, $POCH_3$, ^3J = 11Hz)

δ_C ($CDCl_3$) 50.55 (d. POC, ^2J=7 Hz) 56.3 (m, ring) 56.6, (d, NCH_2P, ^1J= 119 Hz) 129.6 (d, P-C Aromatic ^1J=119 Hz) 128.05, (d, ortho Aromatic, ^2J= 12 Hz) 131.65 (d, meta Aromatic ^3J=10 Hz) 132.2 (br, para Aromatic)

I.R. 2800-3100 cm^{-1} (m, C-H aromatic and aliphatic) 1600 and 1490 cm^{-1} (w, P-Ph) 1440 cm^{-1} (m,POMe) 1170-1300 cm^{-1} (s and br, tertirty amine and P=O) 1120 cm^{-1} (m, POMe) 700-800 cm^{-1} (s, POMe).

M/e (DCI, accurate mass) Found: 634.43 (M^+ +1),

Calculated: 634.60 (M^+ +1)

8 *Trimethyl 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (benzylphosphinate))* [49]

Using the same method as for 5 with 1,4,7,triazacyclononane (0.2g 1.5 mmoles), benzyldiethoxyphosphine (1g, 7mmoles), THF (30 cm3) and paraformaldehyde (0.2g). The mixture was boiled under reflux at 80°C for 18 hours. The remaining solvent was removed and the residue purified

using column chromatography to give a pale yellow oil (0.4g, 37.2%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.55.

δ_P ($CDCl_3$) 48.7 (s)

δ_H ($CDCl_3$) 1.20 (3H, t, $POCH_2\underline{CH_3}$, ^3J = 3 Hz) 2.78, (2H, d, PCH_2N, ^2J = 6Hz) 2.9 (4H, m, ring) 3.18 (2H, d, PCH_2Ar, ^2J = 16Hz) 3.95 (2H, m, $PO\underline{CH_2}CH_3$) 7.24 (5H, m, Aromatic)

δ_C ($CDCl_3$) 16.59 (s, CH_3) 35.12 (d, $P\underline{C}H_2Ar$, ^1J = 84 Hz) 55.83, (d, NCH_2P, ^1J= 105 Hz) 57.2 (m, ring) 60.69 (s. POC,) 129.6 (CH2-$\underline{C}$ Aromatic) 129.67, (ortho Aromatic) 128.51 (d, meta Aromatic, ^3J=10 Hz) 132.2 (br, para Aromatic)

I.R. 3050 cm^{-1} (C-H aromatic) 2950 cm^{-1} (C-H aliphatic) 1400 to 1500 cm^{-1} (m. P-O-Et) 1200 cm^{-1} (br, P=O and tertiary N) 1040 cm^{-1} (s, P[O]O) 960 cm^{-1} (med. P-C)

M/e (DCI, accurate mass) Found: 718.83 (M^+ +1),

Calculated: 718.76 (M^+ +1)

9 Dimethyl 1, 3, Tetrahydroimidazole N, N' bis (methylene (methylphosphinate)) [38]

This reaction was carried out in the same way as for 5 with the same amounts of reagents and purified under the same conditions. However no molecular sieves were used although everything else was dried. Purification was on alumina to give a clear pale yellow oil (0.67g, 54.%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.58.

δp ($CDCl_3$) 51.1

δH ($CDCl_3$) 1.23, (6H, t, OCH_2CH_3) 1.45 (6H, d, PCH_3, ^2J=14 Hz) 2.84 (8H, d, NCH_2P, ^2J=10 Hz) 2.89 (4H, m, amine) 3.53 (2H, s, NCH_2N) 4.02 (4H, p, $POCH_2$)

δ_C ($CDCl_3$) 12.05 (d, PCH_3, ^1J=94 Hz) 15.9, 16.0 (d, OCH_2CH_3, ^3J=6 Hz) 53.35 (d, PCH_2N, ^3J=115 Hz) 53.55,(d, $POCH_2$, ^2J=9 Hz) 59.55 (d, amine, ^3J=8 Hz) 78.65 (d, NCH_2N, ^3J= 5 Hz)

I.R. 2950 cm^{-1} (C-H Ar) 1300 cm^{-1} (P-C) 1220 cm^{-1} (P=O), 1050 cm^{-1} (P-OEt).

M/e (DCI, accurate mass) Found: 313.53 (M^+ +1),

Calculated: 313.29 (M^+ +1)

10 *Dimethyl 1, 3, Tetrahydroimidazole N, N' bis (methylene (phenylphosphinate))*

This reaction was carried out in the same way as for 9, with fully dried equipment. Ethylenediamine (0.24g 4mmoles), phenyldimethoxyphosphine (2.7g 16 mmoles) and parafomaldehyde (0.6g excess) were mixed in THF (30 cm^3). This was heated to reflux at 80 °C for 18 hours. Purification was by column chromatography on alumina to give a clear colourless oil (0.75g, 46%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.68.

δ_P ($CDCl_3$) 39.42

δ_H ($CDCl_3$) 2.53 (4H, m, $N\underline{CH_2}CH_2$) 2.76 (4H, d, NCH_2P, ^2J=9 Hz) 3.18 (2H, d, NCH_2N, ^4J=2 Hz) 3.32 (6H, d, $POCH_3$, ^3J=11 Hz) 7.2 (4H, m, ortho Aromatic) 7.5 (6H, m, meta and para Aromatic)

δ_C ($CDCl_3$) 51.49 (d, $POCH_3$, ^2J=7 Hz) 54.55 (d, NCH_2P, ^1J=122 Hz) 54.59 (d, $N\underline{CH_2}CH_2$, ^4J=8 Hz) 79.65 (t, NCH_2N) 128.8 (d, ^3J=12 Hz, Aromatic) 129.4 (d, ^1J=124 Hz, Aromatic) 132.3 (d, ^2J=10 Hz, Aromatic) 132.78 (d, ^4J=3 Hz).

I.R. 2800-3100 cm^{-1} (m, C-H aromatic and aliphatic) 1600 and 1490 cm^{-1} (w, P-Ph) 1440 cm^{-1} (m,POMe) 1170-1300 cm^{-1} (s and br, tertiary amine and P=O) 1120 cm^{-1} (m, POMe) 700-800 cm^{-1} (s, POMe).

M/e (DCI, accurate mass) Found: 409.64 (M^+ +1),

Calculated: 409.37 (M^+ +1)

11 *Dimethyl Tetrahydropyrimidine N, N' bis (Methylene [Phenyl phosphinate])*

This reaction was carried out in the same way as for 9. 1,3 Diaminopropane (0.29g 4mmoles), phenyldimethoxyphosphine (2.7g 16 mmoles) and parafomaldehyde (0.4g excess) were mixed in THF (30 cm^3). This was heated to reflux at 80°C for 18 hours. Purification was by column chromatography on alumina to give a clear colourless oil (0.68g, 48%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.62.

δ_P ($CDCl_3$) 40.72

δ_H ($CDCl_3$) 1.3 (2H, t, $NCH_2\underline{CH_2}$) 2.5 (4H, m, $N\underline{CH_2}CH_2$) 2.68 (4H, d, NCH_2P, ^2J=9 Hz) 3.17 (2H, d, NCH_2N, ^4J=5 Hz) 3.4 (6H, d, $POCH_3$, ^3J=7 Hz) 7.3 (4H, m, o Ar) 7.6 (6H, m, m&p Ar)

δ_C ($CDCl_3$) 19.67 (s, $NCH_2\underline{CH_2}$) 50.24 (d, $POCH_3$, ^2J=13 Hz) 51.45 (d, NCH_2P, ^1J=122 Hz) 52.35 (d, $N\underline{CH_2}CH_2$, ^4J=6 Hz) 77.2 (NCH_2N) 127.4 (d, ^3J=12 Hz) 128.6 (d, ^1J=123 Hz) 130.1 (d, ^2J=10 Hz) 131.35 (d, ^4J=3 Hz).

I.R. 2800-3100 cm^{-1} (m, C-H aromatic and aliphatic) 1600 and 1490 cm^{-1} (w, P-Ph) 1440 cm^{-1} (m,POMe) 1170-1300 cm^{-1} (s and br, tertiary amine and P=O) 1120 cm^{-1} (m, POMe) 700-800 cm^{-1} (s, POMe).

M/e (DCI, accurate mass) Found: 423.71 (M^+ +1),

Calculated: 423.40 (M^+ +1)

12 *Diethyl Tetrahydropyrimidine N, N' bis (Methylene [Methyl phosphinate])*

This was carried out as for 9 using a solution of 1,3 diaminopropane (0.29g, 4 mmoles) in THF (30 cm^3) and

diethoxymethylphosphine (2g, 16 mmoles). This mixture was heated to reflux 18 hours. A clear colourless oil (0.55g 50.5%) was obtained after purification by column chromatography. Thin layer chromatographic analysis (Al_2O_3, 10% MeOH-CH_2Cl_2) gave R_f = 0.83.

δ_P ($CDCl_3$) 52.23

δ_H ($CDCl_3$) 1.3 (3H, t, $OCH_2C\underline{H}_3$)1.46 (3H, d, PCH_3, ^2J=14 Hz) 1.50 (1H, t, $NCH_2C\underline{H}_2$) 2.63 (2H, m, $NC\underline{H}_2CH_2$) 2.61 (2H, d, NCH_2P, ^2J=10 Hz) 3.35 (1H, br, NCH_2N) 4.02 (2H, p, $OC\underline{H}_2CH_3$)

δ_C ($CDCl_3$) 12.48 (d, PCH_3, ^1J=114 Hz) 16.36 (s, $OCH_2\underline{C}H_3$,) 20.70 (s, $NCH_2\underline{C}H_2$) 52.50 (d, NCH_2P, ^1J=115 Hz) 53.34 (s, $N\underline{C}H_2CH_2$) 59.94 (s, $O\underline{C}H_2CH_3$) 77.2 (m, NCH_2N)

I.R. 2950 cm^{-1} (m, C-H aliphatic) 1400-1450 (m, POEt) 1300 cm^{-1} ($P\text{-}CH_3$) 1220 cm^{-1} (s and br, tertiary amine and P=O), 1050 cm^{-1} (s, P-OEt) 950 cm^{-1} (s, $P\text{-}CH_3$) 800-750 cm^{-1} (s, POEt).

M/e (DCI, accurate mass) Found: 327.73 (M^+ +1),

Calculated: 327.31 (M^+ +1)

13 ***Diethyl Propanediamine N, N' ditosyl N, N' dimethylene (methylphosphinate)***

1,3-Diaminopropane N, N' ditosylamide (0.1g, 0.2mmoles), ethyl [(methanesulfanatomethylene)methyl phosphinate] (0.12g, 0.5mmoles) and caesium carbonate (0.18g, 0.5mmoles) were dissolved in DMF (10 cm3). This was stirred at 60°C for 16 hours. When there was none of the mesylate remaining in the solution the reaction was stopped and the solvent removed. This left a brown oil that could be disolved in dichloromethane and then washed with water. The dichloromethane was then dried and removed under reduced pressure to yield a colourless oil (0.05g, 40%) Rf = 0.35 (Al_2O_3, 10% MeOH-CH_2Cl_2).

δ_P ($CDCl_3$) 49.06

δ_H ($CDCl_3$) 1.3 (6H, t, $OCH_2\underline{CH_3}$) 1.46 (6H, d, PCH_3, ^1J=14 Hz) 1.50 (2H, t, $NCH_2\underline{CH_2}$) 2.43 (6H, s, $\underline{CH_3}$-aromatic) 2.63 (4H, m, $NCH_2\underline{CH_2}$) 2.61 (4H, d, NCH_2P, ^2J=10 Hz) 3.35 (2H, br, NCH_2N) 4.02 (p, $OCH_2\underline{CH_3}$) 7.18 (10H, two doublets, aromatics)

δ_C ($CDCl_3$) 12.48 (d, PCH_3, ^1J=14 Hz) 16.36 (d, $OCH_2\underline{C}H_3$, ^4J=6 Hz) 20.70 (s, $NCH_2\underline{C}H_2$) 23.2 (s, $\underline{C}H_3$-aromatic) 52.50 (d, NCH_2P, ^1J=115 Hz) 53.34 (d, $N\underline{C}H_2CH_2$, ^3J=7 Hz) 59.94 (m, $OCH_2\underline{CH_3}$) 77.2 (m, NCH_2N) 125.4, 129,7, 138.6, 140.8 (s, aromatics)

M/e (DCI) 623 [M^++1]

6.2.3 HYDROLYSIS

14 ***1,4,7 Triazacyclononane N, N', N" tri(methylene (phenylphosphinic)) acid*** **[51]**

Ligand 7 (0.4g) was heated to reflux in 6M hydrochloric acid for 16 hours. After removing the solvent under reduced pressure an off-white solid was obtained (0.34g, 92%), melting point 210-212°C.

δ_P (D_20, pD=0.5) 27.2ppm

δ_H (D_20, pD=0.5) 3.10 (12H, br, ring) 3.25 (6H, d, PCH_2N ^2J=7 Hz) 7.5 (9H, m, meta and para Aromatic) 7.6 (6H, m, ortho Aromatic)

δ_C (D_20, pD=0.5) 51.6 (s, ring) 55.4 (d, PCH_2N, 1J=98 Hz) 129.9 (d, P-C, ^1J=100 Hz) 130 (br, meta Aromatic) 132 (br, ortho Aromatic) 133.8 (br, para Aromatic)

Elemental Analysis; Found: C, 46.01%; H, 5.75%; N, 6.07%; Cl, 9.9%; $C_{27}H_{33}N_3P_3O_6.2HCl.2H_2O$ requires: C, 46.29%; H, 5.57%; N, 6.00%. Cl, 9.3%

15 *1,4,7 Triazacyclononane N, N', N" tri(methylene(benzylphosphinic)) acid* [52]

Ligand 8 (0.3g) was heated to reflux in 6M hydrochloric acid for 16 hours. After removing the solvent under reduced pressure an off-white solid was obtained (0.25g, 95%).

δ_P ($CDCl_3$) 48.70 (s)

δ_H ($CDCl_3$) 3.19 (4H, m, ring) 3.22 (2H, d, PCH_2N, ^2J = 16 Hz) 3.76 (2H, d, PCH_2Ar, ^2J = 6Hz) 7.29 (5H, m, Aromatic)

δ_C ($CDCl_3$) 33.23 (d, PCH_2Ar, ^1J = 83 Hz) 51.92, 51.27 (br, ring) 57.14 (d, NCH_2P, ^1J= 111 Hz) 128.91 and 129.85 (ortho and meta Aromatic) 127.16 (para Aromatic).131.4 (CH2-C Aromatic)

16 ***Ethylenediamine N,N' bis (methylene(methylphosphinic))acid*** [39]

Ligand 9 (0.67g) was heated at reflux for 18 hours in 6M hydrochloric acid. The solvent was removed to leave a white solid (0.62g, 93%), melting point 246-248°C.

δ_P (D_2O, pD= 0.7) 32.13ppm

δ_H (D_2O, pD= 0.7) 1.43 (6H, d, PCH_3, ^2J = 14.2 Hz) 3.27 (4H, d, PCH_2N, ^2J=9.6 Hz) 3.57 (4H, s, amine)

δ_C (D_2O, pD= 0.7) 15.7(d, PCH_3, ^1J=98 Hz) 45.55 (d, amine, ^3J=8 Hz) 47.0 (d, PCH_2N, ^1J= 89Hz) Elemental analysis found: C, 22.68%; H, 6.55%; N, 8.45%; P, 19.0%; Cl, 22.6%;

$C_6H_{18}N_2P_2O_4.2HCl.2H_2O$ requires; C, 22.86%; H, 6.39%; N, 8.89%; P, 19.80%; Cl, 23.3%.

17 ***Tetrahydroimidazole N, N' bis methylene (methylphosphinic acid)***

The ligand 9 (0.2g, 0.6mmoles) was dissolved in a sodium hydroxide solution (2cm^3, 0.1M). This was left at room temperature for 40 hours. After this time the volume of solvent was reduced until

precipitation began. After 24 hours a white solid was obtained, (0.13g, 82%), melting point 244-246°C.

δ_P (NaOD pD=13) 38.0

δ_H (NaOD pD=13) 1.21 (3H, d, PCH_3, ^2J=12 Hz) 2.6 (2H, d, NCH_2P, ^2J=8 Hz) 2.85 (2H, s, NCH_2CH_2N) 3.53 (1H, s, NCH_2N)

δ_C (NaOD pD=13) 13.05 (d, PCH_3, ^1J=89 Hz) 54.8 (d, PCH_2N, ^3J=113 Hz) 58.5 (d, NCH_2CH_2N, ^3J=8 Hz) 78.8 (d, NCH_2N, ^3J= 5 Hz)

M/e (FAB) 257 (M^+ +1)

18 ***Ethylenediamine N,N' bis (Methylene [Phenylphosphinic]) Acid*** **[40]**

Ligand **10** (0.62g) was heated at reflux for 18 hours in 6M hydrochloric acid. The solvent was removed to leave a white solid (0.54g, 98%), melting point 276-278°C.

δ_P (NaOD pD=12.5) 24.78

δ_H (NaOD pD=12.5) 2.50 (4H, t, NCH_2CH_2) 2.79 (4H, d, NCH_2P, ^2J=11 Hz) 7.51 (3H, m, ortho and para Aromatic) 7.70 (2H, m, meta Aromatic)

δ_C (NaOD pD=12.5) 47.36 (NCH_2CH_2) 48.10 (d, NCH_2P, ^1J=113 Hz) 129.1 (d, ^3J=12 Hz, Aromatic) 131.43 (d, ^2J=9 Hz, Aromatic) 132.19 (br, Aromatic) 135.05 (d, ^1J=129 Hz, Aromatic) .

Elemental Analysis found: C, 47.95 %; H, 5.62 %; N, 6.77 %; Cl, 8.8 %;P, 15.49 %. $C_{16}H_{22}N_2P_2O_4$.HCl requires: C, 47.47 %; H, 5.69%; N, 6.92%; Cl, 8.78%P, 15.33 %.

M/e (FAB) [M^++1] for $C_{16}H_{22}N_2P_2O_4$ = 368

19 ***Propanediamine N,N' bis (Methylene [Phenylphosphinic]) Acid*** **[42]**

Ligand **11** (0.44g, 1mmole) was heated at reflux for 18 hours in 6M hydrochloric acid. The solvent was removed to leave a white solid (0.36g, 90%).

δ_P (D_2O pD=0.5) 20.43

δ_H (D_2O pD=0.5) 1.6 (2H, t, NCH_2CH_2) 2.65 (4H, t, NCH_2CH_2) 2.89 (4H, d, NCH_2P, ^2J=10 Hz) 7.14 (m, Aromatic) 7.33 (m, Aromatic)

δ_C (D_2O pD=0.5) 20.91 (s, NCH_2CH_2) 45.5 (d, NCH_2P, ^1J=94 Hz) 45.29 (d, NCH_2CH_2, ^4J=6 Hz) 128.0 (d, Aromatic ^3J=13 Hz) 129 (d, Aromatic ^1J=130 Hz) 130.3 (d, Aromatic ^2J=10 Hz) 131.73

M/e (FAB) [M^++1] for $C_{17}H_{24}N_2P_2O_4$ = 383

20 *Propanediamine N,N' bis (Methylene [Methylphosphinic]) Acid* [41]

Ligand 11 (0.7g, 2mmoles) was heated at reflux for 18 hours in 6M hydrochloric acid. The solvent was removed to leave a white solid (0.52g, 94%), melting point 244-246°C.

δ_P (D_2O pD=0.5) 37.72

δ_H (D_2O pD=0.5) 1.30 (6H, d, PCH_3, ^2J=15 Hz) 1.98 (2H, t, NCH_2CH_2) 3.03 (4H, m, NCH_2CH_2) 3.11 (4H, d, NCH_2P, ^2J=10 Hz)

δ_C (D_2O pD=0.5) 15.0 (d, PCH_3, ^1J=98 Hz) 22.14 (s, NCH_2CH_2) 46.0 (d, NCH_2P, ^1J=89 Hz) 46.4 (d, NCH_2CH_2, ^4J=7 Hz)

Elemental Analysis found: C, 24.99%; H, 6.51%; N, 8.35%; Cl, 22.04%

$C_7H_{20}N_2P_2O_4.2HCl$. requires: C, 25.54%; H, 6.65%; N, 8.50%; Cl, 21.6%

M/e (FAB) [M^++1] for $C_7H_{20}N_2P_2O_4$ = 259

6.2.4 COMPLEX FORMATION

21*Copper complex of 1,4,7 Triazacyclononane N, N', N", tris (methylene(phenylphosphinate))*

Ligand 14 (0.2g) was added to 20 cm^3 of 0.01 molar copper II nitrate solution. [This was using one equivalent of copper to ligand assuming the ligand to be 60% pure (from ^{31}P nmr analysis)]. The solution was heated

to dissolve all of the ligand and left to cool. On standing for 2-3 days crystals formed (0.103g, 80% considering impurity). Elemental analysis: Found a) C, 43.43%; H, 6.18%; N, 5.6%; P, 12.2%; Cu, 8.26%; b) N, 5.74%; C, 43.45%; H, 5.35%; $C_{27}H_{33}N_3P_3O_6Cu.H_3O^+.4H_2O$ requires: C, 43.63%; H, 5.93%; N, 5.66%; P, 12.53%; Cu. 8.55% .

Crystal Data for $[CuL][H_3O^+].4H_2O$ - $C_{27}H_{44}CuN_3O_{11}P_3$:

Trigonal, a = 14.399(3), c = 9.0228(17) Å, V = 1620.0(4) A3 , Dc = 1.522 gcm-3 , F(000) = 778.00, m = 0.88 mm-1. Space group was determined to be P -3. Crystal dimensions : 0.09 × 0.15 × 0.22 mm

Data Collection and Processing Nonius diffractometer, ω/2θ scan mode, (Mo-Kα) radiation ; 3893 reflections were measured of which 2360 were unique. Data were collected to a maximum 2θ of 53.7 degrees. The range of indices was h -15 to 15, k 0 to 18 and l 0 to 11. After correction for Lorentz, polarisation and absorption effects 1254 reflections were used with $I>3\sigma(I)$.

Structure Analysis and Refinement The structure was solved using the Patterson heavy atom method which revealed the position of the copper atom: remaining non-hydrogen atoms were located succeeding difference fourier syntheses. Refinement was by full-matrix, least squares calculations with all non-hydrogen atoms allowed anisotropic motion and with hydrogen atoms riding at calculated positions from the atoms to which they were bonded. The final cycle of refinement included 136 parameters with R=0.04. The highest peak in the final difference map had a height of 0.440 (e $Å^{-3}$).

Final atomic coordinates are given in Appendix

22 Gallium complex of 1,4,7 Triazacyclononane N, N', N", tris (methylene(phenylphosphinate))

Ligand 14 (0.3g) was dissolved in gallium nitrate solution (in 30cm^3 of 0.01 M) with heating. This was left to stand. After 3-4 days crystals formed (0.145g, 72% considering impurity)

δ_H (d4 methanol) 3.25 (m, NCH_2P and amine), 3.35 (doublet of doublets, amine) 3.5 (doublet of doublets, amine), 3.6 (doublet of doublets of doublets, amine), 3.7 (doublet of doublets of doublets, amine), 7.4 (triplet of doublets, meta Aromatic), 7.5 (triplet para Aromatic), 8.1 (doublet of doublets ortho Aromatic)

δ_C (d4 methanol) 53.36 (amine ring), 57.61 (d, amine ring, ^3J=12.5 Hz), 61.6 (s, NCH_2P, ^1J=91 Hz) 133.8 (s, P-C , ^1J= 142 Hz) 133.4 (m, P-C-C and P-C-C-C-C) 129.7 (d, P-C-C-C, ^3J= 13.4 Hz)

δ_P (d4 methanol) 27.36 ppm,

δ_{Ga} (d4 methanol) 132 ppm ($\omega 1/2$ = 557 Hz)

Elemental analysis: found C, 43.31%; H, 5.68%; N, 5.25% P, 11.95%;

$C_{27}H_{33}N_3P_3O_6Ga.5H_2O$ requires: C, 43.16%; H, 5.73%; N, 5.59% P, 12.39%.

Crystal Data for $[GaL].5H_2O$ - $C_{27}H_{43}GaN_3O_{11}P_3$:

Triclinic a = 11.883(3), b = 12.468(4), c = 11.842(5) Å, α =99.39(3), β = 98.47(3), γ = 79.97(2). V = 1691.7(1.0) Å^3 , Dc = 1.469 gcm^{-3} , F(000) = 748.28 , m = 10.057 cm^{-1}. Space group was determined to be P -1. Crystal dimensions : 0.25 × 0.14 × 0.10 mm

Data Collection and Processing Nonius diffractometer, ω /2θ scan mode; 7702 reflections were measured of which 7362 were unique. Data were collected to a maximum 2θ of 54.0 degrees. The range of indices was h -14 to 15, k 0 to 15 and l -15 to 14. After correction for Lorentz, polarisation and absorption effects 3149 reflections were used with I>2.5σ(I).

Structure Analysis and Refinement The structure was solved using the Patterson heavy atom method which revealed the position of the Gallium atom: remaining non-hydrogen atoms were located succeeding difference fourier syntheses.

The position of the carbon hydrogen atoms were calculated on the geometrical ground (C-H 0.95 Å). The water molecule hydrogen atoms were found from a difference Fourier map at R=0.052. There was one exception that had its position calculated as a point on the line between two oxygen atoms. The final cycle of refinement included 415 parameters with R=0.051. The highest peak in the final difference map had a height of 0.500e $Å^{-3}$.

Final atomic coordinates are given in Appendix.

23*Nickel complex of 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (phenylphosphinic)) acid*

Ligand 14 (0.2g) was added to 20 cm^3 of Nickel nitrate solution (0.01 molar). This was heated to dissolve the ligand. On cooling a blue/green precipitate formed, which dissolved easily in methanol but would not dissolve in hot water (0.14g, 64%).

Elemental analysis: found; C, 43.19% ; H, 6.08% ; N,5.61% ; P, 12.77% ; Ni,7.38% ; $C_{27}H_{33}N_3P_3NiO_6.6H_2O$ requires; C,42.87% ; H, 6.09% ; N, 5.56% ; P, 12.31% ; Ni, 7.77% .

Crystal Data for $[NiL].H_3O^{+}.4H_2O$ - $C_{27}H_{44}NiN_3O_{11}P_3$:

Trigonal a = 14.356(1), b = 14.356(1), c = 9.0421(6) Å, α =90, β = 90, γ = 120. V = 1613.9(2) $Å^3$, Dc = 1.519 gcm^{-3} , F(000) = 776 . Space group was determined to be P -3. Crystal dimensions : 0.15 × 0.15 × 0.20 mm

Data Collection and Processing Enraf Nonius diffractometer, ω /2θ scan mode, 3887 reflections were measured of which 2358 were unique. Data were collected to a maximum 2θ of 54.0 degrees. The range of indices was

h -15 to 15, k 0 to 18 and l 0 to 11. After correction for Lorentz, polarisation and absorption effects 1288 reflections were used with $I>2.5\sigma(I)$.

Structure Analysis and Refinement The structure was solved using direct methods, remaining non-hydrogen atoms were located succeeding difference fourier syntheses.

The final cycle of refinement included 137 parameters with R=0.040. The highest peak in the final difference map had a height of 0.32e $Å^{-3}$.

Final atomic coordinates are given in Appendix.

24 *Iron III complex of 1, 4, 7 Triazacyclononane N, N', N'', tris (methylene (phenylphosphinic)) acid*

Ligand 14 (0.1g) was added to 10 cm^3 of 0.01 molar iron II sulphate solution. [This was using one equivalent of iron to ligand assuming the ligand to be 60% pure (from ^{31}P nmr analysis)]. The solution was heated to dissolve all of the ligand and left to cool. On standing for 2-3 days yellow crystals formed (0.073g, 67% considering impurity).

δp (d4 methanol) 31.37 ppm,

Elemental analysis: Found C, 44.17%; H, 5.90%; N, 5.64%; P, 12.33%; Fe, 8.58%; $C_{27}H_{33}N_3P_3O_6Fe.H_3O^+.4H_2O$ requires: C, 44.08%; H, 5.9%; N, 5.71%; P, 12.65%; Fe. 7.62% .

Crystal Data for $[FeL].5H_2O$ - $C_{27}H_{43}NiN_3O_{11}P_3$:

Trigonal a = 11.9417(7), b = 12.4275(8), c = 11.9678(9) Å, α =98.525(6), β = 99.522(6), γ = 79.155(2). V = 1707.7(2) $Å^3$, Dc = 1.43 gcm^{-3} , F(000) = 770 . Space group was determined to be P -1. Crystal dimensions : 0.20 × 0.25 × 0.30 mm

Data Collection and Processing Enraf Nonius diffractometer, ω /2θ scan mode, 7429 reflections were measured of which 7429 were unique. Data were collected to a maximum 2θ of 54.0 degrees. The range of indices was

h -14 to 15, k 0 to 15 and l -15 to 15. After correction for Lorentz, polarisation and absorption effects 4456 reflections were used with I>2.5σ(I).

Structure Analysis and Refinement The structure was solved using direct methods, remaining non-hydrogen atoms were located succeeding difference fourier syntheses.

The final cycle of refinement included 407 parameters with R=0.038. The highest peak in the final difference map had a height of 0.35e $Å^{-3}$.

Final atomic coordinates are given in Appendix.

25 ***Cobalt II complex of 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (phenylphosphinic)) acid***

Ligand 14 (0.1g) was added to 10 cm^3 of 0.01 molar cobalt II chloride solution. [This was using one equivalent of copper to ligand assuming the ligand to be 60% pure (from ^{31}P nmr analysis)]. The solution was heated to dissolve all of the ligand and left to cool. On standing for 18 hours pink crystals formed (0.084g, 77% considering impurity).

Elemental analysis: Found C, 43.45%; H, 6.04%; N, 5.57%; P, 11.96%; Co, 8.55%; $C_{27}H_{33}N_3P_3O_6Co.H_3O^+.4H_2O$ requires: C, 43.90%; H, 5.96%; N, 5.69%; P, 12.50%; Co. 7.99% .

Crystal Data for $[CoL][H_3O^+]\,4H_2O$ - $C_{27}H_{44}CoN_3O_{11}P_3$:

Trigonal, a and b = 14.428, c= 8.911 Å, Volume = 1605.0 (Å3) D_c = 1.528 (gcm^{-3}). Space group determined to be P-3. Crystal dimensions: 0.25 × 0.25 × 0.25 mm.

Data Collection and Processing Rigaku AFC65, (Mo-Kα) radiation; 2153 reflections of which 1896 were unique, of which 1318 were within I>3σ(I). Data collected to a maximum of 54 degrees. The range of indicies were h -14 to 14, k 0 to 17 and l 0 to 10.

Structure Analysis and Refinement The structure was solved by direct methods. Refinement was by the same method as for copper. The final cycle of refinement included 136 parameters with R=0.04. The highest peak in the final difference map had a height of 0.4 (e $Å^{-3}$).

Final atomic coordinates are given in Appendix.

26 *Zinc complex of 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (phenylphosphinic)) acid*

Ligand **14** (0.1g) was dissolved in zinc chloride solution (in $10cm^3$ of 0.01 M) with heating. This was left to stand. After 24 hours colourless crystals formed (0.045g, 41% considering impurity)

δp (d4 methanol) 31.19 ppm,

δ_H (d4 methanol) 2.91 (4H, br, amine ring) 3.32 (2H, d, NCH_2P ^3J=9 Hz), 7.4 (3H, br, meta and para Aromatic), 8.0 (2H, br, ortho Aromatic),

δ_C (d4 methanol) 53.06 (amine ring), 59.05 (amine ring), 61.53 (d, NCH_2P, ^1J=100 Hz) 129.5 (d, P-C-C , ^2J= 13 Hz) 133.0 (br, P-C-C-C-C) 133.34 (d, P-C-C-C, ^3J= 7 Hz) 135.1 (d, P-C, ^1J=140 Hz)

Elemental analysis: found C, 43.51 %; H, 6.03 %; N, 5.67 %; Zn, 8.15 %; $C_{27}H_{33}N_3P_3O_6Zn.H_3O^+.4H_2O$ requires: C, 43.55%; H, 5.91%; N, 5.64%; Zn, 8.75 %.

Crystal Data for $[ZnL].H_3O^+.4H_2O$ - $C_{27}H_{44}ZnN_3O_{11}P_3$:

Trigonal a = 14.412(2), b = 14.412(2), c = 8.937(3) Å, α =90, β = 90, γ = 120. V = 1607.5(6) $Å^3$, Dc = 1.539 gcm^{-3} . Space group was determined to be P -3.

Crystal dimensions : 0.35 × 0.35 × 0.35 mm

Data Collection and Processing Enraf Nonius diffractometer, ω /2θ scan mode, 3495 reflections were measured of which 3133 were unique. Data were collected to a maximum 2θ of 54.0 degrees. The range of indices was h 0 to 20, k -17 to 17 and l 0 to 12. After correction for Lorentz, polarisation and absorption effects 2403 reflections were used with $I>3\sigma(I)$.

Structure Analysis and Refinement The structure was solved using direct methods, remaining non-hydrogen atoms were located succeeding difference fourier syntheses.

The final cycle of refinement included 138 parameters with R=0.031. The highest peak in the final difference map had a height of 0.54e $Å^{-3}$.

Final atomic coordinates are given in Appendix.

27 *Indium complex of 1, 4, 7 Triazacyclononane N, N', N'', tris (methylene (phenylphosphinic)) acid*

Ligand 13 (0.1g) was dissolved in indium chloride solution (in 20cm^3 of 0.01 M) with heating. This was left to stand. After 2 weeks colourless crystals formed (0.015g, 12% considering impurity)

Crystal Data for $[InL].5H_2O$ - $C_{27}H_{43}InN_3O_{11}P_3$;

Triclinic a = 12.061(3), b = 12.261(2), c = 12.128(4) Å, α =96.69(2), β = 101.24(2), γ = 77.72(2). V = 1713.5(7) $Å^3$, Dc = 1.538 gcm^{-3} . Space group was determined to be P -1. Crystal dimensions : 0.3 × 0.4 × 0.45 mm

Data Collection and Processing Rigaku AFC65 diffractometer, ω /2θ scan mode, 8634 reflections were measured of which 8250 were unique. Data were collected to a maximum 2θ of 56.0 degrees. The range of indices was h -15 to 15, k -16 to 16 and l 0 to 16. After correction for Lorentz, polarisation and absorption effects 7458 reflections were used with $I>3\sigma(I)$.

Structure Analysis and Refinement The structure was solved using direct methods, remaining non-hydrogen atoms were located succeeding difference fourier syntheses.

The final cycle of refinement included 578 parameters with R=0.020. The highest peak in the final difference map had a height of 0.38e $Å^{-3}$.

Final atomic coordinates are given in Appendix.

28 *Cobalt III complex of 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (phenylphosphinic)) acid*

Ligand 14 (0.1g) was added to 10 cm^3 of 0.01 molar cobalt II chloride solution. [This was using one equivalent of coblat to ligand assuming the ligand to be 60% pure (from ^{31}P nmr analysis)]. The solution was heated to dissolve all of the ligand and left to cool, before careful addition of 10cm^3 of 100% hydrogen peroxide. On standing for several weeks the solution turned from pink of the Co II complex to a dark blue Co III complex (0.034g, 35% considering impurity).

δ_H (d4 methanol) 3.21 and 3.34 (m, NCH_2P and amine), 3.55 (doublet of doublets, amine) 3.85 (doublet of doublets, NCH_2P), 4.10 (doublet of doublets of doublets, amine), 4.36 (doublet of doublets of doublets, amine), 7.55 (triplet of doublets, meta Aromatic), 7.71 (triplet para Aromatic), 8.33 (doublet of doublets, ortho Aromatic)

δ_C (d4 methanol) 61.55 (s, amine ring), 65.05 (s, amine ring), 65.90 (d, NCH_2P, ^1J=85 Hz) 134.17 (d, P-C , ^1J= 138 Hz) 128.11 (d, P-C-C, ^2J= 12 Hz) 132.30 (s, P-C-C-C-C) 132.66 (d, P-C-C-C, ^3J= 14 Hz)

δ_P (d4 methanol) 58.75 ppm,

29 *Copper complex of 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (methylphosphinic)) acid*

This was formed by dissolving 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (methylphosphinic)) acid [48] (0.05g) adding one equivalent of copper II nitrate solution (12 ml, 0.01 M). It was not needed to heat the solution to dissolve the ligand, however some of the solvent was removed to encourage recrystallisation. This is the solution used for spectrophotometric analysis.

30 *Gallium Complex of 1, 4, 7 Triazacyclononane N, N', N", tris((methylene(methylphosphinic)) acid*

Formed by dissolving 1, 4, 7 Triazacyclononane N, N', N", tris (methylene (methylphosphinic)) acid [48] (0.05g) in an equivalence of gallium III nitrate solution (12 ml, 0.01 M). This sample was used in the NMR experiments as a solution. No solid would crystallise.

δ Ga (D_2O, pD=1) 139 ppm (w1/2 = 200 Hz).

31 *Gallium Complex of 1, 4, 7 Triazacyclononane N, N', N", tris((methylene(benzylphosphinic)) acid*

Formed by dissolving ligand 15 (0.04g) in an equivalence of gallium III nitrate solution (10 cm^3, 0.01 M). This sample was used in the NMR experiments as a solution. No solid would crystallise.

δ Ga (D_2O, pD=1.5) 130.3 ppm (w1/2 = 1000 Hz).

32 *Complex of Ethylene diamine N, N', dimethylene(methylphosphinic) acid*

The formation of three different complexes was attempted. They were with copper, nickel and zinc. Ligand 16 (0.1g) was added to 10 cm^3 of the metal nitrate solution (0.04 molar). This dissolved with little heating. The pH of the solutions was adjusted to be between 5 and 7 using sodium hydroxide solution. Crystallisation of the complexes did not occur.

6.2.5 AROMATIC SYSTEMS

33 *2,9-bis(carboxaldehyde)1,10 phenanthroline*

Following the synthesis in reference[2] without alteration gave the desired product.

34 *2,9-bis(hydroxymethylene)1,10 phenanthroline*

Following the synthesis in reference[2] without alteration gave the desired product.

35 *2,9-bis (bromomethyl)-1,10 phenanthroline*

2,9-bis(hydroxymethylene)1,10 phenanthroline (0.5g, 0.002 moles) was disolved in hydrogen bromide in acetic acid (20 cm^3). The mixture was refluxed at 120°C for 2 hours. On cooling the solvent was removed and the residue disolved in water, this was neutralised by adding potassium carbonate until effervescence stopped. The bromide was extracted into dichloromethane (60 cm^3), dried with magnesium sulphate (1.5g) amd the solvent removed to leave an orange solid.

δ_H ($CDCl_3$) observed: 4.98 (1H, s, Ar-CH_2Br) 7.8 and 7.9 (2H, m, 3,5,6,8 Aromatic) 8.3 (1H, d, 4,7 Aromatic).

Quoted reference*: 4.95 (1H, s, Ar-CH_2Br) 7.75 and 7.85 (2H, m, 3,5,6,8 Aromatic) 8.25 (1H, d, 4,7 Aromatic).

36 ***Diethyl 1,10 phenanthroline 2,9, bis (methylene(methylphosphinate))*** [65]

2,9, bis (bromomethyl) 1,10 phenanthroline (0.6g 2mmoles), methyldiethoxyphosphine (1g, 7mmoles) and acetonitrile (10 cm^3) were mixed under an inert atmosphere at room temperature for 90 minutes. Until the initailly red solution had developed an orange precipitate. After heating at 70°C with refluxing for six hours the solvent was removed under reduced pressure. This also removed any volatile reactants remaining to leave a clear light brown oil which was purified by column chromatography on alumina using dichloromethane with increasing amounts (0-10%) of methanol to give a pale yellow oil (0.42g, 46.7%). Thin layer chromatographic analysis (Al_2O_3, 10% MeOH-CH_2Cl_2) gave R_f= 0.45.

δp ($CDCl_3$) 51.59 ppm,

δ_H ($CDCl_3$) 1.21 (3H, t, $POCH_2\underline{CH_3}$,) 1.55 (3H, d, PCH_3, ^2J=9 Hz), 3.69 (2H, d, NCH_2P, ^2J=8 Hz) 4.05 (2H, m, $PO\underline{CH_2}CH_3$), 7.6 and 7.7 (2H, m, 3,5,6,8 Aromatic) 8.16 (1H, d, 4,7 Aromatic)

δ_C ($CDCl_3$) 13.7 (d, PCH_3, ^1J=96 Hz), 16.4 (t, $POCH_2\underline{CH_3}$,), 41.1 (d, NCH_2P, ^1J=84 Hz) 60.41 ($PO\underline{CH_2}CH_3$,) 124.0 (s, C3) 125.89 (s, C5) 127.2 (s, 4a) 136.68 (s, C4) 145.22 (s, C10b) 153.51 (s, C2)

M/e (DCI, accurate mass) Found: 421.27 (M^+ +1),

Calculated: 421.38 (M^+ +1)

37 1,10 phenanthroline 2,9, bis (methylene(methylphosphinic acid))

The ligand 35 (0.35g, 7.8mmoles) was heated to reflux for 16 hours in 6M HCl. The solvent was then removed under reduced preasure, leaving a pale brown powder (0.23g, 91%), decomposition point 150°C.

δp (D_2O, pD 0.5) 45.32 ppm,

δ_H (D_2O, pD 0.5) 1.58 (3H, d, PCH_3, ^3J=14 Hz), 3.82 (2H, d, $ArCH_2P$, ^3J=17 Hz) 7.64 (1H, s, C5) 7.84 (1H, d, C4 ^3J=4 Hz) 8.43 (1H, d, C3 ^3J=4 Hz)

δ_C(D_2O, pD 0.5) 13.7 (d, PCH_3, ^1J=96 Hz), 41.1 (d, $ArCH_2P$, ^1J=84 Hz) 124.0 (s, C3) 125.89 (s, C5) 127.2 (s, 4a) 136.68 (s, C4) 145.22 (s, C10b) 153.51 (s, C2)

Elemental analysis: found C, 43.51 %; H, 6.03 %; N, 5.67 %; P, 8.15 %; $C_{16}H_{18}N_2P_2O_4.HCl.2H_2O$ requires: C, 43.55%; H, 5.91%; N, 5.64%; P, 8.75 %.

38 2-lithium N,N-diethyltoluamide

This was synthesised following the literature preparation of Beak and coworkers[3], and was used directly in the following synthesis.

38a 2, (N, N, di ethyl 2' toluamide)1,10 phenanthroline [69]

2- lithium N, N diethyl toluamide* (2.2g, 0.012moles) in THF (100cm^3) was stirred at 0°C while a solution of phenanthroline (1.0g,

6mmoles) in THF ($30cm^3$) was slowly added. This was allowed to warm to room temperature and then stirred for 16 hours. The reaciton was then cooled to 0°C and quenched by slowly adding water (10 cm^3). The layers were then separated and the aqueous layer extracted with ether, these fractions were combined with the organic layer. Manganese (IV) oxide (20g) was added and the slurry stirred for 1hour before adding magnesuim sulphate (20g) and stirring for a further hour. This was filtered through a celite plug and the solvent then removed under reduced preasure leaving a dark orange oil. Purification was by column chromatography on silica to give a clear yellow oil (1.25g, 29%). Thin layer chromatographic analysis (SiO_2, Hexane : ethyl acetate, 1 : 3) gave one spot with R_f=0.57, melting point 79-82°C.

δ_H ($CDCl_3$) 1.03, 1.08 (6H, two superimposed triplets) 3.23, 3.39 (4H, two superimposed quartets) 7.45 (9H, multiplet) 7.75 (2H, doublet)

δ_C ($CDCl_3$) 12.03, 13.59 (CH_3 of amide) 38.69, 43.08 (CH_2 of amide) 169.7 ($ArC(O)NEt_2$) 18 aromatic peaks were seen in the region 124.8-138.2 but were not full assigned.

M/e (DCI) 354 (M^+ +1)

*A test reaction was carryied out and quenched with deuterium oxide yield found to be 80%, molecular ratios for this reaction were based on that assumption.

39 *2 Lithio toluene*

This was synthesised following the literature preparation of J. W. Morton[4] and used directly in the following synthesis.

402, *9 di(2' toluene) 1,10 phenanthroline* [5] [73]

2 Lithio toluene (2.4g, 24mmoles) was stirred at 20°C in ether ($70cm^3$) while a solution of phenanthroline (2g, 11mmoles) in THF

($30cm^3$) was added. This was refluxed for 4 hours before leaving to stir for 12 hours. After cooling to 0°C water ($50cm^3$) was added to hydrolyse remaining lithiate. The layers were separated and the aqueous layer was extracted with dichloromethane ($3\times30cm^3$). All the organic fractions were combined and stirred with manganese (IV) oxide (60g) for 2 hours before adding magnesium sulphate (60g) with stirring for a further two hours. This mixture was filtered through a celite plug and the solvent then removed under reduced pressure leaving a dark orange oil. Purification was by recrystallisation from cyclohexane to give a dark yellow powder (0.42g, 48%) melting point 97°C.

δ_H ($CDCl_3$) 1.03/1.08, (3H, $ArC\underline{H}_3$) 7.9 (4H, Aromatic) 8.18 (1H, Aromatic) 8.45 (1H, Aromatic) 8.55 (1H, Aromatic)

δ_C ($CDCl_3$) 21.42 (3H, $ArC\underline{H}_3$) 123.8 (C3) 126.1 (C5) 127.1 (C4a) 125.7, 128.3 and 130.9 (C4', C5' and C6') 130.3 (C3') 136.1 (C4) 136.8 (C2') 140.6 and 145.7 (C1' and C10b) 160.0 (C2)

I.R. 3000-3100 cm^{-1} (m, C-H aromatic) 2900-3000 cm^{-1} (m, C-H aliphatic) 1480 and 1030 cm^{-1} (w, substituted toluene ring)

M/e (DCI) 361 (M^+ +1)

Elemental analysis: found a); C, 86.42%; H, 5.89%; N, 7.59% ; $C_{26}H_{20}N_2$ requires: C, 86.67%; H, 5.55%; N, 7.78%.

41 ***Bromobenzyl(tetrahydropyran)ether*** [6]

2 Bromobenzyl alcohol (10g, 0.05 moles) was disolved in dichloromethane ($100cm^3$) with 3,4-dihydro pyran (5g, 0.06 moles) and a catalytic amount of p-toluene sulphonic acid. This was left to stir at room temperature for one hour, during this time the colour was seem to change from colourlesss to deep blue. The solution was then washed with saturated sodium hydrogen carbonate solution ($2\times40cm^3$) during which

the blue colour faded. The organic layer was dried with magnesium sulphate and concantrated leaving a yellow oil.

δ_H ($CDCl_3$) 1.59, 1.75, 1.89 (6H, m, -C<u>H</u>$_2$- on carbons 9, 10 and 11) 3.58, 3.94 (2H, doublet of triplets, -C<u>H</u>$_2$- on carbon 12) 4.62, 4.56 (1H, d, -CH- on carbon 8) 4.82 (2H, m, -C<u>H</u>$_2$- on carbon 7) 7.15 (1H, t, -C-H on Ar carbon 4 or 5) 7.32 (1H, t, -C-H on Ar carbon 4 or 5) 7.53 (2H, m, -C-H on Ar carbons 3 and 6)

δ_C ($CDCl_3$) 18.83, 25.04, 30.03 (s, carbons 9, 10 and 11) 61.39, 67.90 (s, carbons 12 and 7) 97.73 (s, carbon 8) 122.09 (s, carbon 2) 126.78 (s, carbon 5) 128.18, 128.42 (s, carbons 4 and 6) 131.84 (s, carbon 3) 137.40 (s, carbon 1)

M/e (DCI) 272 (M^+ +1)

42 1,10 Phenanthroline 2, benzyl(tetrahydropyran) ether [71]

Bromobenzyl(tetrahydropyran)ether (5g, 18 mmoles) and TMEDA (2.2g) were disolved in a 1:1 mixture of ether and THF (60 cm^3 total). This was cooled to -78°C under an inert atmosphere, in an acetone/CO_2 bath before adding sec-butyl lithium (15cm^3, 1M). After stirring for three hours a solution of phenanthroline (0.6g, 3.4mmoles) in THF (15 cm^3) was slowly added. This was left stirring at room temperature for 18 hours before adding water (30 cm^3) to hydrolyse any remaining butyl lithium or lithiate. The water was then extracted with ether (2×20cm^3) and all the organic fractions combined, stirred with manganesse (IV) oxide (30g) for three hours before adding magnesium sulphate (30g) and the mixture was then stirred for a further three hours. The slurry was filtered and the solid was washed with ether. The organic fractions were combined and the solvent removed. This gave a dark brown oil which could be purified by column chromatography to give a yellow oil (0.95g, 69%). Thin layer chromatographic analysis (SiO_2, dichloromethane) gave one spot with R_f=0.85.

δ_H ($CDCl_3$) 1.4 (6H, m, ring $C\underline{H_2}$) 3.2 (1H, m, $OC\underline{H_2}$ ring) 3.6 (1H, m, $OC\underline{H_2}$ ring) 4.5 (1H, s) 4.8 (2H, m, $ArC\underline{H_2}O$) 7.8 (12H, m, Aromatic)

δ_C ($CDCl_3$) 18.72, 24,82, 31.23 (s, carbons 9, 10 and 11) 60.65, 67.43 (s, carbons 12 and 7) 96.53 (s, carbon 8) 18 aromatic peaks were seen in the region 124.8-145.7 but were not full assigned.

M/e (DCI) 371 (M^+ +1)

6.2.6 P-S FORMATION

43 *Dimethyl 1, 3, (2 Sulphone) Tetrahydroimidazole N, N' di methylene (methylphosphinate))*

Dimethyl1,3,TetrahydroimidazoleN,N'dimethylene(methylphoshinate) (0.2g, 6.8mmoles) and sulphur (0.25g, excess) were dissolved in pyridine (10 cm^3 each) and then mixed. This was heated at 110°C for 8hours. After this time the solvent was removed under reduced preasure to leave a yellow residue, which was purified using column chromatography to give a pale yellow oil (0.16g, 68%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.75.

δp ($CDCl_3$) 50.37

δ_H ($CDCl_3$) 1.36, (3H, t, $OCH_2\underline{CH_3}$) 1.57 (3H, d, PCH_3, ^2J=14 Hz) 3.77 (2H, d, NCH_2P, ^2J=10 Hz) 4.0 (2H, m, amine) 4.14 (2H, p , $POCH_2$)

δ_C ($CDCl_3$) 13.8 (d, PCH_3, ^1J=87 Hz), 16.67 (d, $OCH_2\underline{C}H_3$, ^3J=12 Hz) 47.64 (d, PCH_2N, ^1J=107 Hz), 47.46 ($N\underline{C}H_2\underline{C}H_2N$) 60.79 (d, $POCH_2$, ^2J=8 Hz) 183.11 (br, NC(S)N)

I.R. 1200cm^{-1} (s, P=O), 1260cm^{-1} and 1310cm^{-1} (m, NC(S)N)

M/e (DCI) 344 (M^+ +1)

44 *Ethyl[(^{t}butyl dimethylsiloxy methylene) methylphosphinate]*

Ethyl[(hydroxymethylene) methylphosphinate] (0.1g, 0.7mmoles), ^{t}butyl dimethylsilylchloride (0.13g, 0.9mmoles) and imidazole (0.12g,

1.8mmoles) were dissolved in DMF (10cm^3). The reaction was stirred at 25°C for 3 hours under an inert atmosphere. The solvents were removed under reduced pressure leaving a brown oily residue, which was purified by dissolving into dichloromethane (20cm^3) and washing with 10% sodium carbonate solution (3×15 cm^3). This was then dried using magnesium sulphate solution and the solvent removed under reduced preasure to give a clear yellow oil (0.11g, 61%). Thin layer chromatographic analysis (Al_2O_3, 10% methanol in dichloromethane) gave one spot with R_f=0.87.

δp ($CDCl_3$) 51.98

δ_H ($CDCl_3$) 0.06 (6H, s, $SiCH_3$) 0.87 (9H, s, ^tBuSi) 1.30, (3H, t, OCH_2CH_3) 1.44 (3H, d, PCH_3, ^2J=14 Hz) 3.81 (2H, d, OCH_2P ^2J=8 Hz) 4.08 (2H, p , $POCH_2$)

δ_C ($CDCl_3$) -6.0 (s, $SiCH_3$) 10.9 (d, PCH_3, ^1J=95 Hz) 16.2 (t, OCH_2C) 25.36 (s, ^tBuSi) 59.3 (d, OCH_2P ^1J=116 Hz) 60.1 (p , POC)

M/e (DCI) 252 (M^+ +1)

46 *Ethyl[(^{t}butyl dimethylsiloxy methylene) methylphosphinthiolate]*

Ethyl [(^{t}butyl dimethylsiloxymethylene) methylphosphinate] (0.1g, 0.7mmoles) and phosphorus pentasulphide (0.25g, excess) were dissolved in toluene (15 cm^3). The reaction was stirred at 25°C for 1 hours under an inert atmosphere. The solution was concentrated under reduced preasure then extracted with the minimum amount of dichloromethane. This gave a yellow solution which could then be filtered to remove unreacted phosphorous pentasulphide.

δp ($CDCl_3$) 87.46

δ_H ($CDCl_3$) 0.06 (6H, s, $SiCH_3$) 0.87 (9H, s, ^tBuSi) 1.30, (3H, t, OCH_2CH_3) 1.44 (3H, d, PCH_3, ^2J=14 Hz) 3.81 (2H, d, OCH_2P ^2J=8 Hz) 4.08 (2H, p , $POCH_2$)

δ_C ($CDCl_3$) 0.06 (6H, s, $SiCH_3$) 0.87 (9H, s, ^tBuSi) 1.30, (3H, t, $OCH_2\underline{CH_3}$) 1.44 (3H, d, PCH_3, ^2J=14 Hz) 3.81 (2H, d, OCH_2P ^2J=8 Hz) 4.08 (2H, p , $POCH_2$)

M/e (DCI) 252 (M^+ +1)

47 Ethyl[(hydroxy methylene) methylphosphinthiolate]

Ethyl[(^{t}butyl dimethylsiloxy methylene) methyl phosphinthiolate] (0.2g, 0.8mmoles) was dissolved in THF (10 cm^3) and cooled in an ice bath to 0°C. Tetrabutyl ammonium fluoride (2 cm^3) was added and the mixture stirred for 15 minutes. Saturated ammonium chloride (20 cm^3) solution was added followed by saturated sodium hydrogen carbonate solution (30 cm^3). The aqueous layer was then extracted with dichloromethane. This was dried with magnesium sulphate and then combined with the THF layer and the solvents removed under reduced preasure to give a pale yellow oil (0.12g, 56%).

δ_P ($CDCl_3$) 91.23

δ_H ($CDCl_3$) 1.28, (3H, t, $OCH_2\underline{CH_3}$) 1.82 (3H, d, PCH_3, ^2J=14 Hz) 4.1 (4H, m , $POCH_2$ and PCH_2O)

δ_C ($CDCl_3$) 1.30, (3H, t, $OCH_2\underline{CH_3}$) 1.44 (3H, d, PCH_3, ^2J=14 Hz) 3.81 (2H, d, OCH_2P ^2J=8 Hz) 4.08 (2H, p , $POCH_2$)

M/e (DCI) 155 (M^+ +1)

6.3 Potentiometric Titrations

6.3.1 Apparatus and Instrumentation

The titration cell was a double walled glass vessel of approximately 5 cm^3 capacity. The temperature of the system was maintained at 25°C using a Techne Tempette Junior TE-8J. The solutions in the titration cell were stirred using a magnetic stirrer. Two systems were used to carry out the titrations. Initially an automatic burette (Mettler DL20) of 1 cm^3

capacity was used and the pH was measured using a Corning 001854 combination microelectrode. The titrations were controlled and data was stored using a BBC microprocessor. The burette functions (volume increments, total volume delivered and time interval allowed for equilibration between each reading) were controlled by the use of basic software stored on a disc. The data was transferred to the MTS mainframe using Kermit.

The second system used was an IBMpc driven autotitrator (Molspin, Newcastle-Upon -Tyne, UK) with a digitally operated syringe. The data was transferred to the UNIX mainframe and was subsequently analysed by two non-linear least-squares programs SCOGS2 and Superquad[7].

6.3.2 Measurements of Acid Disociation Constants

The combination electrode was calibrated by using two NBS buffers: (i) 0.05 mol dm^{-3} KHPH -pH 4.008, 25°C and (ii) 0.025 mol dm^{-3} KH_2PO_4 0.025 mol dm^{-3} Na_2HPO_4 - pH 6.865, 25°C. Stock ligand solutions were made up containing 0.001 mol dm^{-3} ligand and 0.1 mol dm^{-3} tetramethylammonium nitrate to ensure constant ionic strength in 25cm^3 deionised water (MilliQ). The titrant-ligand solution (3 cm^3) was placed in the titration vessel.with the combination electrode and the burette tube. The titrant was tetramethylammonim hydroxide whose exact molarity (0.05 mol dm^{-3}) was determined by titrating against 0.1 mol dm^{-3} HCl. Three separate titrations were performed on each ligand and the results analysed by methods previously outlined.

6.3.3 Measurements of Metal Complexation Constants

Titrant solutions were made up containing 0,001 mol dm^{-3} ligand and 0.1 mol dm^{-3} tetramethylammonium nitrate. The titrant once again

was tetramethylammonium hydroxide (0.05 mol dm^{-3}). Three separate titrations were obtained for each particular ligand/cation combination and data was analysed as before. The cations used were chloride salts, and made up to a 0.01 mol dm^{-3} solution in deionised water (MilliQ). The exact concentration of each cation was established by AAS.. An equivalent amount of the cation solution was added to give a 1:1 ratio with the ligand (usually 0.3 cm^3).

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E. Cole, D. Parker, G. Ferguson, J. F. Gallagher, B. Kaitner.

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C. J. Broan, E. Cole. K. J. Jankowski, D. Parker, K. Pulukkody, B. A. Boyce, N. R. A. Beeley, K. Millar, A. T. Millican.

Courses taken during first year (1990-1991)

Ionic and Molecular Recognition	Prof. D. Parker
Asymmetric Synthesis	Dr. P.G. Steel
Spectroscopy of Reactions	Dr. M. Crampton

Research Colloquia (1990-1991)

October 11th. Dr. W. A. Macdonald	Materials for the Space Age.
October 24th. Dr. M. Bochmann	Synthesis, Reaction and catalytic activity of Cationic Titanium Alkyls.
October 26th. ° Prof. R. Soulen	Chemistry of some Fluorinated Cyclobutenes.
October 31st. ° Dr. R. Jackson	New Synthetic Methods: a-amino acids and small rings.
November 1st Dr. N. Logan	Rocket Propellants
November 6th. ° Dr.P Kocovsky	Stereo-controled Reactions Mediated by Transition and Non-Transition Metals.
November 7th. Dr. G. Gerrand	Raman Spectroscopy for Industrial Analysis.

November 8th ◦ Dr. S. K. Scott	Clocks, Oscillations and Chaos.
November 14th ◦ Prof. T. Bell	Functional Molecular Architecture and Molecular Recognition
November 21st. Prof. J. Pritchard	Copper Surfaces and Catalysts.
November 28th Dr. B. H. Whitaker	Two-dimensional Velocity Imaging of State-selected Reaction Products.
November 29th ◦ Prof. D. Crout	Emzymes in Organic Synthesis.
December 5th. ◦ Dr. P. G. Pringle	Metal Complexes with Functionalised Phosphines.
December 13th Prof. A. H. Cowley	New organometalic Routes to Electronic Materials.
January 15th ◦ Dr. B. J. Alder	Hydrogen in all its Glory
January 17th. ◦ Dr. P. Sarre	Comet Chemistry

January 23rd. Prof. J. S. Higgins	Rheology and molecular Structure of Ionomer Solutions
Januaray 24th. ◦ Dr. P. J. Sadler	Design of Inorganic Drugs: Precious Metals, Hypertension + HIV.
January 30th. Prof. E. Sinn	New Results in T_c Superconductivity.
January 31st. ◦ Dr. D. Lacey	Liquid Crystals
February 6th. ◦ Dr. R. Bushby	Biradicals and Organic Magnets.
February 14th. Dr. M. C. Petty	Molecular Electronics
February 20th. ◦ Prof. B. L. Shaw	New Chemistry with Transition Metal Multihydrides.
February 28th ◦ Dr. J. Brown	Can Chemistry Provide Catalysts Superior to Enzymes
March 6th. ◦ Dr. C. M. Dobson	NMR Studies of Dynamics in Molecular Crystals.
March 7th ◦ Dr. J. Markam	DNA Fingerprinting

April 24th. ◦ Prof. R. R. Schrock	Metal-Ligand Multiple Bonds and Metathesis Initiators.
April 25th, ◦ Prof. T. Hudlicky	Biocatalysis and Symmetry Based Approaches to the Efficient Synthesis of Complex Natural Products.
June 20th. Prof. M. S. Brookhart	Olefin Polymerizations, Oligomerizations and Dimerizations Using Electrophilic Late Transition Metal Catalysts.
July 29th Dr. M. A. Brimble	Synthetic Studies Towards the Antiiotic Griseusin-A

Research Colloquia (1991-1992)

October 17th. ◦ Dr. J. A. Salthouse	Son et Lumiere.
October 31st ◦ Dr. R. Keeley	Modern Forensic Science.
November 6th Prof. B. F. G. Johnson	Cluster-surface Analogues.

November 7th ◦ of Dr. A. R. Butler	Traditional Chinese Herbal Drugs: a different way treating disease.
November 13th ◦ Prof. D. Gani	The Chemistry of PLP Dependant Enzymes.
November 20th ◦ Dr. R. More O'Ferrall	Some Acid-catalysed Rearrangments in Organic Chemistry.
November 28th Prof. I. M. Ward	The Science and Technology of Orientated Polymers.
December 4th ◦ Prof. R. Grigg	Palladium Catalysed Cyclisation and Ion Capture Processes.
Decenber 5th ◦ Prof. A. L. Smith	Soap, Detergents and Black Puddings.
December 11th Dr. W. A. Copper	Colloidal Science, Theory and Practice.
January 22nd. Dr. K. D. M. Harris	Understanding the properties of Solid Inclusion Compounds.
January 29th ◦ Dr. A Holmes	Cycloaddition Reactions in the Service of the Synthesis of Piperipine and Indolizidine Natural Products.

January 30th ○ Dr. M. Anderson	Recent Advances in the Safe and Selective Chemical Control of Insect Pests.
February 12th ○ Dr. D. E. Fenton	Polynuclear Complexes of Molceular Clefts as Models for Copper Biosites.
February 13th ○ Dr. J. Saunders	Molecular Modelling in Drug Discovery.
February 19th ● Prof. E. J. Thomas	Applications of Organic Stannanes to Organic Synthesis.
February 20th ● Prof. E. Vogel	Porphryrins: Molecules of Interdisciplinary Interest.
February 25th. ● Prof. J. F. Nixon	Phosphaalkynes: new building blocks in inorganic and organometallic chemistry.
February 26th Prof. M. L. Hitchman	Chemical Vapour Deposition.
March 5th ● Dr. N. C. Billingham	Degradable Plastics-Myth or Magic?
March 11th ● Dr. S. E. Thomas	Recent Advances in Organoiron Chemistry.
March 12th. Dr. R. A. Hann	Electronic Photography - An Image of the Future.

March 18th ◦ Dr. H. Maskill	Mechanistic Studies of Organic Group Transfer Reactions.
April 7th. Prof. D. M. Knight	Interpreting experiments: the beginning of electrochemistry.
May 13th ◦ Dr. J-C Gehret	Some Aspects of Industrial Agrochemical Research.

Research Colloquia (1992-1993)

October 15th. Dr. M. Glazer & Dr. S. Tarling	It Pays to be British!- The Chemist's Role as an Expert Witness in Patent Litigation.
October 20th. ◦ Dr. H. E. Bryndza	Synthesis, Reaction and Thermochemistry of Metal(alkyl)cyanide Complexes and their Impact on Olefin Hydrocyanation Catalysis.
October 22nd ◦ Prof. A. G. Davies	The Behaviour of Hydrogen as a Pseudometal.
October 28th Dr. J. K. Cockroft	Recent Developments in Powder Diffraction.
October 29th ◦	The Shocking History of Phosphorus.

Dr. J. Emsley

November 4th Dr. T. Kee	Synthesis and Coordination Chemistry of Silylated Phosphites.
November 5th. ○ Dr. C. J. Ludman	Explosions
November 11th ○ Prof. D. Robins	Pyrrolizidine Alkaloids: Biological Activity, Biosynthesis and Benefits.
November 12th ○ Prof. M. R. Truter	Luck and Logic in Host-Guest Chemistry.
November 18th Dr. R. Nix	Characterisation of Heterogeneous Catalysis.
November 25th ○ Prof. Y. Vallee	Reactive Thiocarbonyl Compounds.
November 25th Prof. L. D. Quin	Fragmentation of Phosphorus Heterocycles as a Route to Phosphoryl Species with Uncommon Bonding.
November 26th ○ Dr. D. Humber	AIDS-The Development of a Novel Series of Inhibitors of HIV.
December 2nd. Prof. A. F. Hegarty	Highly Reactive Enols Stabilised by Steric Protection.

December 2nd ◦ Dr. R. A. Aitken	The versatile Cycloaddition Chemistry of $Bu_3P.CS_2$.
December 3rd. ◦ Prof. P. Edwards	What is a Metal?
December 9th Dr. A. N. Burgess	The Structure of Perfluorinated Ionomer Membranes.
January 20th Dr. D. C. Clary	Energy Flow in Chemical Reactions.
January 21st. ◦ Prof. L. Hall	NMR-Window to the human body.
January 27th. ◦ Dr. W. Kerr	Development of the Pauson-Khand Annulation Reaction. Organocobalt Mediated Synthesis of Natural and Unnatural Products.
January 28th. ◦ Prof. J. Mann	Murder, Magic and Medicine.
February 3rd. ◦ Prof. S. M. Roberts	Enzymes in Organic Synthesis.
February 10th Dr. D. Gillies	NMR and Molecular Motion in Solution.

February 10th Dr. D. Gillies	NMR and Molecular Motion in Solution.
February 11th ◦ Prof. S. A. R. Knox	Organic Chemistry at Polynuclear Metal Centres.
February 17th ◦ Dr. R. D. W. Kemmitt	Oxatrimethylenemethane Metal Complexes.
February 18th. ◦ Dr. I. Fraser	Reactive Processing of Composite Materials.
February 22nd Prof. D. M. Grant	Single Crystals, molecular Structure and Chemical-Shift Anisotropy.
February 24th Prof. C. J. M. Stirling	Chemistry on the Flat-Reactivity of Ordered Systems.
March 3rd Dr. K. J. P. Williams	Raman Spectroscopy for Industrial Analysis.
March 10th. Dr. P. K. Baker	An Investigation of the Chemistry of the Highly Versitile 7-Coordinate Complexes $[MI_2(CO)_3(NCMe)_2]$ (M=Mo, W)
March 11th ◦ Dr. R. A. Y. Jones	The Chemistry of Wine Making.

March 24th Prof. I. O. Sutherland	Chromogenic Reagents for Chiral Amine Sensors.
May 13th Prof. J. A. Pople	Application of Molecular Orbital Theory.
May 21st Prof. L. Weber	Metallo-phospha Alkenes as Synthons in Organometallic Chemistry.
June 1st. Prof. J. P. Konopelski	Synthetic Adventures with Enantiomerically Pure Acetals.
June 2nd Prof. F. Ciardelli	Chiral Discrimination in the Stereospecific Polymerisation of Alpha Olefins.
June 7th Prof. R. S. Stein	Scattering Studies of Crystalline and Liquid Crystalline Polymers.
June 16th Prof. A. K. Covington	Use of Ion Selective Electrodes as Detectors in Ion Chromatography.
June 17th Prof. O. F. Nielsen	Low-Frequency IR and Raman Studies of Hydrogen Bonded Liquids.

- Denotes attendance at lecture.

Conferences

International Macrocycles, September 1991, Shefield.°

Stereochemical Symposia, December 1991, Shefield.

Materials and Reactivity, September 1992, Durham.

U.K. Macrocycles, January 1993, Oxford.°

International Macrocycles, July 1993, Holland.°

° Poster presented.

Appendix

Atomic co-ordinates and equivalent isotropic atomic displacement parameters ($Å^2$) Nickel Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Atom	x	y	z	B_{iso}
Ni	2/3	1/3	0.45407(10)	1.52(3)
P	0.42904(8)	0.18347(8)	0.37952(13)	2.10(6)
O(1)	0.52755(21)	0.28728(20)	0.33128(31)	2.2(2)
O(2)	0.33801(21)	0.19105(23)	0.45004(34)	2.9(2)
O(W1)	0.18934(27)	0.03017(25)	0.63622(42)	4.4(2)
O(W2)	0.0	0.0	0.68765(90)	6.5(3)
O(W3)	2/3	1/3	0.05288(87)	9.6(4)
N(1)	0.56741(24)	0.20940(26)	0.60101(38)	1.8(2)
C(2)	0.52495(32)	0.25369(33)	0.71423(48)	2.4(2)
C(3)	0.64035(32)	0.17433(31)	0.66666(47)	2.2(2)
C(4)	0.48190(31)	0.12359(30)	0.51059(47)	2.1(2)
C(11)	0.37542(33)	0.09176(33)	0.22572(48)	2.3(2)
C(12)	0.26605(36)	0.01861(37)	0.21722(56)	3.3(2)
C(13)	0.22355(44)	-0.04858(42)	0.09782(70)	4.7(3)
C(14)	0.28954(56)	-0.04385(44)	-0.01419(64)	4.9(4)
C(15)	0.39707(53)	0.02701(46)	-0.00867(63)	5.0(4)
C(16)	0.44022(39)	0.09424(41)	0.11173(59)	3.9(3)

B_{iso} is the mean of the principle axes of the thermal ellipsoid.

Selected Bond Lenghts and Bond Angles for Nickel Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond Lengths (Å)			Bond Angles (°)	
Ni-O(1)	2.083(3)		O(1)-Ni-O(1)[a]	94.23(12)
P-O(2)	1.506(3)		O(1)-Ni-N(1)[a]	170.43(11)
N(1)-C(2)	1.487(5)		N(1)-Ni-N(1)[a]	84.36(12)
C(2)-C(3)[b]	1.523(9)		O(1)-P-C(4)	104.17(16)
C(11)-C(16)	1.377(7)		O(2)-P-C(4)	109.70(18)
C(14)-C(15)	1.360(9)		C(4)-P-C(11)	106.36(19)
Ni-N(1)	2.104(3)		Ni-N(1)-C(2)	108.80(23)
P-C(4)	1.836(4)		Ni-N(1)-C(4)	106.55(24)
N(1)-C(3)	1.493(5)		C(2)-N(1)-C(4)	113.0(3)
C(3)-C(2)[a]	1.523(5)		N(1)-C(2)-C(3)[b]	112.6(4)
C(12)-C(13)	1.371(7)		P-C(4)-N(1)	109.4(3)
C(15)-C(16)	1.379(8)		P-C(11)-C(16)	121.5(3)
P-O(1)	1.518(3)		C(11)-C(12)-C(13)	120.9(5)
P-C(11)	1.802(4)		C(13)-C(14)-C(15)	120.6(5)
N(1)-C(4)	1.477(5)		O(1)-Ni-N(1)	86.08(11)
C(11)-C(12)	1.388(6)		O(1)-Ni-N(1)[b]	95.29(18)
C(13)-C(14)	1.365(10)		O(1)-P-O(2)	117.83(16)
			O(1)-P-C(11)	110.10(18)
			O(2)-P-C(11)	108.09(18)
			Ni-O(1)-P	115.68(15)
			Ni-N(1)-C(3)	104.1(22)
			C(2)-N(1)-C(3)	112.1(3)
			C(3)-N(1)-C(4)	111.7(3)

N(1)-C(3)-C(2)[a]	110.7(5)
P-C(11)-C(12)	120.3(3)
C(12)-C(11)-C(16)	118.2(4)
C(11)-C(16)-C(15)	120.8(5)
C(12)-C(13)-C(14)	119.7(5)
C(14)-C(15)-C(16)	119.8(5)

a and b represent that following symmetry equivalents:

a = 1-y, x-y, z and b = 1-x+y, 1-x z

Atomic Parameters For Copper Complex of 1,4,7 Triazacyclononanetris(methylene(phenylphosphinic)) Acid

	x	y	z
Cu	1/3	2/3	.45048(10)
P	. 57165(8)	.75481(9)	.37911(14)
O1	.47416(23)	.76031(23)	.3286 (3)
O2	.66168(22)	.85343(23)	.4501 (4)
N1	.43309(23)	.64291(24)	.6026 (4)
C2	.4750 (3)	.7295 (3)	.7158 (5)
C3	.3604 (3)	.5351 (3)	.6672 (5)
C4	.5190 (3)	.6427 (3)	.5119 (5)
C11	.6250 (3)	.7161 (3)	.2252 (5)
C12	.7341 (4)	.7525 (4)	.2173 (6)
C13	.7784 (4)	.7288 (5)	.0993 (4)
C14	.7118 (5)	.6674 (5)	-.0130 (6)
C15	.6033 (5)	.6297 (5)	-.0080 (6)
C16	.5610 (4)	.6353 (4)	.1115 (6)
OW1	1/3	2/3	.0566 (9)
OW2	1	1	.6898 (10)
OW3	.8080 (3)	.8389 (3)	.6369 (4)

Bond Lengths (Å) and Bond Angles (°) for Copper Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond Lenghts (Å)		Bond Angles (°)	
Cu-O(1)	2.099(3)	O(1)-Cu-O(1) [a]	95.06(9)
Cu-N(1)	2.134(3)	O(1)-Cu-N(1)	85.9(11)
Cu.....OW(1)	3.554(8)	O(1)-Cu-N(1) [a]	95.78(11)
P-O(1)	1.515(3)	O(1)-Cu-N(1) [b]	168.99(11)
P-O(2)	1.505(3)	N(1)-Cu-N(1) [a]	83.10(13)
P-C(4)	1.842(4)	O(1)-P-O(2)	117.52(17)
P-C(11)	1.805(4)	O(1)-P-C(4)	104.8(17)
N(1)-C(2)	1.486(5)	O(1)-P-C(11)	109.46(19)
N(1)-C(3)	1.490(5)	O(2)-P-C(4)	109.46(19)
N(1)-C(4)	1.484(5)	O(2)-P-C(11)	108.64(19)
C(2)-C(3) [a]	1.523(10)	C(4)-P-C(11)	106.39(19)
C(11)-C(12)	1.387(6)	Cu-O(1)-P	115.56(17)
C(12)-C(13)	1.369(7)	Cu-N(1)-C(2)	109.36(22)
C(13)-C(14)	1.370(9)	Cu-N(1)-C(3)	103.89(22)
C(14)-C(15)	1.375(9)	Cu-N(1)-C(4)	105.92(25)
C(15)-C(16)	1.364(8)	C(2)-N(1)-C(3)	112.6(3)
C(16)-C(11)	1.372(7)	C(2)-N(1)-C(4)	113.0(3)
		C(3)-N(1)-C(4)	111.4(3)
		N(1)-C(2)-C(3) [a]	112.3(3)
		N(1)-C(3)-C(2) [b]	111.2(3)
		P-C(4)-N(1)	109.6(3)
		P-C(11)-C(12)	120.0(4)
		P-C(11)-C(16)	121.8(3)

C(12)-C(11)-C(16)	118.2(4)
C(11)-C(12)-C(13)	121.8(5)
C(12)-C(13)-C(14)	118.2(5)
C(13)-C(14)-C(15)	121.4(5)
C(14)-C(15)-C(16)	119.2(5)
C(11)-C(16)-C(15)	121.2(5)

Atomic Coordinates and Equivalent Isotropic Displacement Parameters for Cobalt Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

	x	y	z	U(eq)/Å^2
Co(1)	1/3	2/3	0.44623(9)	0.0128(2)
P(1)	0.57355(7)	0.75241(7)	0.3804(1)	0.0140(4)
O(1)	0.4765(2)	0.7589(2)	0.3268(3)	0.018(1)
O(2)	0.6640(2)	0.8506(2)	0.4540(3)	0.021(1)
N(1)	0.4324(2)	0.6412(2)	0.6043(3)	0.012(1)
C(2)	0.4746(3)	0.7279(3)	0.7196(4)	0.014(1)
C(3)	0.3593(3)	0.5341(3)	0.6706(4)	0.014(1)
C(4)	0.5185(3)	0.6403(3)	0.5133(4)	0.015(1)
C(11)	0.6278(3)	0.7137(3)	0.2249(4)	0.017(1)
C(12)	0.7371(3)	0.7500(3)	0.2187(4)	0.021(2)
C(13)	0.7817(3)	0.7257(3)	0.0970(4)	0.029(2)
C(14)	0.7148(3)	0.6639(3)	-0.0188(4)	0.030(2)
C(15)	0.6063(3)	0.6275(3)	-0.0138(4)	0.030(2)
C(16)	0.5628(3)	0.6515(3)	0.1083(4)	0.024(2)
Ow(1)	1/3	2/3	0.0560(7)	0.073(2)
Ow(2)	0	0	0.6939(5)	0.030(1)
Ow(3)	0.8147(2)	0.8408(2)	0.6377(3)	0.026(1)

H(2A)	0.5479	0.7495	0.7411	0.017
H(2B)	0.4341	0.6995	0.8102	0.017
H(3A)	0.3935	0.5228	0.7555	0.016
H(3B)	0.3450	0.4796	0.5976	0.016
H(4A)	0.5743	0.6465	0.5786	0.018
H(4B)	0.4903	0.5739	0.4595	0.018

H(12A)	0.7823	0.7918	0.3000	0.026
H(13A)	0.8572	0.7516	0.0929	0.034
H(14A)	0.7445	0.6461	-0.1031	0.037
H(15A)	0.5612	0.5852	-0.0950	0.036
H(16A)	0.4871	0.6247	0.1122	0.029
HoW(2)	1.0025	1.0566	0.6614	0.036
Ho(3A)	0.8044	0.7798	0.6108	0.032
Ho(3B)	0.7765	0.8553	0.5805	0.032

Selected bond lengths and angles for Cobalt Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond lengths (Å)			Bond angles (°)	
Co(1)-O(1)	2.103(2)		O(1)-Co(1)-O(1A)	96.7(1)
Co(1)-N(1)	2.165(3)		O(1)-Co(1)-N(1)	85.1(1)
P(1)-O(1)	1.527(3)		O(1)-Co(1)-N(1A)	95.6(1)
P(1)-O(2)	1.514(2)		O(1)-Co(1)-N(1B)	167.3(1)
P(1)-C(4)	1.834(3)		N(1)-Co(1)-N(1A)	82.2(1)
P(1)-C(11)	1.811(4)		O(1)-P(1)-O(2)	117.8(2)
N(1)-C(2)	1.493(4)		O(1)-P(1)-C(4)	104.5(2)
N(1)-C(3)	1.490(4)		O(1)-P(1)-C(11)	109.3(2)
N(1)-C(4)	1.489(5)		O(2)-P(1)-C(4)	109.7(1)
C(2)-C(3A)	1.534(6)		O(2)-P(1)-C(11)	108.5(1)
C(11)-C(12)	1.394(5)		C(4)-P(1)-C(11)	106.6(2)
C(11)-C(16)	1.387(5)		Co(1)-O(1)-P(1)	116.3(1)
C(12)-C(13)	1.391(6)		Co(1)-N(1)-C(2)	109.4(3)
C(13)-C(14)	1.389(5)		Co(1)-N(1)-C(3)	104.4(2)
C(14)-C(15)	1.381(7)		Co(1)-N(1)-C(4)	105.8(2)
C(15)-C(16)	1.384(6)		C(2)-N(1)-C(3)	112.1(2)
			C(2)-N(1)-C(4)	112.9(2)
			C(3)-N(1)-C(4)	111.6(3)
			N(1)-C(2)-C(3A)	112.7(3)
			N(1)-C(3)-C(2A)	111.0(3)
			P(1)-C(4)-N(1)	109.8(3)
			P(1)-C(11)-C(12)	119.8(3)
			P(1)-C(11)-C(16)	121.1(3)

C(12)-C(11)-C(16)	119.0(4)
C(11)-C(12)-C(13)	121.0(3)
C(12)-C(13)-C(14)	118.7(4)
C(13)-C(14)-C(15)	120.8(4)
C(14)-C(15)-C(16)	120.0(3)
C(11)-C(16)-C(15)	120.4(4)
HOWA-Ow(2)-HOWB	109.0(1)
HO(3A)-Ow(3)-HO(3B)	106.7(1)

Selected bond lengths and angles for Zinc Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond lengths (Å)			Bond angles (^{0})	
Zn(1)-O(1)	2.072(1)		O(1)-Zn(1)-O(1A)	97.93(4)
Zn(1)-N(1)	2.219(1)		O(1)-Zn(1)-N(1)	85.03(4)
P(1)-O(1)	1.529(1)		O(1)-Zn(1)-N(1A)	95.44(4)
P(1)-O(2)	1.513(1)		O(1)-Zn(1)-N(1B)	165.76(4)
P(1)-C(4)	1.842(1)		N(1)-Zn(1)-N(1A)	80.80(5)
P(1)-C(11)	1.805(1)		O(1)-P(1)-O(2)	117.52(6)
N(1)-C(2)	1.491(2)		O(1)-P(1)-C(4)	104.83(6)
N(1)-C(3)	1.481(2)		O(1)-P(1)-C(11)	109.03(7)
N(1)-C(4)	1.480(2)		O(2)-P(1)-C(4)	109.49(7)
C(2)-C(3A)	1.541(2)		O(2)-P(1)-C(11)	108.51(7)
C(11)-C(12)	1.396(2)		C(4)-P(1)-C(11)	106.97(7)
C(11)-C(16)	1.401(2)		Zn(1)-O(1)-P(1)	117.02(6)
C(12)-C(13)	1.395(2)		Zn(1)-N(1)-C(2)	109.49(8)
C(13)-C(14)	1.390(3)		Zn(1)-N(1)-C(3)	104.11(8)
C(14)-C(15)	1.388(3)		Zn(1)-N(1)-C(4)	104.52(8)
C(15)-C(16)	1.388(3)		C(2)-N(1)-C(3)	112.6(1)
			C(2)-N(1)-C(4)	113.2(1)
			C(3)-N(1)-C(4)	112.2(1)
			N(1)-C(2)-C(3A)	113.0(1)
			N(1)-C(3)-C(2A)	111.6(1)
			P(1)-C(4)-N(1)	110.08(9)
			P(1)-C(11)-C(12)	119.9(1)
			P(1)-C(11)-C(16)	120.7(1)

C(12)-C(11)-C(16)	119.4(1)
C(11)-C(12)-C(13)	120.5(2)
C(12)-C(13)-C(14)	119.6(2)
C(13)-C(14)-C(15)	120.2(2)
C(14)-C(15)-C(16)	120.5(2)
C(11)-C(16)-C(15)	119.9(2)
HOWA-Ow(2)-HOWB	110.8
HO(3A)-Ow(3)-HO(3B)	105.9

Atomic co-ordinates and equivalent isotropic atomic displacement parameters ($Å^2$) Indium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Atom	x/a	y/b	z/c	U(eq)
In(1)	0.189859(7)	0.244942(7)	0.151289(7)	0.0165
P(1)	0.17751(3)	0.14115(3)	-0.10087(3)	0.0206
P(2)	-0.02465(3)	0.26284(3)	0.27033(3)	0.0235
P(3)	0.35659(3)	0.41602(3)	0.23076(3)	0.0201
O(11)	0.18430(9)	0.24862(8)	-0.02243(8)	0.0233
O(12)	0.28369(9)	0.08803(9)	-0.14844(8)	0.0263
O(21)	0.01407(8)	0.27617(9)	0.15927(8)	0.0252
O(22)	-0.08538(9)	0.16844(9)	0.2681(1)	0.0323
O(31)	0.22993(8)	0.40192(8)	0.20870(8)	0.0228
O(32)	0.40758(9)	0.44481(9)	0.35048(8)	0.0275
N(1)	0.21119(9)	0.05422(9)	0.10386(9)	0.0212
N(4)	0.2077(1)	0.1782(1)	0.32375(9)	0.0223
N(7)	0.38667(9)	0.18602(9)	0.19695(9)	0.0202
C(1)	0.1442(1)	0.0440(1)	-0.0126(1)	0.0229
C(2)	0.1569(1)	0.0145(1)	0.1886(1)	0.0249
C(3)	0.2048(1)	0.0559(1)	0.3090(1)	0.0260
C(4)	0.1102(1)	0.2469(1)	0.3749(1)	0.0265
C(5)	0.3213(1)	0.2013(1)	0.3856(1)	0.0239
C(6)	0.4183(1)	0.1569(1)	0.3171(1)	0.0236
C(7)	0.4356(1)	0.2819(1)	0.1758(1)	0.0219
C(8)	0.4146(1)	0.0870(1)	0.1162(1)	0.0227
C(9)	0.3365(1)	0.0020(1)	0.1122(1)	0.0242
C(11)	0.0535(1)	0.1723(1)	-0.2096(1)	0.0229
C(12)	0.0520(1)	0.1170(1)	-0.3173(1)	0.0262

C(13)	-0.0439(1)	0.1438(1)	-0.4014(1)	0.0310
C(14)	-0.1373(1)	0.2246(1)	-0.3783(1)	0.0333
C(15)	-0.1364(1)	0.2788(2)	-0.2713(2)	0.0374
C(16)	-0.0416(1)	0.2532(1)	-0.1867(1)	0.0326
C(21)	-0.1096(1)	0.3952(1)	0.3105(1)	0.0262
C(22)	-0.2040(1)	0.3995(1)	0.3620(1)	0.0302
C(23)	-0.2726(2)	0.5023(2)	0.3883(2)	0.0364
C(24)	-0.2476(2)	0.5998(1)	0.3633(2)	0.0382
C(25)	-0.1526(2)	0.5961(2)	0.3141(2)	0.0479
C(26)	-0.0832(2)	0.4945(2)	0.2879(2)	0.0422
C(31)	0.3656(1)	0.5190(1)	0.1408(1)	0.0231
C(32)	0.4465(2)	0.5870(2)	0.1726(1)	0.0352
C(33)	0.4490(2)	0.6702(2)	0.1047(2)	0.0441
C(34)	0.3721(2)	0.6849(2)	0.0061(2)	0.0388
C(35)	0.2928(2)	0.6171(2)	-0.0268(2)	0.0479
C(36)	0.2887(2)	0.5336(2)	0.0400(2)	0.0408
O(W1)	0.3030(1)	-0.1331(1)	-0.2469(1)	0.0320
O(W2)	0.5732(1)	0.3530(1)	0.5251(1)	0.0359
O(W3)	0.5839(1)	0.1568(1)	0.6138(1)	0.0397
O(W4)	0.2972(1)	-0.0395(1)	-0.4487(1)	0.0411
O(W5)	0.3931(1)	0.1240(1)	-0.3168(1)	0.0452

Selected bond lengths for Indium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

In(1) - O(11)	2.1002(9)		C(1) - H1A	0.95(2)
In(1) - O(21)	2.0921(9)		C(1) - H1B	0.95(2)
In(1) - O(31)	2.0917(9)		C(2) - H2A	0.93(2)
In(1) - N(1)	2.314(1)		C(2) - H2B	0.96(2)
In(1) - N(4)	2.289(1)		C(3) - H3A	0.93(2)
In(1) - N(7)	2.305(1)		C(3) - H3B	0.95(2)
P(1) - O(11)	1.540(1)		C(4) - H4A	0.96(2)
P(1) - O(12)	1.498(1)		C(4) - H4B	0.94(2)
P(1) - C(1)	1.842(1)		C(5) - H5A	0.93(2)
P(1) - C(11)	1.797(1)		C(5) - H5B	0.96(2)
P(2) - O(21)	1.545(1)		C(6) - H6A	0.98(2)
P(2) - O(22)	1.491(1)		C(6) - H6B	0.98(2)
P(2) - C(4)	1.846(1)		C(7) - H7A	0.94(2)
P(2) - C(21)	1.796(1)		C(7) - H7B	0.95(2)
P(3) - O(31)	1.542(1)		C(8) - H8A	0.95(2)
P(3) - O(32)	1.495(1)		C(8) - H8B	0.95(2)
P(3) - C(7)	1.840(1)		C(9) - H9A	0.93(2)
P(3) - C(31)	1.795(1)		C(9) - H9B	0.97(2)
N(1) - C(1)	1.490(2)		C(12) - H12	0.95(2)
N(1) - C(2)	1.495(2)		C(13) - H13	0.94(2)
N(1) - C(9)	1.499(2)		C(14) - H14	0.97(2)
N(4) - C(3)	1.497(2)		C(15) - H15	0.93(3)
N(4) - C(4)	1.489(2)		C(16) - H16	0.93(2)
N(4) - C(5)	1.494(2)		C(22) - H22	0.93(2)

N(7) - C(6)	1.497(2)		C(23) - H23	0.97(2)
N(7) - C(7)	1.490(2)		C(24) - H24	0.93(2)
N(7) - C(8)	1.492(2)		C(25) - H25	0.89(3)
C(2) - C(3)	1.532(2)		C(26) - H26	0.94(3)
C(5) - C(6)	1.536(2)		C(32) - H32	0.92(2)
C(8) - C(9)	1.537(2)		C(33) - H33	0.92(3)
C(11) - C(12)	1.398(2)		C(34) - H34	0.95(2)
C(11) - C(16)	1.397(2)		C(35) - H35	0.94(3)
C(12) - C(13)	1.394(2)		C(36) - H36	0.94(3)
C(13) - C(14)	1.383(2)		O(W1) - HOW1A	0.84(2)
C(14) - C(15)	1.387(3)		O(W1) - HOW1B	0.86(2)
C(15) - C(16)	1.388(2)		O(W2) - HOW2A	0.82(2)
C(21) - C(22)	1.390(2)		O(W2) - HOW2B	0.85(3)
C(21) - C(26)	1.391(2)		O(W3) - HOW3A	0.82(2)
C(22) - C(23)	1.393(2)		O(W3) - HOW3B	0.84(3)
C(23) - C(24)	1.373(3)		O(W4) - HOW4A	0.82(3)
C(24) - C(25)	1.382(3)		O(W4) - HOW4B	0.84(3)
C(25) - C(26)	1.386(3)		O(W5) - HOW5A	0.93(3)
C(31) - C(32)	1.386(2)		O(W5) - HOW5B	0.86(3)
C(31) - C(36)	1.388(2)			
C(32) - C(33)	1.392(2)			
C(33) - C(34)	1.368(3)			
C(34) - C(35)	1.370(3)			
C(35) - C(36)	1.392(3)			

Bond angles for Indium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

O(11) - In(1) - O(21)	101.10(4)		In(1) - N(4) - C(5)	103.86(8)
O(11) - In(1) - O(31)	99.95(4)		C(3) - N(4) - C(4)	113.0(1)
O(11) - In(1) - N(1)	82.29(4)		C(3) - N(4) - C(5)	112.5(1)
O(11) - In(1) - N(4)	160.82(4)		C(4) - N(4) - C(5)	111.7(1)
O(11) - In(1) - N(7)	96.21(4)		In(1) - N(7) - C(6)	109.66(8)
O(21) - In(1) - O(31)	100.84(4)		In(1) - N(7) - C(7)	104.68(7)
O(21) - In(1) - N(1)	97.26(4)		In(1) - N(7) - C(8)	104.86(8)
O(21) - In(1) - N(4)	82.86(4)		C(6) - N(7) - C(7)	113.1(1)
O(21) - In(1) - N(7)	161.32(4)		C(6) - N(7) - C(8)	112.3(1)
O(31) - In(1) - N(1)	160.93(4)		C(7) - N(7) - C(8)	111.6(1)
O(31) - In(1) - N(4)	97.67(4)		P(1) - C(1) - N(1)	110.13(9)
O(31) - In(1) - N(7)	82.85(4)		N(1) - C(2) - C(3)	111.5(1)
N(1) - In(1) - N(4)	78.59(4)		N(4) - C(3) - C(2)	114.0(1)
N(1) - In(1) - N(7)	78.08(4)		P(2) - C(4) - N(4)	110.61(9)
N(4) - In(1) - N(7)	78.49(4)		N(4) - C(5) - C(6)	112.1(1)
O(11) - P(1) - O(12)	116.31(6)		N(7) - C(6) - C(5)	113.5(1)
O(11) - P(1) - C(1)	104.13(6)		P(3) - C(7) - N(7)	111.41(9)
O(11) - P(1) - C(11)	107.40(6)		N(7) - C(8) - C(9)	112.1(1)
O(12) - P(1) - C(1)	109.83(6)		N(1) - C(9) - C(8)	113.7(1)
O(12) - P(1) - C(11)	111.94(6)		P(1) - C(11) - C(12)	120.4(1)
C(1) - P(1) - C(11)	106.54(6)		P(1) - C(11) - C(16)	119.7(1)
O(21) - P(2) - O(22)	115.89(7)		C(12) - C(11) - C(16)	119.8(1)
O(21) - P(2) - C(4)	103.92(6)		C(11) - C(12) - C(13)	119.7(1)
O(21) - P(2) - C(21)	107.01(6)		C(12) - C(13) - C(14)	120.1(1)

O(22) - P(2) - C(4)	111.51(7)		C(13) - C(14) - C(15)	120.2(1)
O(22) - P(2) - C(21)	112.10(6)		C(14) - C(15) - C(16)	120.4(2)
C(4) - P(2) - C(21)	105.60(7)		C(11) - C(16) - C(15)	119.7(1)
O(31) - P(3) - O(32)	116.30(6)		P(2) - C(21) - C(22)	120.4(1)
O(31) - P(3) - C(7)	104.45(6)		P(2) - C(21) - C(26)	120.2(1)
O(31) - P(3) - C(31)	106.98(6)		C(22) - C(21) - C(26)	119.4(1)
O(32) - P(3) - C(7)	111.10(6)		C(21) - C(22) - C(23)	120.0(1)
O(32) - P(3) - C(31)	111.11(6)		C(22) - C(23) - C(24)	120.3(2)
C(7) - P(3) - C(31)	106.22(6)		C(23) - C(24) - C(25)	119.9(2)
In(1) - O(11) - P(1)	119.73(5)		C(24) - C(25) - C(26)	120.5(2)
In(1) - O(21) - P(2)	119.68(6)		C(21) - C(26) - C(25)	119.9(2)
In(1) - O(31) - P(3)	119.62(5)		P(3) - C(31) - C(32)	120.6(1)
In(1) - N(1) - C(1)	104.79(8)		P(3) - C(31) - C(36)	120.0(1)
In(1) - N(1) - C(2)	103.36(8)		C(32) - C(31) - C(36)	119.3(1)
In(1) - N(1) - C(9)	110.05(8)		C(31) - C(32) - C(33)	120.1(2)
C(1) - N(1) - C(2)	112.2(1)		C(32) - C(33) - C(34)	120.2(2)
C(1) - N(1) - C(9)	113.4(1)		C(33) - C(34) - C(35)	120.1(2)
C(2) - N(1) - C(9)	112.3(1)		C(34) - C(35) - C(36)	120.6(2)
In(1) - N(4) - C(3)	109.69(8)		C(31) - C(36) - C(35)	119.7(2)
In(1) - N(4) - C(4)	105.40(8)			

Fractional Atomic Coordinates for Gallium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

	x		y		z	
Ga	.20763(6)		.22413(6)		.16563(7)	
P1	.1871 (2)		.1346 (2)		-.0867	
(2)						
P2	-.0102	(2)	.2562	(2)	.2772	(2)
P3	.3576	(2)	.4008	(2)	.2323	(2)
011	.2061	(4)	.2337	(4)	.0054	(4)
O12	.2885	(4)	.0829	(4)	-.1484	(4)
O21	.0446	(3)	.2532	(4)	.1659	(4)
O22	-.0781	(4)	.1672	(4)	.2781	(5)
O31	.2347	(4)	.3715	(3)	.2202	(4)
O32	.4088	(4)	.4390	(4)	.3498	(4)
N1	.2154	(4)	.0501	(4)	.1137	(5)
N4	.2158	(5)	.1785	(5)	.3318	(5)
N7	.3904	(4)	.1787	(4)	.1967	(5)
C1	.1484	(6)	.0382	(6)	-.0016	(6)
C2	.1604	(6)	.0120	(6)	.2006	(7)
C3	.2080	(6)	.0585	(6)	.3225	(7)
C4	.1169	(6)	.2509	(6)	.3850	(6)
C5	.3289	(6)	.2044	(6)	.3932	(6)
C6	.4242	(6)	.1568	(6)	.3176	(6)
C7	.4396	(6)	.2721	(6)	.3176	(6)
C8	.4200	(6)	.0783	(6)	.1128	(6)
C9	.3381	(6)	-.0043	(6)	.1140	(6)
C11	.0634	(6)	.1735	(6)	-.1870	(6)

C12	-.0250	(7)	-.2526	(7)	-.1527	(7)
C13	-.1189	(7)	-.2816	(7)	-.2313	(8)
C14	-.1243	(7)	.2329	(8)	-.3431	(8)
C15	-.0368	(7)	.1525	(7)	-.3788	(7)
C16	.0581	(6)	.1222	(6)	-.3002	(7)
C21	-.0933	(6)	.3888	(6)	.3079	(6)
C22	-.197	(7)	.3997	(7)	.3536	(7)
C23	-.2650	(7)	.5012	(8)	.3720	(8)
C24	-.2316	(8)	.5915	(7)	.3450	(8)
C25	-.1282	(9)	.5832	(7)	.3021	(9)
C26	-.0585	(7)	.4819	(7)	.2838	(8)
C31	.3556	(6)	.4991	(6)	.1364	(6)
C32	.4300	(7)	.5763	(7)	.1643	(7)
C33	.4242	(8)	.6556	(7)	.0938	(9)
C34	.3490	(10)	.6676	(8)	-.0031	(9)
C35	.2770	(9)	.5809	(9)	-.0317	(8)
C36	.2800	(7)	.5006	(7)	.0375	(7)
OW1	.3019	(5)	-.1387	(5)	-.2387	(6)
OW2	.5693	(6)	.3550	(5)	.5252	(5)
OW3	.5869	(0)	.1619	(0)	.6164	(0)
OW4	.2950	(8)	-.0503	(7)	-.4481	(7)
OW5	.3889	(7)	.1160	(7)	-.3317	(8)

Bond Lenghts for Gallium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond Lengths (Å)			Bond Lengths (Å)	
Ga-O(11)	1.917(4)		N(7)-C(6)	1.485(9)
Ga-O(21)	1.908(4)		N(7)-C(7)	1.481(9)
Ga-O(31)	1.911(4)		N(7)-C(8)	1.491(9)
Ga-N(1)	2.146(5)		C(2)-C(3)	1.530(11)
Ga-N(4)	2.121(5)		C(5)-C(6)	1.525(10)
Ga-N(7)	2.139(5)		C(8)-C(9)	1.538(10)
P(1)-O(11)	1.533(5)		C(11)-C(12)	1.369(10)
P(1)-O(12)	1.489(5)		C(11)-C(16)	1.385(11)
P(1)-C(1)	1.846(5)		C(12)-C(13)	1.381(12)
P(1)-C(11)	1.803(7)		C(13)-C(14)	1.361(14)
P(2)-O(21)	1.546(5)		C(14)-C(15)	1.375(13)
P(2)-O(22)	1.484(5)		C(15)-C(16)	1.393(11)
P(2)-C(4)	1.828(7)		C(21)-C(22)	1.394(11)
P(2)-C(21)	1.784(7)		C(21)-C(26)	1.382(11)
P(3)-O(31)	1.546(5)		C(22)-C(23)	1.382(12)
P(3)-O(32)	1.473(5)		C(23)-C(24)	1.355(14)
P(3)-C(7)	1.825(7)		C(24)-C(25)	1.379(14)
P(3)-C(31)	1.797(7)		C(25)-C(26)	1.388(13)
N(1)-C(1)	1.475(9)		C(31)-C(32)	1.387(11)
N(1)-C(2)	1.476(9)		C(31)-C(36)	1.368(11)
N(1)-C(9)	1.496(9)		C(32)-C(33)	1.382(12)
N(4)-C(3)	1.499(10)		C(33)-C(34)	1.348(15)
N(4)-C(4)	1.502(9)		C(34)-C(35)	1.362(15)

N(4)-C(5)	1.492(9)		C(35)-C(36)	1.387(12)

Bond Angles for Gallium Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

O(11)-Ga-O(21)	96.2(2)		Ga-N(4)-C(5)	104.9(4)
O(11)-Ga-O(31)	95.7(2)		C(3)-N(4)-C(4)	112.5(5)
O(11)-Ga-N(1)	86.1(2)		C(3)-N(4)-C(5)	111.7(5)
O(11)-Ga-N(4)	168.3(2)		C(4)-N(4)-C(5)	111.5(5)
O(11)-Ga-N(7)	94.7(2)		Ga-N(7)-C(6)	109.9(4)
O(21)-Ga-O(31)	96.5(2)		Ga-N(7)-C(7)	105.6(4)
O(21)-Ga-N(1)	95.2(2)		Ga-N(7)-C(8)	106.0(4)
O(21)-Ga-N(4)	86.4(2)		C(6)-N(7)-C(7)	112.8(5)
O(21)-Ga-N(7)	168.5(2)		C(6)-N(7)-C(8)	111.5(5)
O(31)-Ga-N(1)	168.0(2)		C(7)-N(7)-C(8)	110.7(5)
O(31)-Ga-N(4)	95.3(2)		P(1)-C(1)-N(1)	108.5(4)
O(31)-Ga-N(7)	86.0(2)		N(1)-C(2)-C(3)	110.6(6)
N(1)-Ga-N(4)	82.3(2)		N(4)-C(3)-C(2)	111.6(6)
N(1)-Ga-N(7)	82.0(2)		P(2)-C(4)-N(4)	108.7(5)
N(4)-Ga-N(7)	82.2(2)		N(4)-C(5)-C(6)	110.0(6)
O(11)-P(1)-O(12)	116.2(3)		N(7)-C(6)-C(5)	112.0(5)
O(11)-P(1)-C(1)	101.8(3)		P(3)-C(7)-N(7)	109.1(4)
O(11)-P(1)-C(11)	108.7(3)		N(7)-C(8)-C(9)	109.7(4)
O(12)-P(1)-C(1)	111.0(3)		N(1)-C(9)-C(8)	112.1(5)
O(12)-P(1)-C(11)	111.0(3)		P(1)-C(11)-C(12)	121.0(6)
C(1)-P(1)-C(11)	107.4(3)		P(1)-C(11)-C(16)	119.0(5)
O(21)-P(2)-O(22)	116.3(3)		C(12)-C(11)-C(16)	120.0(7)

O(21)-P(2)-C(4)	101.2(3)		C(11)-C(12)-C(13)	119.9(8)
O(21)-P(2)-C(21)	108.2(3)		C(12)-C(13)-C(14)	120.6(8)
O(22)-P(2)-C(4)	112.4(3)		C(13)-C(14)-C(15)	120.3(7)
O(22)-P(2)-C(21)	111.4(3)		C(14)-C(15)-C(16)	119.6(8)
C(4)-P(2)-C(21)	106.5(4)		C(11)-C(16)-C(15)	119.6(7)
O(31)-P(3)-O(32)	116.5(3)		P(2)-C(21)-C(22)	120.2(6)
O(31)-P(3)-C(7)	102.3(3)		P(2)-C(21)-C(26)	121.0(6)
O(31)-P(3)-C(31)	107.7(3)		C(22)-C(21)-C(26)	118.8(7)
O(32)-P(3)-C(7)	111.4(3)		C(21)-C(22)-C(23)	120.6(8)
O(32)-P(3)-C(31)	111.4(3)		C(22)-C(23)-C(24)	120.1(8)
C(7)-P(3)-C(31)	106.8(3)		C(23)-C(24)-C(25)	120.3(8)
Ga-O(11)-P(1)	120.7(3)		C(24)-C(25)-C(26)	120.3(8)
Ga-O(21)-P(2)	121.1(3)		C(21)-C(26)-C(25)	119.9(7)
Ga-O(31)-P(3)	120.4(3)		P(3)-C(31)-C(32)	119.6(6)
Ga-N(1)-C(1)	105.3(4)		P(3)-C(31)-C(36)	121.0(6)
Ga-N(1)-C(2)	105.0(4)		C(32)-C(31)-C(36)	119.4(7)
Ga-N(1)-C(9)	110.2(4)		C(31)-C(32)-C(33)	119.6(8)
C(1)-N(1)-C(2)	112.2(5)		C(32)-C(33)-C(34)	120.9(8)
C(1)-N(1)-C(9)	113.1(5)		C(33)-C(34)-C(35)	119.7(8)
C(2)-N(1)-C(9)	110.6(5)		C(34)-C(35)-C(36)	120.9(8)
Ga-N(4)-C(3)	110.4(4)		C(31)-C(36)-C(35)	119.5(8)
Ga-N(4)-C(4)	105.3(4)			

Fractional Atomic Coordinates for Iron Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Atom	x	y	z	B_{iso}
Fe	0.19986(4)	0.23370(4)	0.15897(4)	2.27(2)
P(1)	0.18390(8)	0.13557(7)	-0.0916(7)	2.67(4)
P(2)	-0.01353(8)	0.25736(8)	0.27672(8)	2.99(4)
P(3)	0.35943(8)	0.40433(7)	0.23097(7)	2.58(3)
O(11)	0.19883(20)	0.23629(17)	-0.00269(18)	2.78(10)
O(12)	0.28689(20)	0.08361(19)	-0.14831(20)	3.31(10)
O(21)	0.03653(18)	0.25931(18)	0.16633(19)	2.8(10)
O(22)	-0.07888(21)	0.16660(20)	0.27592(24)	4.17(13)
O(31)	0.23622(19)	0.37821(17)	0.21649(18)	2.66(9)
O(32)	0.41107(22)	0.44014(19)	0.34907(20)	3.58(11)
N(1)	0.21424(23)	0.05292(21)	0.11044(23)	2.62(12)
N(4)	0.213647(23)	0.17800(22)	0.32691(22)	2.79(12)
N(7)	0.38777(22)	0.18038(21)	0.19508(22)	2.47(11)
C(1)	0.14568(30)	0.04170(27)	-0.00528(30)	3.09(15)
C(2)	0.15891(31)	0.01339(27)	0.19554(32)	3.29(16)
C(3)	0.20703(32)	0.05750(29)	0.31564(31)	3.47(16)
C(4)	0.11721(30)	0.24811(30)	0.3812(29)	3.22(16)
C(5)	0.3271(29)	0.20216(29)	0.38867(28)	3.08(15)
C(6)	0.42172(29)	0.15587(29)	0.31627(30)	3.22(15)
C(7)	0.43878(28)	0.27405(27)	0.17129(29)	2.82(15)
C(8)	0.41724(28)	0.08078(27)	0.11315(31)	3.14(15)
C(9)	0.33714(31)	-0.0018(27)	0.11123(31)	3.26(16)
C(11)	0.06013(29)	0.17265(26)	-0.19400(28)	2.78(14)
C(12)	0.05407(32)	0.12136(30)	-0.30528(31)	3.42(16)

C(13)	-0.03983(37)	0.15135(35)	-0.38521(33)	4.21(19)
C(14)	-0.1279(36)	0.23231(38)	-0.35468(39)	4.76(21)
C(15)	-0.12361(37)	0.28192(38)	-0.24501(43)	5.31(22)
C(16)	-0.03036(35)	0.25357(33)	-0.16390(35)	4.17(18)
C(21)	-0.09734(29)	0.39052(29)	0.31089(29)	3.07(15)
C(22)	-0.19854(34)	0.39913(32)	0.35667(34)	3.97(18)
C(23)	-0.26629(38)	0.50133(36)	0.37708(38)	4.82(21)
C(24)	-0.23472(42)	0.59325(34)	0.35213(39)	5.03(23)
C(25)	-0.13374(47)	0.58662(36)	0.30965(46)	6.05(27)
C(26)	-0.06464(38)	0.48489(330	0.28889(40)	4.83(21)
C(31)	0.35955(29)	0.50414(26)	0.13672(28)	2.79(15)
C(32)	0.43308(36)	0.57956(35)	0.16530(35)	4.48(20)
C(33)	0.42851(44)	0.66031(38)	0.09408(44)	5.59(25)
C(34)	0.35326(47)	0.66463(38)	-0.00160(42)	5.52(24)
C(35)	0.28007(48)	0.58896(45)	-0.03233(39)	6.25(27)
C(36)	0.28339(39)	0.50760(36)	0.03690(34)	4.72(21)

Bond Lengths (Å) for Iron Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

Bond Lengths (Å)			Bond Lengths (Å)	
Fe-O(11)	2.938(2)		Fe-O(21)	1.931(2)
Fe-N(1)	2.217(3)		Fe-N(4)	2.192(3)
P(1)-O(11)	1.535(2)		P(1)-O(12)	1.496(2)
P(1)-C(11)	1.792(3)		P(2)-O(21)	1.542(2)
P(2)-C(4)	1.828(4)		P(3)-C(7)	1.826(3)
P(3)-O(32)	1.465(2)		N(1)-C(2)	1.486(4)
N(1)-C(1)	1.489(4)		N(4)-C(4)	1.487(4)
N(4)-C(3)	1.50(4)		N(7)-C(7)	1.493(4)
N(7)-C(6)	1.50(4)		C(5)-C(6)	1.513(5)
C(2)-C(3)	1.519(5)		C(11)-C(16)	1.386(5)
C(11)-C(12)	1.385(5)		C(14)-C(15)	1.362(7)
C(13)-C(14)	1.368(7)		C(21)-C(26)	1.377(5)
C(21)-C(22)	1.387(5)		C(24)-C(25)	1.368(7)
C(23)-C(24)	1.355(7)		C(31)-C(36)	1.377(5)
C(31)-C(32)	1.372(5)		C(34)-C(35)	1.373(8)
C(33)-C(34)	1.335(8)		C(35)-C(36)	1.390(6)
C(32)-C(33)	1.398(6)		C(25)-C(26)	1.387(6)
C(22)-C(23)	1.384(6)		C(15)-C(16)	1.379(6)
C(12)-C(13)	1.380(5)		C(8)-C(9)	1.524(5)
N(7)-C(8)	1.486(4)		N(4)-C(5)	1.492(4)
N(1)-C(9)	1.496(4)		P(3)-C(31)	1.796(3)
P(3)-O(31)	1.542(2)		P(2)-C(21)	1.794(4)
P(2)-O(22)	1.486(3)		P(1)-C(1)	1.83(3)

Fe-O(31)	1.928(2)		Fe-N(7)	2.206(3)

Bond Angles (°) for Iron Complex of 1,4,7 Triazacyclononane tris(methylene(phenylphosphinic)) Acid

O(11)-Fe-O(21)	100.5(1)		O(11)-Fe-O(31)	99.7(1)
O(11)-Fe-N(1)	83.7(1)		O(11)-Fe-N(4)	163.0(1)
O(11)-Fe-N(7)	94.6(1)		O(21)-Fe-O(31)	100.6(1)
O(21)-Fe-N(1)	95.4(1)		O(21)-Fe-N(4)	83.8(1)
O(21)-Fe-N(7)	163.2(1)		O(31)-Fe-N(1)	162.7(1)
O(31)-Fe-N(4)	95.6(1)		O(31)-Fe-N(7)	83.9(1)
N(1)-Fe-N(4)	79.4(1)		N(1)-Fe-N(7)	78.9(1)
N(4)-Fe-N(7)	79.6(1)		O(11)-P(1)-O(12)	116.1(1)
O(11)-P(1)-C(1)	101.2(1)		O(11)-P(1)-C(11)	108.5(1)
O(12)-P(1)-C(1)	111.5(2)		O(12)-P(1)-O(11)	111.6(2)
C(1)-P(1)-C(11)	107.1(2)		O(21)-P(2)-O(22)	115.9(2)
O(21)-P(2)-C(4)	101.0(1)		O(21)-P(2)-C(21)	108.0(2)
O(22)-P(2)-C(4)	112.6(2)		O(22)-P(2)-C(21)	112.0(2)
C(4)-P(2)-C(21)	106.5(2)		O(31)-P(3)-O(32)	116.3(1)
O(31)-P(3)-C(7)	101.8(1)		O(31)-P(3)-C(31)	107.9(1)
O(32)-P(3)-C(7)	112.0(2)		O(32)-P(3)-C(31)	111.3(2)
C(7)-P(3)-C(31)	106.7(2)		Fe-O(11)-P(1)	122.7(1)
Fe-O(21)-P(2)	123.0(1)		Fe-O(31)-P(3)	122.7(2)
Fe-N(1)-C(1)	104.1(2)		C(1)-N(1)-C(2)	111.2(2)
Fe-N(1)-C(9)	111.5(2)		C(2)-N(1)-C(9)	111.6(3)
C(1)-N(1)-C(9)	112.6(3)		Fe-N(4)-C(4)	105.3(2)

Fe-N(4)-C(3)	111.0(1)		C(3)-N(4)-C(4)	112.3(3)
Fe-N(4)-C(5)	105.1(2)		C(4)-N(4)-C(5)	110.9(3)
C(3)-N(4)-C(5)	111.9(3)		Fe-N(7)-C(7)	104.9(2)
Fe-N(7)-C(6)	110.4(2)		Fe-N(1)-C(2)	105.2(2)
Fe-N(7)-C(8)	106.7(2)		C(6)-N(7)-C(7)	112.5(3)
C(6)-N(7)-C(8)	111.4(2)		C(7)-N(7)-C(8)	110.6(2)
P(1)-C(1)-N(1)	108.9(2)		N(1)-C(2)-C(3)	110.1(3)
N(4)-C(3)-C(2)	112.4(3)		P(2)-C(4)-N(4)	109.0(2)
N(4)-C(5)-C(6)	110.5(3)		N(7)-C(6)-C(5)	112.3(3)
P(3)-C(7)-N(7)	109.5(2)		N(7)-C(8)-C(9)	110.8(3)
N(1)-C(9)-C(8)	112.2(3)		P(1)-C(11)-C(12)	120.3(3)
P(1)-C(11)-C(16)	120.8(3)		C(12)-C(11)-C(16)	118.9(3)
C(11)-C(12)-C(13)	120.5(3)		C(12)-C(13)-C(14)	119.9(4)
C(13)-C(14)-C(15)	119.9(4)		C(14)-C(15)-C(16)	121.1(4)
C(11)-C(16)-C(15)	119.6(4)		P(2)-C(21)-C(22)	120.0(3)
P(2)-C(21)-C(26)	120.8(3)		C(21)-C(22)-C(26)	119.1(3)
C(21)-C(22)-C(23)	119.9(4)		C(22)-C(23)-C(24)	120.4(4)
C(23)-C(24)-C(25)	120.4(4)		C(24)-C(25)-C(26)	119.9(4)
C(21)-C(26)-C(25)	120.2(4)		P(3)-C(31)-C(32)	120.2(3)
P(3)-C(31)-C(36)	120.2(3)		C(32)-C(31)-C(36)	119.5(3)
C(31)-C(32)-C(33)	119.8(4)		C(32)-C(33)-C(34)	120.6(4)
C(33)-C(34)-C(35)	120.5(4)		C(34)-C(35)-C(36)	120.0(4)
C(31)-C(36)-C(35)	119.7(4)			

"This is not the end.

It is not even the begining of the end.

But it is, perhaps, the end of the beginning."

10th November 1942

Winston Churchill