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New Chelating Systems for Radiopharmaceutical Diagnosis

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ABSTRACT

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NEW CHELATING SYSTEMS FOR RADIOPHARMACEUTICAL DIAGNOSIS

by Paul Saunders Walker

This thesis concerns the design of novel binding agents for radioisotopes having potential application in radiopharmaceutical imaging systems. The first section reviews the currently available methods of radioimaging with particular emphasis on the limitations of the pharmaceutical reagents currently used for this important medical diagnostic tool.

The main focus of the work concerns: (i) the design and study of a particular class of novel radiopharmaceutical hosts based on a well-established group of polydentate ligands, the propylene amine oximes (PnAOs); and (ii) the evaluation of various techniques for the quantification of host binding efficiency.

Modelling studies have been used to design a series of novel, multi-functional PnAO complexes of Tc(V). In particular, substitution of the PnAO skeleton with pendant arms containing hetero-atom substituted aromatic rings was investigated with a view to increasing the co-ordination number of the ligand, thereby leading to complexes which would be more stable within the body. Six novel PnAO ligands substituted with tethered methoxybenzene and pyridinyl moieties have been prepared and fully characterised. A number of these ligands have been successfully complexed with the Tc(V) mimicking metals Co(III) and Cu(II) and their crystal structures solved.

Extraction experiments have been used to determine the strength of the association between polydentate ligand hosts and their metal guests. A series of oxonol dye salts based on the Tc(V) mimicking metals Mn(II), Co(III) , and Cu(II) have been prepared in high purity. Their use as extraction experiment indicators was, however, precluded by the insoluble nature of the PnAO-oxonol salt complexes formed.

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2 Acknowledgements

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Debs, I couldn't have done it without you. I Love You.

3 Abbreviations

CT ..... X-Ray Computed Tomography
DCM ..... Dichloromethane
DMAP ..... *N*,*N*-Dimethylaminopyridine
DMSA ..... Dimercaptosuccinic Acid
ITLC ..... Instant Thin Layer Chromatography
RBC ..... Red Blood Cell
MRI ..... Magnetic Resonance Image
PET ..... Positron Emission Tomography
PnAO ..... Propylene Amine Oxime
SD ..... Standard Deviation
SPECT ..... Single Photon Emission Computed Tomography
TCNQ ..... Tetracyanoquinodimethane
THF ..... Tetrahydrofuran

SECTION 1

Introduction

Aims and Objectives

"An expert is someone who has
made all the mistakes that can be made
in a narrow field"

Niels Bohr

4 Introduction

4.1 Nuclear Medicine

Nuclear medicine is an enormously useful discipline wherein diagnostic and prognostic information is obtained by an essentially non-invasive (i.e. nonsurgical) procedure.[1] In its practice, some chemical form of an emitting isotope, a radiopharmaceutical, is administered to a patient (usually by intravenous injection) with the goal of the isotope becoming localised in a specific organ. Subsequent visualisation of the organ with suitable imaging equipment provides information about both the structure and functioning of that organ.

The use of radiopharmaceuticals as imaging tools has a fundamental advantage over the more routinely used techniques of nuclear magnetic resonance and ultrasound imaging. Whilst the latter provide high resolution images and are able to easily delineate anatomical features, they give only limited information on biological function. The radiopharmaceutical exploits the nuclear properties of the radionuclide and the pharmacological properties of the associated pharmaceutical. In this way the strength of nuclear medicine lies in its use for monitoring anatomical, biochemical and physiological functions *in vivo*. This information, especially with respect to organ function, is currently difficult or impossible to obtain by other means.

Diagnostic nuclear medicine thus provides a unique way of both assessing disease states and monitoring the effects of treatment, and has therefore become a very widely employed technique. Routinely used diagnostic radiopharmaceuticals are currently under investigation for use in the treatment of disease.[2]

4.2 Radionuclides in Nuclear Medicine

Since the field of tissue-specific organic pharmaceuticals is very broad and very successful it is important to understand why there is so much interest in the use of inorganic radionuclides in the radiopharmaceuticals that are used for imaging. It would certainly be easier to substitute a non-radioactive carbon for one of its radioactive isotopes. However, the radionuclides with physical and nuclear properties suitable for use in either diagnostic or therapeutic radiopharmaceuticals are predominantly metals.[2] A number of radionuclides with differing physical and chemical properties are used today. The precise properties of a

radionuclide often determine the theatre of its application as an imaging tool. The element can be infused as a naked ion or be part of a larger complex.

4.2.1 Examples of Radionuclides Employed in Nuclear Medicine

4.2.1.1 ^{201}Tl

$^{201}Tl^{+}$ (Thallous chloride Tl 201, duPont-NEN; Mallinckrodt; MediPhysics) is approved for use as a myocardial perfusion agent for determining the state of the myocardium during stress and rest exercises. Although not a co-ordination compound, ^{201}Tl is a very important radiopharmaceutical having been in use since 1975. $^{201}Tl^{+}$ acts as a K^{+} mimic by accumulating in viable myocardium via the Na-K-ATPase pump. Scans show damaged or infarcted tissue as unlabelled or 'cold' regions under imaging conditions.[2]

4.2.1.2 ^{111}In

^{111}In-Oxine (Indium In 111 Oxyquinoline Solution, Amersham International, Figure 4.1) and ^{111}In-DTPA (MPI Indium DTPA I 111, MediPhysics, Figure 4.1) are co-ordination compounds that form very stable complexes.

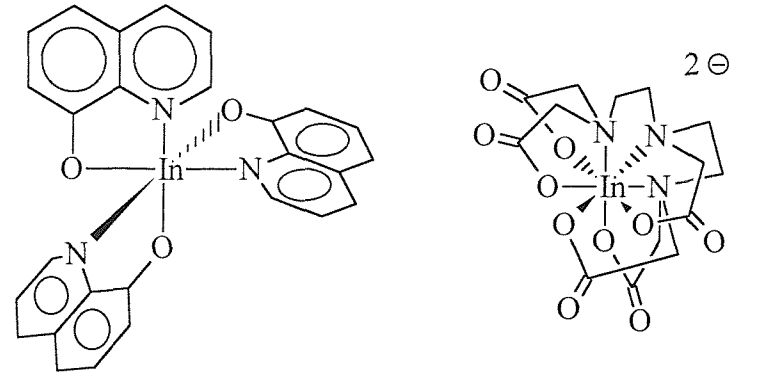


Figure 4.1 ^{111}In-Oxine ^{111}In-DTPA

^{111}In-oxine is used to label leukocytes (white blood cells) and thus images sites of infection or inflammation. It is a neutral, lipid-soluble complex that is able to penetrate the cell membrane. Once inside the cell the ^{111}In becomes displaced and binds to other cytoplasmic components thus becoming trapped in the cell. Cells are labelled *in vitro* and re-introduced to the patient's blood-stream for imaging purposes.[3]

^{111}In-DTPA is used to evaluate the cerebral spinal fluid pathways.[4] The complex has an overall charge of 2- and a very high stability constant (K_{LM} = 29.0 at pH 7.4).[5]

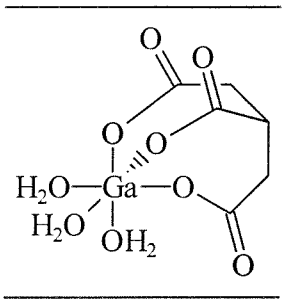


Figure 4.2 ^{67}Ga-Citrate

4.2.1.3 ^{67}Ga

^{67}Ga-Citrate (Neoscan, Mediphysics; Gallium Citrate Ga 67 Injection, Mallinckrodt; Gallium Citrate Ga 67 Injection, U.S.P., duPont-NEN, Figure 4.2) concentrates in certain viable primary and metastatic tumours as well as some focal infection sites. The mechanism of this concentration, like the structure of the compound, remains largely undiscovered, a situation which is common for many of the radiopharmaceuticals in routine use. It is known however that ^{67}Ga accumulates in lysosomes by binding to intracellular protein. The weak complex dissociates immediately in the blood-stream and the ^{67}Ga is transchelated to transferrin. Ga^{3+} mimics the ferric ion in its binding to molecules in serum but unlike the ferric ion it is not reduced *in vivo* and does not become incorporated into haemoglobin.[3]

4.2.1.4 ^{57}Co

^{57}Co-cyanocobalamin (Rubatope-57, Bristol-Myers Squibb; Cyanocobalamin Co57 Capsules, Mallinckrodt, Figure 4.3) is used in the diagnosis of pernicious anaemia and intestinal vitamin B_{12} absorption abnormalities. The complex is administered orally and is absorbed by the gastrointestinal system in the same way as Vitamin B_{12}. The ^{57}Co activity of the urine is then monitored for 24 hours. This is one of the few instances where a radiopharmaceutical is the exact copy of a native molecule. In this instance ^{57}Co is isotopically substituted for non-radioactive Co in the vitamin B_{12} molecule.[6]

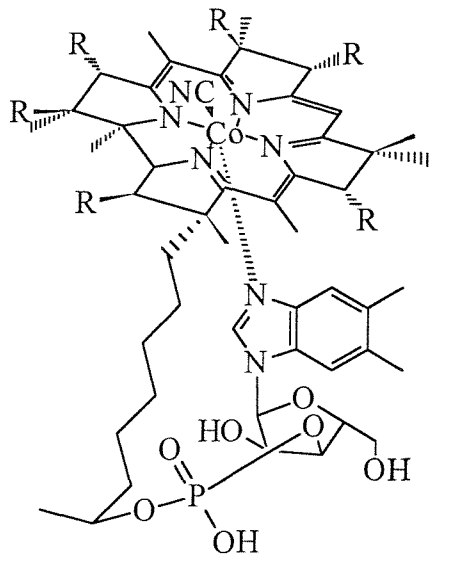


Figure 4.3 ^{51}Co-Cyanocobalamin

4.2.1.5 ^{51}Cr

$Na^{51}CrO_4$ (Chromitope Sodium, Bristol-Myers Squibb; Sodium Chromate Cr 51 Injection, Mallinckrodt) is used to determine RBC (red blood cell) volume or mass, the study of RBC survival time, and the evaluation of blood loss in patients. RBCs are labelled *in vitro* then injected back into the patient where they are allowed to equilibrate. Samples are then withdrawn and studied *in vitro*.[7]

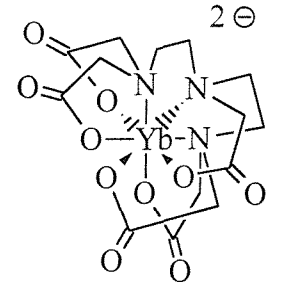


Figure 4.4 ^{169}Yb-DTPA

4.2.1.6 ^{169}Yb

^{169}Yb-DTPA (Figure 4.4) images cerebral spinal fluid pathways in much the same way as ^{111}In-DTPA.[2] No structural determination has been performed, and whether the co-ordination number is 8 or less is not yet known.

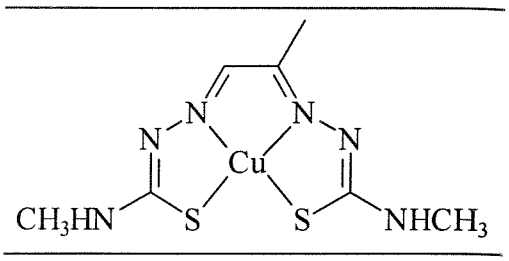


Figure 4.5 ^{62}Cu-PTSM

4.2.1.7 ^{62}Cu

^{62}Cu-PTSM (Figure 4.5) is a positron emitting complex that is used as a perfusion tracer. It is neutral and lipophilic and has been found to distribute as a chemical microsphere which is retained by all mammalian cells. The complex is not retained in the blood and is therefore rapidly cleared from the body leaving clear images of infused tissue.[8]

4.2.1.8 ^{186}Re, ^{153}Sm

^{186}Re and ^{153}Sm are both β^- emitting radionuclides. As such they are used in the field of radiotherapeutic medicine to treat rather than diagnose illness. In particular they are employed as diphosphonate complexes (Figure 4.17) which have a high affinity for sites of actively growing bone. In this way the lethal radiation is directed towards areas under attack by metastatic bone cancer.[2]

4.2.1.9 ^{11}C

Some isotopes of carbon do however have the right properties for use in radiopharmaceuticals. The isotope ^{11}C (20 min, β^+) for example, has potential use for incorporation into diagnostic radiopharmaceuticals. However, a cyclotron is required for its preparation and because of this isotope's short half-life the cyclotron must be located at the hospital at which it will be used. The short half-life additionally requires very efficient and high yield incorporation of ^{11}C into the potential drug. For these reasons the use of this particular radionuclide has been limited to research applications.[2]

4.2.2 Complimentarity of Radionuclide Properties

The metal radionuclides described above have very different chemical and physical properties but they are all used routinely in approved radiopharmaceuticals because of their radiation emitting properties. Radionuclides can be divided into two groups relating

to their specific field of use: radiodiagnosis and radiotherapy. Radionuclides have the potential to be used as diagnostic and therapeutic agents, but it is only the former which have been extensively developed. This reflects the differing nature of the two types of application.[9]

In radiodiagnosis it is only necessary to detect the location of the radionuclide in the body. This requires that the radionuclide emit photons of energy greater than 35 KeV and preferably 80 KeV.[2] Since extremely sensitive devices are available for the detection of such ionising radiation, useful diagnostic information may be obtained with relatively low patient radiation doses.

Radiotherapeutic agents however need to deliver high doses of radiation to target tissues. This demands that the radionuclides decay by particle emission and have a half-life in the range of 1-10 days.[2] The precise emission energy and half-life is dependent on the particular radiotherapeutic application. If unacceptably high whole-body radiation doses are to be avoided, highly selective agents must be found which localise rapidly at the target site, and clear very rapidly from the body if unabsorbed. Further to this it is preferable for the absorbed material to remain in place until radioactive decay is virtually complete or, if broken down, to give rise to radioactive products which are rapidly excreted from the body. As such the specifications for radiotherapeutic agents are so exacting that their development poses a much greater technical challenge than does that of radiodiagnostic agents.[9]

4.2.3 Ionising Radiation Emissions

The ionising radiations emitted by all radionuclides may be divided into four basic types, three of which are in use in diagnostic medicine:[9]

4.2.3.1 α-Particles

These are heavy, energetic, dipositive ions (helium nuclei) which penetrate tissue to the order of 0.1 mm. α-Particles cause the death of any cells through which they pass, and consequently are highly radiotoxic and clearly unsuitable for diagnostic use. However, under certain circumstances they may be used in radiotherapy.[9]

4.2.3.2 β-Particles

These are electrons which have been ejected from the core of radionuclide during the breakdown of a neutron. As such they are much lighter and less energetic than α-particles and penetrate further through tissue with a range of 1 μm - 1 mm. This small range means that β-emitting radionuclides cannot be monitored externally. Instead, like α-particles, they too find use in radiotherapy; ^{131}I for instance is a β-emitter used in the treatment of cancer of the thyroid since this is where iodine collects in the body.[9] Other examples of β-emitters include: ^{24}Na, ^{67}Cu and ^{203}Hg.

4.2.3.3 β^+-Particles (Positrons)

Positrons are positively charged electrons and their characteristics are identical to β-particles except that positron emitting radionuclides can be monitored externally. One very important aspect of positron emitting radionuclides is that when a positron is emitted the chances are that it will impact with an electron. If this happens a positron-electron annihilation event takes place. This results in the emission of two, perfectly anti-parallel γ-rays each with an energy of 510 KeV which can be visualised using special equipment.[9] Examples of β^+-emitters include: ^{52}Fe, ^{64}Cu and ^{68}Ga.

4.2.3.4 γ-Rays

γ-Rays are not, as the name suggests, particles but electro-magnetic waves produced by internal nuclear transitions. As such they often accompany particle emissions but can occur in isolation. Although γ-rays can be high in energy their ionising potential is very low and hence they are ideally suited to radiodiagnosis.[9] Examples of γ-emitters include: ^{57}Co, ^{99m}Tc and ^{201}Tl.

4.2.4 Detecting Ionising Emissions

Ionising emissions are only as good as the equipment used to image them. Fortunately the technology exists that allows us not only to detect various emission types but also to build complex and detailed three dimensional pictures from them. However, not all forms of imaging require the emission of ionising radiation. There are three basic types of non-emission imaging:

4.2.4.1 Non-emission Imaging

4.2.4.1.1 Ultrasound

Ultrasound is a very simply applied and widely used method of imaging both soft and hard tissue. The principle is based on the application of a sound-generating pad to the epidermis. Sound waves in the frequency range 3.5 - 7.5 MHz are passed into the body and the pad simultaneously receives any reflected waves. These reflections are passed to a detector attached to a computer which reassembles the echoes into a picture of the area being scanned. Tissues of varying density reflect the sound waves to different extents; bone for instance reflects sound waves very well and gives sharp images whereas organs and particularly soft, fatty tissues reflect fewer waves giving blurred or soft-focused images. The usability of ultrasound (like all imaging modalities) reflects the quality of the images it affords. Thus it is commonly employed to gain information about bone shape and morphology and to determine the integrity of organs or the activity and health of developing embryos.

4.2.4.1.2 MRI

Magnetic resonance imaging relies on detecting the spatially localised NMR signals of protons in water.[10] Since the body is composed of approximately 60% water, this is the most abundant and sensitive resonance to detect *in vivo*. Spatial information is obtained by making the resonance frequency position independent. This is achieved by imposing a gradient magnetic field unlike the static field used in laboratory pulsed NMR spectrometers. Water protons in the tissue resonate at slightly different frequencies according to their position in the gradient field. This gives a spatially encoded signal which is computationally decoded to give a digitised image.[11] MRI gives much more detail than ultrasound and can easily delineate different tissue types. Anatomically, MRI is a high resolution scanning technique but offers very limited information about the physiological functioning of the body.

4.2.4.1.3 CT

X-ray computed tomography or 'CAT Scans' utilise an external source of ionising radiation. Tissues absorb incident X-rays to varying degrees, bone in particular absorbing more strongly than blood or soft tissue because it contains Ca and P. The X-ray source and

detector are aligned and data are collected in segments at many angles. The absorption data are resolved into images by solving the resultant simultaneous equations. The result is a series of digitised images representing thin slices of tissue. Each image is made up of thousands of small 'picture elements', each of which represents approximately 1 mm^3 of tissue. The signal intensity in each picture element is governed by the extent to which the incident X-rays have been absorbed. Occasionally, contrast agents such as $BaSO_4$ (given orally or rectally) or a triiodinated aromatic compound such as iopamidol (Figure 4.6) are given to patients intravenously at doses of up to 50 g. The heavy elements Ba and I present in these contrast agents absorb X-rays strongly and are easily distinguished from background absorption.[11]

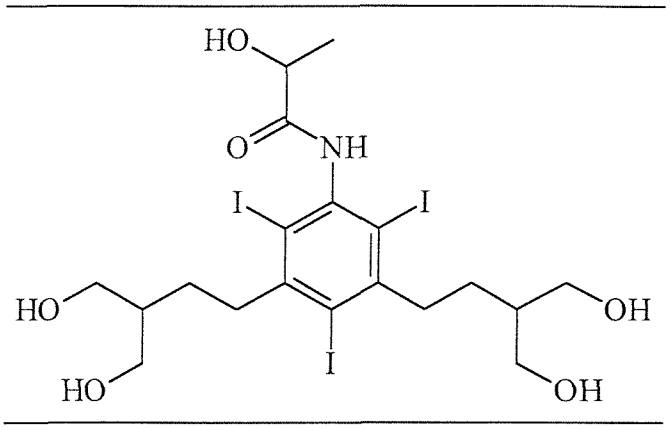


Figure 4.6 Iopamidol

X-ray computed tomography offers the highest resolution of all imaging modalities but again it is unable to monitor biological function. There are two techniques in common use that allow the visualisation of physiological events as they occur:

4.2.4.2 Emission Imaging

4.2.4.2.1 PET

Positron Emission Tomography exists purely as a consequence of the β^+ decay event. As already outlined the positively charged electron impacts with a valence electron and the two become annihilated. The two collinear γ-rays are detected simultaneously at each side of the patient confining the annihilation event to a single line joining the two detectors. In this way the data provided by PET isotopes can be processed without physical collimation. Instead, a distribution plot of the radioisotope throughout a particular volume element or

'slice' is constructed from the pattern of coincidences gained from a series of static or mobile Anger camera scans. The resolution of PET is about 3 mm which is better than can be gained from SPECT scans.[11] The use of PET is, however, limited by its prohibitive cost. The installation of a complete PET system costs around $ 5-6 million (US) and includes the whole body camera (multiple crystal based Anger cameras), a cyclotron and auxiliary equipment.[12]

4.2.4.2.2 SPECT

Single Photon Emission Computed Tomography is currently the technique of choice for the detection and localisation of radiopharmaceutical based emissions. SPECT scanners generate sectional slides of the variation in radioactivity throughout the body. Imaging selected planes within the body makes lesions more obvious, separates them from the radioactivity of superficial structures and gives information about their depth.[13] The resolution and sensitivity of the technique is highly dependent on the design of the collimators and the geometry of detector array.[14]

SPECT images planes within the body; this is a specific use for a much more general technique, that of the detection of γ-emitting radionuclides within the body. The γ-rays emitted from the radioisotope are detected by an Anger camera. Unlike PET, the radionuclides used in SPECT are γ-emitters, each event resulting in the emission of a single photon in a random direction. As such, a lead collimator is required to localise the radiation on the detector. The detector itself consists of a Tl-doped NaI crystal. Crystals doped in this way absorb a significant fraction of γ-radiation below 500 KeV.[14] The incident γ-rays can be in the range 80 and 300 KeV but should ideally fall within the 100-200 KeV band which is optimal for this kind of hardware.[2] Absorption of the radiation results in the ejection of a core electron which imparts its kinetic energy to the crystal matrix. The resulting emission of light photons is directly proportional to the number and energies of the incident γ-rays. The flashes of light are amplified using photomultipliers or photodiodes into electrical pulses in proportion to the amount of light produced. These electrical pulses are converted into a graphical display which can be stored digitally and retrieved later. The area monitored by the crystal is inversely proportional to the length of the collimator whereas the resolution of the display is directly proportional to it. Small, easily located organs near the surface, such as thyroids, are imaged using a high-resolution

collimator focusing on a single wide crystal. Large organs, such as kidneys, which also vary in location are best studied through an array of smaller crystals each with a relatively short collimator.[14] The resolution of this technique is about 1-2 cm, an order of magnitude lower than CT. A three-dimensional image is obtained by mounting the Anger camera on a rotating gantry and recording images at different angles. The images are then combined to give a reconstruction of activity distribution.[11] Anger cameras are now used to perform most of the high-resolution and rapid-scan studies in nuclear medicine. These consist of an array of NaI(Tl) detectors each having a single-hole collimator. This array is sufficiently wide to cover the width of the body. Accordingly, moving the array from head to toe provides a whole-body scan.[14]

4.2.5 Sources of Radionuclides

The availability and cost of a radionuclide are almost as important as its properties for potential use in radiopharmaceuticals.[2] Combined with this any radionuclide which is destined for medical applications must be available in a radiochemically pure form. That is, it must be free of other radiation sources. This requirement of very high radiochemical purity has a bearing on the way in which the radionuclide is produced. There are essentially three routes to obtaining radiochemically pure nuclides:[9]

4.2.5.1 Nuclear Fission

Nuclear fission of a heavy element has the advantage that 'carrier free' radioisotopes of high specific activity may be produced. Such a process however produces a complex mixture of fission-products and painstaking separation and purification of the desired radionuclide becomes necessary. This problem can be simplified by using a pure target isotope to produce a fission product which has unique properties. For instance, the fission of ^{235}U produces ^{131}I which may be separated from other fission-products by virtue of its volatility. Involatile fission-products of ^{235}U include ^{99}Mo, ^{103}Ru and ^{132}Te.

4.2.5.2 Neutron Capture

Neutron capture reactions are used to generate radionuclides from non-fissile parents. A high purity target isotope is used and the process yields unconverted target material, the desired radionuclide and its decay products. The problem of fission-product impurities does not arise with the neutron capture method. The technique is however very sensitive to

any impurities in the target material.

4.2.5.3 Cyclotron Sources

Cyclotron production of radionuclides involves irradiating target nuclides with accelerated ions. An example of this is the production of ^{68}Ge which decays with a 280 day half-life to the positron emitter ^{68}Ga. This is achieved by the proton irradiation of ^{69}Ga to produce ^{68}Ge. Cyclotron production of radionuclides is expensive compared with reactor irradiations, but higher specific activities are possible than with those obtained from material derived from the neutron capture process. Further, radionuclides with particularly useful properties which cannot be produced in a reactor, may be prepared by cyclotron irradiation. An example of this is ^{52}Fe, a positron emitter suitable for the radioimaging of bone marrow whereas the reactor produced isotope is ^{59}Fe, which is a β-emitter and therefore unsuitable for such purposes.

4.2.5.4 Generators

For the radionuclides to be of use to the clinicians in hospitals they must be packaged or presented in such a way as to make them rapidly and safely accessible. To this end many generator systems have been developed which present clinicians with pure samples of radionuclides in suitable solvents for incorporation into radiopharmaceutical kits. Examples of parent-daughter generator systems are shown in Table 4.1. Parent-daughter generators have increased the availability of several radionuclides that would not otherwise have received such widespread use.

Parent	Daughter	Radiopharmaceutical	Application
^{68}Ge (288 days)	^{68}Ga (68.1 min)	^{68}Ga-DTPA aerosols	Lung Ventilation
^{82}Sr (25 days)	^{82}Rb (26 min)	$^{82}Rb^{+}$ (K^{+} analogue)	Myocardial Blood Flow
^{62}Zn (9.2 hrs)	^{62}Cu (9.73 min)	^{62}Cu-PTSM	Cerebral Blood Flow

Table 4.1 Parent/Daughter Generator Systems

A generator (Figure 4.7) usually consists of a reservoir of sterile saline, an alumina or silica column, shielding for the column and a suitable outlet. The column is loaded with a target isotope which decays to generate the radionuclide of interest. Internal transitions tend to leave the mass of the core unchanged but reduce the nuclear charge. A result of this is a change in the ion's chemical properties (overall charge) which allows the daughter

isotope to be eluted from the column with saline. Generators use the product of all three production routes (nuclear fission, neutron capture and cyclotron) and often the nuclide is present as an oxide or soluble salt.

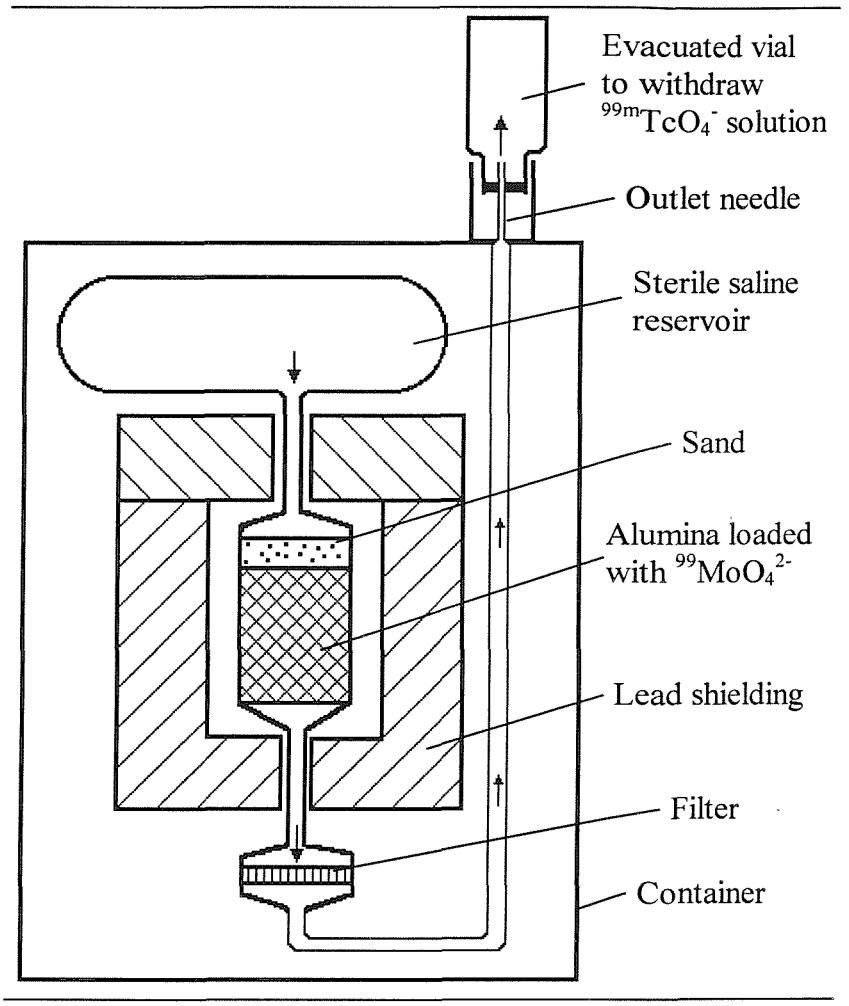


Figure 4.7 Structural Arrangement of a $^{99m}TcO_4^-$ Generator

4.3 Technetium

Technetium was discovered relatively recently in 1937 by Perrier and Segrè.[15] There are over 30 known isotopes of technetium ranging in mass from 90 to 108. Technetium is essentially a synthetic element and as such has no stable isotopes. The most stable isotopes have half-lives on the order of only 10^6 years. Interestingly since the age of the earth is of the order of 10^9 years, all primordial technetium has long since decayed. However, traces of ^{99}Tc are formed naturally by the spontaneous fission of ^{238}U and have been isolated in nanogram quantities from pitchblende.[16] Since the advent of the nuclear age ^{99}Tc has been generated on a tonne scale since this isotope is obtained in about 6% yield from the

neutron-induced fission of ^{235}U. This artificial build-up means that there is now more ^{99}Tc in existence than naturally occurring rhenium.

4.3.1 Important Technetium Isotopes

By far the most important isotope of technetium is ^{99m}Tc. It has been estimated that some chemical form of ^{99m}Tc is used in more than 90% of the diagnostic scans performed in nuclear medicine departments in the United States.[17] The radiophysical properties of this nuclide, which exists in a metastable nuclear excited state, are nearly ideal for diagnostic radioscintigraphy.[14] It decays via the emission of monoenergetic γ-rays with no accompanying α- or β-particle emission which would increase the radiation dose to the patient. The energy of this γ-ray is 140 KeV which is sufficiently high for escaping deeply seated organs but suitably low to allow collimation by lead and efficient trapping by NaI(Tl) crystals in γ-cameras. The physical half-life of ^{99m}Tc is only 6 hours and thus relatively large doses can be administered to patients without generating an unacceptably high radiation risk.[1] ^{99m}Tc decays to the long-lived isotope ^{99}Tc. This nuclide has a half-life of 2.1×10^5 years and decays by the emission of β-particles with a maximum energy of 292 KeV. This long half-life coupled with the low emission energy means that residual ^{99}Tc in the body poses a negligible radiation risk. The widespread availability and low cost of man-made ^{99}Tc has permitted the investigation and development of the chemistry of technetium.[18]

4.3.2 Sources of Technetium

The development of the technetium-generator has revolutionised the nuclear medicine industry. Nuclear medicine clinics which are remote or isolated from nuclear installations now have access to ^{99m}Tc in a pure and safe to handle form. The technetium-generator is based on the decay of enriched ^{99}Mo which is prepared either by neutron irradiation of ^{98}Mo or by fission of ^{235}U.

Figure 4.8 outlines the decay sequence of ^{99}Mo that allows it to be incorporated into a generator system.

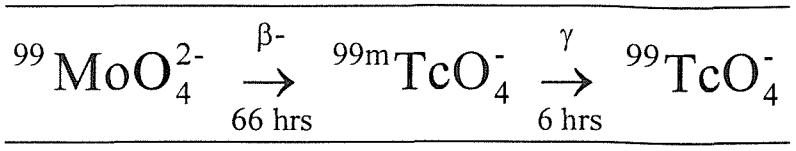


Figure 4.8 The Decay Sequence of ^{99}Mo to ^{99}Tc

The generator contains freshly prepared $[^{99}MoO_4]^{2-}$ adsorbed at the top of a lead-shielded alumina ion-exchange column. The ^{99}Mo decays with 67 hour half-life by β-emission to give $[^{99m}TcO_4]^-$. As a result of the difference in charges between the molybdate and pertechnetate ions, only the latter elutes from the column with physiological saline solution (0.15 M NaCl). An evacuated vial is placed over the outlet needle which connects via a tube to the bottom of the column. This draws out a defined volume of saline containing the pertechnetate usually as the ammonium salt. Since the ^{99m}Tc undergoes further decay to ^{99}Tc, the eluant contains both nuclides. The activity of the eluant and the relative quantities of ^{99m}Tc and ^{99}Tc depend on the age of the column and the period of time since it was previously 'milked'. Total technetium concentrations in the eluant are variable but usually lie in the range 10^{-8} to 10^{-6} M. The minimum quantity of pure ^{99m}Tc necessary for adequate imaging is on the order of a few nanograms so that even with several times this amount of ^{99}Tc present, the chemical toxicity is negligible.[14] There are few drawbacks to the use of ^{99m}Tc in the nuclear medicine industry but the accepted use of generators does define two salient features of the chemical and physical form of technetium that is available:[1]

1) As outlined above, the nuclide is a mixture of ^{99m}Tc and ^{99}Tc dependant on generator age and last elution time.
2) The starting material for all ^{99m}Tc radiopharmaceutical preparations is an aqueous NaCl solution of the high-oxide pertechnetate.

4.4 The Supramolecular Chemistry of Technetium

Technetium containing radiopharmaceuticals can be divided into two classes:

1) In some cases the co-ordination characteristics of the ligand, the nature of the technetium core and the properties of the resultant complex dictate biological localisation. These complexes are usually small and maybe charged; they are considered to be "technetium essential".

2) The other general case derives its target specificity by attachment of the technetium complex to a biologically active molecule. An example of this is an antibody or an enzyme with the technetium-ligand complex bound in a passive role and effectively carried along for the ride. The target specificity arises out of the interaction of the biologically active part with the host's natural processes. Radiopharmaceuticals of this type are considered to be "technetium tagged".[2]

4.4.1 Chemical Properties of Technetium

The position of technetium in the middle of the second-row transition series imparts to it a very diverse chemistry. Many complexes of technetium are known and range in oxidation state from -I to VII. These complexes have co-ordination geometries varying from 4 to 9, and utilise a variety of chelating ligands that satisfy the crystal-field requirements.

Such diversity allows for high specificity in the targeting of radiopharmaceuticals containing ^{99m}Tc by careful design of the ligand system.[2] The nature, shape, and size of the many ^{99m}Tc ligands already characterised vary greatly and graphically demonstrate the versatility of this radionuclide as a tool for radiodiagnosis and radiotherapy. Technetium also possesses a large donor set; indeed many of the approved radiopharmaceutical drugs in use today employ a combination of N, O, S, P and halide donors. This allows both hard and soft ligands to be employed, sometimes within the framework of a single, specifically designed ligand.[2]

4.4.2 Ligand Types used in Approved Radiopharmaceuticals

Below is a small selection of the currently approved ^{99m}Tc radiopharmaceuticals. They display the varied nature of ^{99m}Tc complexes and emphasise the design possibilities of ^{99m}Tc as an imaging tool.

4.4.2.1 Square Planar Tc(V) Complexes

The square pyramidal Tc(V) mono-oxo complex is very important in the co-ordination chemistry of technetium. It usually exists with the technetium atom sitting slightly above the plane of the immediate ligand field and the oxygen positioned apically.

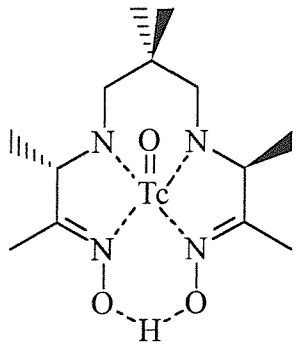
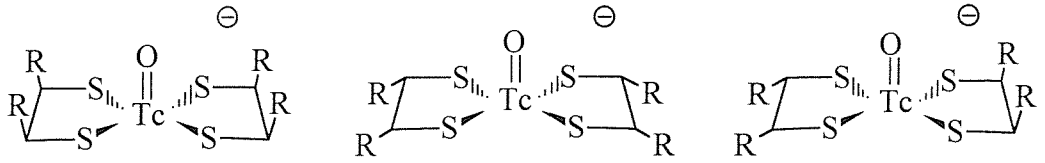


Figure 4.9 ^{99m}Tc-*d,l*-HM-PAO

^{99m}Tc-*d,l*-HM-PAO[19] (Ceretec, Amersham International, Figure 4.9) is an approved cerebral perfusion imaging agent for the evaluation of stroke. ^{99m}Tc-*d,l*-HM-PAO may also have a use in monitoring other cerebral diseases such as hematomas and Alzheimer's disease. The ligand loses two amine protons and one oxime proton on co-ordination of the Tc(V) monooxo core giving a neutral complex. This neutral complex is able to pass through the blood brain barrier where it is metabolised thereby blocking diffusion back out of the brain.[20] The mechanism of metabolism remains largely unknown but is peculiar to the *d,l* isomer, the meso isomer is metabolised very slowly in comparison and does not therefore result in localisation.



syn endo	syn exo	anti
R = COOH	R = COOH	R = COOH

Figure 4.10 ^{99m}Tc-Succimer

Succimer[21] (MPI DMSA Kidney Reagent, MediPhysics, Figure 4.10) is an imaging agent which concentrates in the renal cortex and is therefore suitable for the evaluation of kidney morphology. Once co-ordinated, the meso-DMSA (dimercaptosuccinic acid) can adopt any one of the above isomer configurations; all three isomers have been observed by HPLC but they all act in the same way.[22]

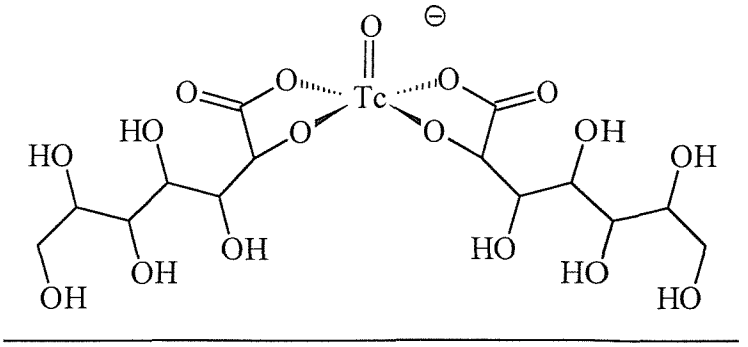


Figure 4.11 ^{99m}Tc-Gluceptate

Gluceptate[21] (Glucoscan, duPont-NEN; TechneScan Gluceptate, Mallinckrodt, Figure 4.11) is marketed for imaging kidneys and brain lesions and to assess renal and brain perfusion. The ligands bind weakly and an excess is required for the complex to persist. Gluceptate is often used as a donor Tc(V) complex to synthesise thermodynamically more stable but kinetically slower forming complexes.

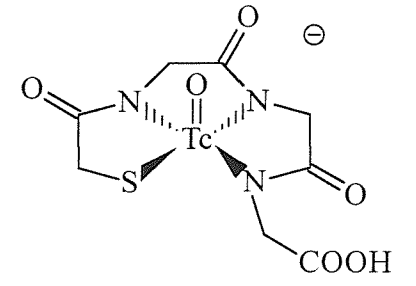


Figure 4.12 ^{99m}Tc-MAG$_3$

MAG$_3$[23] (TechneScan MAG$_3$, Mallinckrodt, Figure 4.12) is marketed as a renal imaging agent. It is injected intravenously and monitored during its passage through the kidneys to assess renal function. On co-ordination of MAG$_3$ to the Tc(V) monooxo core, the sulphur and three amide nitrogens deprotonate giving a square-pyramidal, anionic complex.[24] The carboxylate group does not bind even loosely[25] but ensures efficient renal excretion via the dianionic pathway.[26]

4.4.2.2 Octahedral Tc Complexes

Technetium, in a variety of oxidation states exists in a number of octahedral complexes.

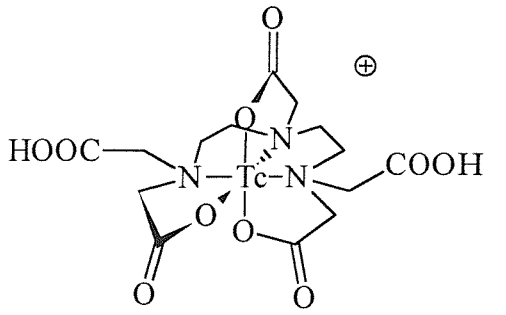


Figure 4.13 ^{99m}Tc-Penetate

Penetate[27] (AN-DTPA, Syncor International; MPI DTPA Kit, MediPhysics; Techniplex, Bristol-myers Squibb; DTPA, duPont-NEN, Figure 4.13) is approved for kidney and brain imaging and to allow assessment of renal perfusion and glomerular filtration rate. There is some question as to whether the technetium core is in a IV or V oxidation state. As drawn above (Figure 4.13) the technetium core is Tc(IV)[28] but the alternative in which there are three free acid groups and the familiar Tc(V)[29] monooxo core is also a likely possibility. However, until its crystal structure is solved the precise nature of this material will remain in question but there is no doubt that the complex is monocationic.

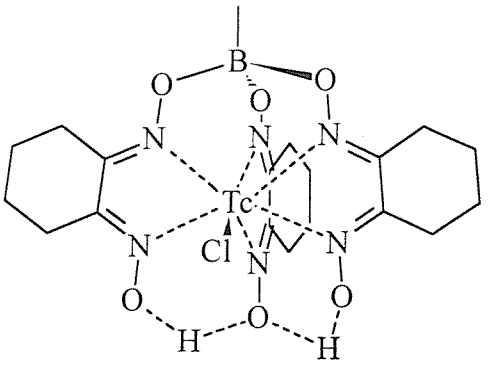


Figure 4.14 ^{99m}Tc-Teboroxime

Teboroxime[30] (Cardiotec, Bristol-Myers Squibb, Figure 4.14) is a neutral, seven co-ordinate Tc(III) complex. The oxime moieties form an approximately trigonal cage with chloride directly balancing the residual charge on the Tc(III). It is marketed as a myocardial perfusion agent for evaluating coronary artery diseases such as ischemia and infarction. Teboroxime is unusual in that it is a neutral myocardial perfusion agent. The teboroximes are a member of a larger class of complexes, the BATO's (boronic acid adducts of

technetium dioximes) and all have the basic formula $TcCl(CDO)(CDOH)_2BMe$ where CDOH = cyclohexanedione-dioxime.[31] Under physiological conditions a chloro-hydroxy exchange takes place but this does not affect the efficacy of Teboroxime as a myocardial perfusion agent.[32] It has been reported[33] that the basicity of the co-ordinated hydroxyl group in $TcOH(CDO)(CDOH)_2BMe$ is such that at physiological pH there may be an equilibrium *in vivo* resulting in the formation of $[Tc(OH_2)(CDO)(CDOH)_2BMe]^+$. It is probably this cationic species which is retained in the heart, the neutral species being quickly washed out.

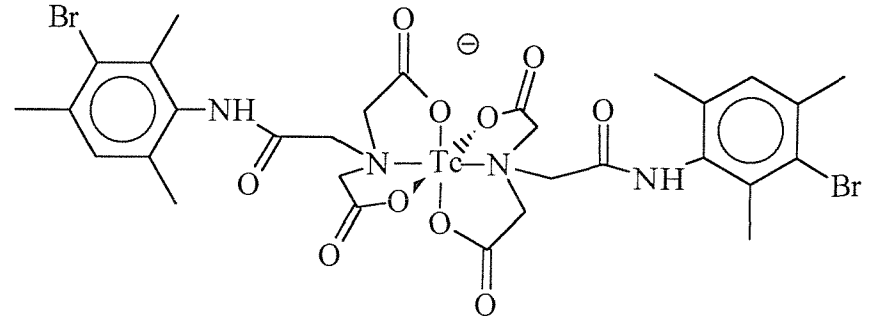


Figure 4.15 ^{99m}Tc-Mebrofenin

Mebrofenin[34] (Choletec, Bristol-Myers Squibb, Figure 4.15) is a member of the HIDA (hepatobiliary iminodiacetic acid) class of compounds. This group of radiopharmaceuticals was found to have biological characteristics suitable for imaging the hepatobiliary system (liver, gall bladder, bile duct and intestines).[34] There are three close analogues in the HIDA class which vary only in ring substituents. There is as yet no evidence for the given structure but the Tc(III) core is believed to be octahedral.

Sestambi[35] (Cardiolite, duPont-NEN, Figure 4.16) is an octahedral, cationic Tc(I) complex developed as a myocardial perfusion agent for evaluating the integrity of the myocardium. Although a cationic complex, Sestambi is not believed to be taken up by the myocardium via the Na-K-ATPase pump[36] but rather acts as a K^+ complex mimic.[37] The first complex of this kind to show promise was $Tc(t\text{-butylisonitrile})_6^+$ (TBI).[38] TBI was too lipophilic and suffered from high activity in the lungs and liver which precluded good myocardial images.

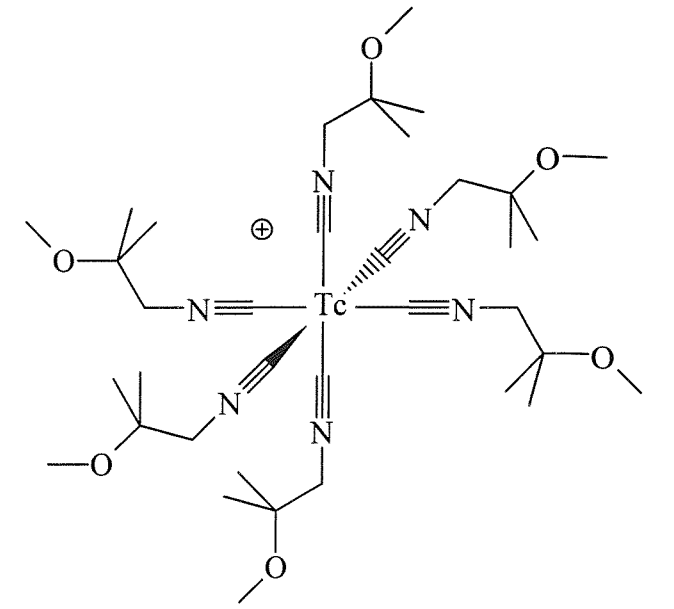


Figure 4.16 ^{99m}Tc-Sestambi

Research led to Sestambi which is a derivatised isonitrile ligand that is cleared quickly from non-target tissues after first pass metabolism of the methoxy group to a hydroxy group.[39] This is a good example of radiopharmaceutical development utilising *in vivo* biochemical processes to enhance the attributes of the first generation drug.

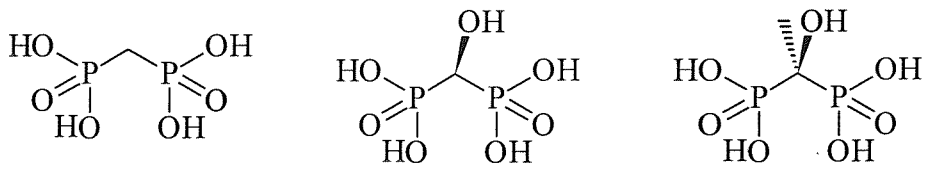


Figure 4.17 Phosphonate Ligands

Technetium phosphate derivatives (Figure 4.17) have long been used to image bone and myocardial infarcts.[40] The ^{99m}Tc complexes can be considered to exist as bis-bidentate or bidentate-tridentate ligands systems, depending on the ligand substituents, with the ability to complex two metals simultaneously. When prepared, each technetium atom is bound to two ligands and each ligand is co-ordinated to two technetium centres. The complex is an octahedral polymer with two hydroxides per technetium acting as Tc-O-Tc bridges. The absolute oxidation state of the Tc cannot be definitively assigned because the degree of protonation of the Tc-O-Tc bridge cannot be determined. Polyphosphates and

pyrophosphates are very unstable *in vivo* because of enzymatic cleavage of the P-O-P bond. Phosphonates overcome this problem by having an enzyme stable P-C-P linkage. These complexes localise in bone reflecting the affinity of the co-ordinated diphosphonate ligand for calcium in actively growing bone tissue.[41]

4.4.3 Technetium Complex Core Types

The relationship between the ligand donor set and the common Tc(V) core is very flexible. The nature of the ligand set will also affect the stability of the complex in aqueous media. Hard ligands are labile and therefore prone to ligand exchange or hydrolysis while soft ligands, such as dithiolate, give inert complexes containing the TcO^{3+} core. Table 4.2 summarises the extent of observed Tc-complex cores and their associated ligand sets.

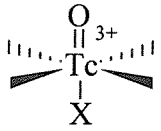
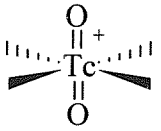
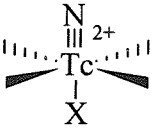
Tc(V) Core Type	Donor Atom Set	Co-ordinating Groups (X)
	$(S^-)_4$ $(S^-)_2(O^-)_2$ $(O^-)_4$ $(S^-)_2(N^-)_2$ $(O^-)_2NCl^-$ $(Cl^-)_4$ $(Br^-)_4$	
	$(S^-)_2N_2$ $(O^-)_2N_2$ $O^-N_2Cl^-$ P_4 $(CN^-)_4$	O^- Cl^- H_2O μO^- $(O^-)_2$ O^- HO^- CN^- CH_3O^-
	N_4 P_4 $(CN^-)_4$	
	$(S^-)_2S_2$ $(S^-)_2N_2$ P_4 $(Cl^-)_2P_2$	
	$P_2(N^-)_2$ $(Cl^-)_2P_2$	CH_3CN PPh_3

Table 4.2 Tc(V) Core Types and Associated Ligand Sets

4.4.4 Technetium Analogues

Since technetium does not exist in any isotopic form stable to decay, the study of its chemistry has so far been limited to those laboratories capable of handling radioactive material at very low concentrations (10^{-7}-10^{-8} M). Indeed since the properties of technetium make it an ideal nuclide for use in nuclear medicine, it has been the development of suitable ligand systems for this purpose that has provided the majority of our knowledge about this element.

The growth potential of ^{99m}Tc radiopharmaceuticals is so great that interest has been focused on completing our understanding of technetium's supramolecular chemistry. Particular interest has been shown by industry and research groups alike in the possibility of using analogues that mimic the size and co-ordination chemistry of technetium. In this way new ligands can be designed, synthesised and complexed to safer, more abundant metals by a wider range of institutions in order that their potential as technetium chelators and ultimately ^{99m}Tc radiopharmaceuticals can be evaluated.

With such a diverse array of transition metals and oxidation states available it would at first appear to be a simple matter of selecting the ion of a metal whose size, charge and crystal-field requirements match those of the corresponding technetium ion. However, other questions also need to be addressed:

1) does the mimic have a similar redox potential?

and 2) does the mimic support oxidised cores in its complexes?

Of concern to the pharmaceutical industry is the availability of the mimic in a highly oxidised form. Technetium is available to research institutions and hospitals in the form of a pertechnetate which is chemically reduced in the presence of the ligand to form the complex. The ability to model and refine this procedure with readily available and safe materials would be an invaluable commodity.

No one particular metal can satisfy all these criteria so it is important to decide which area of technetium's behaviour is to be mimicked. The most important criteria for a technetium analogue is that it should have a similar ionic radius and chemical reactivity. Table 4.3

summarises the suitability of a number of transition metals as technetium analogues. The metal centres of choice for modelling Tc(V) are Cu(II) and Co(III). Also mirroring some aspects of Tc(V) behaviour are Re(V) and Ru(IV). These metals were initially selected either because of their ionic radii or because of their similar chemical properties. Much of what was already known about the chemistry of the analogues has been applied to technetium. In many cases it was found that technetium forms strong complexes with ligand classes that are salient in the chemistry of the analogue and X-ray crystallographic analysis has shown that the technetium ion is bound in a similar manner.

Metal	Ionic Radius / pm	Tc(X) / pm	Suitability as Analogue
Mn(II)	67	64.5	Reasonable Tc(IV)
Mn(III)	64.5	64.5	Not very accessible
Co(II)	65	64.5	Excellent Tc(IV)
Co(III)	61	60	Excellent Tc(V)
Co(IV)	60	60	Not very accessible
Cu(II)	73	64.5	Poor size match Tc(IV)
Re(IV)	63	64.5	Good Tc(IV)
Re(V)	58	60	Reasonable Tc(V)
Ru(IV)	62	60	Reasonable Tc(V)

Table 4.3 Properties of some Technetium Analogues[42]

4.4.5 ReO^{3+} as a Tc(V) Analogue

The ionic radius of Re(V) (Table 4.3) is comparable to Tc(V) because of the third-row contraction phenomenon. Since these elements occupy the same group of the Periodic Table it is reasonable to assume that they also share very similar chemical reactivity. There is indeed one similarity that makes Re(V) an ideal Tc(V) analogue: its ability to exist as ReO^{3+}, the isoelectronic analogue of the widely observed TcO^{3+} core. The ReO^{3+} core is potentially an invaluable research tool as it allows a direct comparison of the effect of the additional oxygen on its preferred binding geometry and stability. However, to date very little work appears to have been reported that explores the ReO^{3+} core as an analogue of TcO^{3+}. This is probably because much of the work done so far has been carried out by specialist branches of industry and academia who have access to suitable facilities that allow direct use of Tc isotopes. It remains to be seen whether the further exploration of the chemistry of rhenium reveals a suitable role for this potentially superb technetium mimic.

4.5 Current Problems in Nuclear Medicine

Two major problems dog the field of radiopharmaceutical research and development. There is the obvious need for improvement in the range of currently available radiopharmaceuticals and a desire to design and synthesise new alternatives that increase the scope of radiodiagnosis and radiotherapy. Alongside these concerns there remains a problem which is in many ways unique to the world of nuclear medicine, our ability to produce useful quantitative information about active metal complex behaviour is severely hampered by stringent safety procedures.

4.5.1 Complex Characterisation

Much of the work currently being carried out in the field of new radionuclide ligand discovery is at the stage where novel ligands are being rationally designed and synthesised. In addition, well-established ligands for more common metals are being experimented with in order to determine their compatibility with radionuclides. The consequence of this, as in all new fields of chemical research, is that current experimentation is only on a qualitative basis that lacks any quantitative methodology. Ligands which appear to efficiently complex radionuclides or their safely accessible models are elaborated further and those which appear not to, and are therefore apparently unsuitable, remain undeveloped.

In order to establish whether a particular ligand or ligand type does in fact offer a viable target for further research, the question: "Does this ligand bind?" should be changed to: "How well does this ligand bind?". However, in contrast with conventional metal-ligand chemistry the absolute amounts of active material that can be safely handled is very low. This presents difficulties both in physical manipulation and in our ability to determine useful information such as binding constants and active metal-ligand complex geometries. Techniques such as NMR titration, solvent based extractions and X-ray crystallography can only be applied by workers equipped with suitable protection.

Only simple tests are currently available to determine the stability of metal-ligand complexes: ITLC tests rely on simple paper chromatographic techniques through the measurement of the radioactive count of paper strips. A quantitative answer gives the research chemist much more information such as donor type (neutral or charged), the number of donors, and may even hint at a binding geometry. Armed with quantitative data

about a particular metal-ligand complex, the chemist can devise a logical and constructive approach to synthesising better, suitably modified ligands. The binding data from any new complexes can be analysed to determine whether structural modifications have been beneficial regarding the direction in which the chemist wishes to take the ligand co-ordination properties. Since the ultimate use of any quantitative technique will be to determine how well a given ligand complexes nanomolar concentrations of a radionuclide, that technique must be easy to apply, safe to use, and very sensitive.

4.5.2 Radiopharmaceutical Deficiencies

Much has been written about the problems involved with introducing drugs of any kind into the body. All such substances are treated as hostile invaders and are quickly attacked by the immune system and converted into forms which are rapidly cleared from the body. Building resistance into drugs is often impossible because of the nature of the compound and its mode of action or because such a step simply compromises efficacy.

Extra care has to be taken when introducing metal complexes into the body. As a result of the biochemical dependency on metals to perform just about all cellular processes, trace metals are extracted from the blood by naturally occurring macrocycles and metal chelating ligands which bind very strongly and with a high degree of specificity. Species like technetium which display a wide range of shapes, sizes and oxidation states can be mistaken for other metals by agents such as transferrin and displaced from the formulated complex via competitive transchelation. The very nature of physiological processes means that the complex is likely to encounter high and low pH environments in salt solutions of varying concentration. These denaturing conditions often lead to simple dissociation of the metal from its ligand.

These factors have the potential effect of rendering the radiopharmaceutical useless because its properties arise out of the nature of the complex. In the case of technetium-essential radiopharmaceuticals, target specificity will have been lost and the active nuclide remains in the blood, as either a salt or as part of a new complex, until it is excreted. Technetium-tagged radiopharmaceuticals are inherently target specific but if they lose their radioactive marker, the ligand goes on to the target site and the active technetium again remains in the blood. 100% breakdown is unlikely in either case but any freely distributed technetium will

add significantly to the background radiation count resulting in poorly resolved, over exposed scans. For these reasons a main thrust of current investigations has been to increase the binding constant of active metal-ligand complexes to limit the breakdown of the radiopharmaceutical in the body.

The other major issue associated with radiopharmaceutical efficacy is that of target specificity. The mechanisms of action of the urogenital system, the hepatobiliary system and the circulation are well known. Based on knowledge of how these and other major physiological systems of the body work, it has been shown that it is relatively simple to program biological behaviour into a substance using the shape, size and charge of a metal-ligand complex. It is not so easy, however, to develop systems that can localise in specific tissues or organs of the body or in incidental sites such as infection, disease or tumour. Researchers are now widely turning to the attachment of strongly bound metal-ligand complexes to biologically active molecules as a means of delivering ionising radiation to remote parts of the body. Biologically active molecules such as enzymes, antibodies, proteins and peptides are already being tested as radioimaging or radiotherapeutic vehicles. Consequently there is a need to develop new chelating ligands, possibly via the modification of established ones, that provide suitable active groups as attachment points for larger molecules.

5 Aims and Objectives

The aims and objectives of this research project are based on observations made by the radiopharmaceutical industry. This relatively young but highly specialised branch of chemistry is rapidly maturing and continues to ask many questions of the research base in its field.

The main objectives of this project were:

1 **To develop an analytical technique suitable for determining the potential strengths and weaknesses of new chelating ligands.** It was intended to develop a quantitative assay system that allows us to determine useful thermodynamic data, such as binding constants, for novel complexes of ^{99m}Tc and its easily accessible analogues.

2 **To synthesise novel chelating systems designed to increase the life of radiopharmaceuticals in the body.** It was intended to design novel chelating systems and modify existing ones to increase the stability of ^{99m}Tc complexes to produce radiopharmaceuticals with greater resistance to *in vitro* denaturing.

3 **To elaborate the chelating systems to allow the attachment of prefabricated, biologically active molecules.** By synthesising novel chelating systems with remote functional groups it was intended to allow the rapid attachment of a wide range of biologically active molecules via a one-step convergent reaction.

SECTION 2

Results and Discussion

Conclusions

"A conclusion is simply the place where
either time, funding or interest runs out."

Scholars Everywhere

6 Results and Discussion

6.1 Achieving the Objectives

At the outset there were clearly pre-defined chemical targets: it was clear that the chemistry would be based around ^{99m}Tc and the common ligand types that were already available for binding it. A suitable system for determining the binding strength of technetium complexes would also have to be investigated.

6.1.1 Determining Complex Binding Strength

In the field of quantitative analysis of complex binding strength there are a number of options available. Techniques such as NMR titration and competitive chelation are commonly used but rely on the presence of radioactive material. For that reason alone neither of the techniques was suitable so attention was turned to solvent-based extraction experiments as a measure of ligand suitability.

Building upon our knowledge of technetium mimics it was envisaged that extraction experiments could be performed using salts of those particular metals with indicating anions. To this end, extraction experiments have classically been carried out using metal 2,4,6-trinitrophenoxide salts. Cram[43] made extensive use of 2,4,6-trinitrophenoxide salts during his characterisation of macrocyclic compounds. The group I metal salt of 2,4,6-trinitrophenol was synthesised and dissolved in water to a known concentration. This was combined with a solution of the macrocycle in a suitable, water-immiscible organic solvent (usually deuterochloroform) also at a known concentration. The mixture was shaken for a given time to allow equilibration and then centrifuged to separate the layers. During the equilibration process the discreetly ionised metal cations are complexed by the macrocycle which remains dissolved in the organic layer upon separation. To maintain the charge balance 2,4,6-trinitrophenoxide anion associates itself with the metal complex and in this way also becomes dissolved in the organic phase. The 2,4,6-trinitrophenoxide anion has a distinctive UV chromophore which allows its concentration in solution to be monitored by UV spectroscopy. Knowledge of the concentration of 2,4,6-trinitrophenoxide ion in aqueous and organic solution at equilibrium allows certain fundamental constants to be calculated. The method is reproducible and well tested but has one major drawback: 2,4,6-trinitrophenoxide salts are highly explosive. Dicationic metal 2,4,6-trinitrophenoxide salts

(such as calcium and cobalt) are particularly sensitive to detonation and since the known technetium mimics are all multicationic this raised an important safety issue. An alternative anion had to be found. One possibilty was 2,4-dinitrophenoxide as its salts are less explosive but instead a much safer dye based system was explored.

Previous work by Grossel and co-workers[44] saw the development of an extraction technique for complexation studies using oxonol dyes (Figure 6.1), a number of which were synthesised by D. J. Edwards[45] following methods originally reported in the Patent literature by ICI and Ilford Ltd.[46]

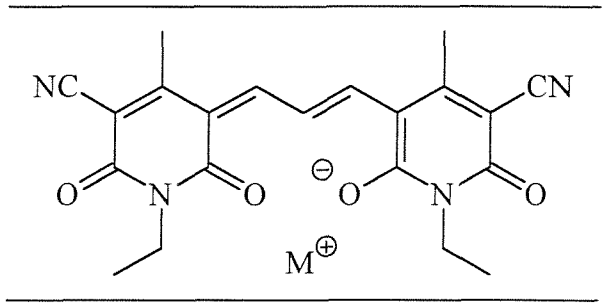


Figure 6.1 *N*-Ethyl Oxonol

The synthesis of a series of oxonol dye salts based on technetium mimicking metals was proposed. Oxonol dye salts are only moderately soluble in water but sufficiently to achieve the concentration ranges required for such studies (approximately 10^{-5}-10^{-7} M). These dyes have very high extinction coefficients and a chromophore which is simple to monitor using UV/Visible spectroscopy.

Since workable concentrations of technetium isotopes are at best in the 10^{-7}-10^{-8} M region the synthesis and isolation of enough material for use as described above is not practicable. Once the procedure had been verified using technetium mimics at low concentrations it was intended to metathesise a technetium oxonol *in situ*. By making the aqueous phase of the extraction system a mixture of a simple technetium salt (available from pertechnetate), and the oxonol salt of a cation poorly bound or completely unbound by the target ligand (tetraalkylammonium or lithium), it was hoped that technetium oxonol would be extracted preferentially. There was a number of assumptions made at this point such as oxonol being the extracted anion but this was to be investigated.

Once the extraction technique had been refined it would to be used to determine the stability of a number of potential technetium ligands previously synthesised elsewhere. It would also play a key rôle during this project assisting in the rational design of novel ligands and the modification of suitable existing ligands.

6.1.2 New Ligands

There are many chelators, ligand systems and binding agents that are suitable for modification to become radiopharmaceuticals. It was decided however to concentrate efforts on the PnAO class of ligands (Figure 6.2). This was because Amersham International had already gained a great deal of experience in this field through their development of Ceretec[19] a modified PnAO.

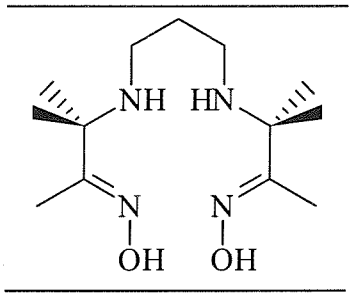


Figure 6.2 PnAO

The PnAO (propylene amine oxime) ligand has many of the features associated with macrocycles. It is polydentate, kinetically and thermodynamically stable and strongly binds a wide range of metals. The nature of the ligand also imparts to it many very desirable properties in relation to its application in the field of radiopharmaceuticals. Since the accepted preparation time (synthesis and purification) of a radiopharmaceutical is ideally less than 20 minutes, ligands must be kinetically "fast binders". In this respect true macrocycles are problematic since they are often incorrectly pre-organised for binding and require a relatively large energy input over a long time to successfully co-ordinate metal cations. PnAO ligands overcome this by being a freely rotatable, linear molecule in solution which quickly wraps around technetium. The final step is loss of one of the oxime protons and the formation of an intramolecular hydrogen bond giving rise to a thermodynamically stable pseudo-macrocycle. It is also chemically compatible with Sn(II), the reducing agent used to prepare Tc(V) from the widely available Tc(VII) pertechnetate. Finally, PnAO ligand complexes of Tc(V) are neutrally charged species. This is because

all PnAO ligands stabilise the often observed TcO^{3+} core by deprotonation of the two amines (which then co-ordinate as amides) as well as one of the oximes (Figure 6.3).

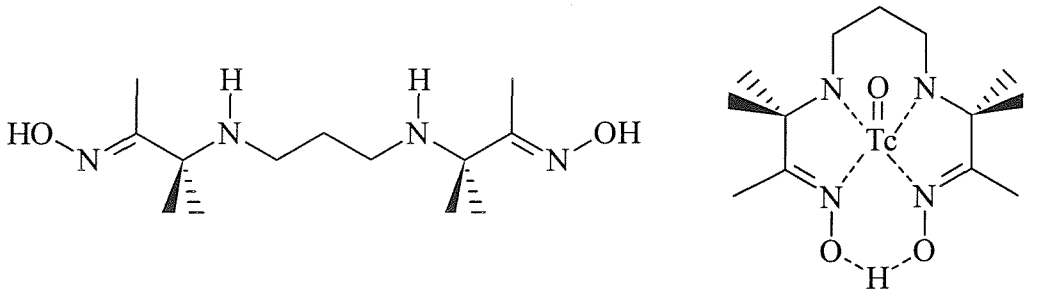
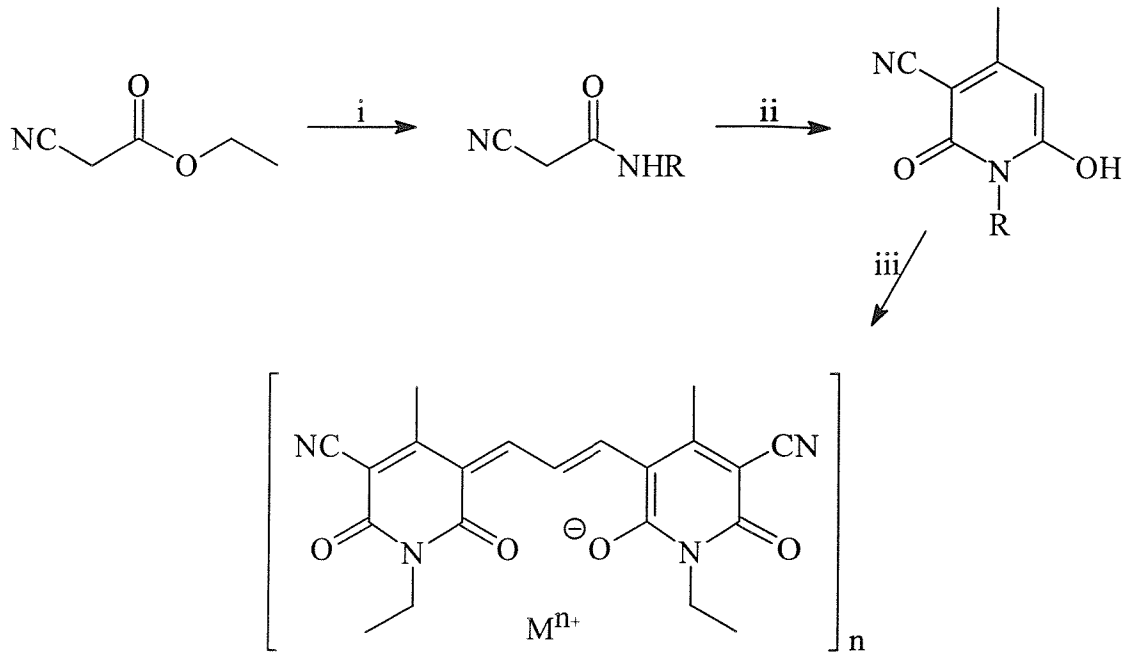


Figure 6.3 Linear PnAO Neutral Complex with TcO^{3+}

In addition to excellent physical properties, PnAO ligands also offer a superb system for further elaboration. Modification of the backbone allows the substitution of reactive groups that either assist in co-ordination of the technetium or create attachment points for large biologically active molecules. Novel PnAO ligands could be complexed with ^{99m}Tc on the tracer level in the hope of making available improved radiopharmaceuticals for use in radioimaging and radiotherapy.

6.2 Synthesis Of Extraction Experiment Indicators

The first synthetic targets were oxonol dye salts of technetium mimics. Scheme 6.1 outlines the synthetic route to their preparation. The overall scheme is based on work carried out previously within the research group by D. J. Edwards[45] which was directed at producing backing layer dyes for the photographic film industry[46] based on the preparation of both group I and group II metal oxonol salts.

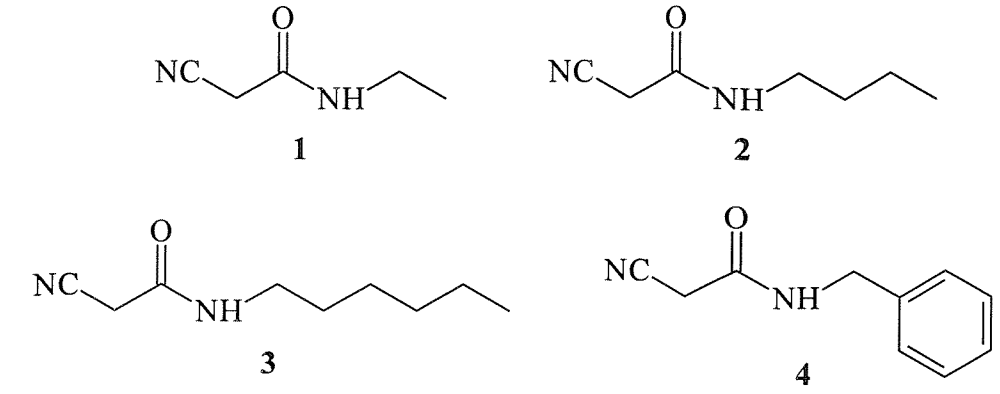


Scheme 6.1 Synthetic Route to Oxonol Dyes

i NH_2R, EtOH; *ii* $CH_2COCH_2CO_2R$, KOH, MeOH; H_2O, concHCl (pH1); *iii* $(CH_3O)_2(CH_2)_3(OCH_3)_2$, $M^{n+}(OAc)_n$, EtOH

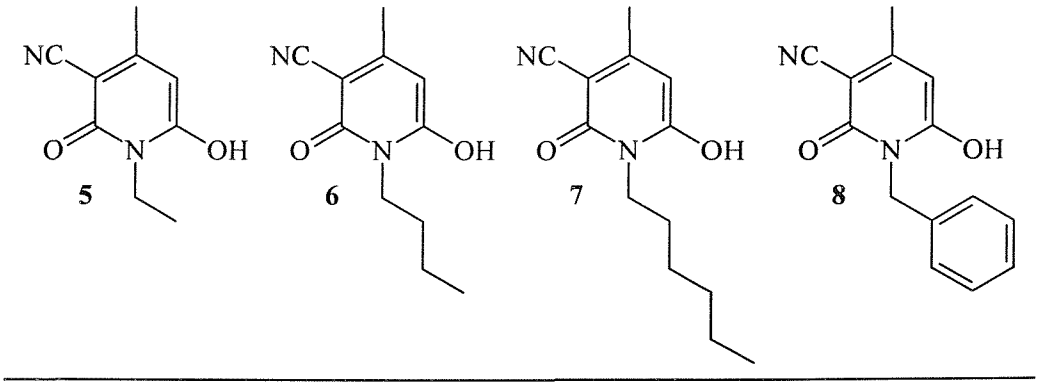
6.2.1 *N*-Substituted Cyanoethanamides

In the current work it was desirable to synthesise a series of oxonols which varied not only on the metal present but on the substitution of the backbone. Thus an array of oxonols could be prepared with varying degrees of aqueous and organic solubility. This was accomplished by varying the nature of the alkyl group at the cyclic nitrogen. Introduction of this group was via the primary alkylamine used to synthesise the *N*-substituted cyanoethanamides:[47] *N*-ethyl cyanoethanamide (**1**), *N*-butyl cyanoethanamide (**2**), *N*-hexyl cyanoethanamide (**3**) and *N*-benzyl cyanoethanamide (**4**). Each substitution proceeded in good yield and the crystalline products were recrystallised from either ethanol (**1**, **2** and **4**) or toluene (**3**). Exothermic substitution at the unactivated ester proceeded via a highly reactive ketene intermediate in less than 1 hour in all cases. This relies on the acidic nature of the extracted proton and the subsequent stabilisation of the anion by the nitrile and ester groups. The base was present as excess alkylamine, more of which quenched the ketene giving the less reactive cyanoethanamide.



6.2.2 *N*-Substituted Hydroxypyridones

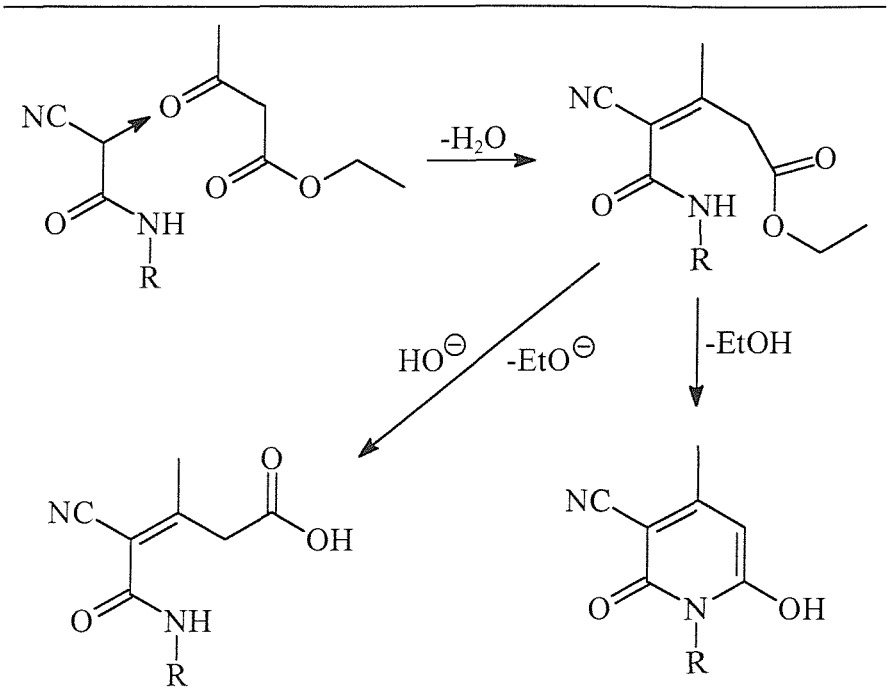
The next step was synthesis of the corresponding *N*-substituted hydroxypyridones. Further elaboration of the oxonol structure was possible here by varying the nature of the β-keto ester. By using β-keto acids with extended alkyl or aryl chains it was effectively possible to add increasingly organic soluble substituents at the 4-position of the heterocyclic ring. However, as Scheme 6.1 suggests, ethyl 3-oxobutanoate was chosen firstly because of its availability as a cheap reagent and secondly because it would keep the structure of the final oxonol relatively simple. Four *N*-substituted hydroxypyridones were prepared at this stage:[48] 1-ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**), 1-butyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**6**), 1-hexyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**7**) and 1-benzyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**8**).



The reactions were carried out in basic methanol yielding the pyridinolate potassium salts which were precipitated nearly pure from water by careful acid work-up.

Hydroxypyridones **5** and **8** were synthesised in reasonable yield and purified by recrystallisation from ethanol and methanol respectively; however, **6** and **7** presented

problems. ^{1}H and ^{13}C NMR spectra showed that along with each of the desired products (recrystallised from ethanol and methanol respectively) there was an accompanying compound which was in many respects similar to the product. IR spectroscopy showed that the mixtures contained *N*-substituted hydroxypyridone and an organic acid. This evidence led to the conclusion that heterocycle annulation was in competition with a side reaction. A likely mechanism for this reaction involves ring closure via both an aldol condensation and an ester substitution (Scheme 6.2).



Scheme 6.2 Probable Mechanism for Hydroxypyridone Formation

The aldol condensation was identical for each of the different cyanoethanamides and always proceeded successfully. The next step, however, appeared to be sensitive to the nature of the *N*-substituted group. With ethyl and benzyl substituents the required substitution took place, but with butyl and hexyl substituents the greater steric bulk made the substitution step more difficult. The result was that the usually much slower step of base-catalysed ester hydrolysis occurred in preference yielding the uncyclised acid upon work-up (Scheme 6.2).

In order to optimise the reaction and avoid ester hydrolysis two modifications were introduced. The butyl derivative was resynthesised using: (i) a non-nucleophilic base (triethylamine) that would catalyse the reaction but not hydrolyse the ester; and (ii) ethoxide as a base so that any attack at the ester would simply regenerate the same ester.

The triethylamine variation yielded a green solid a crude sample of which was found to be the desired product free of open chain by-products. Purification by any means proved to be very difficult because of the presence of triethylammonium salts. The ethoxide ion variation (from sodium metal in ethanol) gave the intended hydroxypyridone and an open chain ethyl ester terminated adduct. It appeared that ethoxide ion was catalysing the initial condensation but that ring-closure was still proceeding slowly. The reaction was ~66% complete, the remaining product was identified as the open chain intermediate.

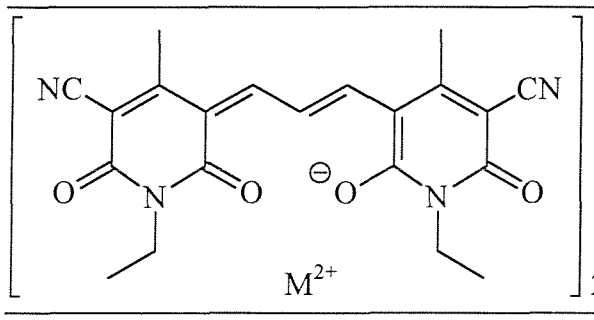
Other variations were attempted such as increasing the reflux time of the pyridone reaction from 8 hours to 24 hours but to no avail. It was noted that the success of those reactions involving the ethyl and benzyl substituents was probably because of the smaller steric bulk of the ethyl group and the increased nucleophilicity of the *N*-benzyl amide group.

6.2.3 Oxonols

Oxonol dye salts are prepared by the double condensation of two hydroxypyridone molecules with 1,1,3,3-tetramethoxypropane in the presence of the desired cationic component[45] (usually the ethanoate for metals or the chloride for tetraalkylammonium salts, Scheme 6.1). By manipulating the reaction stoichiometry correctly it is possible to synthesise unsymmetrical oxonols[45] but this was not pursued. Instead, use was only made of the convenient one-pot symmetrical oxonol synthesis.

Two different types of oxonol were to be synthesised reflecting their intended ultimate use. A series was to be prepared based on technetium mimics so that modelling of potential ^{99m}Tc ligands could be carried out without recourse to the stringent safety procedures governing the handling of radioactive material. Additionally, a series of oxonols would be required which when in solution presented a cation that was not efficiently bound by target ligand systems. This would allow the *in situ* metathesis of ^{99}Tc or ^{99m}Tc oxonol so that extraction experiments could be performed on the tracer level.
The two most available and convenient technetium mimics were Cu(II) and Co(II). Their ethanoates were procured and the synthesis of their oxonol salts was undertaken. It was decided that *N*-ethyl oxonols should be prepared first since their synthesis was already well documented[46] for group I and group II metals.

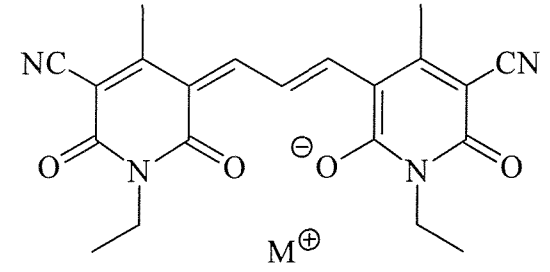
The reaction of metal(II) ethanoate, 1,1,3,3-tetramethoxypropane and 1-ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone was carried out in a 10% solution of glacial ethanoic acid in ethanol. After refluxing, the Cu(II) solution was dark green with an accompanying dark green solid and the Co(II) solution very dark blue with an accompanying dark blue solid. Both solids were filtered giving copper(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate] (**9**) as a dark green powder and cobalt(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate] (**10**) as a dark blue powder.



9 Cu(II)
10 Co(II)
17 Mn(II)

After vacuum desiccation, **9** was a fine, brown powder and **10** a fine, violet powder. Crude NMR spectra of both products indicated the presence of the required oxonol dyes plus starting materials although each was very broad due to the paramagnetic nature of the cations. An initial attempt was made at recrystallising **9** and **10** from hot ethanol in which the dyes dissolved to give a deep blue solution. Neither dye was very soluble in an excess of boiling ethanol, indeed it was discovered that they were not soluble in most common solvents except acetonitrile (sparingly) and dimethyl sulphoxide. The samples of highest purity were obtained from refluxing solutions of ethanol. Extended ethanol-based soxhlet extractions of **9** and **10** were performed but only succeeded in bleaching any extracted oxonol dye.[45] Although complete dissolution was never achieved, the particles of the samples that were refluxed in ethanol were slowly broken down freeing the trapped impurities. This gave rise to very fine powders 90 - 95% pure by NMR, the chief impurity being **5**. As expected the elemental analyses of these samples were very poor indicating that they were not suitable for incorporation into extraction experiments at that stage. Previous work[45] had indicated that oxonol salts of dicationic metals were difficult to purify so an attempt was made to synthesise some *N*-ethyl oxonol salts of group I metals and tetraalkylammonium cations. After stoichiometric adjustment the reaction conditions were

exactly the same as for **9** and **10**. Lithium ethanoate was used to prepare lithium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**11**) as a shiny yellow/green metallic crystalline solid.



11 Li
12 K
13 $N(CH_3)_4$

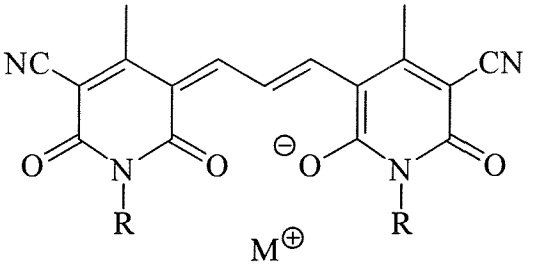
This monocationic oxonol salt was considerably more soluble in ethanol than **9** and **10** which allowed it to be completely purified. Elemental analysis data was still considerably different from the calculated results but by all other methods **11** appeared to be pure.

To complete the Group I metal series of oxonols an attempt was made to purify some dyes synthesised previously within the research group. Amongst the samples were *N*-ethyl oxonols based on sodium, potassium, magnesium and calcium all of which had supposedly been recrystallised from refluxing ethanol. The dyes based on dicationic metals (magnesium and calcium) acted very much like **9** and **10** in that they were not very soluble. At best they were harvested as very fine dark blue powders which NMR showed to contain unreacted hydroxypyridone **5**. As expected from the result with **11** the sodium and potassium dyes proved to be much more soluble in hot ethanol giving dark green/blue metallic crystalline solids. However, the potassium oxonol was observed to contain a white powdery solid amongst the metallic crystals, NMR later showed this to be unreacted hydroxypyridone which was also present in the sodium oxonol. Eventually the sodium oxonol was recrystallised to high purity but the slightly less soluble potassium oxonol remained ~85% pure. In order to obtain a pure sample of the potassium oxonol the synthesis was repeated using potassium ethanoate to give potassium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**12**) in moderate yield. Recrystallisation from refluxing ethanol gave **12** in ~95% purity.

It was becoming clear that many oxonol dyes were not easy to purify, previous work[45] had frequently involved the use of organic cations, salts which are easier to purify. Unless the reaction went to very near completion it was very difficult to remove the last traces of hydroxypyridone **5**. It was decided therefore to prepare a number of oxonols that could be more easily purified by recrystallisation. Two possibilities of adding increasingly organic soluble components were investigated (i) tetraalkylammonium cations and (ii) oxonols synthesised from *N*-substituted hydroxypyridones with lipid soluble substituents.

The first attempted modification involved the use of tetramethylammonium as the cation. The oxonol synthesis was carried out using tetramethylammonium chloride and yielded a tiny amount of green/blue microcrystalline solid from the concentrated reaction filtrate. NMR showed this to be the required tetramethylammonium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**13**). However, the majority of reaction product was found to be tetramethylammonium chloride. It would have been possible to have experimented with different alkylammonium salts since this might have increased the reaction yield and could have had the effect of making the oxonol more soluble in organic solvents. Unfortunately, an increasingly organic soluble oxonol would have been detrimental to its qualities as an extraction indicator since the dye should be virtually insoluble in the organic phase.

The synthesis of oxonols **14** - **16** based on hydroxypyridones with *N*-butyl and *N*-benzyl substituents was attempted using the method previously employed for the synthesis of **9** and **10.** Potassium 1-butyl-3-(3-(1-butyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**14**) was obtained in very low yield. The characteristic oxonol dye blue colour was present but the majority of the product mixture was unreacted hydroxypyridone **6**. It was not possible to recover even a small amount of pure **14**.



14 K (R = Butyl)
15 K (R = Benzyl)
16 Li (R = Benzyl)

Potassium 1-benzyl-3-(3-(1-benzyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**15**) was synthesised in ~63% yield. This approximation was based on ^{1}H NMR assignments which showed that approximately half the hydroxypyridone **8** had undergone condensation. The reflux times for the reaction were increased in order to allow more time for the condensation to go to completion but results indicated that ~63% was the maximum yield under these conditions. As before it did not prove possible to remove the unreacted hydroxypyridone from the product mixture. Following earlier results with **11** it was hoped that the lithium salt of *N*-benzyl oxonol would be more soluble and hence be purifiable by recrystallisation. Lithium 1-benzyl-3-(3-(1-benzyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (**16**) was prepared in ~70% yield (cf. **15**) as a crude mixture of mid-green shiny crystalline needles and fine crystals. The remainder of this crude product was found to be hydroxypyridone **8** but frustratingly, all attempts to further purify **16** including various ethanol based recrystallisations failed. With **14**, **15** and **16** there was no doubt that oxonol was being formed in the reaction. It seemed however that manipulating the organic solubility of the oxonol anion was having a detrimental effect on its solubility in both aqueous and organic solvents, and it was concluded that variation of the *N*-substituent was not going to provide extraction indicators with enhanced performance.

In light of those results it was decided to concentrate on preparing pure samples of the *N*-ethyl substituted oxonols. Since the only 100% pure sample at that stage was the lithium salt **11**, it was decided to attempt UV extraction experiments using a solution of this treated with a suitable technetium mimic in order to generate the required oxonol *in situ*. Development of this technique was important as it was to be used for the preparation of ^{99}Tc and ^{99m}Tc oxonols as described earlier. Whilst preparing these solutions it was noted that addition of dicationic metal salts was immediately followed by the precipitation of a

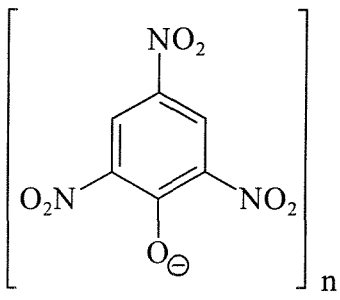
dark, flaky solid. Analysis of these solids showed them to be almost pure samples of dicationic metal oxonols which had been metathesised in solution and precipitated out by virtue of their insolubility.

6.2.4 Oxonol Metathesis

A fortuitous method had been discovered for the preparation of potentially pure dicationic oxonol salts. Metathesis reactions were devised using very stringently purified water, pure samples of metal(II) salts and **11**. The metathesis of **9** and **10** was attempted by the slow addition of a dilute solution of **11** to an equally dilute solution of metal(II) chloride with rapid stirring. Yields of 92% and 94% were achieved for **9** and **10** respectively. Characterisation showed the samples to be 100% pure with elemental analysis confirming that the shiny metallic, purple flakes contained water of crystallisation. The manganese salt of *N*-ethyl oxonol was also metathesised. The use of manganese as a technetium mimic had not been previously discussed but there was some evidence that it might be a useful analogue (Table 4.3). Manganese is also a congener of both technetium and rhenium and is potentially very important for modelling the lower oxidation state range. Manganese(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate] (**17**) was recovered 100% pure in 84% yield from the ethanoate as a shiny metallic, purple solid. **17** like **9** and **10** gave a very broad ^{1}H NMR spectra due to the paramagnetic nature of the cation.

6.2.5 2,4,6-Trinitrophenoxides

As well as comparing extraction experiment results from the oxonol salts with those previously published[71] for other metal salts, a more direct method of validating their usefulness was sought. The explosive nature of 2,4,6-trinitrophenoxide salts, as discussed earlier, precludes their safe usage as large scale extraction indicators. However, if small amounts of correctly handled 2,4,6-trinitrophenoxide salts could be synthesised they would be of use during the initial phase of oxonol testing as experiments could be performed under identical conditions. In this way league tables of extraction efficiency could be built up for well-studied ligand types with a range of metal cations. Correlation of the results from the oxonol and the 2,4,6-trinitrophenoxide studies would further vindicate the use of oxonols as extraction indicators.



M^{n+}

18 Na (n = 1)
19 K (n = 1)
20 Li (n = 1)
21 Mg (n = 2)
22 Cu (n = 2)
23 Co (n = 2)

For safety reasons 2,4,6-trinitrophenol is stored under water. This makes the preparation of salt solutions of known concentration very difficult. For this reason it was necessary to attempt the synthesis of solid 2,4,6-trinitrophenoxide salts. The methodology involved is very simple; 2,4,6-trinitrophenol and the relevant metal carbonate are dissolved in water and on evaporation of the solvent, crystals of the product salt form.[49] Sodium 2,4,6-trinitrophenoxide (**18**) and potassium 2,4,6-trinitrophenoxide (**19**) were prepared accordingly as bright yellow needles and pale yellow prismatic needles respectively.

Difficulties arose trying to prepare lithium 2,4,6-trinitrophenoxide (**20**) because lithium carbonate is only sparingly soluble in water. The method relies heavily on the complete dissolution of both of the solid starting materials so the reaction was repeated with the mixture being heated to achieve the solution of lithium carbonate. At 85 °C the lithium carbonate dissolved but on cooling and standing the product did not crystallise. The observed precipitate was a crude, powdery mixture of product and reagents. A 1:1 stoichiometry of 2,4,6-trinitrophenol and lithium carbonate had the same effect so lithium hydroxide was used as the lithium source. Addition of aqueous lithium hydroxide to a solution of 2,4,6-trinitrophenol instantaneously precipitated dark orange rhombic crystals. Curiously however, all attempts to recrystallise the crude and impure product were unsuccessful; once the crystalline material dissolved it would not recrystallise.

2,4,6-Trinitrophenoxide salts of the dicationic metals magnesium (**21**), copper (**22**) and cobalt (**23**) proved as difficult to prepare as **20** and for the same reasons, that is the carbonates were virtually insoluble in water. The difficulty was that neither reagent was achieving complete solution and hence not helping to solubilise the other component. To overcome this problem other salts were used namely the sulphates and hydroxides but all were similarly insoluble in water. The use of metal nitrates was also tried since it was

known that these were highly water soluble. Whilst the reaction appeared to work without a basic component (carbonate or hydroxide), the most insoluble product was 2,4,6-trinitrophenol which recrystallised on cooling. Various other solvent systems were experimented with such as ethanol, aqueous ethanol and acetone but one or other of the solid reagents always remained insoluble.

For reasons of either solvent incompatibility (lipid soluble *N*-substituted oxonols) or synthetic complexity (2,4,6-trinitrophenoxides) the synthesis of extraction experiment indicators concluded with pure samples of *N*-ethyl oxonol salts of lithium, sodium, potassium, manganese(II), cobalt(II) and copper(II).

6.3 Synthesis of Modified PnAO Ligands

The second set of synthetic targets were new PnAO-derived structures with enhanced, second-generation modifications. The PnAO skeleton lends itself to elaboration as it is possible to substitute the carbon backbone at almost any point (Figure 6.4). Work on the understanding of PnAO ligand types was instigated by R. K. Murmann,[50] their synthesis (Scheme 6.3) has changed little since that time.

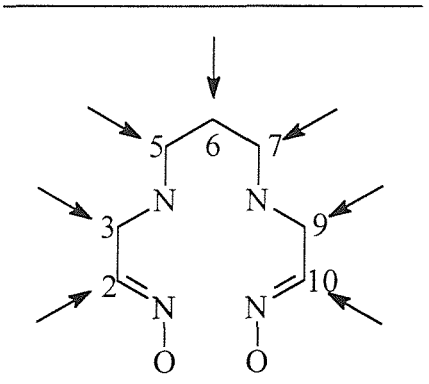


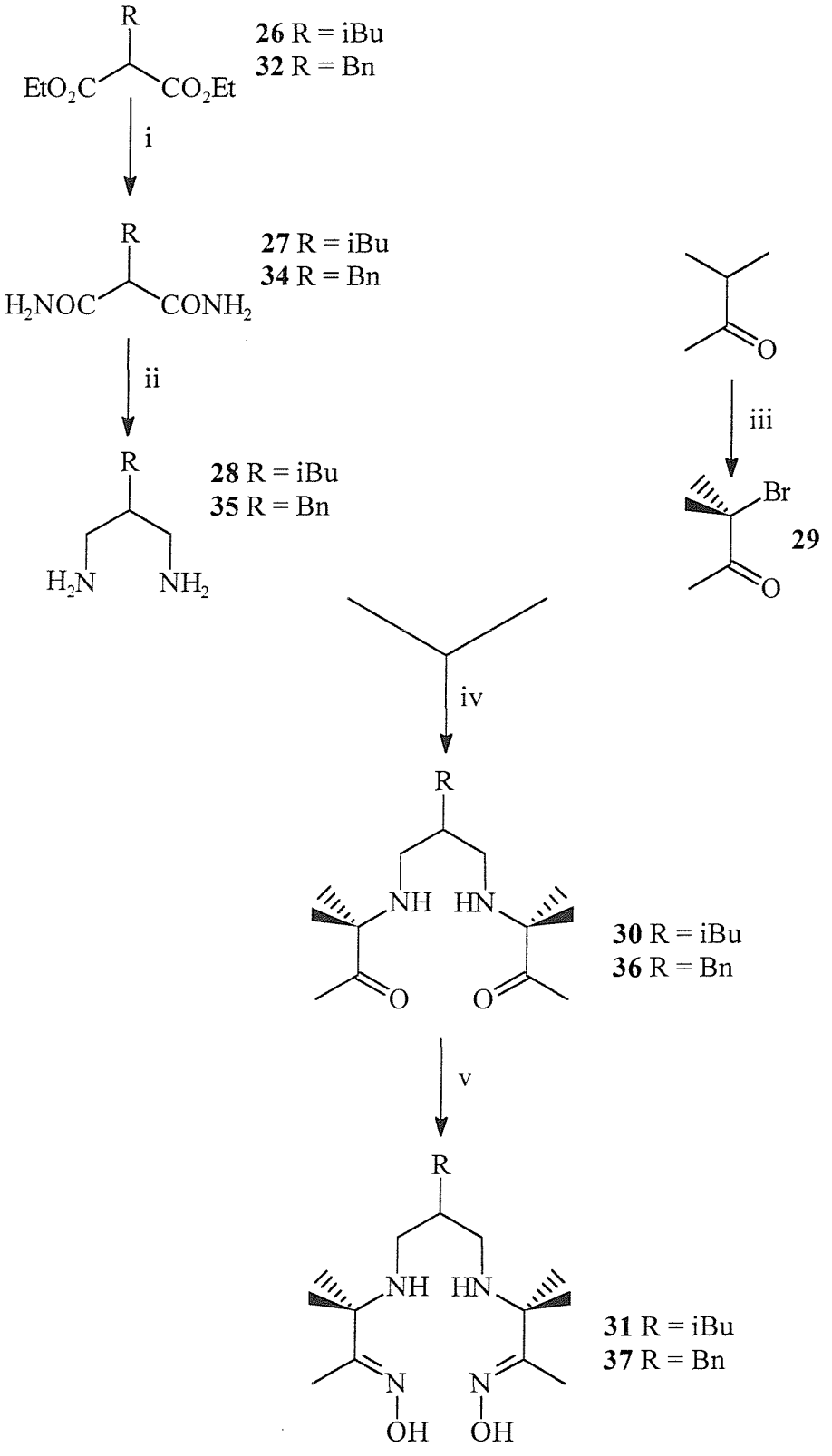
Figure 6.4 PnAO Substitution

Substitution of the ethylene unit between the amine and oxime nitrogens is wholly dependant on the nature of the α-bromoketone unit used in the convergent step. The use of different α-bromoketones allows for substitution at that point in the final structure, and it is also possible to prepare unsymmetrical PnAO ligands[51] by manipulating the stoichiometry of the convergent step. Similarly, the propylene bridge of the ligand comes from diethyl 1,3-propanedioate. Substitution at the 2-position of this 3-carbon fragment

subsequently provides PnAO ligands with modifications at the apical 6-position. Since it is known that the substitution pattern between the amine and oxime nitrogens has a stabilising effect on Tc(V) complexes, much of the recent work carried out on the enhancement of the PnAO ligand system has been directed at elaboration of the apical 6-position. For this reason it was decided to concentrate the efforts of this project into preparing novel PnAO ligand systems with modified apical sites. These would have the ability to further co-ordinate the complexed metal cation or provide attachment points for large biologically active molecules.

6.3.1 PnAO Ligands

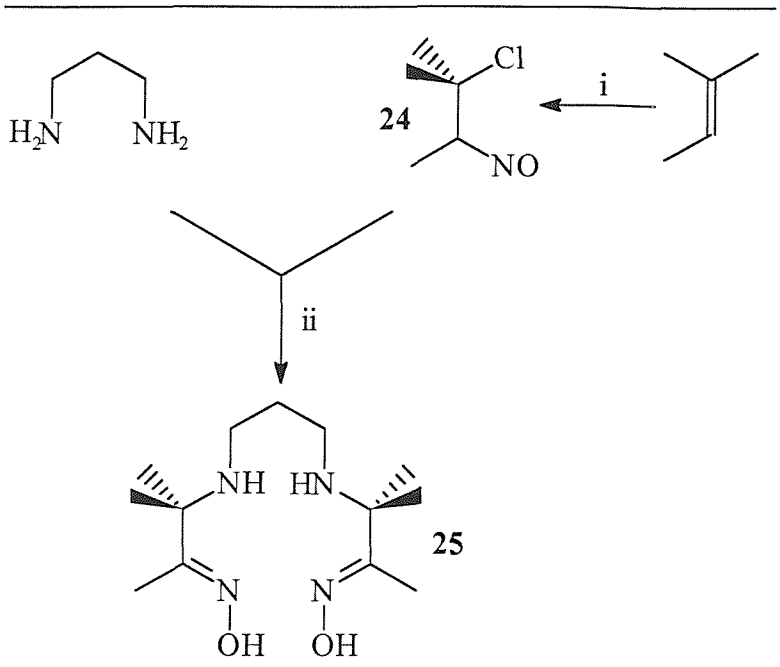
In order to gain some experience in the synthesis of PnAO ligands the first target was the preparation of PnAO (Figure 6.2). The method[50] used was different from that currently accepted in that 2-chloro-2-methyl-3-nitrosobutane (**24**) was used to functionalise 1,3-propanediamine, rather than an α-bromoketone (Scheme 6.4). This approach leads to 6-substituted PnAO ligands from 2-substituted 1,3-propanediamines in a single step.



Scheme 6.3 Synthetic Route To PnAO Ligands

i NH_3, $NaOCH_3$, CH_3OH; *ii* BH_3.THF; *iii* Br_2, CCl_4; *iv* Na_2CO_3, DMF; *v* NH_2OH, CH_3OH

However, the overall reaction is not as efficient as the route given in Scheme 6.3 and the nitrosobutane **24** is difficult to purify and store. In either case the resulting PnAO substitution pattern has a stabilising effect on ligand complexes formed with Tc(V).



Scheme 6.4 Nitroso Route To PnAO Ligands
i 3-Methylbutyl nitrite, concHCl; *ii* CH_3OH

The nitrosobutane **24** is obtained by reaction of 3-methyl-2-butene with nitrosyl chloride, a process which is usually avoided because preparation of nitrosyl chloride from various reagents[52] although straightforward gives a low yield of the product which is difficult to store. 3-Methylbutyl nitrite was used as an alternative nitroso source because it is more convenient to handle and store.[53] The nitrite is reacted with 3-methyl-2-butene in the presence of an acid catalyst (Scheme 6.4). Both ^{1}H and ^{13}C NMR spectra of the product seemed to indicate the presence of impurities even after recrystallisation. However, nitroso compounds exist as dimers (Figure 6.5) and since **24** has a chiral centre, the dimer is diastereomeric. The R,R and S,S enantiomers are of equivalent energy but the R,S diastereomer is different hence the NMR spectra appeared to indicate impurities. The energy difference between the diastereomers is small so that the NMR signals overlap except for the proton peak corresponding to the chiral centre. This proton is very close to and therefore influenced by the other chiral centre in the complex.

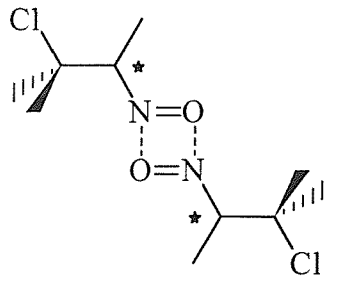


Figure 6.5 Nitroso Dimers

3,3,9,9-Tetramethyl-4,8-diaza-2,10-undecanedione dioxime (**25**) was prepared in moderate yield from 1,3-propanediamine and a slight excess of **24**. Solvation in methanol encouraged the isomerisation of the nitroso groups into the more stable oximes.[54] This reaction was worked up in aqueous base which had the effect of tautomerising the remaining nitroso groups and the crude product was purified by recrystallisation from hot methanol.

6.3.2 PnAO Substitution

Alkyl substitution at the 2-position of diethyl 1,3-propanedioate permits the elaboration of 3-carbon fragments. It also provides a convenient entry route into an apically substituted PnAO skeleton (Scheme 6.3). A method[55] was found for the preparation of PnAO ligands in this manner and was used, as a model run, to synthesise the 2-methyl-1-propyl variant (Figure 6.6).

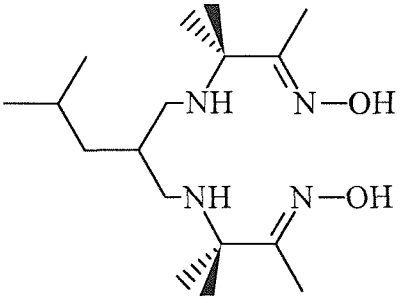


Figure 6.6 6-(2-Methyl-1-propyl)-PnAO

Diethyl 2-(2-methyl-1-propyl)-1,3-propanedioate (**26**) was prepared from diethyl 1,3-propanedioate and 1-chloro-2-methylpropane using ethoxide as a base. Distillation at reduced pressure provided the product oil in good yield.

Conversion of **26** to the corresponding diamide was achieved by reaction with methanolic ammonia in the presence of a catalytic amount of sodium methoxide. The resulting 2-(2-methyl-1-propyl)-1,3-propanediamide (**27**) was recrystallised to give a colourless solid in good yield.

Reduction of **27** to 2-(2-methyl-1-propyl)-1,3-propanediamine (**28**) with borane in THF initially gave the intermediate borate ester. Careful work-up with concHCl followed by basification and distillation provided **28** as a colourless, viscous oil.

3-Bromo-3-methyl-2-butanone[56] (**29**) was prepared by the bromination of 3-methyl-2-butanone in CCl_4 in good yield.

The combination of **28** and **29** was achieved via base catalysed substitution carried out in DMF. 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-methyl-1-propyl)-2,10-undecanedione (**30**) was purified by column chromatography to yield a light orange waxy solid ~95% pure. Attempts to further purify **30** did not succeed so it was stored cold under nitrogen and used as it was in the next step.

Two methods for the final step of the scheme, the oximation of the ketone groups, have been reported,[55] one of these involves the use of *O*-(trimethylsilyl)hydroxylamine in DCM and gives higher yields than the considerably cheaper alternative of hydroxylamine. However, as well as being economically efficient, hydroxylamine hydrochloride was much easier to store so its use was preferred. 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-methyl-1-propyl)-2,10-undecanedione dioxime (**31**) was prepared by the reaction of **30** with a methanolic solution of hydroxylamine hydrochloride, which had previously been neutralised with sodium hydroxide, in moderate yield and purified by recrystallisation.

6.3.3 Novel PnAO Ligands

After familiarisation with the techniques involved in synthesising 6-substituted PnAO ligands a search was made of the available literature to ascertain the nature of all of the 6-substituted PnAO ligands that had previously been made. This detailed search also included the unpublished library of compounds that had been synthesised by Amersham International. It was discovered that an apparently novel PnAO ligand would be one which

was substituted at the 6-position with a benzyl group (Figure 6.7), and this became the next synthetic target.

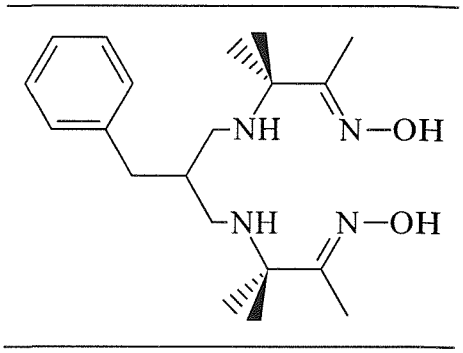


Figure 6.7 6-Benzyl PnAO

A scheme identical to the one outlined for the synthesis of **31** was used. Diethyl 2-benzyl-1,3-propanedioate[57] (**32**) was prepared from diethyl 1,3-propanedioate and (bromomethyl)benzene by the action of ethoxide in ethanol. Numerous other methods for preparing **32** were attempted to determine whether or not a more efficient method could be found. The reaction conditions and yields are summarised in Table 6.1.

Base Reagent	Solvent	Other Reagents	% Yield
Sodium Hydride	1,2-Dimethoxyethane	(chloromethyl)benzene	31
Sodium Ethoxide	Ethanol	"	49
Sodium Ethoxide	Ethanol	(bromomethyl)benzene	71
Potassium Carbonate	Acetone	"	36
"	Acetonitrile	"	63
"	THF	"	29
"	THF (Room Temp)	"	34
Sodium Hydroxide	DCM / Water	" + TEBACl†	< 1

Table 6.1 Methods for Preparing Diethyl 6-benzyl-1,3-propanedioate
(† Triethylbenzylammonium chloride, phase-transfer catalyst)

By far the most successful method was that involving the use of ethoxide in ethanol, it was also one of the more easily applied.

An alternative route for preparing the required 2-substituted 1,3-propanediamine was also investigated. This involved the substitution of 1,3-propanedinitrile by the action of sodium hydride and (chloromethyl)benzene. 2-Benzyl-1,3-propanedinitrile (**33**) was formed in low yield but recrystallised well to give near perfect elemental analysis results. Problems arose

however whilst trying to find a suitable reductant. Literature reports[58] state that borane in THF will accomplish the reduction in approximately 16 - 35% yield depending on the nature of the 2-substituent and that attempts to reduce 1,3-propandinitriles by catalytic hydrogenation (5% rhodium on alumina, 5 atm.), lithium aluminium hydride and lithium aluminium hydride-aluminium chloride among other reagents are singularly unsuccessful. Reduction of **33** was therefore not attempted.

Conversion of **32** to the corresponding diamide (**34**) and subsequent reduction to the diamine (**35**) were carried out by the same method as had been used for **27** and **28**. **35** was obtained in good yield from borane reduction so the same reduction was attempted using lithium aluminium hydride as a comparison. Although an easier reaction to set-up and work-up this latter failed to achieve complete reduction of the substrate. Lithium aluminium hydride has been used in the literature method[55] to reduce 2-substituted-1,3-propanediamides with only sterically small or chemically simple groups but it is reported[55] that borane in THF is more suitable for larger and increasingly complex 2-substituents.

Alkylation of **35** with **29** to give the diketone proceeded as for **30**. 3,3,9,9-Tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione (**36**) was provided in good yield and purified by column chromatography but like **30** could not be completely purified.

Oximation of **36** was by the preferred method of freshly prepared methanolic hydroxylamine. 3,3,9,9-Tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione dioxime (**37**) was purified by recrystallisation to give a glassy white solid in reasonable yield.

6.3.4 Rational Design of Enhanced PnAO Ligands

The substitution of a benzyl group at the 2-position of PnAO did not actually satisfy any of the project criteria: the benzyl group was never expected to co-ordinate the cationic centre of any complexes and neither would it act as an attachment point for other molecules. Being an aromatic ring however, it did lend itself readily to further modification. However, before consideration of the nature of possible substituents which might be incorporated, it was important to establish the precise binding geometry favoured by **37**. For this reason it was necessary to solve the X-ray crystal structure of its complex with suitable metals.

Section 6.5 reports in detail the preparation and X-ray crystallographic study of a number of 6-substituted PnAO complexes. The results of the X-ray analysis of the first two such complexes are relevant here and will be briefly discussed in the context of the design of modified synthetic targets.

Figure 6.8 and Figure 6.9 show the complexes of **37** with Co(III) and Cu(II) respectively. In both cases the PnAO ligand is deprotonated once at an oxime which results in the formation of a strong hydrogen bond to the remaining oxime proton. The residual complex charge is made up of two directly co-ordinated nitrite anions in the case of Co(III) and one tetrafluoroborate anion in the case of Cu(II). Additionally, the oxygen directly bound to the Cu(II) centre is part of a water molecule, this was an important result for the process of designing extra co-ordinating groups.

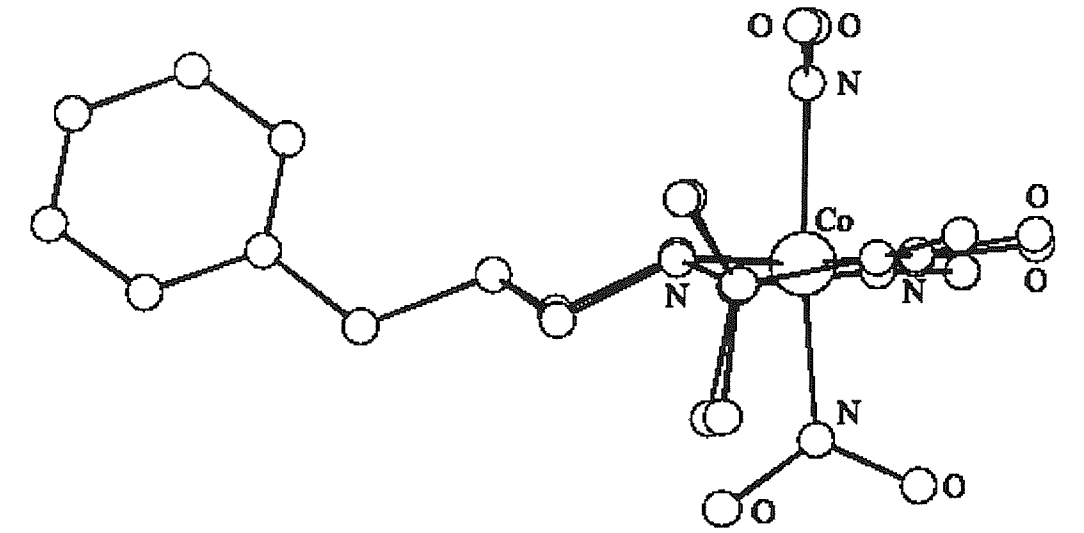


Figure 6.8 Structure of Co(III)BnPnAO$(NO_2)_2$

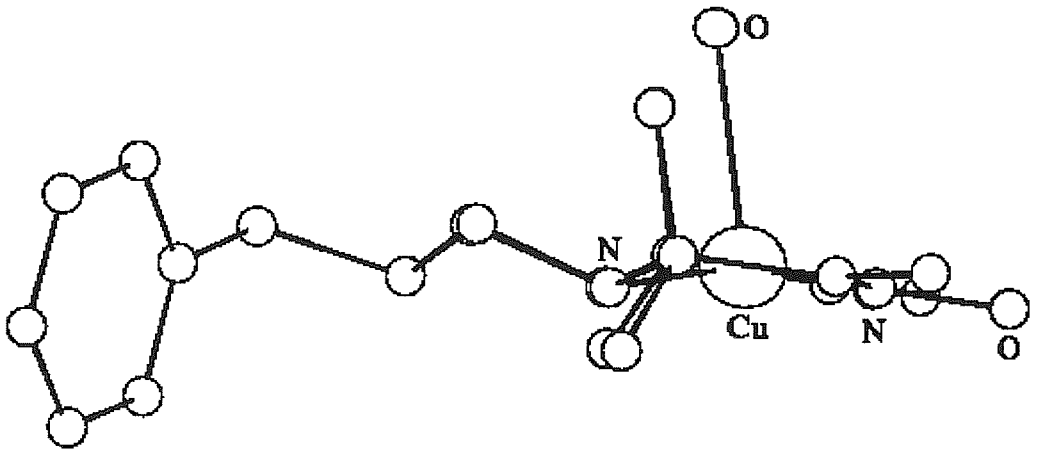


Figure 6.9 Structure of [Cu(II)BnPnAO(H_2O)]BF_4

Each of these complexes is viewed from its side looking through the plane defined by the four nitrogen atoms. These results indicated that any additional co-ordinating groups would have to occupy similar positions in the complex to those favoured by the nitrogens of the nitrite anions in the case of Co(III)BnPnAO(NO_2)$_2$ or the oxygen of the water molecule in [Cu(II)BnPnAO(H_2O)]BF_4.

CPK models of the complexes indicated that the phenyl ring could not easily approach the co-ordination centre of the complex because of steric constraints. It appeared that the alkyl chain joining the apical 6-position of the ligand to the aromatic ring (in these cases one methylene unit) was not long enough to allow the pendant arm to interact with the metals co-ordination sphere. Therefore, substitution of the phenyl ring alone would not allow the new co-ordinating group to interact with the metal.

Two solutions to this problem were considered; one involved substituting the phenyl ring by a long alkyl chain with a co-ordinating group at the end, the other involved only slightly increasing the length of the spacer unit and substituting additional functionality into the phenyl ring. Since much research had already been devoted by Amersham International to preparing PnAO ligands with straight alkyl chains of varying length with attached groups, the latter route was investigated.

Substitution of the phenyl ring presented quite a flexible approach for the addition of extra co-ordinating groups. Amine and hydroxyl functions attached directly to the electron rich

ring would provide excellent co-ordinating groups as would heterocyclic substituents such as the nitrogen of a pyridine moiety. In order to visualise these modifications the proposed new ligands were constructed from CPK models. This provided the initial insight into how long the tethering chain needed to be and at which position(s) the ring should be substituted. It became clear that the length of the tethering chain would have to be two or three units and substitution of the ring would ideally be at the 2- or 3-positions.

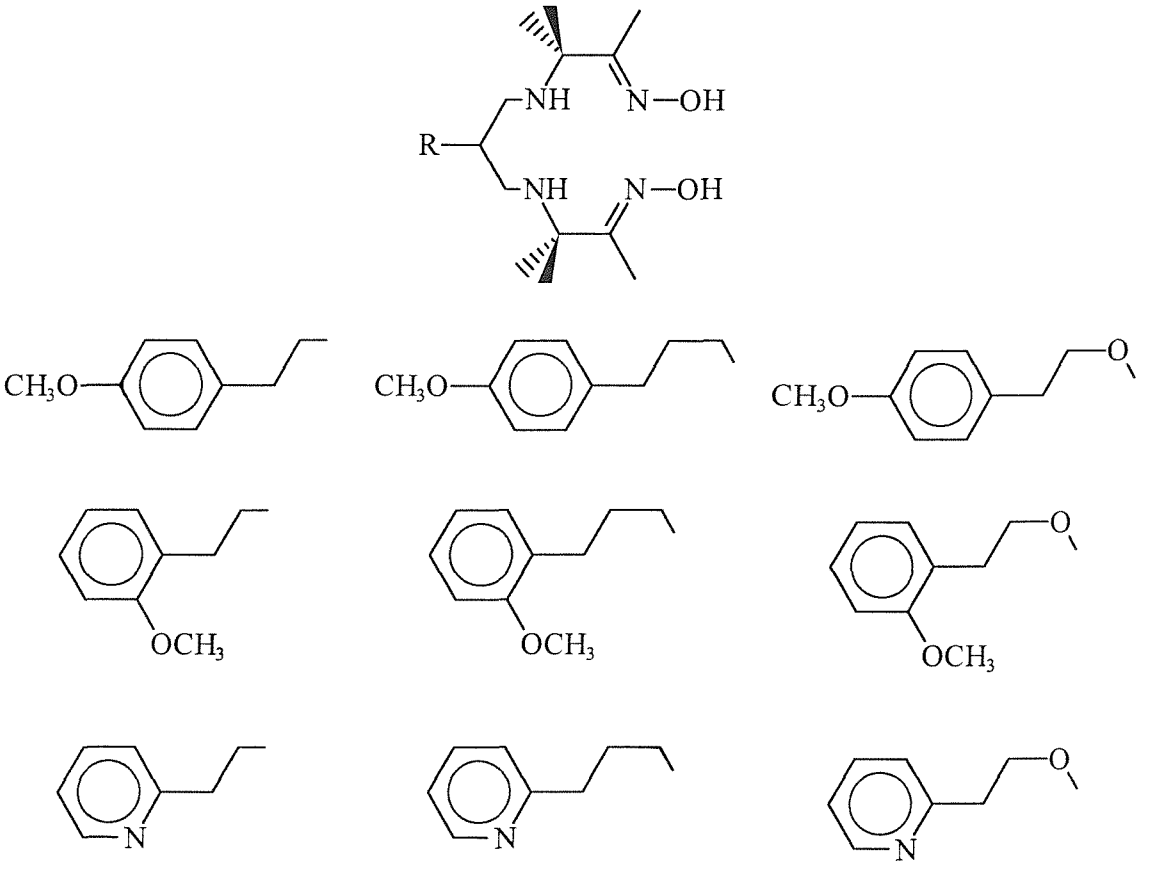


Figure 6.10 Proposed Modifications to **37**

Figure 6.10 represents the nine synthetic targets selected. These involve three types of modification:

1) Variation of the length of tethering chain.
2) Alteration of the position of the hetero atom on aromatic ring.
3) Changes in the nature of the hetero atom.

Tethering chain lengths of two and three atoms were chosen in order to see which if either was preferred. A 2-position for the hetero atom appeared to be most favourable for orthogonal co-ordination into the complex centre. It was also decided to prepare analogues which had the co-ordinating group in the 4-position which appeared to make it impossible for direct co-ordination to the complex centre. They would be useful in acting as controls for extraction experiments to gauge the effect of increased lipophilicity on the behaviour of the complex. The final problem concerned the nature of the co-ordinating groups themselves. Methoxy groups were chosen by analogy to crown ether chemistry and because the unreactive ether groups would facilitate synthesis of the ligands. If these behaved favourably it was envisaged that the methoxy group could be substituted for a hydroxyl group which has the potential to be deprotonated and thus co-ordinate as a phenoxide moiety. This would have important implications on the biodistribution of potential radiopharmaceuticals as it might be possible to prepare anionic ^{99m}Tc complexes. The pyridine moiety is widely known as a superb co-ordinating group and can be further manipulated through conversion into its *N*-oxide with implications similar to those of a phenoxide moiety. The pyridinium salt may also be of particular use when we consider that the final employment of this ligand will be the chelation of the ^{99m}TcO core. Since it is likely then that any donating group will not see the metal centre but must interact instead with the oxygen, it is possible that an intracomplex hydrogen bond could be formed between the pyridinium hydrogen and the core oxygen.

As well as tethering chains comprised of methylene units, the target modifications include analogues of the three unit spaced ligands which contain an oxygen atom. CPK models of ligands with propylene tethers indicated that steric crowding at the junction of the PnAO backbone was a problem. Substitution of the first methylene for an oxygen appeared to greatly reduce the steric bulk in that region without losing any of the flexibility of the propylene chain. Indeed, of the nine proposed ligands, the 2-pyridinyl derivative with an ether-linked three unit spacer displayed the best binding geometry with the five hetero atoms lying in a near perfect square based pyramid. A possible representation of its complex is given in Figure 6.11 (protons omitted for clarity).

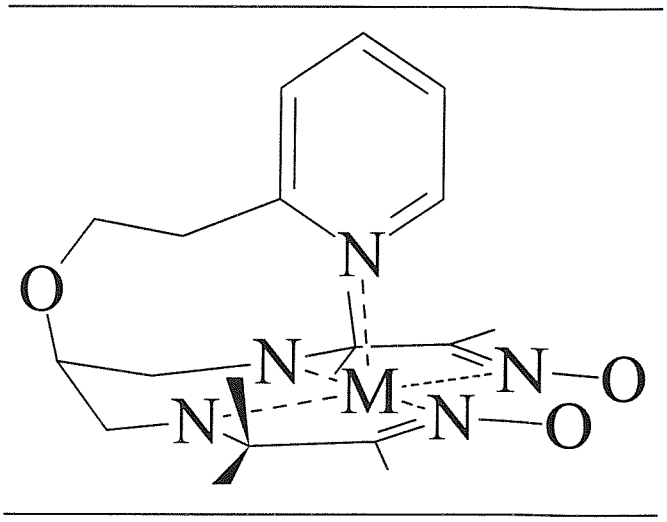


Figure 6.11 Complex of Ideal Target

To further test the assumptions that were made about the suitability of these modifications it was decided to build the complexes in a software molecular modelling package. The CACHE[59] software suite was used to determine the lowest energy configuration possible assuming that co-ordination by the pendant group had occurred. By keeping bond lengths and angles to within acceptable parameters it was found that a tether of three or four units would be required for the complex to successfully form. The binding geometry of all the variants agreed with the CPK models in all aspects except that an extra unit in the tether was required. The results also suggested that the presence of an oxygen atom in the chain at the PnAO junction should help to relieve steric crowding. However, the particular version of the software used was not specifically tailored to performing energy minimisations on metal complexes, but rather was a package intended for dealing with large (particularly biological) organic molecules. Otherwise the results seemed to indicate that the modifications tested did represent viable targets for the elaboration of the PnAO skeleton.

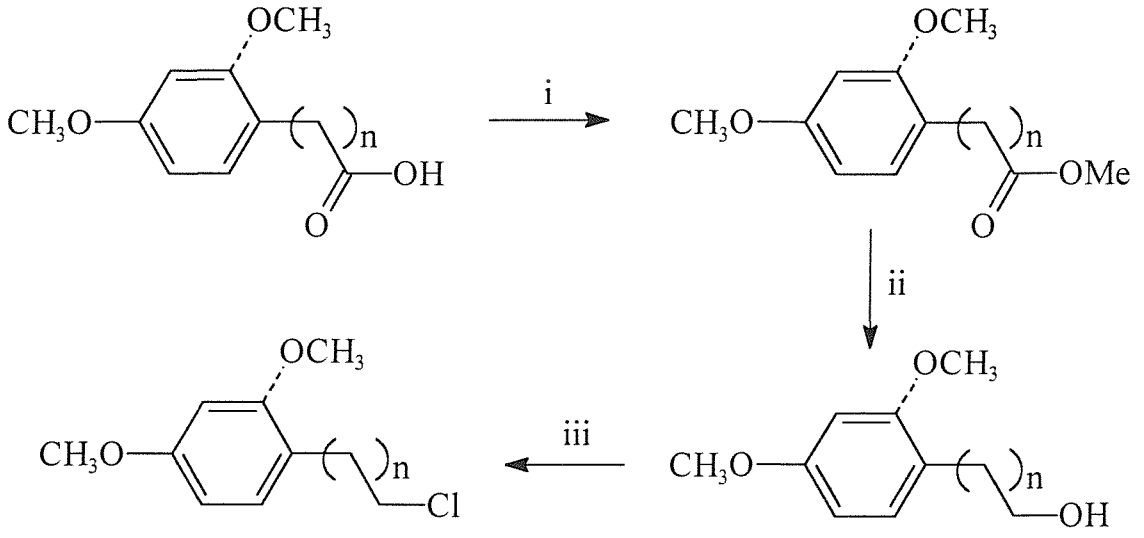
6.3.5 Enhanced PnAO Ligands with -(CH_2)-$_n$ Tethers

For the six new target ligands with ethylene and propylene tethers it was intended that the synthetic route to **31** (Scheme 6.3) would be employed as it was for the preparation of **37**. With **31** and **37** the substituent groups were sourced directly as their chlorides but this was not possible for any of the six target groups. Therefore, the primary task became preparation of the six substituent groups with suitable leaving groups for substitution onto diethyl 1,3-propanedioate. Chloride as a leaving group was chosen because of the success

of the diethyl 1,3-propanedioate substitution reactions involving 1-chloro-2-methylpropane and (chloromethyl)benzene.

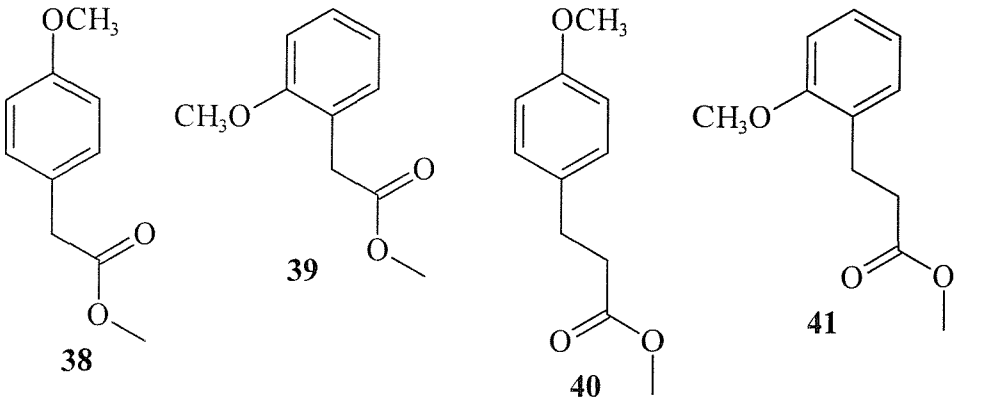
6.3.6 (Methoxyphenyl)alkyl Chlorides

The first syntheses to be attempted were those of the (methoxyphenyl)alkyl substituted analogues. A scheme for the preparation of the (methoxyphenyl)alkyl groups as their chlorides was devised (Scheme 6.5). The starting material acids were all commercially available.

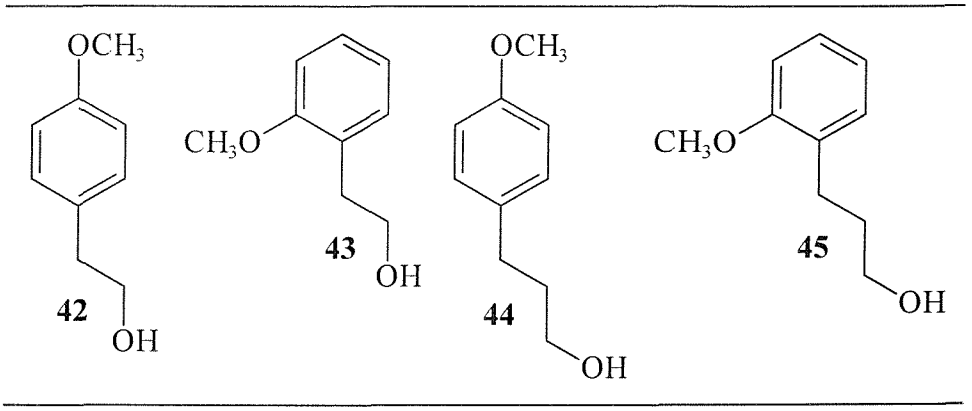


Scheme 6.5 Synthetic Route To (Methoxyphenyl)alkyl Chlorides (n = 1,2)
i $ClCO_2CH_3$, DMAP, DCM; *ii* $LiAlH_4$, Et_2O; *iii* $SOCl_2$, DCM

Methyl chloromethanoate, rather than simple esterification, was used to convert the acids to their methyl esters[60] (**38** to **41**) because the reaction is very quick and clean. It proceeds via the formation of a mixed carboxylic-carbonic anhydride, an isolatable intermediate which is decomposed in a controlled manner by the addition of catalytic quantities of *N,N*-dimethyl 4-aminopyridine. Attack of the pyridinyl nitrogen at the carboxyl carbon leads to loss of carbon dioxide and the formation of the activated ester and methanol. The activated ester is quenched by methanol forming the methyl ester and recycling the catalyst. The methyl esters **38** to **41** were prepared in good yield and purified by distillation at reduced pressure.



Reduction of the methyl esters **38** to **41** to the corresponding alcohols (**42** to **45**) was carried out using lithium aluminium hydride.[61] Alcohols **42** to **45** were prepared in excellent yield and purified by column chromatography.



The next step in the scheme was to convert the alcohols **42** to **45** to the corresponding chlorides. Thionyl chloride was used to perform the conversion[62] but the majority of the reaction product was the symmetrical sulphite (Figure 6.12) with between only 13 and 19% of the desired alkyl chloride. It was therefore decided to investigate a different leaving group so a series of 4-methylbenzenesulphonate esters was prepared instead.

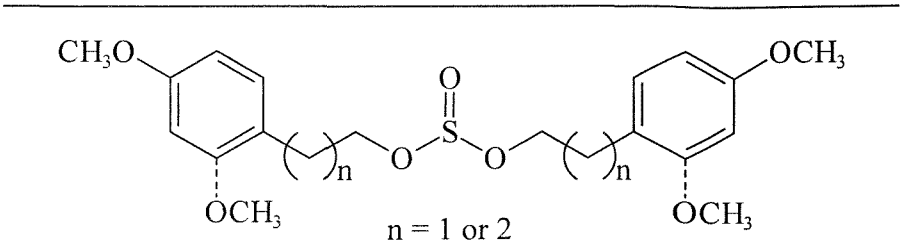
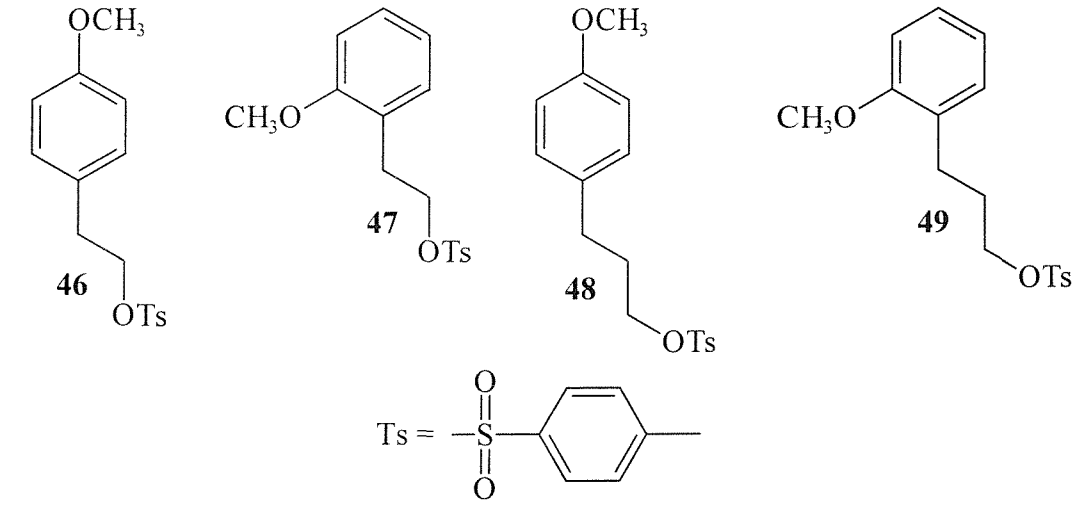


Figure 6.12 Symmetrical Sulphites of (Methoxyphenyl)alkyl Analogues

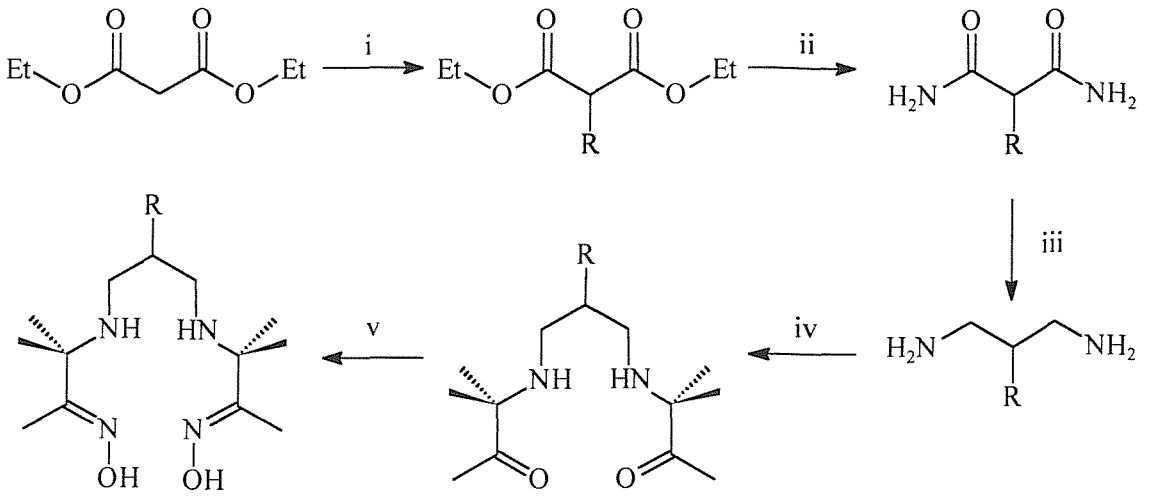
4-Methylbenzenesulphonation[63] of alcohols **42** to **45** proceeded smoothly to give methylbenzenesulphonates **46** to **49** in good yield.



The solid products were purified by column chromatography. They were then further purified by recrystallisation because column chromatography did not adequately remove ethyl 4-methylbenzenesulphonate, a known reaction by-product. This impurity was present because ethanol (which is used to stabilise the reaction solvent; chloroform) is also a substrate for 4-methylbenzenesulphonyl chloride. Being an oil however, it was easily removed by recrystallisation.

6.3.7 (Methoxyphenyl)alkyl PnAO Ligands

With suitable precursors in hand preparation of the (methoxyphenyl)alkyl PnAO ligands was then investigated (Scheme 6.6).



Scheme 6.6 Scheme For The Preparation Of (Methoxyphenyl)alkyl PnAO Ligands

i Methylbenzenesulphonates; *ii* NH_3, $NaOCH_3$, CH_3OH; *iii* BH_3.THF; *iv* Bromoketone **29** ,Na_2CO_3, DMF; *v* NH_2OH, CH_3OH

The next step in the scheme, substitution of diethyl 1,3-propanedioate, corresponded to the first step in the synthetic scheme for **31** and **37.** It was assumed that substitution using the (methoxyphenyl)alkyl 4-methylbenzenesulphonates would proceed just as successfully under the same conditions. However, experimentation showed that the 4-methylbenzenesulphonates were not very soluble in ethanol so instead the reaction was performed in THF using sodium hydride as the base. The diethyl 2-((methoxyphenyl)alkyl)-1,3-propanedioates **50** to **53** were all prepared in good yield and purified by distillation at reduced pressure.

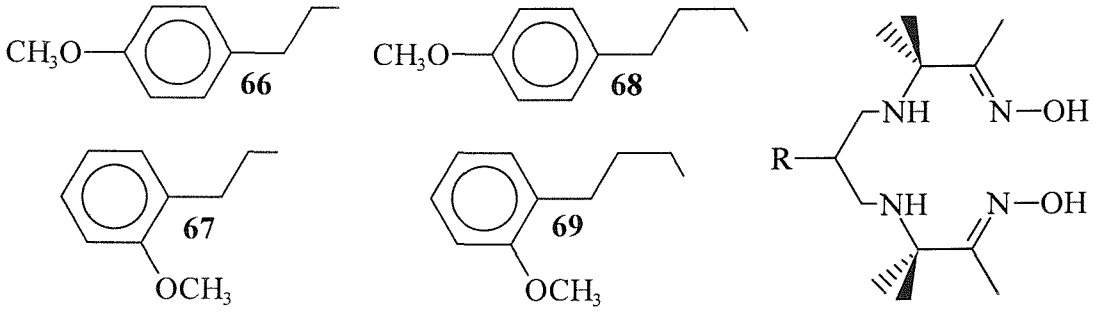
The substitution was also carried out using the bisalkyl sulphite (Figure 6.12) of the reaction involving **42** and thionyl chloride. The reaction proceeded in 65% yield when the sulphite was freshly prepared; in this way the sulphite was acting as an alternative to the desired chloride. In cases where preparation of the chloride, 4-methylbenzenesulphonate or other common leaving group derivative might not be possible it was thought that sulphites might prove to be viable alternatives.

Conversion of the substituted diesters to the corresponding diamides was initially attempted as before using methanolic ammonia and sodium methoxide. However, this method was only successful for one of the four analogues, 2-(2-(4-methoxyphenyl)ethyl)-1,3-propanediamide (**54**) which was purified by recrystallisation in good yield. The

remaining analogues were only converted to their half ester half amide derivative. It seems that changing the position of the ring substituent or increasing the length of the tether by one unit significantly decreases the solubility of the intermediate half ester half amide sufficiently that further substitution does not take place. A series of experiments was conducted to force the reaction to completion through the use of ultra-dry apparatus and solvents and by varying the amount and nature of catalyst present. The only significant variations in yield were observed when the solvent itself was changed. The choice of solvent for the reaction was a compromise since it had to be able to successfully solvate the starting materials and intermediates as well as dissolve a high concentration of ammonia gas. In general it was found that many solvents carried out either one or the other function but alcohols seemed to provided the most suitable compromise. Diamide **55** was eventually prepared in a mixture of ethanol and toluene, diamide (**56**) in 2-propanol and diamide **57** in a mixture of 2-propanol and toluene. All were recovered in poor yield and purified by recrystallisation.

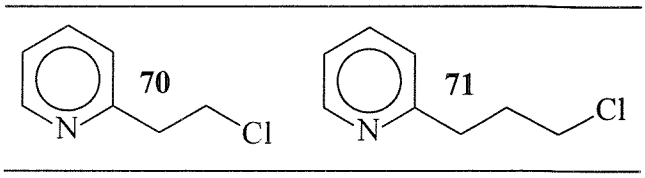
Reduction of the diamides to the corresponding diamines by borane in THF did not prove problematic. Since the reaction is carried out in refluxing THF the issue of decreased solubility did not arise. The diamines **58** to **61** were all prepared in good yield and purified by distillation at reduced pressure.

Alkylation of the diamines with **29** gave the diketones **62** to **65** in reasonable yield, each being recovered in good purity by column chromatography. The final step, oximation with hydroxylamine, again suffered problems resulting from the poor solubility of the substrates in methanol at room temperature. This was reflected in lower yields in comparison to the corresponding step for PnAOs **31** and **37**, **66** to **69** all being prepared in poor to moderate yields. These were each recrystallised to provide the desired products as white powders.



6.3.8 Pyridinylalkyl Chlorides

The remaining ethylene- and propylene-tethered targets were those which incorporated a pyridine moiety as the co-ordinating group. As with the (methoxyphenyl)alkyl derivatives the first task was preparation of the substituent groups as their chlorides.



2-(2-Pyridinyl)ethanol and 3-(2-pyridinyl)-1-propanol were converted into their corresponding chlorides with thionyl chloride. The inherently basic nature of the products meant that they were prone to decomposition. **70**[62] undergoes elimination to give 2-ethenylpyridinium chloride whilst **71**[64] rearranges to give 1,2-dihydro-3*H*-pyrrocolinium chloride[65] (Figure 6.13). To overcome this problem the products can either be stabilised by preparation and storage as the hydrochloride salt or they can be used immediately after preparation.

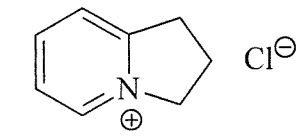


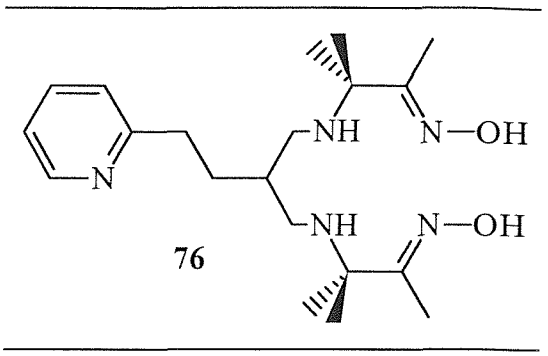
Figure 6.13 1,2-Dihydro-3*H*-pyrrocolinium chloride

In addition to preparation of the chlorides, an attempt was made to synthesise the 4-methylbenzenesulphonates of 2-(2-pyridinyl)ethanol and 3-(2-pyridinyl)-1-propanol. Since 4-methylbenzensulphonates are less prone to elimination than chlorides[66], and after previous experience with the (methoxyphenyl)alkyl derivatives, it was envisaged that the chlorides may have again been problematic but unfortunately, all attempts at preparing the 4-methylbenzenesulphonates were unsuccessful.

6.3.9 Pyridinylalkyl PnAO Ligands

As suspected from the base sensitivity of the chloride precursors, all attempts at substitution of diethyl 1,3-propanedioate succeeded only in catalysing the decomposition of the starting materials to either 2-ethenylpyridinium chloride or 1,2-dihydro-3*H*-

pyrrocolinium chloride. Alternatives routes to the 2-substituted diethyl 1,3-propanedioates had to be found.



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However, a method[67] for the substitution of diethyl 1,3-propanedioates with ethyl tethered pyridine units was found which exploits 2-ethenylpyridine as the electrophile and relies on the heterocyclic nitrogen as a charge sink which encourages nucleophilic addition at the unsubstituted double bond terminus. Diethyl 2-(2-(2-pyridinyl)ethyl)-1,3-propanedioate (**72**) was prepared in 45% yield (very good in comparison with the literature[67] yield of 26%) and purified by distillation at reduced pressure. A method for the preparation of diethyl 2-(3-(2-pyridinyl)-1-propyl)-1,3-propanedioate could not however be found and time did not permit further experimentation to devise a route to it.

Conversion of **72** to the corresponding diamide proceeded without the complications observed previously for other 2-substituted diethyl 1,3-propanedioates. The diamide (**73**) was provided in high yield and purified by recrystallisation and this was reduced to the diamine (**74**) in good yield, **74** being purified by distillation at reduced pressure. Alkylation of **74** with **29** gave 3,3,9,9-tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)ethyl)-2,10-undecanedione (**75**) in moderate yield. Purification by column chromatography provided **75** as the familiar light orange wax which was ~95% pure by ^{1}H NMR.

Oximation of **75** with hydroxylamine gave 3,3,9,9-tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)ethyl)-2,10-undecanedione dioxime (**76**) in poor yield. Problems arose during purification of **76** which was the first PnAO to be synthesised that was not a white powder. It could not be easily recrystallised being a low melting solid (~25 °C) but ^{1}H NMR indicated that the sample was ~85-90% pure.

6.3.10 Enhanced PnAO Ligands with $-OCH_2CH_2-$ Tethers

It was suspected that the target ligands incorporating an ether functionality at the junction of the PnAO backbone and the tether would have to be synthesised in a slightly different way from that used for their C-linked analogues. Since conventional substitution of diethyl 1,3-propanedioate was not possible, alternative three-carbon synthons (Figure 6.15) were sought that could be elaborated and ultimately end up as the propylene bridge of the PnAO skeleton. Two possible schemes were investigated both of which were based on the alcohol derivatives of the proposed substituents (Figure 6.14).

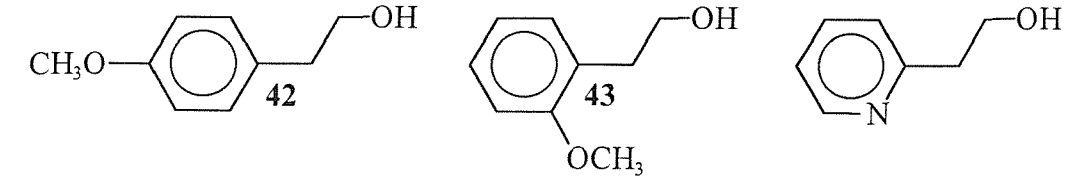


Figure 6.14 Alcohol Precursors for $-OCH_2CH_2-$ Tethered Targets

A method[68] was found for nucleophilic substitution at C_2 of diethyl 1,3-propanedioate. This involved reaction with bromine[69] to give diethyl 2-bromo-1,3-propanedioate (77) followed by substitution of the bromide for an alkoxide. The second possible method involved the use of 1,3-diamino-2-propanol. Deprotonation of the hydroxyl group would allow the fragment to act as a nucleophile and substitute the chloride or 4-methylbenzenesulphonate of the precursor in a similar manner to diethyl 1,3-propanedioate. Alternatively, conversion of 1,3-diamino-2-propanol to the methylsulphonate would allow it to act as an electrophile and be substituted by the deprotonated alcohol in a reaction similar to that using diethyl 2-bromo-1,3-propanedioate. Due to the potential problem of polysubstitution in such a species it was envisaged that the amine functions would require prior protection.

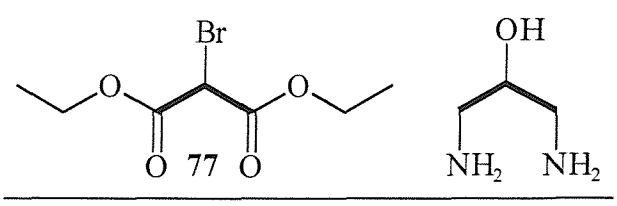


Figure 6.15 Alternative 3-Carbon Synthons

Diester (77) was prepared in high yield and purified by distillation. An attempt was made to substitute **77** with 2-pyridinylethanol following the literature procedure.[68] 2-pyridinylethanol and **77** were combined in dry acetone and a suspension of potassium carbonate, after refluxing the reaction yielded only a dimer of diethyl 1,3-propanedioate (Figure 6.16). The reaction was repeated at differing temperatures and also in the absence of base but the only detectable product was the same dimer. It was thought that the competitive substitution and elimination was occurring much faster than the intended substitution so the reaction was repeated using sodium hydride in THF to deprotonate to alcohol.

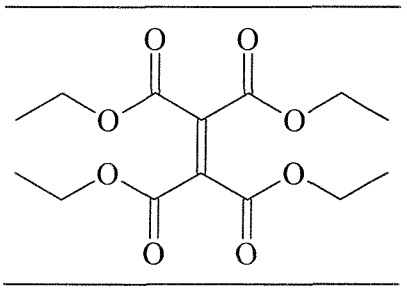


Figure 6.16 Diester Dimer

Slow addition of the deprotonated alcohol to **77** and vice-versa had the inevitable effect of speeding up the undesired dimerisation. It was reported[68] that the use of butanone as a solvent could considerably assist the promotion of the desired substitution over dimerisation but time did not permit further experimentation.

The use of 1,3-diamino-2-propanol in the preparation of PnAO derivatives has been studied previously.[70] Alkylation of the hydroxyl group provides the diamine which can then be alkylated and converted by oximation to the product PnAO. An initial attempt was made to alkylate 1,3-diamino-2-propanol with **70** by deprotonating the hydroxyl group with sodium hydride in THF. However, instead of the intended substitution taking place, base-catalysed elimination occurred preferentially to give 2-ethenylpyridine.

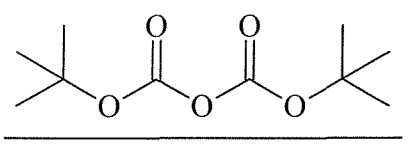
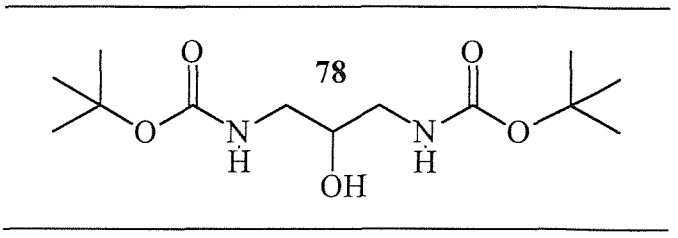
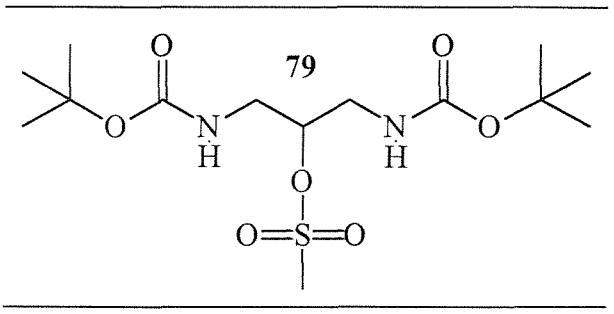


Figure 6.17 "BOC Anhydride"

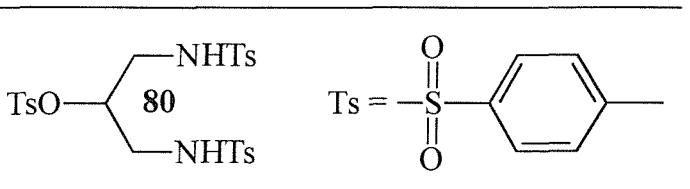
Following the described procedure, preparation of the methylsulphonate derivative was preceded by protection of the two amine functionalities with "di-*t*-butyl dicarbonate" (Figure 6.17). The dicarbamate **78** was prepared in very high yield and purified by recrystallisation.



Conversion of **78** to the methylsulphonate with methylsulphonyl chloride proceeded with similarly high yield to provide the BOC-protected methylsulphonate **79** which was also purified by recrystallisation.



A precursor analogous to **79** was also prepared in which 2-hydroxy-1,3-propanediamine was protected as the *N,N',O*-tris-4-methylbenzenesulphonate (**80**) in moderate yield and purified by column chromatography.



80 provides identical functionality to **79** but was prepared in only one step, it was thought however that deprotection of the sulphonamide would not be as facile as that for the carbamate. It was intended that **80** would be used in parallel with **79** to see which was the more suitable for substitution at the 2-position.

The first attempted substitution involved **79** and 2-pyridinylethanol. The alcohol was deprotonated using sodium hydride in THF and the resulting mixture was slowly added to a solution of **79**. After overnight stirring at room temperature there was no reaction and time did not permit an investigation of different reaction conditions. Substitution of the *N,N',O*-tris-4-methylbenzenesulphonate **80** was not attempted for the same reason.

6.4 Complex Stability Studies

The use of oxonol dyes as extraction indicators has not previously been examined in any detail. Existing work from within the research group was carried out using impure samples of mainly group I metal oxonols. For this reason the use of oxonol dyes as extraction indicators had to be validated. The first set of experiments was performed using the slightly impure dyes prepared by the one-pot multiple condensation reaction. The dyes prepared included the *N*-ethyl oxonol salts of lithium, sodium, potassium, magnesium, calcium, cobalt(II) and copper(II). The magnesium, calcium and copper(II) oxonols were too impure for even a preliminary study so the study began using the lithium, sodium, potassium and cobalt(II) derivatives. Assessment of the dyes during extraction-related processes was to be by measurement of the UV/Visible spectra of the relevant solutions, the procedure used to determine further thermodynamic data being adopted from the work of Cram[43] and used without modification. The Appendix (section 9.1) contains a note of the associated constants (K_d, K_e, K_a and ΔG_a).

6.4.1 UV/Visible Characteristics

Lithium, sodium, potassium and cobalt(II) oxonol were dissolved in pure water at a concentration of 1.0×10^{-5} M. These standard solutions allow the direct determination of the UV/Visible region peak maxima (λ_{max}) and the corresponding extinction coefficients (ε_{max}).

6.4.2 Partition Experiments

Dichloromethane was chosen as the organic solvent and from this the partition constant (K_d) was calculated. 10 mL of oxonol solution was added to 10 mL of DCM and the mixture was shaken for 10 minutes. After a separation time of 10 minutes triplicate aliquots of the aqueous phase were removed and tested.

6.4.3 Extraction Experiments

Using the same stock solutions, the dyes were extracted into equimolar solutions of three different crowns: tetra-aza-14-crown-4 (**A**), dibenzo-18-crown-6 (**B**) and tetrathia-14-crown-4 (**C**) (Figure 6.18). The experiments were otherwise identical to the partition experiments and from them it was possible to determine the extraction constant (K_e).

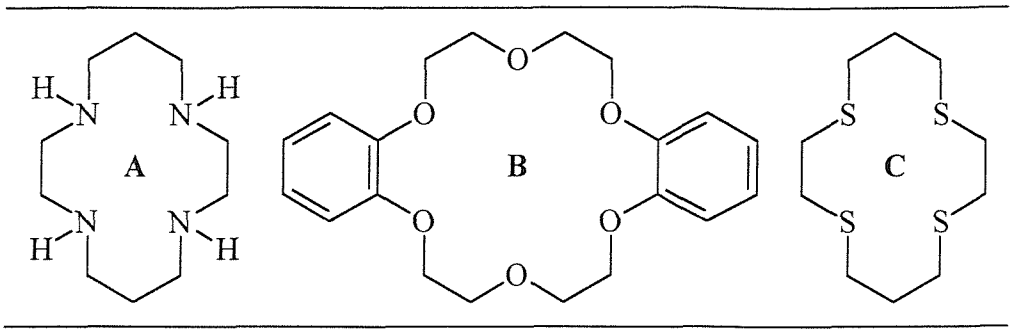


Figure 6.18 Crowns used in Preliminary Extraction Experiments

6.4.4 Results

The data do not directly provide any useful information but can be manipulated to the give standard thermodynamic constants such as the association constant K_a (Table 6.3). This allows a direct comparison of the results with published figures. Of particular value is a reference work by Izatt and co-workers[71] which reports extensively on a wide range of cations and macrocyclic ligands. It contains a nearly exhaustive list of all of the reported macrocycle-based extraction experiments and provides information such as binding affinities and the corresponding thermodynamic data. This report was used as a comparison for all of the results determined in this project.

A summary of the data collected for the experiments is given in Table 6.2. A number of assumptions were made about the extraction process: i) that there was stoichiometric cation to crown binding; ii) that the dyes were fully ionised in the aqueous phase; and iii) that the extraction of polyationic species was accompanied by UV active dye anions only. Moving from lithium to potassium, the value of the constants should be similar but that for cobalt(II) should be different as a result of it being dicationic. The partition constant (K_d) for sodium oxonol is three orders of magnitude lower than those for sodium and potassium oxonol so it was clearly not behaving as it should be, probably because the dye salt was very impure.

		Li Oxonol	Na Oxonol	K Oxonol	Co(II) Oxonol
ε_{max} ($dm^3mol^{-1}cm^{-1}$)		1.20 ±0.01 x 10^5	1.30 ±0.01 x 10^5	8.06 x ±0.01 10^4	1.04 ±0.01 x 10^5
K_d (M^{-1})		2.92 ±0.45 x 10^4	6.97 ±1.05 x 10^2	6.48 ±0.81 x 10^5	5.82 ±0.86 x 10^9 M^{-2}
K_e (M^{-2})	A	5.86 ±1.35 x 10^{11}	2.67 ±0.53 x 10^{11}	1.65 ±0.38 x 10^{12}	1.31 ±0.29 x 10^{16} M^{-3}
	B	1.44 ±0.35 x 10^{10}	7.87 ±1.75 x 10^9	1.23 ±0.25 x 10^{11}	3.07 ±0.83 x 10^{14} M^{-3}
	C	7.70 ±1.52 x 10^9	---	2.26 ±0.57 x 10^{10}	9.05 ±2.08 x 10^{14} M^{-3}

Table 6.2 Observable data for impure oxonol dyes ±SD

The results (Table 6.3) show that in some cases the cation binding constants obtained using oxonol dye salts are in very good agreement with the literature figures but in others the figures are a long way out. In particular the association constants (K_a) derived for sodium oxonol are about two orders of magnitude higher than those for lithium and potassium oxonol. This was to be expected following the low partition constant observed for sodium oxonol. In some cases there were no data available for comparison and for others the data had been determined by various other, non-extraction based, methods.

		Li Oxonol	Na Oxonol	K Oxonol	Co(II) Oxonol
K_a (M^{-1})	A	2.01 ±0.77 x 10^7	3.83 ±1.34 x 10^8	2.55 ±0.91 x 10^6	2.26 ±0.83 x 10^6
	B	4.93 ±1.96 x 10^5	1.13 ±0.42 x 10^7	1.89 ±0.62 x 10^5	5.28 ±2.21 x 10^4
	C	2.64 ±0.93 x 10^5	---	3.48 ±1.31 x 10^4	1.55 ±0.59 x 10^5
ln K_a (Lit.[71])	A	16.86 (16.21)	19.76 (---)	14.75 (---)	14.63 (29.27)
	B	13.11 (10.36)	16.24 (16.35)	12.15 (17.78)	10.87 (6.68)
	C	12.48 (---)	--- (---)	10.46 (---)	11.95 (---)

Table 6.3 Thermodynamic data calculated from K_e and K_d ±SD

Where possible the literature figure included is from an extraction experiment (usually the di- or trinitrophenoxide) but the published figures vary wildly for a given system depending on the nature of the determining experiment. However, considering the impure nature of the dyes, the tests showed that the oxonols did present a possibility for developing self-indicating extraction experiments without recourse to trinitrophenoxides.

Immediately following the success of the preliminary experiments an attempt was made to extract oxonol dyes into a solution of PnAO (**25**). Unfortunately **25** was not soluble in DCM so it was thought that an investigation into the use of different organic solvents would help. Firstly, however, it was important to determine whether or not the oxonols were suitable as extraction indicators.

6.4.5 Mixed Metal Extraction Experiments

In order to produce impurity free solutions of the oxonols it was decided to attempt mixed metal extractions. Since lithium *N*-ethyl oxonol (**11**) was 100% pure it was used as the basis for preparing solutions of technetium mimic oxonols. This was to be achieved by mixing **11** with the salt of a technetium mimic which it was hoped would be preferentially bound by the target ligand. However, previous work had indicated the fact that oxonol dyes in solution may be aggregated. To test this theory an aqueous solution of **11** was prepared, serial dilutions of which were used to determine whether or not ε_{max} remained the same at different concentrations. The solution was diluted in tenfold steps between 1.0×10^{-3} and 1.0×10^{-7} M during which time the apparent ε_{max} for each concentration was increasing. This meant that the absorbance was changing only slightly in response to large changes in concentration, typical behaviour of an aggregated system. But since the extraction experiment protocol calls for samples from the organic phase to be removed and tested, an experiment to determine the nature of the dye in DCM was sought. **11** was the most aqueous soluble of the oxonols which had been prepared and it was also the most organic soluble. It was not however soluble in DCM at a concentration of 2.0×10^{-4} M so a 25x excess of 15-crown-5 was added to assist solvation. The final dye concentration was 8.0×10^{-5} M which was of a similar order of magnitude to the maximum usable aqueous concentration of oxonol dye. Serial dilutions were made and the resultant solutions tested.

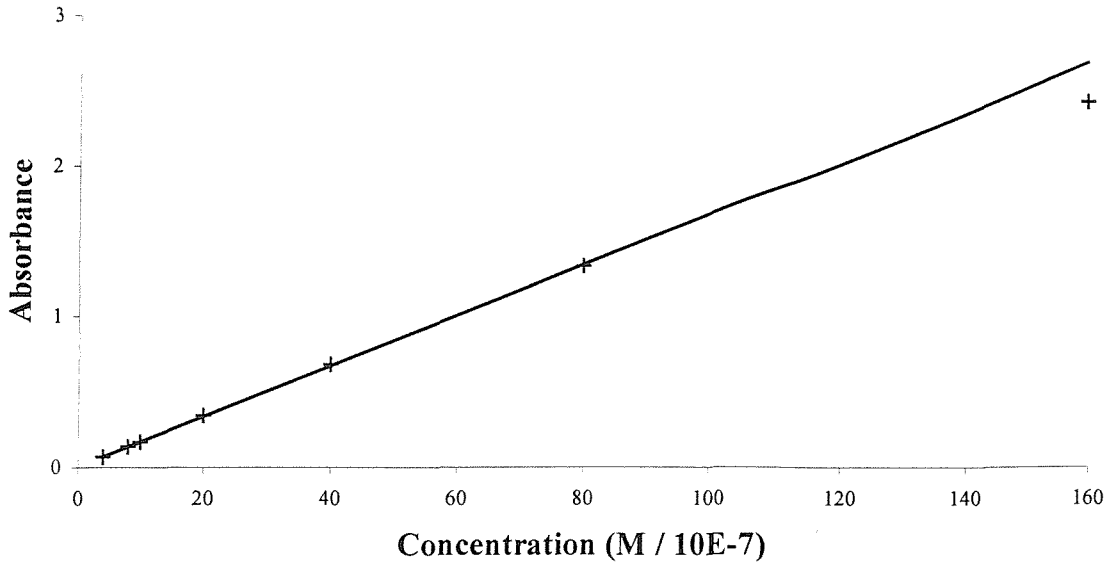


Figure 6.19 Plot of Absorbance versus Concentration for **11** in DCM

A graph of the results (Figure 6.19) showed that the relationship between absorbance and concentration was linear over most of the concentration range considered. The highest concentration (1.60×10^{-5} M) had an apparently lower absorbance than it should, this evidence suggested that aggregation was taking place. The result however, showed that as long as the concentration of the dye in the organic phase of an extraction system was less than 8.0×10^{-6} M it could be reliably used to determine the extraction constant. Since the maximum concentrations of the aqueous stock solutions of oxonols were 1.0×10^{-5} M, it would require over 80% extraction for the results to be affected through direct measurement of the organic phase. If this happened to be the case then an aliquot of the organic phase could be diluted to bring the concentration below the aggregation threshold limit. From the data, ε_{max} was calculated (Table 6.4).

11 was also partitioned into DCM in quadruplicate so that the K_d could be determined. The partition behaved reproducibly and from the previously determined ε_{max}, K_d was calculated (Table 6.4).

Cobalt was chosen as an example of a technetium mimic in order to test the theory. An aqueous solution was made up containing **11** (2.0×10^{-5} M) and cobalt(II) chloride (1.0×10^{-5} M). This was also partitioned into DCM and K_d calculated.

Both sets of solutions were then extracted into a DCM solution of tetra-aza-14-crown-4 at a concentration of 1.0×10^{-5} M. For each experiment K_e and subsequently K_a were calculated (Table 6.4).

	E_{max} ($dm^3mol^{-1}cm^{-1}$)	K_d (M^{-1})	K_e (M^{-2})	K_a (M^{-1})	ln K_a
11	$1.67 \pm 0.01 \times 10^5$	$5.78 \pm 0.97 \times 10^2$	$3.18 \pm 0.75 \times 10^8$	$5.50 \pm 2.22 \times 10^5$	13.22
11+$CoCl_2$	$1.68 \pm 0.01 \times 10^5$	$6.70 \pm 1.00 \times 10^7$	$1.3 \pm 0.33 \times 10^{14}$	$1.54 \pm 0.72\ 10^6$	14.25

Table 6.4 Results of mixed metal extraction experiments ±SD

The results were calculated on the assumption that the behaviour of the dye in DCM was cation independent. Hence ε_{max} calculated for the DCM solution of **11** was used for the mixed metal solution.

The association constant (K_a) for **11** is very similar to that determined during the preliminary extractions (Table 6.3) as would be expected. This was also very close to the published figure. The result for the mixed metal extraction is very similar to the value determined previously but was still very different from the published data[71] for Co(II). More importantly however the result is not significantly different from the extraction of **11**. There are two possible reasons for this:

1) Assuming that cobalt is being extracted preferentially, the extracted species may be different from the expected e.g. it may be that only one oxonol anion is being extracted with the dicationic cobalt, the charge balance being made up by chloride. Even accounting for this by doubling the calculated concentration of extracted cobalt the numbers just did not match up.

2) Alternatively the more organic soluble **11** is being extracted purely as a consequence of its solubility rather than by any specificity of the host. Literature to date suggests that tetra-aza-14-crown-4 binds cobalt far more favourably than lithium. For this reason it was concluded that host specific extraction from mixed metal oxonol systems was not possible.

A time based extraction was also performed to gain an understanding of the kinetics of the system. Aliquots of the organic phase of a mixed metal extraction experiment were taken over twenty minutes to determine when, if at all, the system came to equilibrium (Figure 6.20).

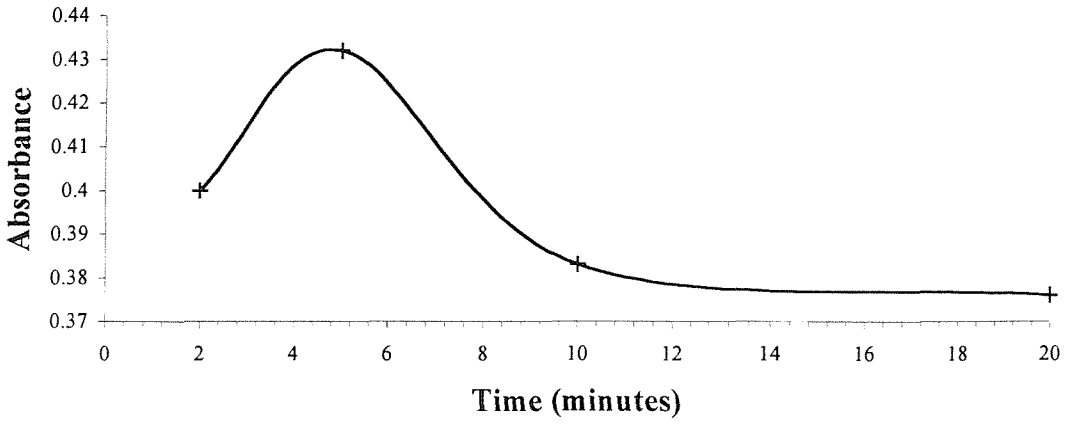


Figure 6.20 Plot of absorbance versus time for mixed metal extraction experiment

The results of the mixed metal extraction experiment showed that the system reached an absorbance maximum at approximately 5 minutes after which time the absorbance quickly dropped. It was possible that the extraction system was binary in nature, initially the lithium may have bound kinetically to the host giving rise to the absorbance maximum. Competing with this trend would be binding of the thermodynamically stable cobalt which it was presumed would have eventually given rise to a new, stable absorbance for the cobalt-host complex. Alternatively it was possible that the oxonol was being bleached by reaction with the host. The highly conjugated nature of the dye makes it very susceptible to attack by electrophiles, this was intended since the original role of the dyes was as backing layers for photographic film[45,46]. For that application it was important that the dyes could quickly and easily be bleached by agents such as thiosulphate. In the present case such a reaction would occur with the secondary amines of the host. In either case, binary competition or bleaching, an unknown factor was being introduced which rendered the experiment irreproducible and therefore unsuitable.

6.4.6 Extraction Experiments with Pure Oxonols

With pure samples of *N*-ethyl oxonols based on copper(II), cobalt(II) and manganese(II)

(**9**, **10** and **17**) it was possible to repeat the extraction experiments without complications. Aqueous stock solutions of **9**, **10** and **17** were prepared at a concentration of 1 x 10^{-5} M and their UV/Visible properties were determined. It was discovered that these dyes displayed aggregation behaviour as had **11** so their UV/Visible properties in DCM were investigated. Using the previously established procedure the dyes were solubilised in DCM by the addition of a 25-times excess of crown ether and found to show no evidence for aggregation (Figure 6.21). It was noted that the extinction coefficient (given by the gradient) for each species was markedly different in DCM. This suggests that the earlier assumption that the behaviour of oxonol dyes was cation independent in DCM was wrong. It was also noted that after a few days the blue DCM solutions bleached to a pale green colour. Aqueous solutions at identical concentrations differed very slightly in their absorbance probably because the oxonol anion is then not cation associated.

The next step was to partition the dyes between water and DCM in order to assess their solubility in the organic phase with no ionophore host present. With **9**, **10** and **17** being soluble in water at only very high dilution it was suspected that very little would partition into an organic solvent. There was no detectable concentration of dye in the organic phase which, although a situation which is ideal for this kind of experiment, meant that the partition constant (K_d) and the association constant (K_a) could not be determined.

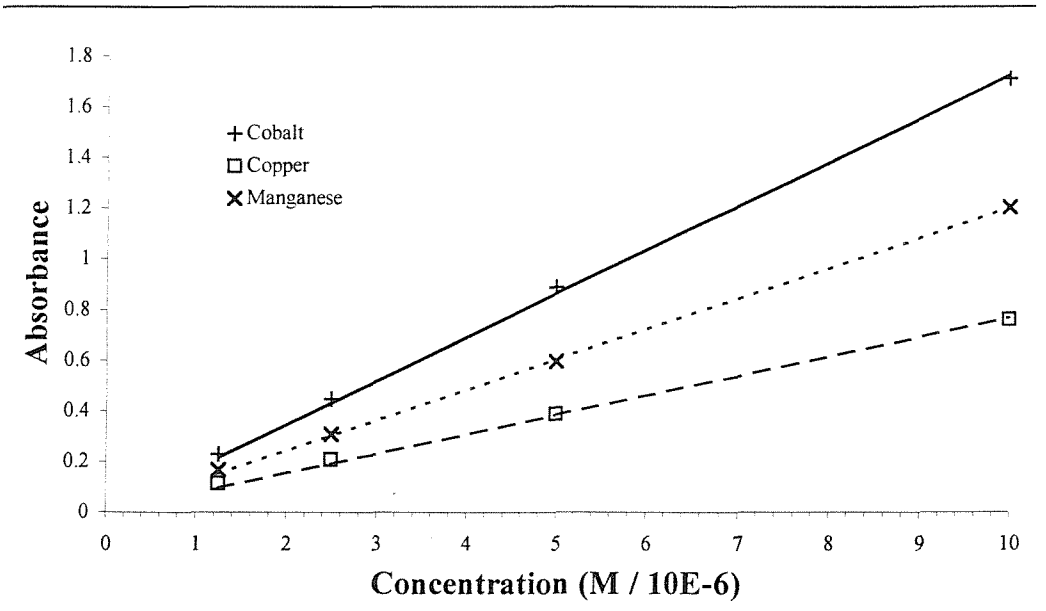


Figure 6.21 Plot of Absorbance versus Concentration for **9**, **10** and **17** in DCM with added dibenzo-18-crown-6.

	Manganese	Cobalt	Copper
Extinction Coefficient ε_{max}	$1.20 \times 10^5 \pm 925$	$1.72 \times 10^5 \pm 1474$	$7.65 \times 10^4 \pm 1219$
Extraction Constant K_e	$3.33 \pm 0.32 \times 10^{11}$	$9.27 \pm 1.04 \times 10^{10}$	$2.51 \pm 0.25 \times 10^{11}$

Table 6.5 Data for pure oxonol extraction experiments ±SD

To avoid the complication of bleaching by free amine bases, the first extraction experiments to be carried out were performed using dibenzo-18-crown-6. 1×10^{-5} M aqueous solutions of **9**, **10** and **17** were extracted into 2×10^{-2} M crown ether DCM solutions. Blue colour was transferred to the organic phase, the aqueous phase remained purple and there was no precipitate present at the interface. The extraction constant (K_e) was calculated for each of the experiments (Table 6.5).

The extraction experiments were performed in quadruplicate and proved to be very reproducible. Without being able to determine the partition constants and hence the association constants, the results were not directly comparable with published results. They would, however, form a useful reference for future work assuming that it was all carried out in the same solvents and with identical concentrations of dye and host. The results showed that Mn(II), Co(II) and Cu(II) all behaved very similarly which would be expected for those particular cations, this was further evidence that the oxonol dyes were behaving as ideal extraction indicators.

The dibenzo-18-crown-6 experiment was repeated using tetra-aza-14-crown-4. At concentrations on a similar order of magnitude to the dyes (1×10^{-5} M), the experiments yielded a blue precipitate at the solvent interface which appeared to slowly dissolve back into the aqueous phase over the course of an hour. During the preliminary round of extraction experiments this problem of precipitation was overcome by using a higher ratio (100x excess) of crown. When repeated with the pure samples of **9**, **10** and **17** nearly all of the blue colouration moved into the organic phase but was quickly bleached at a rate that appeared to be accelerated by UV/Visible spectroscopy. This meant that the experiments could not be repeated and so were of little use.

A similar problem was encountered when the same extraction was repeated with PnAO (**25**). A blue precipitate was formed at the interface which did not slowly dissolve back

into the aqueous phase as had been observed for tetra-aza-14-crown-4. With a 100x excess of **25** only a very little blue colour was transferred to the organic phase but it did not appear to be readily bleachable. Time did not allow for an investigation of different extraction conditions which may have provided a more suitable organic solvent.

6.4.7 Radioactive Metal Extraction Experiments

The lack of success thus far with using oxonols as extraction experiment indicators led to the investigation of the employment of radioactive metals in their place. Ultimately ^{99m}technetium would be the radionuclide used for imaging and although this was available it was thought desirable to use radionuclide isotopes of the technetium mimics (manganese, cobalt and copper). ^{57}Co was chosen because it is a low energy γ-emitter and relatively safe to handle. The use of ^{57}Co acts as a bridge between concentrations of cobalt oxonol (1×10^{-5} M) and the much lower concentrations of available ^{99m}Tc (~ 1×10^{-8} M).

Whereas oxonol salts act as extraction indicators for large scale experiments, the inherent activity of the radionuclide can be used to assess the degree of metal transfer in micro extractions. The use of radioactivity as an extraction indicator is more reliable than inactive oxonols because it determines the amount of metal present directly. UV/Visible spectroscopy determines oxonol concentration which can be related to metal concentration only if the assumption is made that the oxonol anion remains associated with metal cation. Results gained from the use of $^{57}CoCl_2$ should be identical to those from cobalt(II) *N*-ethyloxonol (**10**) assuming:

1) Extraction is anion independent.
2) Extraction is concentration independent.

and 3) The cobalt species are chemically identical.

The nature of the extractions was identical to those carried out with metal oxonol salts, the full details of each is given in the experimental. An aqueous solution of $^{57}CoCl_2$ was shaken with a chloroform solution of ligand. A potential problem was envisaged in that the active material was supplied in an aqueous solution of 0.01 M hydrochloric acid. Since manipulation of the radioactive material is cumbersome and to some degree blind, the extractions were carried out under acidic conditions to see what sort of results would be

obtained (if necessary it would be possible to neutralise the stock solution for future experiments). Typically the experiments involved 2 mL each of water and chloroform, 100 - 500 μL aliquots being withdrawn for testing. The activity of each phase was determined using a γ-counter calibrated for determining the activity of ^{57}Co samples, the Appendix (section 9.2) contains a discussion of the error analysis involved in the counting procedure. The results are summarised in Table 6.6.

Experiment	Aqueous Activity	Organic Activity	% Extraction
1	2745778 ± 0.12%	764 ± 7.24%	0.028 ± 0.002
2	2347921 ± 0.13%	29984 ± 1.56%	1.261 ± 0.021
(20 minutes extra shaking)	(2349258) ± 0.13%	(8280) ± 2.20%	(0.351) ± 0.008
3	2541506 ± 0.13%	33054 ± 1.10%	1.284 ± 0.016
(buffered to pH 7.4)	---	(5076) ± 2.81%	(0.197) ± 0.006
4	2619363 ± 0.13%	20660 ± 1.39%	0.783 ± 0.012
5	2916148 ± 0.12%	1616 ± 4.98%	0.055 ± 0.003
6	2726227 ± 0.12%	8652 ± 2.15%	0.316 ± 0.007
(activity added before water)	(2951682) ± 0.12%	(3800) ± 3.24%	(0.129) ± 0.004

Table 6.6 Results of Extraction Experiments using Radioactive ^{57}Co. Figures quoted are counts per second (cps).

Experiment 1 Partitioning of $^{57}CoCl_2$

2 mL each of water and chloroform were mixed and 10 μL of $^{57}CoCl_2$ solution was added. The mixture was shaken for 10 minutes and then left to settle for 5 minutes. 500 μL of each phase was removed and placed in a counter for determination of activity. The result indicated that virtually none of the salt was partitioned into chloroform.

Experiment 2 Extraction into tetra-aza-14-crown-4

As experiment 1 except $^{57}CoCl_2$ was extracted into an equivalent concentration of tetra-aza-14-crown-4 in chloroform. After initial sampling the system was shaken for a further 20 minutes then a second sample was removed and counted. There was very little extraction of active cobalt. After further shaking the extraction ratio decreased whereas it would have been expected to have either increased or remained the same. This may have reflected a change in the sensitivity of the counting apparatus. The correct alignment of samples in the counter by the automated feeder may also have contributed to the difference. Another possibility was handling errors associated with manipulating very small quantities of radioactive liquid (10 μL).

Experiment 3 Extraction into an increased concentration of tetra-aza-14-crown-4

Experiment 2 was repeated with 3 mL phases and a 10-fold excess of crown. After samples were taken an excess of sodium phosphate buffer (pH 7.4) was added to neutralise the acid and decrease ligand protonation thus increasing cobalt uptake.The increased crown concentration led to an increase in cobalt extraction which should reduce errors. However, the observed increase was very slight. After buffering it was again noted that the extraction ratio had decreased possibly as a result of the addition of excess sodium to the extraction system. Competition between the two metals for binding by cyclam would have favoured sodium by virtue of its much increased concentration over ^{57}Co.

Experiment 4 Extraction of Co(II) oxonol (**10**) into tetra-aza-14-crown-4

As experiment 3, a 1 x 10^{-5} M solution of cobalt *N*-ethyl oxonol (**10**) was extracted into a 10-fold excess of tetra-aza-14-crown-4. The same experiment was repeated with the addition of a spike of $^{57}CoCl_2$. Visually half of the purple aqueous colour was transferred to the organic phase. The assumption was made that this represented a movement of **10** into the organic phase. After spiking, the active and inactive cobalt cations should both be extracted to the same degree assuming equal mixing. Although considerable blue colouration was transferred only 0.783% of the activity was extracted. This result possibly indicated that active cobalt was not freely exchanged with the inactive cobalt and that there was a solubility problem with the active cobalt source. More likely however was that the oxonol anion was being protonated at the low pH conditions and had dissolved in the organic phase.

Experiment 5 Extraction into dibenzo-18-crown-6

It was suspected that protonation of tetra-aza-14-crown-4 was hampering efforts to extract cobalt. To avoid this experiment 4 was repeated using dibenzo-18-crown-6 at a 4000-fold excess. The active cobalt was only 0.055% extracted even though half of the blue oxonol colour had been transferred to the organic phase. The persisting problem of both ligand and oxonol protonation probably explain the poor result.

Experiment 6

The extraction of ^{57}Co into dibenzo-18-crown-6 was performed under forcing conditions. A 545,777 : 1 excess of crown ether was used. In addition the reaction conditions were

varied by first adding the active spike to the crown ether solution, shaking, and then adding the aqueous phase and extracting as normal. An increase in extraction was noted compared to experiment 5 but it was only slight and well within the apparent errors of the experiment. Under such forcing conditions it is reasonable to assume that all of the active cobalt would be extracted. When the active cobalt solution (10 μL) was added to the crown solution and shaken before the addition of water still very little extraction took place.

To prove that the pH of the extraction system was the likely cause of the poor results obtained, two further experiments were performed. Solutions of tetra-aza-14-crown-4 and PnAO (**25**) were made up in 0.1 M HCl and to them was added a spike of $^{57}CoCl_2$. The solutions were stirred rapidly in the presence of a pH probe and titrated with aliquots of 0.1 M sodium hydroxide. Samples of the solution were taken when appropriate and spotted directly onto ITLC paper. These papers were then chromatographed in saline which separated bound radionuclide from the free radionuclide (this latter did not move from the baseline). The papers were dried, cut in half and the radioactive count of free and bound ^{57}Co was determined for each sample. An overlay plot was drawn showing both the pH of the system and the percentage of bound activity (RadioChemical Purity, RCP) plotted against the volume of added base. The plots for tetra-aza-14-crown-4 (Figure 6.22) and PnAO (Figure 6.23) both indicated that as the pH increased, so did the percentage of bound radionuclide as expected.

The results of the extraction experiments carried out using $^{57}CoCl_2$ suggested that it would be possible to assess the degree of extraction by measuring the activity of the two phases directly. Equally, however, it was made very clear that in order to achieve this, any active metal sample would first have to be neutralised to avoid ligand protonation. The method of neutralisation would have to be considered carefully because the introduction of different cations to the system may have an unquantifiable effect. For this reason it was considered that addition of inactive $Co(OH)_2$ would be appropriate. Since the active and inactive cobalt nuclides would be chemically equivalent a measure of the extraction of activity would also be an exact measure of cobalt distribution.

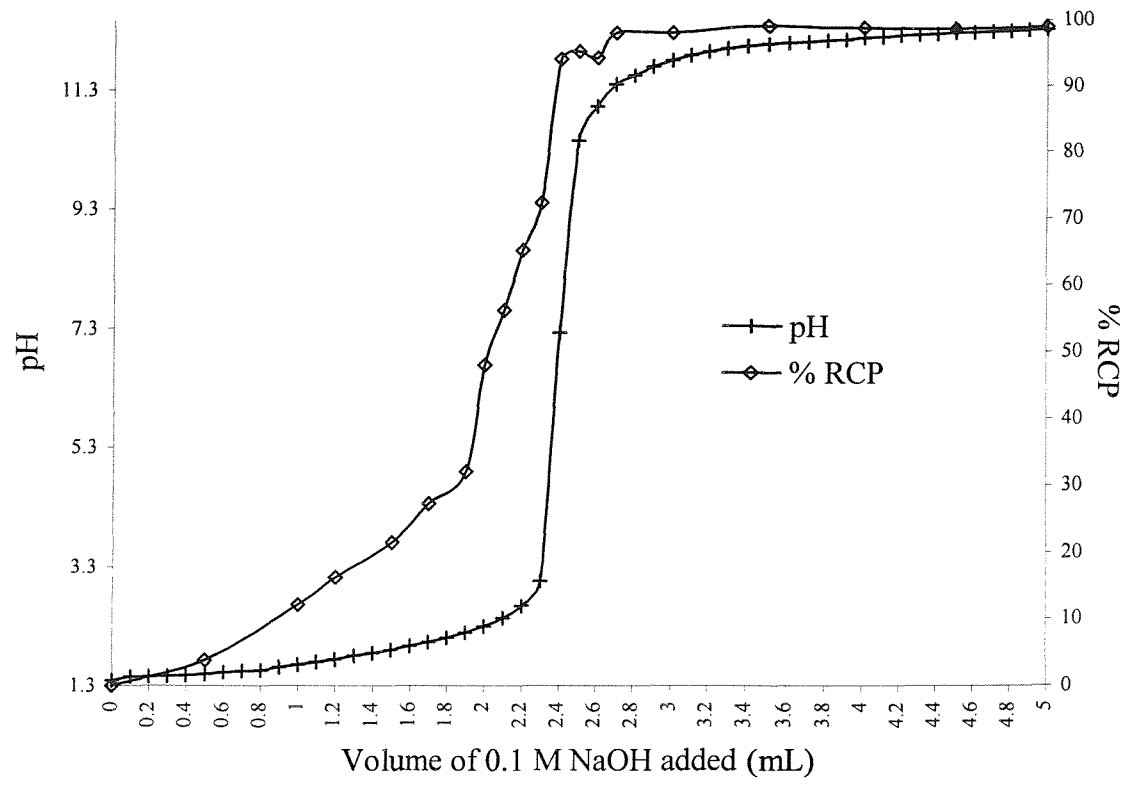


Figure 6.22 Plot of pH and % RCP for tetra-aza-14-crown-4 and $^{57}CoCl_2$

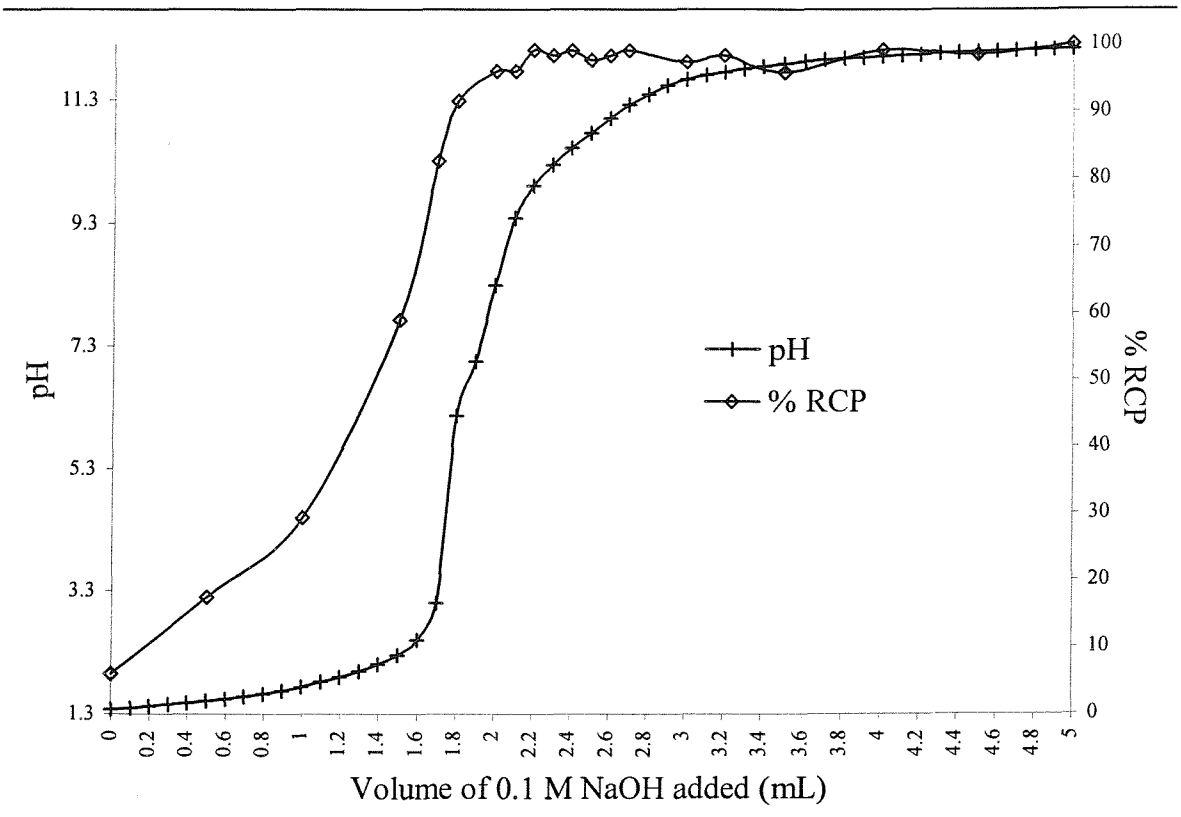


Figure 6.23 Plot of pH and % RCP for PnAO and $^{57}CoCl_2$

6.5 Crystallographic Studies of PnAO Complexes

The modelling of ligands is an excellent tool for gaining an improved understanding of the consequences of modifications to a ligand structure in order to achieve a specific goal such as enhanced complexation through the addition of extra co-ordinating groups. However, once a new ligand design has been synthesised one excellent test of its ability to further interact with its guest is to examine its crystal structure. X-ray crystallography has featured prominently in the published literature relating to PnAO ligands. Many different metallic cations and various co-ordinating anions have been employed to further the understanding of the behaviour of this ligand class. Particular studies have focused on determining the optimum length of the apical methylene chain unit and the effect of this on the strength of the hydrogen bond. There has however, been very little published X-ray structural work concerning modified PnAO ligands, much higher priority being given to the investigation of the stability of the potential ^{99m}Tc radiopharmaceutical in the body in order to push the complex through the rigorous proceedings of medical usage approval. X-ray crystallography is however the decisive tool for determining whether or not the complex formed between a cation and a novel PnAO ligand is binding through its extra co-ordinating group and thereby gaining an improved insight into any stability changes observed.

6.5.1 Precursors For Complexation Studies

The chemistry of PnAO ligand complexes has much in common with that of tetra-aza-14-crown-4. Precursors are prepared whereby the metal is complexed with the ligand as its chloride. Such preparations use the inexpensive metal chloride and are performed on a relatively large scale thus making purification simple. The complex chlorides made in this way often provide enough information about ligand behaviour but the chloride ion can be a problem as it is a co-ordinating anion. For projects such as the present one the co-ordination of the extra donor group to the cation is through the same site occupied by the chloride ion. In order to optimise this interaction the chloride can be replaced by a non-co-ordinating anion thus leaving the cation free for further intracomplex binding. An initial study of both PnAO and tetra-aza-14-crown-4 binding of cobalt was undertaken. The chlorides of the two complexes were prepared according to literature procedures to give Co(III)(PnAO)Cl_2[72] and [Co(III)(cyclam)Cl_2]Cl[73] in good yield. The oxidation of cobalt in PnAO complexes occurs in air at room temperature and has been observed in all of the

known cobalt-PnAO complexes.

6.5.2 Crystallographic Studies of Novel PnAO Ligand Complexes

After the preparation of 6-benzyl PnAO (**37**) a series of models of the complex were created. Using both CPK models and the Cache[59] molecular modelling suite, an attempt was made to predict where on the ligand extra co-ordinating groups should be added to enhance its complexation ability. To give further weight to the model studies it was decided to grow crystals of the complex salts of **37** starting with cobalt and copper. Not only would this provide two new species for examination and proof that the binding model was correct but it would also give a valuable insight into the preparation of crystals suitable for X-ray crystallography. This latter point was very important since upon the synthesis of any new, enhanced ligands the best way to determine whether or not the extra donor group was co-ordinating or not to the cation in the complex would be by use of X-ray crystallography. The Appendix (section 9.3) contains further information regarding the collection and processing of all data relating to the following structures.

The chloride precursors [Co(III)BnPnAO]Cl_2 and [Cu(II)BnPnAO(H_2O)]Cl of the intended complexes were prepared as described[72] and from those the target complexes were prepared with suitable non-co-ordinating anions.

The cobalt complex of **37** was crystallised as its nitrite salt. Following a method[72] used to prepare the similar complex Co(III)PnAO(NO_2)$_2$, an aqueous solution of the dichloride was made basic by the addition of potassium hydroxide and to this was added an excess of potassium nitrite. After stirring, the mixture was acidified to pH 5 by the addition of dilute HCl and heated at 50°C for 30 minutes during which time a dark orange solid precipitated. The product was filtered and recrystallised from ethanol to give Co(III)BnPnAO(NO_2)$_2$ as orange slates.

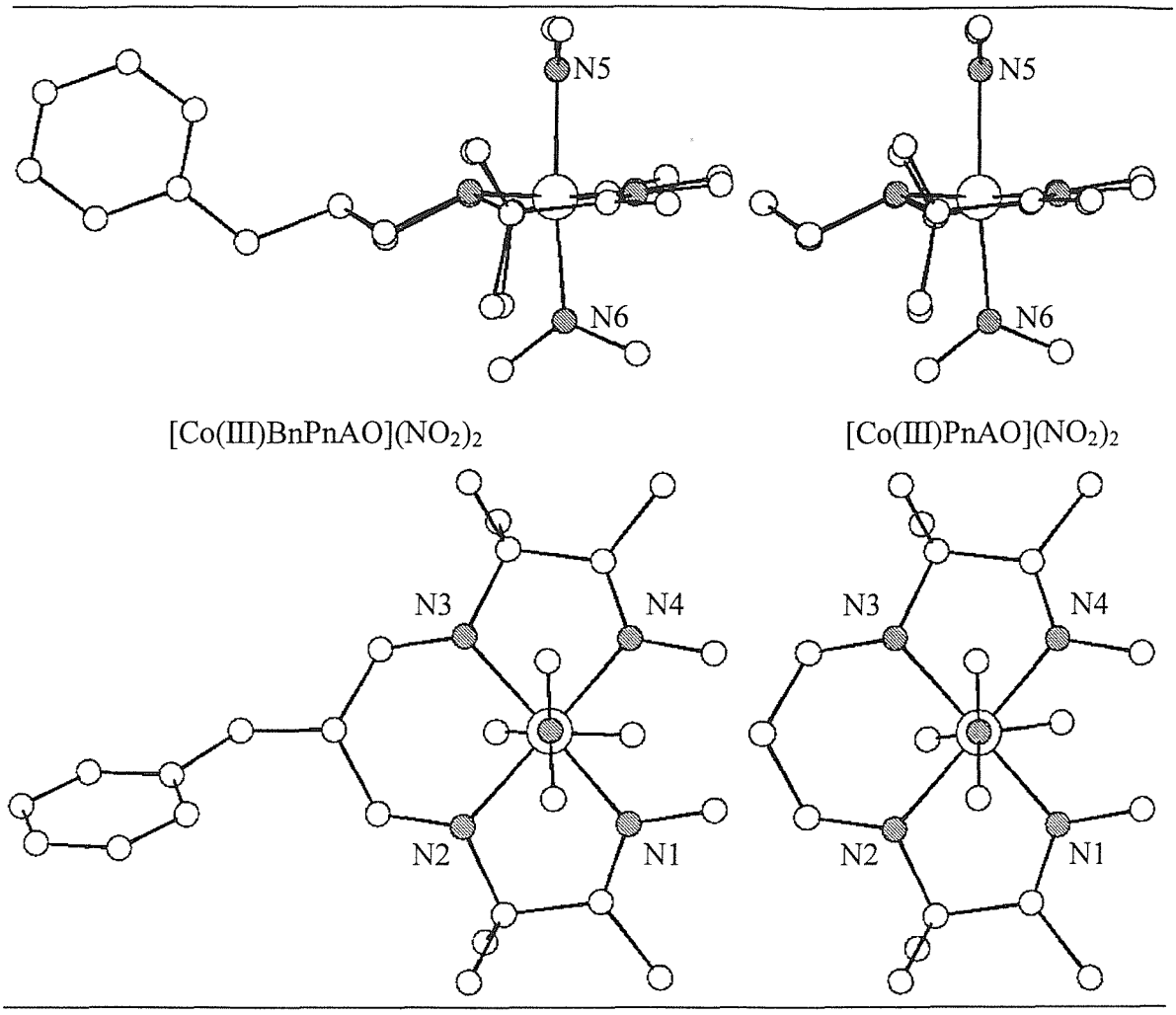


Figure 6.24 The solid-state geometries of the complexes of [Co(III)BnPnAO](NO$_2$)$_2$ and [Co(III)PnAO](NO$_2$)$_2$

Figure 6.24 shows views of [Co(III)BnPnAO](NO$_2$)$_2$ alongside [Co(III)PnAO](NO$_2$)$_2$ the crystal structure[74] of which has been previously solved. Since the benzyl substituent of **37** does not in anyway interact with the core, the binding geometry around the cobalt is almost identical to that found in its unsubstituted analogue; the cobalt is bound octahedrally and there are no solvent molecules present.

Within this structure it should be noted that the Co-N5 distance is slightly longer than that for Co-N6. It is thought that the four equatorial nitrogens of the PnAO ligand system stabilise the cation so well that the complex tends towards a square-planar configuration. Kinetic studies[74] on the unsubstituted complex indicated that the nitro group with the longer Co-N bond may be very weakly hydrogen bonded to the two secondary amines on the ligand. As expected it was also shown that this nitro group was considerably more labile than the other which prompted the publication[72] of a structural study of a similar

complex [Co(III)PnAO(NO_2)(H_2O)]ClO_4. This was prepared by dissolving the dinitrite salt in water and precipitating it with silver perchlorate. For this reason it seemed feasible that a substituted hetero atom on the phenyl ring might also replace the loosely bound nitro group in the presence of a non-co-ordinating anion.

The copper complex of **37** was crystallised as its tetrafluoroborate salt. Following a method[75] previously used to prepare a similar complex [Cu(II)6,6-dimethyl-PnAO(H_2O)]ClO_4, a methanolic solution of the dichloride [Cu(II)BnPnAO(H_2O)]Cl was treated with a methanolic solution of copper(II) tetrafluoroborate. The purple solid which precipitated on cooling was filtered and recrystallised from water to give [Cu(II)BnPnAO(H_2O)]BF_4 as purple blocks.

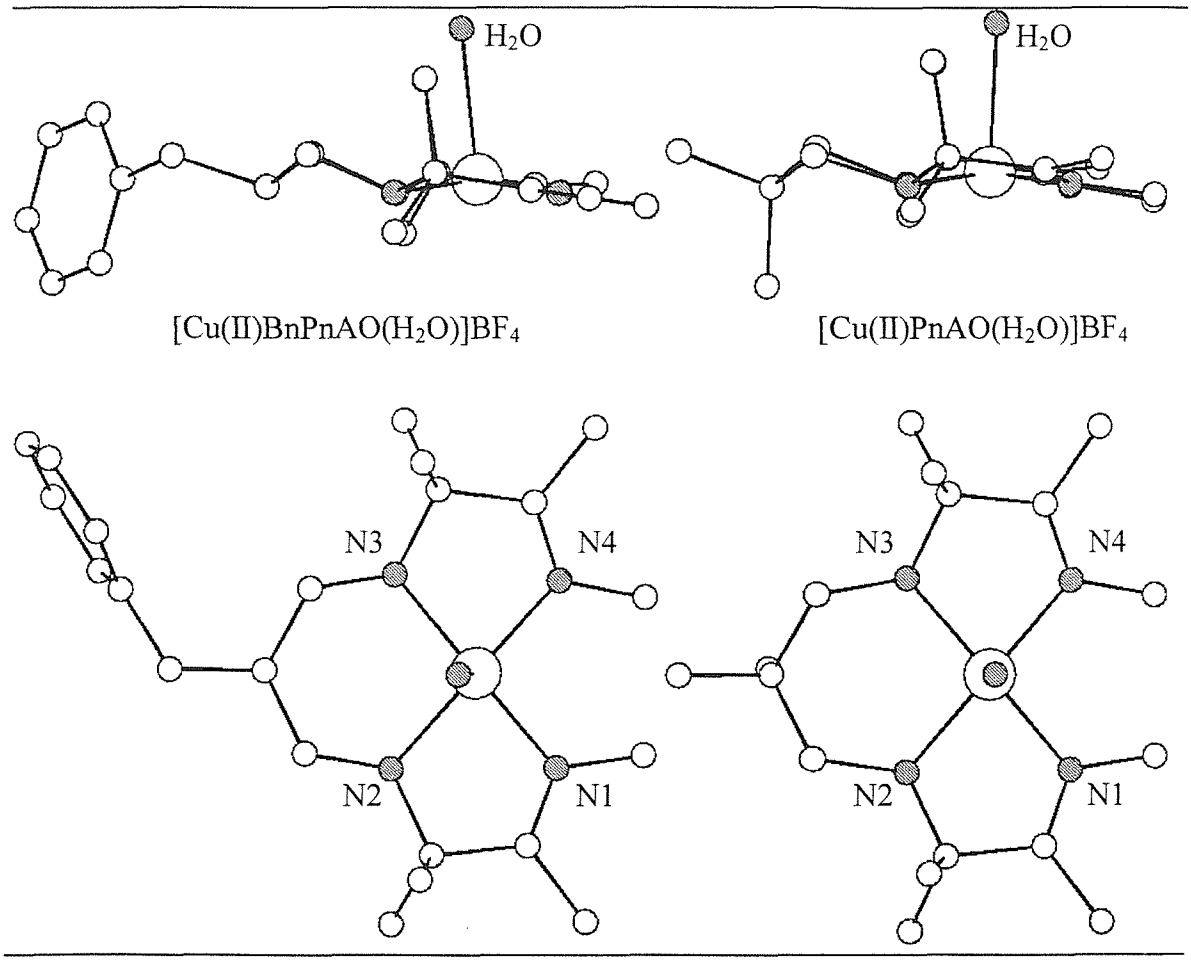


Figure 6.25 The solid-state geometries of the complexes of [Cu(III)BnPnAO(H_2O)]BF_4 and [Cu(III)PnAO(H_2O)]BF_4

Figure 6.25 shows views of [Cu(II)BnPnAO(H_2O)]BF_4 alongside [Cu(II)6,6-dimethylPnAO(H_2O)]ClO_4 the crystal structure[75] of which has been previously solved.

The copper sits in a distorted square pyramidal geometry and slightly out of the plane of the nitrogens. Literature[19] data has shown that in PnAO ligand complexes of TcO^{3+} the carbons in the chelate ring all lie above the plane of the nitrogens. Cu(II) complexes of PnAO ligands previously reported[76] have displayed similar behaviour. In $[Cu(II)BnPnAO(H_2O)]BF_4$, however, the sp^2 carbons lie in the plane of the nitrogens. The bonding of the aqua group also differs in that it is parallel to the methyl groups which lie above the nitrogen plane.

As with $Co(III)BnPnAO(NO_2)_2$ the benzyl substituent of $[Cu(II)BnPnAO(H_2O)]BF_4$ does not interact with the core but unlike $Co(III)BnPnAO(NO_2)_2$ there are two molecules in the unit cell. These molecules are linked via hydrogen bonding to one of the two BF_4 anions (Figure 6.26).

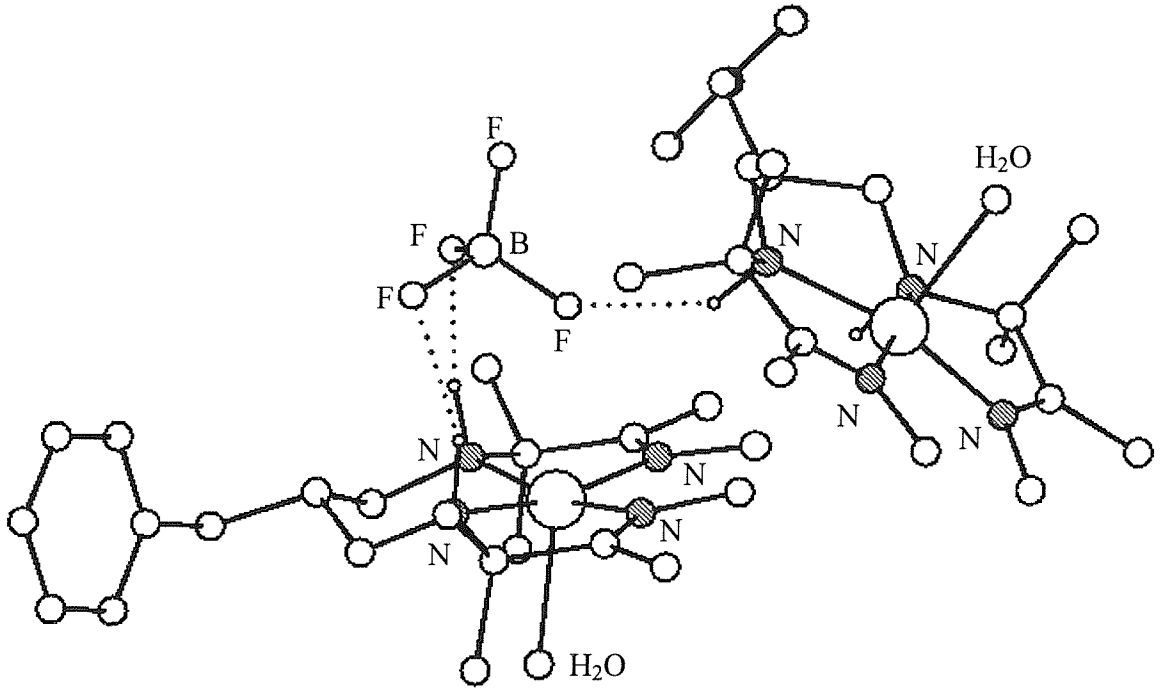


Figure 6.26 Hydrogen bonding in $[Cu(II)BnPnAO(H_2O)]BF_4$

Of the two complexes, $[Cu(II)BnPnAO(H_2O)]BF_4$ has more in common with TcO^{3+} PnAO ligand complexes because it adopts a square pyramidal geometry which is capped by an oxygen ligand. Hydrogen bonding to or direct substitution of the water molecule was considered to represent an ideal method for modelling the interaction of extra co-ordinating groups with the oxo-technetium core.

Only one of the novel ligands prepared in this project has to date afforded a crystalline complex, MeOBnPnAO (**66**). The copper complex of **66** was prepared in an identical fashion to that used for[Cu(II)BnPnAO(H_2O)]BF_4. [Cu(II)MeOBnPnAO(H_2O)]BF_4 was recrystallised from water to give purple needles.

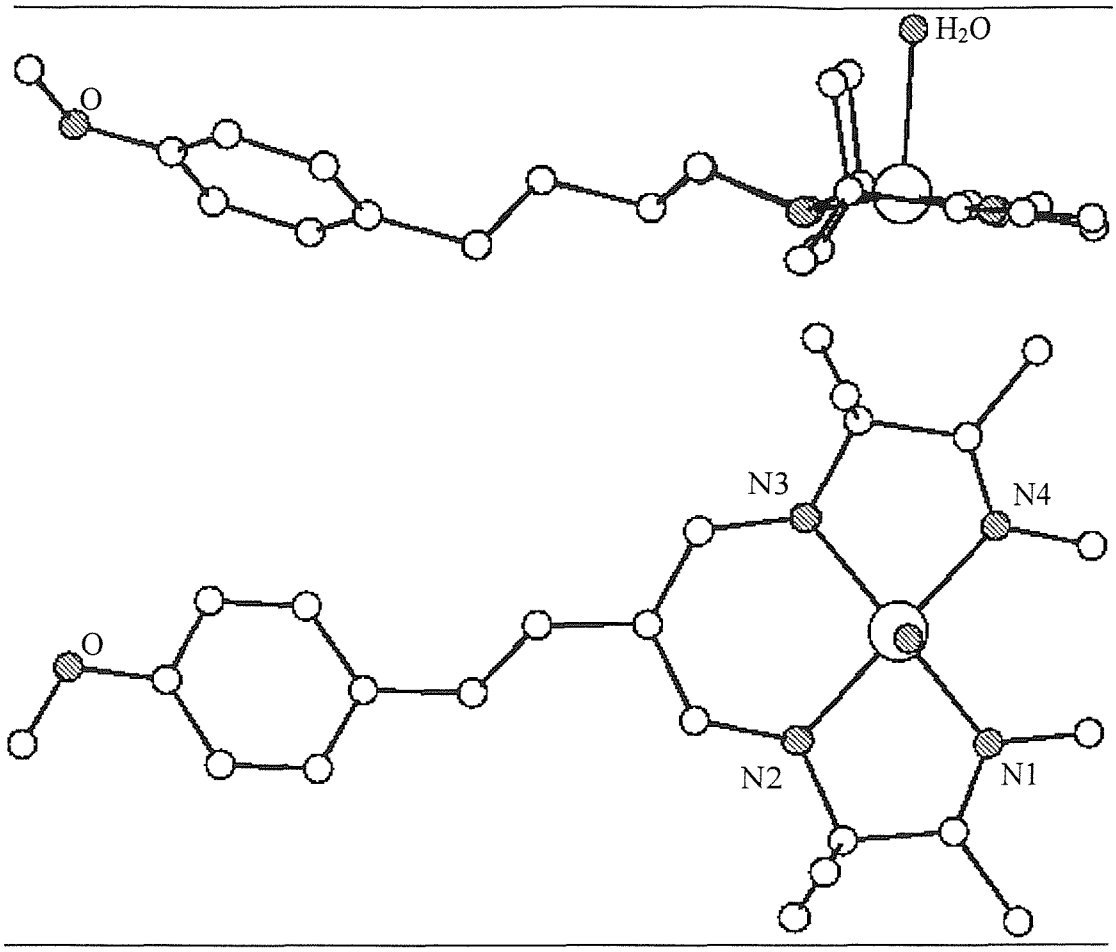


Figure 6.27 The solid-state geometry of the complex [Cu(III)MeOBnPnAO(H_2O)]BF_4

Figure 6.27 shows views of the solid-state geometry of [Cu(II)MeOBnPnAO(H_2O)]BF_4. As expected the 4-methoxyphenyl substituted ligand adopts a conformation that places the bulky substituent away from the co-ordinating centre. The co-ordination environment around the copper is the expected slightly distorted, square pyramid. Unlike [Cu(II)BnPnAO(H_2O)]BF_4 there is only one molecule in the unit cell and the overall geometry is similar to that observed for Co(III)BnPnAO(NO_2)$_2$ in that the substituent chain is not bent. In common with [Cu(II)BnPnAO(H_2O)]BF_4 the sp^2 carbons in the chelate ring lie in the plane of the nitrogen atoms of the PnAO pincer.

Attempts at crystallising the copper complexes of the remaining target ligands proved troublesome. The salts were not sufficiently soluble in water to allow aqueous recrystallisation to take place yet they were too soluble in organic solvents. Time did not permit an investigation of the use of different anions or cobalt in the place of copper.

6.5.3 TCNQ Salts of PnAO and Tetra-aza-14-crown-4 Complexes

A non-co-ordinating anion that additionally displays electrical conducting behaviour in some of its complexes is TCNQ. An attempt was made to prepare the TCNQ salts of the complex precursors following a metathesis scheme previously reported[77] whereby aqueous solutions of the precursors and of lithium TCNQ were mixed leading to precipitation of a TCNQ salt. This scheme had originally been intended to provide samples for electrical resistivity testing and gave little information about the nature or purity of the product. In both cases the precipitated products were blue or black amorphous solids which resisted recrystallisation from any solvent.

7 Conclusions And Further Work

7.1 Synthesis of Oxonol Dye Extraction Indicators

Very pure samples of a number of dicationic oxonol dyes have been metathesised. Previously the products of one-pot dicationic oxonol dye syntheses proved difficult to purify by recrystallisation owing to their insolubility. This problem has now been overcome through the use of the corresponding lithium oxonol species which is itself readily purified by recrystallisation. Metathesis in water allows exchange of the cation to yield the much less soluble dicationic oxonol dye salts with a much greater level of purity than was previously possible.

Variation of the *N*-alkyl substituent of the oxonol appeared to have a detrimental effect on the solubility of such dyes in both aqueous and organic solvents. This had the effect of lowering reaction yields and making the products even more difficult to purify by recrystallisation.

7.2 Extraction Experiments

It has been shown that oxonol dyes do represent an alternative to di- and trinitrophenoxide salts as extraction indicators. *N*-Ethyl oxonol salts of manganese(II), cobalt(II) and copper (II) all behaved reproducibly under extraction conditions and provided thermodynamic data on the process which were comparable with published results based on similar techniques. Extractions performed on crown macrocycles bearing only oxygen donors were successful at concentrations $> 1 \times 10^{-3}$ M.

Limitations to the usefulness of oxonol dyes in this process were also discovered. The sensitivity of the oxonol anion to attack by nucleophiles means that the species can be quickly bleached, especially in chlorinated organic solvents. It was also discovered that at concentrations $\geq 1 \times 10^{-5}$ M, complexes formed with ligands bearing primary or secondary amines were insoluble in either the aqueous or organic phases. This problem could be avoided at concentrations $\leq 1 \times 10^{-7}$ M. An investigation must also be carried out into which organic solvents are most suited to oxonol-based extraction systems.

In the present study, it has been found that the use of mixed metal extraction systems had serious drawbacks. Whilst it was hoped that the desired metal ion would be complexed preferentially over weakly bound cations such as lithium or various tetraalkylammonium ions, it was discovered that the solubility of a given species in the organic solvent controlled the behaviour observed in the extraction experiments and that this far outweighed any binding preference of the ligand. Since lithium oxonol was usually the most organic soluble salt, this species made a significant contribution to the amount of oxonol anion present in the organic phase of extraction experiments through a combination of complexation with the ligand and the natural solubility of the salt in the solvent.

Progress has been made on the use of radioactivity as an extraction experiment indicator. The use of ^{57}Co in both extraction experiments and pH-dependency studies has shown that very small scale work with radionuclides is both possible and reproducible. Future work in this area must concentrate on the pH of the media in which the radionuclide is present. ^{57}Co was purchased as its dichloride in 0.1 M HCl. The subsequently low pH conditions caused protonation of all of the subject ligands which meant that extraction could not take place, therefore neutralisation of the radionuclide media must be a high priority. One possible method of neutralising the acid would be through the use of solid cobalt(II) hydroxide. The resultant solution would simply be cobalt(II) chloride some of which would be present as the active ^{57}Co isotope. Since the isotopes are chemically identical, direct measurement of the active species would be representative of all the cobalt species present.

7.3 Synthesis of New PnAO Based Ligands

A series of novel ligands based on the PnAO structure have been prepared. These incorporate structural changes at the apical 6-position of the ligand backbone by the attachment of tethered aromatic rings, it being hoped that the presence of methoxy groups attached to or a nitrogen atom in these pendant rings would allow the substituent to interact with the cationic core of metal complexes thus increasing the dentition of the ligand and further stabilising its metal complexes.

Five of the targets were successfully prepared, four of which were based on methoxyphenylalkyl substituted ligands, the remainder being an ethyl tethered 2-pyridinyl variant. Attempts to make the remaining alkyl tethered target, the propyl tethered 2-pyridinyl variant were hampered by the competing reaction of 3-(2-pyridinyl)propyl chloride cyclising to give the pyrrocolinium salt. A route to its successful preparation must be found which either overcomes this problem or avoids it by utilising a different approach. The remaining three targets are PnAO ligands with ethoxy tethered rings, their preparation will be based on one of two strategies. For the methoxybenzene derivatives the same alcohols that were employed in the preparation of the alkyl tethered ligands could be deprotonated and used as alkoxides to nucleophilically attack a suitable three carbon synthon. Three such synthons were prepared: diethyl 2-bromopropanedioate (**77**), *N*,*N*'-di-BOC-*O*-methylsulphonyl-2-hydroxy-1,3-propanediamine (**79**) and *N*,*N*',*O*-tris-4-methoxybenzenesulphonyl-2-hydroxy-1,3-propanediamine (**80**). Substitution of diethyl 2-bromopropanedioate in this way failed when propanone was used a the solvent, however, it has been reported[68] that the use of butanone favours substitution over elimination. Use of the two protected 2-hydroxy-1,3-propanediamines was not fully explored, an investigation of suitable reaction conditions must be carried out in order to determine whether or not successful substitution of these synthons is possible. Preparation of the ethoxy tethered 2-pyridinyl variant may be possible by using 2-ethenylpyridine in a similar manner to its use in the preparation of the ethyl tethered 2-pyridinyl variant. Instead of using the diethyl propanedioate anion, 2-hydroxy-1,3-propanediamine could be deprotonated at the oxygen and used as the nucleophile for attack at the electrophilic double bond terminus. Solubility of the deprotonated species and subsequent purification of the product would probably benefit from the prior protection the two amine groups as their BOC carbamate derivatives.

7.4 Crystallographic Studies of PnAO Complexes

The crystal structures of three new PnAO-based ligands have been determined. 6-Benzyl PnAO complexes of Co(III) and Cu(II) were shown to have very similar bonding geometries to otherwise identical, unsubstituted PnAO complexes.[74,75] This was expected because the benzyl substituent positioned itself as far away as possible from the co-ordination centre. The information gained from solving the structure of the benzyl substituted PnAO complexes was used to assist in the design of novel ligands with extra co-ordinating groups.

The only target ligand to be successfully complexed, crystallised and solved had the co-ordinating group in a position which was chosen to avoid contact with the co-ordination sphere. This Cu(II) complex had very similar geometries to that of the Cu(II) complex of 6-benzyl PnAO as it also placed the PnAO substituent away from the co-ordination sphere.

Further work should concentrate on the preparation of complexes of the remaining target ligands that are able to crystallise. Attempts were made to prepare complexes of the remaining ligands with Cu(II) and although this undoubtedly worked, it was not possible to crystallise the complexes in a form suitable for X-ray diffraction. Tetrafluoroborate was used as a non-co-ordinating anion as it had been in the previous two Cu(II) complexes but failed to crystallise with any of the Cu(II) complexes. Alternative non-co-ordinating anions must be sought such as perchlorate and pentafluorophenoxide, this combined with an evaluation of different solvents should make the crystallisation of Cu(II) complexes possible. No attempt was made to crystallise the target ligands with Co(III) since the previous complex employed two nitrite anions which are co-ordinating species. However, use can be made of the nature of the cobalt co-ordination environment which is not perfectly octagonal. It has been reported[72] that dissolving the cobalt(III) dinitrite complex of PnAO in water allows it to be recrystallised by the addition of silver perchlorate. The resulting complex has one directly co-ordinated nitrite anion and one non-co-ordinated perchlorate anion, the remaining octahedral site was taken up by a water molecule. Using this principle it should be possible to prepare crystals suitable for X-ray crystallography in three steps. First would be the preparation of the very stable cobalt(III) dichloride salt which would hopefully, as before, be easy to purify. The chlorides would then be exchanged for nitrites in a metathesis reaction. This may yield the desired co-ordinated complex by virtue of the weakness of the long cobalt-nitrite bond, the nitrite would be forced to take up a non-co-ordinating position in the unit cell to make way for direct co-ordination of a PnAO substituent. If, as suspected, both nitrites occupied the co-ordinating sites the complex could be dissolved in water and crystallised as the nitrite-perchlorate salt. In this case, however, rather than water occupying the remaining co-ordination site it might instead be filled by the co-ordinating group of the substituent.

SECTION 3

Experimental

"Why," said the Dodo, "the best way to explain it is to do it."
(And as you might like to try the thing yourself, some winter day,
I will tell you how the Dodo managed it.)

Lewis Carroll, *Alice in Wonderland*

8 Experimental

8.1 Physical Measurements

Melting points were recorded on an Electrothermal melting point apparatus and are uncorrected.

Elemental analyses were performed either by Microanalytical Service, Department of Chemistry, Imperial College of Science, Technology and Medicine, London or C.H.N. Analysis Ltd., Alpha House, Countesthorpe Road, South Wigston, Leicester, LE8 2PJ.

UV-Visible spectra were recorded with three different instruments: an ATI-UNICAM UV3 UV-Visible spectrophotometer, a Shimadzu UV-1601 UV-Visible spectrophotometer and a Hewlett-Packard 8452A Diode Array spectrophotometer.

IR spectra were recorded on either a Perkin-Elmer 1600 Series FTIR spectrometer or a Perkin-Elmer Paragon 1000 FTIR spectrometer.

^{1}H NMR spectra were recorded with three different instruments: a Jeol GX270 spectrometer (270 MHz), a Bruker AC300 spectrometer (300 MHz) and a Bruker AM360 spectrometer (360 MHz) all using tetramethylsilane (TMS) as an internal standard. Coupling frequencies are given in hertz.

^{13}C NMR spectra were recorded on a Bruker AC300 spectrometer (75 MHz).

ES (electrospray) mass spectra were recorded on a Micromass Platform quadrupole mass analyser. The instrument was calibrated with a mixture of sodium and caesium iodide, the operating conditions were capillary 3.50 kV, HV lens 0.5 kV, cone voltage 20 V, source temperature 110 °C, ES eluent: 100% acetonitrile at 100 μL min^{-1}, nitrogen drying gas 300 L h^{-1} and nebulising gas 20 L h^{-1}. 10 μL injections of ~1-10 μg mL^{-1} solutions were made using a Hewlett-Packard HP 1050 autosampler.

APCI (atmospheric pressure chemical ionisation) spectra operating conditions were capillary 3.5 kV, HV lens 0 kV, cone voltage 20 V, source temperature 150 °C, probe

temperature 450 °C, ES eluent: 100% acetonitrile at 200 μL min^{-1}, nitrogen drying gas 250 L h^{-1} and APCI sheath gas 50 L h^{-1}. Negative ion data were recorded under identical conditions except for different polarity voltages and capillary voltages of -3.0 kV for ES and APCI.

FAB (fast atom bombardment) mass spectra were recorded on a VG analytical 70-250-SE normal geometry double focusing mass spectrometer, fitted with an Ion-Tech saddle-field gun running at 6 kV, with the gun current monitored at 1.6 mA, using argon as bombarding gas. Data were acquired at 6 kV accelerating voltage, at a scan rate of 3 s per decade over a mass range of 1400 amu to 50 amu, with an interscan delay of 1 second. 1 μL of matrix and NBA (3-nitrobenzyl alcohol) was loaded onto the stainless steel FAB probe tip to which 1 μL of solution containing the analyte was added.

8.2 Materials

Unless otherwise stated all chemicals were of reagent grade and were purchased from either Aldrich Chemical Company or Avocado. Solvents, and where necessary chemicals, were all purified and dried according to literature procedures.[78] In particular:
THF (65.4 °C) was distilled from sodium/benzophenone.
DCM (40.0 °C) was distilled from calcium hydride.
Ethanol (78.3 °C) and methanol (64.5 °C) were distilled from magnesium/iodine.

8.3 Preparative Methodologies

All enclosed reactions were carried out under a nitrogen atmosphere or with a nitrogen bubbler.

8.3.1 *N*-Ethylcyanoethanamide[47] (1)

Ethyl cyanoethanoate (113.1 g, 1.0 mol) and ethylamine (96.6 g, 1.5 mol, 70% w/w aq) were mixed and stirred vigorously. The mixture warmed quickly, clouded and then subsequently clarified. The reaction was monitored by TLC and after completion the solution was cooled to 30 °C, filtered and placed in an ice bath. A solid formed which was separated by filtration to yield cream-yellow crystals. The crude solid was purified by recrystallisation from hot ethanol to give the title compound **1** as a colourless crystalline solid (68.01 g, 61%), mp 73.5-75.5 °C (lit.[47] 72.0 °C); δ_H(300 MHz, DMSO-d_6) 1.03 (3 H,

t, J 7.7, CH_3), 3.09 (2 H, d of q, J_d 7.7, J_q 7.7, CH_2), 3.58 (2 H, s, CH_2) and 8.21 (1 H, br s, NH).

8.3.2 *N*-Butylcyanoethanamide[79] (2)

Ethyl cyanoethanoate (113.1 g, 1.0 mol), butylamine (88.0 g, 1.2 mol) and ethanol (50 mL) were mixed and stirred vigorously. The mixture warmed quickly, clouded and then subsequently clarified. The reaction was monitored by TLC and after completion the solution was cooled to 30 °C, filtered and placed in an ice bath. A solid formed which was separated by filtration to yield cream crystals. The crude solid was purified by recrystallisation from hot ethanol to give the title compound **2** as a colourless crystalline solid (95.53 g, 67%), mp 69.0-70.0 °C (lit.[79] 68.0 °C, benzene); δ_H(300 MHz, DMSO-d_6) 0.86 (3 H, t, J 8.0, CH_3), 1.10 (2 H, m, CH_2), 1.38 (2 H, m, CH_2), 3.07 (2 H, d of t, J_d 8.0, J_t 8.0, CH_2), 3.57 (2 H, s, CH_2) and 8.18 (1 H, br s, NH).

8.3.3 *N*-Hexylcyanoethanamide[80] (3)

Ethyl cyanoethanoate (56.55 g, 0.50 mol), hexylamine (60.70 g, 0.60 mol) and ethanol (50 mL) were mixed and stirred vigorously. The mixture warmed quickly, clouded and then subsequently clarified. The reaction was monitored by TLC and after completion the solution was cooled to 30 °C, filtered and placed in an ice bath. A solid formed which was separated by filtration to yield cream crystals. The crude solid was purified by recrystallisation from hot toluene to give the title compound **3** as an off-white crystalline solid (71.99 g, 86%), mp 56.0-57.0 °C (lit.[80] 74-75 °C); δ_H(300 MHz, DMSO-d_6) 0.88 (3 H, t, J 8.0, CH_3), 1.12-1.42 (8 H, m, CH_2), 3.05 (2 H, d of t, J_d 8.0, J_t 8.0, CH_2), 3.58 (2 H, s, CH_2) and 8.18 (1 H, br s, NH).

8.3.4 *N*-Benzylcyanoethanamide[81] (4)

Ethyl cyanoethanoate (56.56 g, 0.50 mol), benzylamine (58.94 g, 0.55 mol) and ethanol (70 mL) were mixed and stirred vigorously. The mixture warmed quickly, clouded and then subsequently clarified. The reaction was monitored by TLC and after completion the solution was cooled to 30 °C, filtered and placed in an ice bath. A solid formed which was separated by filtration to yield cream crystals. The crude solid was purified by recrystallisation from hot ethanol to give the title compound **4** as an colourless crystalline solid (72.74 g, 84%), mp 121.0-123.0 °C (lit.[81] 117-119 °C); δ_H(300 MHz, DMSO-d_6)

3.70 (2 H, s, CH_2), 4.30 (2 H, s, CH_2), 7.23-7.49 (5 H, m, Ar-H) and 8.75 (1 H, br s, NH).

8.3.5 1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone[45] (5)

N-Ethylcyanoethanamide (1) (30.0 g, 0.27 mol) and ethyl 3-oxobutanoate (35.14 g, 0.27 mol) were mixed in methanol (60 mL) and warmed to achieve solution. KOH (16.27 g, 0.29 mol) in methanol (14 mL) was added to the mixture over 10 minutes. The mixture was magnetically stirred and refluxed for 8 hours. The solution was cooled and the solid separated by filtration. The potassium salt product was dissolved in warm water, filtered, cooled, cautiously acidified to pH 1 with concHCl, and then cooled on an ice bath. The desired product was separated by filtration and washed with methanol, water, methanol again, and then dried at 60 °C to yield a white, chalky product. A further crop of product was isolated by cautiously acidifying the mother-liquor to pH 1 with concHCl, the solid was treated as above. The crude product was purified by recrystallisation from hot ethanol to give the title compound **5** as a fine, white powdery solid (24.4 g, 53%), mp 247-249 °C (lit.[45] 245-246 °C); δ_H(300 MHz, DMSO-d_6) 1.10 (3 H, t, *J* 7.7, CH_3), 2.20 (3 H, s, CH_3), 3.92 (2 H, q, *J* 7.7, CH_2), 5.65 (1 H, s, CH) and 7.40 (1 H, br s, OH).

8.3.6 1-Butyl-3-cyano-4-methyl-6-hydroxy-2-pyridone[45] (6)

N-Butylcyanoethanamide (2) (2.0 g, 1.40 x 10^{-2} mol) and ethyl 3-oxobutanoate (1.86 g, 1.40 x 10^{-2} mol) were mixed in ethanol (50 mL) containing sodium metal (0.33 g, 1.40 x 10^{-2} mol) and warmed to achieve solution. The mixture was magnetically stirred and refluxed for 24 hours. The solution was cooled and the solid separated by filtration. The sodium salt product was dissolved in warm water, filtered, cooled, cautiously acidified to pH 1 with concHCl, and then cooled on an ice bath. The desired product was separated by filtration and washed with methanol, water, methanol again, and then dried at 60 °C to yield an off-white, crumbly product. A further crop of product was isolated by cautiously acidifying the mother-liquor to pH 1 with concHCl, the solid was treated as above. The crude product was purified by recrystallisation from hot ethanol to give the title compound **6** as a fine, off-white powdery solid (0.18 g, 6%), mp 195-198 °C (lit.[45] 205-207 °C); δ_H(300 MHz, DMSO-d_6) 0.88 (3 H, t, *J* 8.0, CH_3), 1.28 (2 H, m, CH_2), 1.48 (2 H, m, CH_2), 2.13 (3 H, s, CH_3), 3.86 (2 H, t, *J* 8.0, CH_2), 5.43 (1 H, s, CH) and 7.25 (1 H, br s, OH).

8.3.7 1-Hexyl-3-cyano-4-methyl-6-hydroxy-2-pyridone[45] (7)

N-Hexylcyanoethanamide (**3**) (25.0 g, 0.15 mol) and ethyl 3-oxobutanoate (19.50 g, 0.15 mol) were mixed in methanol (60 mL) and warmed to achieve solution. KOH (10.10 g, 0.18 mol) in methanol (14 mL) was added to the mixture over 10 minutes. The mixture was magnetically stirred and refluxed for 8 hours. The solution was cooled and the solid separated by filtration. The potassium salt product was dissolved in warm water, filtered, cooled, cautiously acidified to pH 1 with concHCl, and then cooled on an ice bath. The product was a sticky brown dough which was dissolved in DCM and washed with water. The organic phase was dried ($MgSO_4$) and evaporated at reduced pressure to give a brown foam. The crude product was purified by recrystallisation from hot methanol to give the title compound **7** as an amorphous white solid (10.43 g, 30%), mp 210-214 °C (lit.[45] 212-214 °C); δ_H(300 MHz, DMSO-d_6) 0.86 (3 H, t, *J* 8.0, CH_3), 1.10-1.48 (8 H, m, CH_2), 2.15 (3 H, s, CH_3), 3.63 (2 H, t, *J* 8.0, CH_2) and 6.03 (1 H, s, CH).

8.3.8 1-Benzyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (8)

N-Benzylcyanoethanamide (**4**) (25.00 g, 0.14 mol) and ethyl 3-oxobutanoate (18.70 g, 0.14 mol) were mixed in methanol (40 mL) and warmed to achieve solution. KOH (8.40 g, 0.15 mol) in methanol (20 mL) was added to the mixture over 10 minutes. The mixture was magnetically stirred and refluxed for 8 hours. The solution was cooled and the solid separated by filtration. The potassium salt product was dissolved in warm water, filtered, cooled, cautiously acidified to pH 1 with concHCl, and then cooled on an ice bath. The desired product was separated by filtration and washed with methanol, water, methanol again, and then dried at 60 °C to yield a white, chalky product. A further crop of product was isolated by cautiously acidifying the mother-liquor to pH 1 with concHCl, the solid was treated as above. The crude product was purified by recrystallisation from hot ethanol to give the title compound **8** as a fine, white powdery solid (14.34 g, 43%, Found: C, 64.6; H, 4.8; N, 10.9%; $C_{14}H_{12}N_2O_2$ requires: C, 70.0; H, 5.0; N, 11.7%), mp 247-250 °C; ν(Nujol)/cm^{-1} 2218, 1647 and 1535; δ_H(300 MHz, DMSO-d_6) 2.22 (3 H, s, CH_3), 5.11 (2 H, s, CH_2), 5.69 (1 H, s, CH), 6.87 (1 H, br s, OH) and 7.10-7.30 (5 H, m, Ar-H); δ_C(75 MHz, DMSO-d_6) 20.6 (q), 43.5 (t), 88.2 (s), 92.4 (d), 117.5 (s), 127.1 (d), 127.3 (d), 128.3 (d), 136.8 (s), 158.4 (s), 160.5 (s) and 160.7 (s).

8.3.9 Copper(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate][45] (9)

1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**) (4.98 g, 2.80 x 10^{-2} mol), 1,1,3,3-tetramethoxypropane (2.30 g, 1.40 x 10^{-2} mol) and copper(II) ethanoate monohydrate (1.40 g, 7.00 x 10^{-3} mol) were mixed in a solution of ethanol/ethanoic acid (9:1, 50 mL). The mixture was refluxed for 2 hours, cooled, and the dark brown product was separated by filtration. The product was dried at reduced pressure over silica gel to give the title compound **9** as a light brown powder (3.20 g, 54%), mp >355 °C (lit.[45] >360 °C); δ_H(300 MHz, DMSO-d_6) 1.05 (6 H, br s, CH_3), 2.42 (6 H, s, CH_3), 3.84 (4 H, br s, CH_2), 7.76 (2 H, d, *J* 12.9, CH) and 9.03 (1 H, t, *J* 12.9, CH).

By metathesis

Lithium *N*-ethyloxonol (**11**) (0.50 g, 1.26 x 10^{-3} mol) and $CuCl_2$ (0.09 g, 6.70 x 10^{-4} mol) were each dissolved in de-ionised water (250 mL). After both solutions had been filtered, the $CuCl_2$ solution was stirred vigorously whilst the lithium *N*-ethyloxonol (**11**) solution was slowly added dropwise. After the addition was complete the mixture was left to stir overnight. The solid was separated by filtration and dried at reduced pressure over silica gel to give the title product **11** as shiny, metallic purple flakes (0.49 g, 92%, Found: C, 57.6; H, 4.8; N, 12.8%; $C_{42}H_{38}N_8O_8Cu.1½H_2O$ requires: C, 57.8; H, 4.7; N, 12.8), mp >360°C; λ_{max}(water)/nm 588 and 543sh (ε/dm^3 mol^{-1} cm^{-1} 181 300 and 107 400); ν(Nujol)/cm^{-1} 2215, 1670 and 1616; δ_H(300 MHz, DMSO-d_6) 1.04 (6 H, br s, CH_3), 2.39 (6 H, br s, CH_3), 3.81 (4 H, br s, CH_2), 7.74 (2 H, br s, CH) and 9.03 (1 H, br s, CH); δ_C(75 MHz, DMSO-d_6) 13.2 (q), 18.7 (q), 34.0 (t), 92.3 (s), 110.5 (s), 121.0 (d), 157.7 (d), 158.1=4 (s), 161.5 (s) and 162.1 (s).

8.3.10 Cobalt(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate][45] (10)

1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**) (4.98 g, 2.80 x 10^{-2} mol), 1,1,3,3-tetramethoxypropane (2.30 g, 1.40 x 10^{-2} mol) and cobalt(II) ethanoate tetrahydrate (1.74 g, 7.00 x 10^{-3} mol) were mixed in a solution of ethanol/ethanoic acid (9:1, 50 mL). The mixture was refluxed for 2 hours, cooled, and the dark blue product was separated by

filtration. The product was dried at reduced pressure over silica gel to give the title compound **10** as a dark purple powder (4.92 g, 84%), mp >355 °C (lit.[45] >360 °C); δ_H(300 MHz, DMSO-d_6) 0.95 (6 H, t, *J* 6.4, CH_3), 2.29 (6 H, s, CH_3), 3.75 (4 H, q, *J* 6.4, CH_2), 7.68 (2 H, d, *J* 15.0, CH) and 8.92 (1 H, t, *J* 15.0, CH).

By metathesis

Lithium *N*-ethyloxonol (**11**) (0.50 g, 1.26 x 10^{-3} mol) and cobalt(II) ethanoate tetrahydrate (0.17 g, 6.70 x 10^{-4} mol) were each dissolved in de-ionised water (250 mL). After both solutions had been filtered, the cobalt(II) ethanoate solution was stirred vigorously whilst the lithium *N*-ethyloxonol (**11**) solution was slowly added dropwise. After the addition was complete the mixture was left to stir overnight. The solid was separated by filtration and dried at reduced pressure over silica gel to give the title product **10** as shiny, metallic purple flakes (0.50 g, 94%, Found: C, 56.4; H, 4.9; N, 12.6%; $C_{42}H_{38}N_8O_8Co.3H_2O$ requires: C, 56.3; H, 5.0; N, 12.5%), mp >360°C; λ_{max}(water)/nm 588 and 543sh (ε/dm^3 mol^{-1} cm^{-1} 178 200 and 104 500); ν(Nujol)/cm^{-1} 2236, 1671, 1653 and 1614; δ_H(300 MHz, DMSO-d_6) 0.89 (6 H, br s, CH_3), 2.22 (6 H, br s, CH_3), 3.69 (4 H, br s, CH_2), 7.55 (2 H, br s, CH) and 8.83 (1 H, br s, CH); δ_C(75 MHz, DMSO-d_6) 13.1 (q), 18.6 (q), 33.9 (t), 92.3 (s), 110.4 (s), 121.0 (d), 157.5 (d), 158.1 (s), 161.3 (s) and 161.9 (s).

8.3.11 Lithium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate[45] (11)

1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**) (15.00 g, 8.40 x 10^{-2} mol), 1,1,3,3-tetramethoxypropane (6.90 g, 4.20 x 10^{-2} mol), lithium ethanoate dihydrate (4.35g, 4.20 x 10^{-2} mol) and ethanol (100 mL) were mixed and refluxed for 3 hours. After cooling, the solid was separated by filtration, recrystallised from boiling ethanol and dried at reduced pressure over silica gel to give the title compound **11** as shiny, metallic yellow-green, cubic crystalline solid (11.86 g, 71%), mp 357 °C (lit.[45] 357 °C); δ_H(300 MHz, DMSO-d_6) 1.08 (6 H, t, *J* 7.0, CH_3), 2.42 (6 H, s, CH_3), 3.85 (4 H, q, *J* 7.0, CH_2), 7.79 (2 H, d, *J* 13.0, CH) and 9.02 (1 H, t, *J* 13.0, CH).

8.3.12 Potassium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate[45] (12)

1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**) (3.56 g, 2.00 x 10^{-2} mol), 1,1,3,3-tetramethoxypropane (1.64 g, 1.00 x 10^{-2} mol), potassium ethanoate (0.98g, 1.00 x 10^{-2} mol) and ethanol (40 mL) were mixed and refluxed for 20 hours. After cooling, the solid was separated by filtration, recrystallised from boiling ethanol and dried at reduced pressure over silica gel to give the title compound **12** as dark blue-green, crystalline solid (2.63 g, 61%), mp >355 °C dec. at 250 °C due to presence of **5** (lit.[45] >360 °C); δ_H(300 MHz, DMSO-d_6) 0.99 (6 H, t, *J* 7.4, CH_3), 2.40 (6 H, s, CH_3), 3.83 (4 H, q, *J* 7.4, CH_2), 7.75 (2 H, d, *J* 12.7, CH) and 8.98 (1 H, t, *J* 12.7, CH).

8.3.13 Tetramethylammonium 1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate[45] (13)

1-Ethyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**5**) (2.00 g, 1.10 x 10^{-2} mol), 1,1,3,3-tetramethoxypropane (0.90 g, 5.50 x 10^{-2} mol), tetramethylammonium chloride (0.60g, 5.50 x 10^{-2} mol) and ethanol (10 mL) were mixed and refluxed for 24 hours. After cooling, the reaction mixture was filtered and the filtrate evaporated at reduced pressure. The resulting sticky blue solid was recrystallised from boiling ethanol and dried at reduced pressure over silica gel to give the title compound **13** as dark blue-green, crystalline solid (~1%), mp 348 °C dec. (lit.[45] 345 °C, dec.); δ_H(300 MHz, DMSO-d_6) 1.09 (6 H, t, *J* 8.0, CH_3), 2.43 (6 H, s, CH_3), 3.89 (4 H, q, *J* 8.0, CH_2), 7.77 (2 H, d, *J* 13·0, CH), 90.2 [1 H, t, *J* 13.0,CH).

8.3.14 Potassium 1-butyl-3-(3-(1-butyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (14)

Prepared similarly to **15** using 1-butyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**6**) instead but provided a negligible amount of product.

8.3.15 Potassium 1-benzyl-3-(3-(1-benzyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (15)

1-Benzyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**8**) (1.00 g, 4.20 x 10^{-3} mol), 1,1,3,3-tetramethoxypropane (0.34 g, 2.10 x 10^{-3} mol), potassium ethanoate (0.20g, 2.10 x 10^{-3} mol) and ethanol (75 mL) were mixed and refluxed for 24 hours. After cooling, the solid was separated by filtration, recrystallised from boiling ethanol and dried at reduced pressure over silica gel to give the title compound **15** as a pale violet, powdery solid (1.24 g, 63%), mp >355 °C; δ_H(300 MHz, DMSO-d_6) 2.50 (6 H, s, CH_3), 5.03 (4 H, s, CH_2), 7.18-7.30 (10 H, m, Ar-H), 7.84 (2 H, d, *J* 13·2, CH), 9.02 (1 H, t, *J* 13·2, CH).

8.3.16 Lithium 1-benzyl-3-(3-(1-benzyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate (16)

1-Benzyl-3-cyano-4-methyl-6-hydroxy-2-pyridone (**8**) (1.00 g, 4.20 x 10^{-3} mol), 1,1,3,3-tetramethoxypropane (0.34 g, 2.10 x 10^{-3} mol), lithium ethanoate (0.077 g, 1.05 x 10^{-3} mol) and ethanol (25 mL) were mixed and refluxed for 24 hours. After cooling, the solid was separated by filtration, recrystallised from boiling ethanol and dried at reduced pressure over silica gel to give the title compound **16** as dark green needles (1.33 g, 70%), mp 339 °C; δ_H(300 MHz, DMSO-d_6) 2.47 (6 H, s, CH_3), 5.01 (4 H, s, CH_2), 7.16-7.31 (10 H, m, Ar-H), 7.79 (2 H, d, *J* 13·0, CH), 8.87 (1 H, t, *J* 13·0, CH).

8.3.17 Manganese(II) bis[1-ethyl-3-(3-(1-ethyl-2,6-dioxo-4-methyl-5-cyano-1,2,3,6-tetrahydro-3-pyridinylidene)-1-propenyl)-4-methyl-5-cyano-6-oxo-1,6-dihydro-2-pyridinolate] (17)

Lithium *N*-ethyloxonol (**11**) (0.50 g, 1.26 x 10^{-3} mol) and manganese(II) ethanoate tetrahydrate (0.164 g, 6.70 x 10^{-4} mol) were each dissolved in de-ionised water (250 mL). After both solutions had been filtered, the manganese(II) ethanoate solution was stirred vigorously whilst the lithium *N*-ethyloxonol (**11**) solution was slowly added dropwise. After the addition was complete the mixture was left to stir overnight. The solid was separated by filtration and dried at reduced pressure over silica gel to give the title product **17** as shiny, metallic purple flakes (0.44 g, 84%, Found: C, 57.3; H, 4.9; N, 12.7%; $C_{42}H_{38}N_8O_8Mn.2½H_2O$ requires: C, 57.1; H, 4.9; N, 12.7%), mp >360°C; λ_{max}(water)/nm

588 and 543sh (ε/dm^3 mol^{-1} cm^{-1} 188 200 and 117 100); ν(Nujol)/cm^{-1} 3433, 2219, 1668, 1613 and 1585; δ_H(360 MHz, DMSO-d_6) 0.95 (6 H, br s, CH_3), 2.33 (6 H, br s, CH_3), 3.85 (4 H, br s, CH_2), 7.73 (2 H, br s, CH) and 8.96 (1 H, br s, CH); δ_C(90 MHz, DMSO-d_6) 13.4 (q), 18.8 (q), 34.1 (t), 92.4 (s), 110.6 (s), 121.0 (d), 157.7 (d), 158.4 (s), and 162.2 (s).

8.3.18 Metal Trinitrophenoxides[49] (18 - 23)

Stoichiometric amounts of 2,4,6-trinitrophenol and metal carbonate were dissolved in water. The precipitate was collected, washed with ethanol and recrystallised from hot water. Sodium trinitrophenoxide **18** was prepared as small, yellow needles. Potassium trinitrophenoxide **19** was prepared as bright yellow plates. Lithium trinitrophenoxide **20** was prepared as orange, rhomboids. The preparation of magnesium (**21**), copper (**22**) and cobalt (**23**) trinitrophenoxide was not pursued because of the highly insoluble nature of the respective metal carbonate.

8.3.19 2-Chloro-2-methyl-3-nitrosobutane[53] (24)

2-Methyl-2-butene (20.11 g, 2.80 x 10^{-4} mol) and 3-methylbutyl nitrite (33.49 g, 2.80 x 10^{-4} mol) were mixed and stirred at -15 °C under nitrogen. concHCl (31.1 mL) was added dropwise at a rate that maintained the reaction temperature <0 °C. After the addition was complete the mixture was stirred for 30 minutes. The precipitate was separated by filtration on a coarse sinter and washed with cold ethanol (-20 °C, 4 x 5 mL) until all traces of blue colouration had gone giving the title compound **24** as a flaky, white crystalline solid which was air dried and stored under nitrogen in a fridge (21.54 g, 57%), mp 71-72 °C (lit.[53] 75 °C); δ_H(300 MHz, DMSO-d_6) 1.48 (3 H, m, CH_3), 1.68 (6 H, m, CH_3), 5.85 and 5.95 (1 H, q, *J* 6.6, CH).

8.3.20 3,3,9,9-Tetramethyl-4,8-diaza-2,10-undecanedione dioxime[50] (25)

2-chloro-2-methyl-3-nitrosobutane (**24**) (1.00 g, 7.38 x 10^{-3} mol), 1,3-propanediamine (0.25 g, 3.37 x 10^{-3} mol) and methanol (20 mL) were mixed and stirred for 2 hours at 0 °C, 2 hours at room temperature and 15 hours at reflux. After cooling, the solvent was removed at reduced pressure and the solid dissolved in water and filtered. The filtrate was poured into an excess of sodium carbonate solution and made up to pH11 with concentrated NaOH solution. The precipitate was separated by filtration, washed with cold

water, recrystallised from boiling methanol to give the title compound **25** as a colourless, crystalline solid (0.46 g, 50%), mp 190-191 °C (lit.[50] 180-181 °C); δ_H(300 MHz, DMSO-d_6) 1.10 (12 H, s, CH_3), 1.40 (2 H, quin, *J* 6.7, CH_2), 1.70 (6 H, s, CH_3), 2.22 (4 H, t, *J* 6.7, CH_2), 3.37 (4 H, br s, NH) and 10.35 (2 H, s, OH).

8.3.21 Diethyl 2-(2-methyl-1-propyl)-1,3-propanedioate[55] (26)

Sodium metal (3.92 g, 0.17 mol) was dissolved in ethanol (90 mL). To the rapidly stirring solution was slowly added diethyl-1,3-propanedioate (28.09 g, 0.175 mol), stirring was continued for 30 minutes during which time a thick white precipitate formed. To this mixture was slowly added 1-bromo-2-methylpropane (23.30 g, 0.17 mol) which was then refluxed overnight. After sufficient further refluxing to neutralise the solution (moist litmus paper) the ethanol was removed at reduced pressure. The crude oil was distilled at reduced pressure to give the title compound **26** as a colourless oil (19.54 g, 53%), bp 82 °C @ 1.0 mmHg (lit.[55] 100-102 °C @ 10.0 mmHg); δ_H(300 MHz, $CDCl_3$) 0.92 (6 H, d, J 6.7, CH_3), 1.27 (6 H, t, *J* 7.0, CH_3), 1.58 (1 H, non, *J* 6.7, CH), 1.80 (2 H, t, *J* 7.4, CH_2), 3.41 (1 H, t, *J* 7.7, CH) and 4.19 (4 H, q, *J* 7.0, CH_2).

8.3.22 2-(2-Methyl-1-propyl)-1,3-propanediamide[55] (27)

Diethyl 2-(2-methyl-1-propyl)-1,3-propanedioate (**26**) (20.94 g, 9.70 x 10^{-2} mol) was dissolved in methanol (50 mL), treated with sodium methoxide (0.01 g, 2.55 x 10^{-4} mol) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot ethanol to give the title compound **27** as a colourless solid (9.70 g, 63%), mp 190-193 °C (lit.[55] 191-192 °C); δ_H(300 MHz, DMSO-d_6) 0.87 (6 H, d, *J* 6.6, CH_3), 1.47 (1 H, non, *J* 6.6, CH), 1.56 (2 H, t, *J* 7.0, CH_2), 3.08 (1 H, t, *J* 7.4, CH), 7.06 (2 H, s, NH_2) and 7.28 (2 H, s, NH_2).

8.3.23 2-(2-Methyl-1-propyl)-1,3-propanediamine[55] (28)

2-(2-Methyl-1-propyl)-1,3-propanediamide (**27**) (9.68 g, 6.10 x 10^{-2} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 450 mL, 0.46 mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-

evaporated with methanol (5 x 200 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **28** as a colourless oil (5.93 g, 75%); δ_H(300 MHz, $CDCl_3$) 0.90 (6 H, d, *J* 6.6, CH_3), 1.11 (2 H, t, *J* 7.2, CH_2), 1.38 (1 H, m, CH), 1.54 (1 H, m, CH), 2.10 (4 H, br s, NH_2), 2.65 (2 H, d of d, *J* 6.4, *J* 12.7, CH_2) and 2.71 (2 H, d of d, *J* 5.1, *J* 12.5, CH_2).

8.3.24 3-Bromo-3-methyl-2-butanone[56] (29)

2-Methyl-2-butanone (50.0 g, 0.58 mol) was dissolved in CCl_4 (100 mL) and cooled in an ice bath. Bromine (92.78 g, 0.58 mol) in CCl_4 (50 mL) was added slowly and the solution stirred overnight at room temperature. The CCl_4 was removed at reduced pressure and the product fractionally distilled until pure giving the title compound **29** as a colourless liquid (66.0 g, 69%), bp 138 °C (lit.[56] 139-142 °C); δ_H(300 MHz, $CDCl_3$) 1.88 (6 H, s, CH_3) and 2.44 (3 H, s, CH_3).

8.3.25 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-methyl-1-propyl)-2,10-undecanedione[55] (30)

To a suspension of K_2CO_3 (15.62 g, 0.113 mol) in dry DMF (56 mL) was added 2-(2-methyl-1-propyl)-1,3-propanediamine (**28**) (5.90 g, 4.50 x 10^{-2} mol) and 3-bromo-3-methyl-2-butanone (**29**) (18.65 g, 0.113 mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (50 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **30** as a pale orange wax (9.13 g, 68%); δ_H(300 MHz, $CDCl_3$) 0.87 (6 H, d, *J* 6.6, CH_3), 1.09 (2 H, t, *J* 7.2, CH_2), 1.28 (12 H, s, CH_3), 1.59 (1 H, sep, *J* 6.7, CH), 1.71 (1 H, non, *J* 3.6, CH), 2.19 (6 H, s, CH_3), 2.33 (2 H, d of d, *J* 7.9, *J* 11.2, CH_2) and 2.51 (2 H, d of d, *J* 4.1, *J* 11.0, CH_2).

8.3.26 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-methyl-1-propyl)-2,10-undecanedione dioxime[55] (31)

Hydroxylamine hydrochloride (14.21 g, 0.205 mol) was added to NaOH (7.64 g, 0.191 mol) in methanol (200 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-tetramethyl-4,8-diaza-6-(2-

methyl-1-propyl)-2,10-undecanedione (**30**) (8.14 g, 2.70 x 10^{-2} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from hot ethyl ethanoate to give the title compound **31** as a shiny, colourless solid (3.24 g, 40%), mp 189-190 °C (lit.[55] 190-192 °C); δ_H(300 MHz, DMSO-d_6) 0.87 (6 H, d, *J* 6.6, CH_3), 1.05 (2 H, m, CH_2), 1.32 (12 H, s, CH_3), 1.56 (1 H, sep, *J* 6.4, CH), 1.80 (6 H, s, CH_3), 1.86 (1 H, m, CH), 2.62 (6 H, m, CH_2, NH) and 10.89 (2 H, s, OH).

8.3.27 Diethyl 2-benzyl-1,3-propanedioate[57] (32)

Sodium metal (1.394 g, 6.06 x 10^{-2} mol) was dissolved in ethanol (30 mL). To the rapidly stirring solution was slowly added diethyl-1,3-propanedioate (10.00 g, 6.24 x 10^{-2} mol), stirring was continued for 30 minutes during which time a thick white precipitate formed. To this mixture was slowly added (bromomethyl)benzene (10.398 g, 6.06 x 10^{-2} mol) which was then refluxed overnight. After sufficient further refluxing to neutralise the solution (moist litmus paper) the ethanol was removed at reduced pressure. The crude oil was distilled at reduced pressure to give the title compound **32** as a colourless oil (10.43 g, 69%), bp 120-140 °C @ 2.0 mmHg (lit.[57] 145-155 °C @ 5.0 mmHg); δ_H(300 MHz, $CDCl_3$) 1.12 (6 H, t, *J* 7.4, CH_3), 3.14 (2 H, d, *J* 7.4, CH_2), 3.57 (1 H, t, *J* 8.1, CH), 4.08 (4 H, q, *J* 7.4, CH_2) and 7.09-7.18 (5 H, m, Ar-H).

8.3.28 2,2-Dibenzyl-1,3-propanedinitrile[82] (33)

1,3-Propanedinitrile (1.00 g, 1.51 x 10^{-2} mol) in THF (10 mL) was added dropwise to a suspension of sodium hydride (0.60 g, 1.51 x 10^{-2} mol) in THF (20 mL) and the mixture stirred for 30 minutes. (Chloromethyl)benzene (2.01 g, 1.59 x 10^{-2} mol) in THF (10 mL) was added dropwise to the mixture which was stirred overnight. The mixture was worked up with water which was added to excess (100 mL) to obtain a cloudy solution. The aqueous solution was extracted with DCM (3 x 100 mL) and the organic phases combined and dried ($MgSO_4$). The dry solution was separated by filtration and the solvent was removed at reduced pressure to yield the product as a yellow oil which turned into a yellow crystalline solid on cooling. The solid was recrystallised from hot ethanol to give the title product **33** as colourless, tiny needles (0.64 g, 27%) mp 152-153 °C (lit.[82] 131-132 °C); δ_H (300 MHz, $CDCl_3$) 3.26 (4 H, s, CH_2) and 7.27 (10 H, s, Ar-H).

8.3.29 Benzyl-1,3-propanediamide[83] (34)

Diethyl 2-benzyl-1,3-propanedioate (**32**) (10.11 g, 4.00 x 10^{-2} mol) was dissolved in methanol (25 mL), treated with sodium methoxide (0.004 g, 7.80 x 10^{-5} mol) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot ethanol to give the title compound **34** as small colourless needles (4.56 g, 59%) mp 228-229 °C (lit.[83] 224-226°C); δ_H(300 MHz, DMSO-d_6) 2.97 (2 H, d, *J* 8.0, CH_2), 3.31 (1 H, t, *J* 7.4, CH), 7.05 (2 H, s, NH_2) and 7.14-7.30 (7 H, m, Ar-H, NH_2).

8.3.30 2-Benzyl-1,3-propanediamine (35)

2-Benzyl-1,3-propanediamide (**34**) (7.28 g, 3.80 x 10^{-2} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 288 mL, 0.29 mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-evaporated with methanol (5 x 100 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **35** as a colourless oil (4.13 g, 66%, Found: C, 71.1; H, 8.7; N, 16.5%; $C_{11}H_{16}N_2$ requires: C, 73.1; H, 9.8; N, 17.1%); ν(film)/cm^{-1} 3371, 3289, 1974, 1878, 1811 and 1602; δ_H(300 MHz, $CDCl_3$) 1.58 (4 H, s, NH_2), 1.73 (1 H, sep, *J* 6.2, CH), 2.61 (2 H, d, *J* 7.4, CH_2), 2.69 (2 H, d of d, *J* 6.1, *J* 12.7, CH_2), 2.74 (2 H, d of d, *J* 5.5, *J* 12.5, CH_2) and 7.17-7.31 (5 H, m, Ar-H); δ_C(75 MHz, $CDCl_3$) 36.8 (t), 43.6 (t), 46.1 (d), 126.0 (d), 128.4 (d), 129.1 (d) and 140.7 (s).

8.3.31 3,3,9,9-Tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione (36)

To a suspension of K_2CO_3 (8.71 g, 6.30 x 10^{-2} mol) in dry DMF (32 mL) was added 2-benzyl-1,3-propanediamine (**35**) (4.13 g, 2.50 x 10^{-2} mol) and 3-bromo-3-methyl-2-butanone (**29**) (10.40 g, 6.30 x 10^{-2} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (50 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **36** as a

pale yellow wax (5.86 g, 71%); ν(film)/cm^{-1} 3321, 2961 and 1708; δ_H(300 MHz, $CDCl_3$) 1.22 (12 H, s, CH_3), 1.91 (1 H, m, CH), 2.12 (6 H, s, CH_3), 2.31 (2 H, br s, NH_2), 2.38 (2 H, d of d, *J* 7.0, *J* 11.4, CH_2) and 2.47 (2 H, d of d, *J* 4.4, *J* 11.0, CH_2), 2.60 (2 H, d, *J* 7.4, CH_2) and 7.14-7.29 (5 H, m, Ar-H); δ_C(75 MHz, $CDCl_3$) 24.5 (q), 24.8 (q), 38.0 (t), 41.8 (d), 46.6 (t), 63.1 (s), 126.1 (d), 128.4 (s), 129.1 (s), 140.5 (s) and 213.6 (s).

8.3.32 3,3,9,9-Tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione dioxime (37)

Hydroxylamine hydrochloride (7.82 g, 0.113 mol) was added to NaOH (4.20 g, 0.105 mol) in methanol (115 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-tetramethyl-4,8-diaza-6-benzyl-2,10-undecanedione (**36**) (4.96 g, 1.50 x 10^{-2} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from hot ethyl ethanoate/ethanol to give the title compound **37** as a glassy, colourless solid (1.77 g, 33%), mp 176-177 °C; ν(film)/cm^{-1} 3316, 3173, 1636, 1600 and 1495; δ_H(300 MHz, DMSO-d_6) 1.33 (12 H, s, CH_3), 1.79 (6 H, s, CH_3), 2.22 (1 H, m, CH), 2.59 (6 H, m, CH_2, NH), 7.21-7.35 (5 H, m, Ar-H) and 10.88 (2 H, s, OH); δ_C(75 MHz, DMSO-d_6) 10.9 (q), 25.1 (q), 37.8 (t), 38.6 (d), 46.8 (t), 60.5 (s), 127.4 (d), 129.6 (d), 130.2 (d) and 140.6 (s); m/z(ES+) 363 (M + H^+, 100%).

8.3.33 Methyl 4-methoxyphenylethanoate[84] (38)

4-Methoxyphenylethanoic acid (10.0 g, 6.00 x 10^{-2} mol) and triethylamine (6.39 g, 6.30 x 10^{-2} mol) were stirred in DCM (300 mL) and cooled in an ice bath. Methyl chloromethanoate (5.67 g, 6.00 x 10^{-2} mol) was carefully added dropwise and the mixture stirred for a further 10 minutes. *N*,*N*-Dimethyl-4-aminopyridine (0.73 g, 6.00 x 10^{-3} mol) was added and the mixture stirred for a further 30 minutes. After warming to room temperature the mixture was diluted with DCM (300 mL) and washed with sat. $NaHCO_3$ (150 mL), HCl (0.1 mol dm^{-3}, 100 mL) and sat. NaCl (150 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was distilled at reduced pressure to give the title compound **38** as a very pale yellow oil (8.43 g, 78%), bp 139-140 °C @ 10.5 mmHg (lit.[84] 114-116 °C @ 10 mmHg); δ_H(300 MHz, $CDCl_3$) 3.55 (2 H, s, CH_2), 3.65 (3 H, s, CH_3), 3.75 (3 H, s, CH_3), 6.84 (2 H, d, *J* 8.8, CH) and 7.18 (2 H, d, *J* 8.8, CH).

8.3.34 Methyl 2-methoxyphenylethanoate[85] (39)

2-Methoxyphenylethanoic acid (3.0 g, 1.80 x 10^{-2} mol) and triethylamine (1.92 g, 1.90 x 10^{-2} mol) were stirred in DCM (100 mL) and cooled in an ice bath. Methyl chloromethanoate (1.70 g, 1.80 x 10^{-2} mol) was carefully added dropwise and the mixture stirred for a further 10 minutes. *N*,*N*-Dimethyl-4-aminopyridine (0.22 g, 1.80 x 10^{-3} mol) was added and the mixture stirred for a further 30 minutes. After warming to room temperature the mixture was diluted with DCM (100 mL) and washed with sat. $NaHCO_3$ (50 mL), HCl (0.1 mol dm^{-3}, 40 mL) and sat. NaCl (50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was distilled at reduced pressure to give the title compound **39** as a light yellow oil (2.20 g, 65%), bp 131 °C @ 9 mmHg (lit.[85] 120 °C @ 20 mmHg); δ_H(300 MHz, $CDCl_3$) 3.63 (2 H, s, CH_2), 3.67 (3 H, s, CH_3), 3.79 (3 H, s, CH_3), 6.84-6.93 (2 H, m, Ar-H) and 7.16-7.27 (2 H, m, Ar-H).

8.3.35 Methyl 3-(4-methoxyphenyl)propanoate[86] (40)

3-(4-Methoxyphenyl)propanoic acid (6.0 g, 3.30 x 10^{-2} mol) and triethylamine (3.54 g, 3.50 x 10^{-2} mol) were stirred in DCM (200 mL) and cooled in an ice bath. Methyl chloromethanoate (3.12 g, 3.30 x 10^{-2} mol) was carefully added dropwise and the mixture stirred for a further 10 minutes. *N*,*N*-Dimethyl-4-aminopyridine (0.40 g, 3.30 x 10^{-3} mol) was added and the mixture stirred for a further 30 minutes. After warming to room temperature the mixture was diluted with DCM (200 mL) and washed with sat. $NaHCO_3$ (100 mL), HCl (0.1 mol dm^{-3}, 70 mL) and sat. NaCl (100 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was distilled at reduced pressure to give the title compound **40** as a light yellow oil (3.42 g, 53%), bp 150 °C @ 10 mmHg (lit.[86] 154-156 °C @ 16 mmHg); δ_H(300 MHz, $CDCl_3$) 2.59 (2 H, t, *J* 7.7, CH_2), 2.89 (2 H, t, *J* 7.7, CH_2) 3.65 (3 H, s, CH_3), 3.77 (3 H, s, CH_3), 6.82 (2 H, d, *J* 8.8, CH) and 7.11 (2 H, d, *J* 8.8, CH).

8.3.36 Methyl 3-(2-methoxyphenyl)propanoate (41)

3-(2-Methoxyphenyl)propanoic acid (3.0 g, 1.70 x 10^{-2} mol) and triethylamine (1.77 g, 1.75 x 10^{-2} mol) were stirred in DCM (100 mL) and cooled in an ice bath. Methyl chloromethanoate (1.57 g, 1.70 x 10^{-2} mol) was carefully added dropwise and the mixture stirred for a further 10 minutes. *N*,*N*-Dimethyl-4-aminopyridine (0.20 g, 1.70 x 10^{-3} mol)

was added and the mixture stirred for a further 30 minutes. After warming to room temperature the mixture was diluted with DCM (100 mL) and washed with sat. $NaHCO_3$ (50 mL), HCl (0.1 mol dm^{-3}, 40 mL) and sat. NaCl (50 mL). The combined organic phases were dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The residue was distilled at reduced pressure to give the title compound **41** as a light yellow oil (2.58 g, 80%), bp 142.5 °C @ 10.5 mmHg (lit.[87] 146-147 °C @ 10 mmHg); δ_H(300 MHz, $CDCl_3$) 2.60 (2 H, t, *J* 7.7, CH_2), 2.94 (2 H, t, *J* 7.7, CH_2) 3.65 (3 H, s, CH_3), 3.80 (3 H, s, CH_3), 6.81-6.89 (2 H, m, CH) and 7.12-7.21 (2 H, m, CH).

8.3.37 2-(4-Methoxyphenyl)ethanol[88] (42)

Methyl 4-methoxyphenylethanoate (**38**) (6.48 g, 3.60 x 10^{-2} mol) was dissolved in THF (150 mL) and carefully added dropwise into a suspension of lithium aluminium hydride (3.42 g, 9.00 x 10^{-2} mol) in THF (150 mL). After stirring for 1 hour, water was carefully added until effervescing was complete and then 10% H_2SO_4 was added until the mixture clarified. The organic phase was washed with water and sat. $NaHCO_3$ solution then dried ($MgSO_4$). After evaporation of the solvent at reduced pressure the crude oil was chromatographed with DCM/ethyl ethanoate (85:15) on silica to give the title product **42** as a colourless oil (4.65 g, 85%), bp 135 °C @ 10 mmHg (lit.[88] 121 °C @ 7 mmHg); δ_H(300 MHz, $CDCl_3$) 1.97 (1 H, s, OH), 2.81 (2 H, t, *J* 6.6, CH_2), 3.80 (3 H, s, CH_3), 3.81 (2 H, t, *J* 6.8, CH_2), 6.87 (2 H, d, *J* 8.5, CH) and 7.16 (2 H, d, *J* 8.8, CH).

8.3.38 2-(2-Methoxyphenyl)ethanol[89] (43)

Methyl 2-methoxyphenylethanoate (**39**) (1.94 g, 1.08 x 10^{-2} mol) was dissolved in diethyl ether (50 mL) and carefully added dropwise into a suspension of lithium aluminium hydride (1.02 g, 2.70 x 10^{-2} mol) in diethyl ether (50 mL). After stirring for 1 hour, water was carefully added until effervescing was complete and then 10% H_2SO_4 was added until the mixture clarified. The organic phase was washed with water and sat. $NaHCO_3$ solution then dried ($MgSO_4$). After evaporation of the solvent at reduced pressure the crude oil was chromatographed with DCM/ethyl ethanoate (85:15) on silica to give the title product **43** as a colourless oil (1.43 g, 87%), bp 134 °C @ 10 mmHg (lit.[89] 132-134 °C @ 6 mmHg); δ_H(300 MHz, $CDCl_3$) 2.01 (1 H, s, OH), 2.93 (2 H, t, *J* 6.4, CH_2), 3.84 (2 H, t, *J* 6.4, CH_2), 3.84 (3 H, s, CH_3), 6.88-6.96 (2 H, m, Ar-H) and 7.17-7.27 (2 H, m, Ar-H).

8.3.39 3-(4-Methoxyphenyl)-1-propanol[90] (44)

Methyl 3-(4-methoxyphenyl)propanoate (**40**) (3.21 g, 1.70 x 10^{-2} mol) was dissolved in diethyl ether (100 mL) and carefully added dropwise into a suspension of lithium aluminium hydride (1.57 g, 4.13 x 10^{-2} mol) in diethyl ether (100 mL). After stirring for 1 hour, water was carefully added until effervescing was complete and then 10% H_2SO_4 was added until the mixture clarified. The organic phase was washed with water and sat. $NaHCO_3$ solution then dried ($MgSO_4$). After evaporation of the solvent at reduced pressure the crude oil was chromatographed with DCM/ethyl ethanoate (85:15) on silica to give the title product **44** as a colourless oil (2.47 g, 90%), bp 166 °C @ 10 mmHg (lit.[90] 113 °C @ 0.45 mmHg); δ_H(300 MHz, $CDCl_3$) 1.84 (2 H, quin, *J* 7.1, CH_2), 2.09 (1 H, br s, OH), 2.63 (2 H, t, *J* 7.7, CH_2), 3.63 (2 H, t, *J* 6.6, CH_2), 3.77 (3 H, s, CH_3), 6.82 (2 H, d, *J* 8.8, CH) and 7.10 (2 H, d, *J* 8.8, CH).

8.3.40 3-(2-Methoxyphenyl)-1-propanol[91] (45)

Methyl 3-(2-methoxyphenyl)propanoate (**41**) (2.33 g, 1.20 x 10^{-2} mol) was dissolved in diethyl ether (75 mL) and carefully added dropwise into a suspension of lithium aluminium hydride (1.14 g, 3.00 x 10^{-2} mol) in diethyl ether (75 mL). After stirring for 1 hour, water was carefully added until effervescing was complete and then 10% H_2SO_4 was added until the mixture clarified. The organic phase was washed with water and sat. $NaHCO_3$ solution then dried ($MgSO_4$). After evaporation of the solvent at reduced pressure the crude oil was chromatographed with DCM/ethyl ethanoate (85:15) on silica to give the title product **45** as a colourless oil (1.71 g, 88%), bp 140 °C @ 10 mmHg (lit.[91] 118-120 °C @ 1.9-2.0 mmHg); δ_H(300 MHz, $CDCl_3$) 1.84 (2 H, quin, *J* 6.8, CH_2), 2.11 (1 H, br s, OH), 2.71 (2 H, t, *J* 7.4, CH_2), 3.59 (2 H, t, *J* 6.3, CH_2), 3.82 (3 H, s, CH_3), 6.84-6.92 (2 H, m, Ar-H) and 7.12-7.20 (2 H, m, Ar-H).

8.3.41 2-(4-Methoxyphenyl)ethyl 4-methylbenzenesulphonate[92] (46)

2-(4-Methoxyphenyl)ethanol (**42**) (11.87 g, 7.80 x 10^{-2} mol) was dissolved in $CHCl_3$ (60 mL) and cooled in an ice bath. Pyridine (12.34 g, 0.156 mol) was added followed by 4-methylbenzenesulphonyl chloride (22.30 g, 0.117 mol) in portions. The reaction was monitored by TLC and when complete was extracted into diethyl ether and washed with 10 % HCl, 5% $NaHCO_3$ solution and water. The organic phase was dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The crude product was chromatographed with

diethyl ether/40-60 petroleum ether (20:80) on silica then recrystallised from the same solvent mixture to give the title compound **46** as colourless blocks (17.77 g, 74%), mp 57 °C (lit.[92] 57.8-58.8 °C); δ_H(300 MHz, $CDCl_3$) 2.37 (3 H, s, CH_3), 2.83 (2 H, t, *J* 7.0, CH_2), 3.72 (3 H, s, CH_3), 4.11 (2 H, t, *J* 7.0, CH_2), 6.72 (2 H, d, *J* 8.8, CH), 6.96 (2 H, d, *J* 8.1, CH), 7.22 (2 H, d, *J* 8.1, CH) and 7.63 (2 H, d, *J* 8.8, CH).

8.3.42 2-(2-Methoxyphenyl)ethyl 4-methylbenzenesulphonate[93] (47)

2-(2-Methoxyphenyl)ethanol (**43**) (10.11 g, 6.60 x 10^{-2} mol) was dissolved in $CHCl_3$ (60 mL) and cooled in an ice bath. Pyridine (10.56 g, 0.133 mol) was added followed by 4-methylbenzenesulphonyl chloride (18.99 g, 9.90 x 10^{-2} mol) in portions. The reaction was monitored by TLC and when complete was extracted into diethyl ether and washed with 10 % HCl, 5% $NaHCO_3$ solution and water. The organic phase was dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The crude product was chromatographed with diethyl ether/40-60 petroleum ether (20:80) on silica then recrystallised from the same solvent mixture to give the title compound **47** as colourless blocks (15.04 g, 75%), mp 53 °C (lit.[93] 54.6-55.2 °C); δ_H(300 MHz, $CDCl_3$) 2.40 (3 H, s, CH_3), 2.95 (2 H, t, *J* 7.7, CH_2), 3.70 (3 H, s, CH_3), 4.21 (2 H, t, *J* 7.7, CH_2), 6.75 (1 H, d, *J* 8.5, CH), 6.82 (1 H, t, *J* 8.5, CH), 7.06 (1 H, d, *J* 8.5, CH), 7.20 (1 H, t, *J* 8.5, CH), 7.27 (2 H, d, *J* 8.5, CH) and 7.68 (2 H, d, *J* 8.8, CH).

8.3.43 3-(4-Methoxyphenyl)-1-propyl 4-methylbenzenesulphonate[94] (48)

3-(4-Methoxyphenyl)-1-propanol (**44**) (11.51 g, 6.90 x 10^{-2} mol) was dissolved in $CHCl_3$ (60 mL) and cooled in an ice bath. Pyridine (10.95 g, 0.138 mol) was added followed by 4-methylbenzenesulphonyl chloride (19.80 g, 0.10 mol) in portions. The reaction was monitored by TLC and when complete was extracted into diethyl ether and washed with 10 % HCl, 5% $NaHCO_3$ solution and water. The organic phase was dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The crude product was chromatographed with diethyl ether/40-60 petroleum ether (20:80) on silica then recrystallised from the same solvent mixture to give the title compound **48** as colourless blocks (16.48 g, 75%), mp 41-44 °C (lit.[94] 41-43 °C); δ_H(300 MHz, $CDCl_3$) 1.93 (2 H, quin, *J* 6.8, CH_2), 2.45 (3 H, s, CH_3), 2.58 (2 H, t, *J* 7.7, CH_2), 3.77 (3 H, s, CH_3), 4.01 (2 H, t, *J* 6.3, CH_2), 6.77 (2 H, d, *J* 8.8, CH), 6.98 (2 H, d, *J* 88, CH), 7.34 (2 H, d, *J* 8.1, CH) and 7.79 (2 H, d, *J* 8.1, CH).

8.3.44 3-(2-Methoxyphenyl)-1-propyl 4-methylbenzenesulphonate[91] (49)

3-(2-Methoxyphenyl)-1-propanol (**45**) (9.41 g, 5.70 x 10^{-2} mol) was dissolved in $CHCl_3$ (60 mL) and cooled in an ice bath. Pyridine (8.69 g, 0.113 mol) was added followed by 4-methylbenzenesulphonyl chloride (16.19 g, 8.50 x 10^{-2} mol) in portions. The reaction was monitored by TLC and when complete was extracted into diethyl ether and washed with 10 % HCl, 5% $NaHCO_3$ solution and water. The organic phase was dried ($MgSO_4$) and evaporated to dryness at reduced pressure. The crude product was chromatographed with diethyl ether/40-60 petroleum ether (20:80) on silica to give the title compound **49** as a low melting, colourless solid (14.66 g, 80%); δ_H(300 MHz, $CDCl_3$) 1.92 (2 H, quin, *J* 6.8, CH_2), 2.45 (3 H, s, CH_3), 2.63 (2 H, t, *J* 7.7, CH_2), 3.77 (3 H, s, CH_3), 4.03 (2 H, t, *J* 6.3, CH_2), 6.78-7.19 (4 H, m, Ar-H), 7.33 (2 H, d, *J* 8.8, CH) and 7.79 (2 H, d, *J* 8.1, CH).

8.3.45 Diethyl 2-(2-(4-methoxyphenyl)ethyl)-1,3-propanedioate[95] (50)

Diethyl 1,3-propanedioate (9.08 g, 5.66 x 10^{-2} mol) was carefully added dropwise to a suspension of NaH (2.16 g, 5.40 x 10^{-2} mol) in THF (100 mL) and the mixture was stirred for 1 hour. 2-(4-Methoxyphenyl)ethyl 4-methylbenzenesulphonate (**46**) (16.54 g, 5.40 x 10^{-2} mol) in THF (100 mL) was added dropwise and the mixture stirred for a further 1 hour, then the mixture was refluxed for sufficient time to neutralise the solution (moist litmus paper). Water was carefully added to added to neutralise any remaining NaH then the organic phase was washed with water (3 x 100 mL), dried ($MgSO_4$) and evaporated at reduced pressure. The crude product was distilled at reduced pressure to give the title compound **50** as a colourless oil (10.90 g, 69%), bp 201-230 °C @ 12 mmHg (lit.[95] 130-132 °C @ 0.1 mmHg); δ_H(300 MHz, $CDCl_3$) 1.27 (6 H, t, *J* 7.0, CH_3), 2.18 (2 H, q, *J* 8.0, CH_2), 2.60 (2 H, t, *J* 8.0, CH_2), 3.33 (1 H, t, *J* 7.4, CH), 3.78 (3 H, s, CH_3), 4.19 (4 H, q, *J* 7.0, CH_2), 6.83 (2 H, d, *J* 9.0, CH) and 7.10 (2 H, d, *J* 9.0, CH).

8.3.46 Diethyl 2-(2-(2-methoxyphenyl)ethyl)-1,3-propanedioate[96] (51)

Diethyl 1,3-propanedioate (8.65 g, 5.40 x 10^{-2} mol) was carefully added dropwise to a suspension of NaH (1.96 g, 4.90 x 10^{-2} mol) in THF (100 mL) and the mixture was stirred for 1 hour. 2-(2-Methoxyphenyl)ethyl 4-methylbenzenesulphonate (**47**) (15.04 g, 4.90 x 10^{-2} mol) in THF (100 mL) was added dropwise and the mixture stirred for a further 1 hour, then the mixture was refluxed for sufficient time to neutralise the solution (moist litmus paper). Water was carefully added to added to neutralise any remaining NaH then

the organic phase was washed with water (3 x 100 mL), dried ($MgSO_4$) and evaporated at reduced pressure. The crude product was distilled at reduced pressure to give the title compound **51** as a colourless oil (12.55 g, 87%), bp 190-215 °C @ 12 mmHg (lit.[96] 204-206 °C @ 15 mmHg); δ_H(300 MHz, $CDCl_3$) 1.26 (6 H, t, *J* 7.1, CH_3), 2.19 (2 H, q, *J* 7.6, CH_2), 2.67 (2 H, t, *J* 7.4, CH_2), 3.34 (1 H, t, *J* 7.7, CH), 3.80 (3 H, s, CH_3), 4.19 (4 H, q, *J* 7.1, CH_2) and 6.82-7.27 (4 H, m, Ar-H).

8.3.47 Diethyl 2-(3-(4-methoxyphenyl)-1-propyl)-1,3-propanedioate[97] (52)

Diethyl 1,3-propanedioate (9.16 g, 5.70 x 10^{-2} mol) was carefully added dropwise to a suspension of NaH (2.08 g, 5.70 x 10^{-2} mol) in THF (100 mL) and the mixture was stirred for 1 hour. 3-(4-Methoxyphenyl)-1-propyl 4-methylbenzenesulphonate (**48**) (16.48 g, 5.20 x 10^{-2} mol) in THF (100 mL) was added dropwise and the mixture stirred for a further 1 hour, then the mixture was refluxed for sufficient time to neutralise the solution (moist litmus paper). Water was carefully added to added to neutralise any remaining NaH then the organic phase was washed with water (3 x 100 mL), dried ($MgSO_4$) and evaporated at reduced pressure. The crude product was distilled at reduced pressure to give the title compound **52** as a colourless oil (13.41 g, 84%), bp 225-230 °C @ 16 mmHg (lit.[97] 189-190 °C @ 1.0 mmHg); δ_H(300 MHz, $CDCl_3$) 1.25 (6 H, t, *J* 7.4, CH_3), 1.62 (2 H, quin, *J* 7.9, CH_2), 1.92 (2 H, q, *J* 7.8, CH_2), 2.58 (2 H, t, *J* 7.7, CH_2), 3.33 (1 H, t, *J* 7.4, CH), 3.77 (3 H, s, CH_3), 4.18 (4 H, q, *J* 7.1, CH_2), 6.81 (2 H, d, *J* 8.8, CH) and 7.08 (2 H, d, *J* 8.1, CH).

8.3.48 Diethyl 2-(3-(2-methoxyphenyl)-1-propyl)-1,3-propanedioate (53)

Diethyl 1,3-propanedioate (8.06 g, 5.00 x 10^{-2} mol) was carefully added dropwise to a suspension of NaH (1.83 g, 4.60 x 10^{-2} mol) in THF (100 mL) and the mixture was stirred for 1 hour. 3-(2-methoxyphenyl)-1-propyl 4-methylbenzenesulphonate (**49**) (14.66 g, 4.60 x 10^{-2} mol) in THF (100 mL) was added dropwise and the mixture stirred for a further 1 hour, then the mixture was refluxed for sufficient time to neutralise the solution (moist litmus paper). Water was carefully added to added to neutralise any remaining NaH then the organic phase was washed with water (3 x 100 mL), dried ($MgSO_4$) and evaporated at reduced pressure. The crude product was distilled at reduced pressure to give the title compound **53** as a colourless oil (11.59 g, 82%), bp 215-220 °C @ 18 mmHg; ν(film)/cm^{-1} 1749, 1600, 1588 and 1494; δ_H(300 MHz, $CDCl_3$) 1.25 (6 H, t, *J* 7.4, CH_3), 1.62 (2 H,

quin, *J* 7.7, CH_2), 1.94 (2 H, q, *J* 7.6, CH_2), 2.64 (2 H, t, *J* 7.4, CH_2), 3.37 (1 H, t, *J* 7.4, CH), 3.80 (3 H, s, CH_3), 4.18 (4 H, q, *J* 7.1, CH_2), 6.81-6.89 (2 H, m, Ar-H) and 7.10-7.19 (2 H, m, Ar-H); δ_C(75 MHz, $CDCl_3$) 14.2 (q), 27.7 (t), 28.7 (t), 29.9 (t), 52.1 (d), 55.3 (q), 61.4 (t), 110.3 (d), 120.5 (d), 127.3 (d), 130.0 (d), 130.3 (s), 157.6 (s) and 169.7 (s).

8.3.49 2-(2-(4-Methoxyphenyl)ethyl)-1,3-propanediamide[98] (54)

Diethyl 2-(2-(4-methoxyphenyl)ethyl)-1,3-propanedioate (**50**) (10.90 g, 3.70 x 10^{-2} mol) was dissolved in methanol (50 mL) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot methanol to give the title compound **54** as a colourless solid (6.33 g, 72%), mp 219-221 °C (lit.[98] 212-213 °C); δ_H(300 MHz, DMSO-d_6) 1.92 (2 H, q, *J* 7.6, CH_2), 2.45 (2 H, q, *J* 7.7, CH_2), 3.00 (1 H, t, *J* 7.4, CH), 3.73 (3 H, s, CH_3), 6.86 (2 H, d, *J* 8.8, CH), 7.09 (2 H, s, NH_2), 7.10 (2 H, d, *J* 8.8, CH) and 7.30 (2 H, s, NH_2).

8.3.50 2-(2-(2-Methoxyphenyl)ethyl)-1,3-propanediamide (55)

Diethyl 2-(2-(2-methoxyphenyl)ethyl)-1,3-propanedioate (**51**) (2.60 g, 1.11 x 10^{-2} mol) was dissolved in ethanol/toluene (1:1, 50 mL) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot toluene to give the title compound **55** as a colourless solid (0.52 g, 20%, Found: C, 61.0; H, 6.8; N, 11.81%; $C_{12}H_{16}N_2O_3$ requires: C, 61.0; H; 6.8, N, 11.9%), mp 232-235 °C; ν(Nujol)/cm^{-1} 3377, 3187 and 1667; δ_H(300 MHz, DMSO-d_6) 1.90 (2 H, q, *J* 7.8, CH_2), 2.47 (2 H, q, *J* 8.1, CH_2), 2.98 (1 H, t, *J* 7.4, CH), 3.76 (3 H, s, CH_3), 6.86 (1 H, t, *J* 7.4, CH), 6.93 (1 H, d, *J* 8.1, CH), 7.06 (2 H, s, NH_2), 7.09 (1 H, d, *J* 7.6, CH), 7.18 (1 H, t, *J* 7.6, CH) and 7.27 (2 H, s, NH_2); δ_C(75 MHz, DMSO-d_6) 29.7 (t), 30.6 (t), 52.9 (d), 55.1 (q), 110.5 (d), 120.2 (d), 127.2 (d), 129.1 (s), 129.3 (d), 157.0 (s) and 171.4 (s); m/z(ES+) 237 ($M + H^+$).

8.3.51 2-(3-(4-Methoxyphenyl)-1-propyl)-1,3-propanediamide (56)

Diethyl 2-(3-(4-methoxyphenyl)-1-propyl)-1,3-propanedioate (**52**) (4.00 g, 1.61 x 10^{-2} mol) was dissolved in 2-propanol (50 mL) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot toluene to give the title compound **56** as a colourless solid (1.12 g, 28%, Found: C, 61.9; H, 6.0; N, 8.9%; $C_{13}H_{18}N_2O_3$ requires: C, 62.4; H; 7.3, N, 11.2%), mp 200-202 °C; ν(Nujol)/cm^{-1} 3408, 3159 and 1655; δ_H(300 MHz, DMSO-d_6) 1.47 (2 H, m, CH_2), 1.65 (2 H, m, CH_2), 2.50 (2 H, q, *J* 7.7, CH_2), 2.98 (1 H, t, *J* 7.4, CH), 3.71 (3 H, s, CH_3), 6.83 (2 H, d, *J* 8.1, CH), 7.05 (2 H, s, NH_2), 7.07 (2 H, d, *J* 8.8, CH) and 7.28 (2 H, s, NH_2); δ_C(75 MHz, DMSO-d_6) 29.2 (t), 30.6 (t), 33.8 (t), 52.8 (d), 54.9 (q), 113.6 (d), 129.1 (d), 133.7 (s), 157.3 (s) and 171.8 (s); m/z(ES+) 251 ($M + H^+$).

8.3.52 2-(3-(2-Methoxyphenyl)-1-propyl)-1,3-propanediamide (57)

Diethyl 2-(3-(2-methoxyphenyl)-1-propyl)-1,3-propanedioate (**53**) (4.05 g, 1.63 x 10^{-2} mol) was dissolved in 2-propanol/toluene (1:1, 50 mL) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot toluene/60-80 petroleum ether to give the title compound **57** as a colourless solid (1.38 g, 32%, Found: C, 62.5; H, 7.0; N, 11.0%; $C_{13}H_{18}N_2O_3$ requires: C, 62.4; H; 7.3, N, 11.2%), mp 159-169 °C; ν(Nujol)/cm^{-1} 3394, 3184 and 1674; δ_H(300 MHz, DMSO-d_6) 1.48 (2 H, m, CH_2), 1.67 (2 H, m, CH_2), 2.53 (2 H, q, *J* 7.7, CH_2), 2.98 (1 H, t, *J* 7.4, CH), 3.76 (3 H, s, CH_3), 6.85 (1 H, t, *J* 7.4, CH), 6.93 (1 H, d, *J* 8.1, CH), 7.04 (2 H, s, NH_2), 7.09-7.19 (2 H, m, Ar-H) and 7.27 (2 H, s, NH_2); δ_C(75 MHz, DMSO-d_6) 29.3 (t), 30.0 (t), 30.6 (t), 52.9 (d), 55.1 (q), 110.5 (d), 120.1 (d), 127.1 (d), 129.5 (d), 129.7 (s), 157.0 (s) and 171.8 (s); m/z(ES+) 251 ($M + H^+$).

8.3.53 2-(2-(4-Methoxyphenyl)ethyl)-1,3-propanediamine (58)

(4-Methoxyphenyl)ethyl)-1,3-propanediamide (**54**) (3.00 g, 1.30 x 10^{-2} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 100 mL, 0.10 mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and

concentrated by evaporation at reduced pressure. The residue was repeatedly co-evaporated with methanol (5 x 50 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **58** as a colourless oil (1.95 g, 72%); ν(film)/cm^{-1} 3371, 3292, 1611, 1583 and 1512; δ_H(300 MHz, $CDCl_3$) 1.24 (4 H, br s, NH_2), 1.44 (1 H, sep, *J* 5.9, CH), 1.59 (2 H, q, *J* 7.6, CH_2), 2.59 (2 H, t, *J* 7.7, CH_2), 2.73 (2 H, d of d, *J* 5.5, *J* 15.8, CH_2), 2.78 (2 H, d of d, *J* 5.9, *J* 16.2, CH_2), 3.78 (3 H, s, CH_3), 6.82 (2 H, d, *J* 8.1, CH) and 7.11 (2 H, d, *J* 8.8, CH); δ_C(75 MHz, $CDCl_3$) 32.1 (t), 32.6 (t), 43.6 (d), 43.9 (t), 55.4 (q), 114.0 (d), 129.3 (d), 134.7 (s) and 157.9 (s); m/z(ES+) 209 ($M + H^+$).

8.3.54 2-(2-(2-Methoxyphenyl)ethyl)-1,3-propanediamine (59)

2-(2-(2-Methoxyphenyl)ethyl)-1,3-propanediamide (**55**) (0.51 g, 2.16 x 10^{-3} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 17.3 mL, 1.73 x 10^{-2} mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-evaporated with methanol (5 x 20 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **59** as a colourless oil (0.32 g, 71%); ν(film)/cm^{-1} 3358, 3289, 1600 and 1586; δ_H(300 MHz, $CDCl_3$) 1.47 (1 H, m, CH), 1.57 (2 H, q, *J* 7.6, CH_2), 1.88 (4 H, br s, NH_2), 2.62 (2 H, t, *J* 7.9, CH_2), 2.75 (2 H, d of d, *J* 5.9, *J* 13.2, CH_2), 2.80 (2 H, d of d, *J* 3.9, *J* 13.2, CH_2), 3.80 (3 H, s, CH_3), 6.82-6.91 (2 H, m, Ar-H) and 7.11-7.21 (2 H, m, CH); δ_C(75 MHz, $CDCl_3$) 27.4 (t), 29.8 (t), 43.4 (d), 43.6 (t), 55.2 (q), 110.2 (d), 120.4 (d), 127.0 (d), 129.6 (d), 130.8 (s) and 157.2 (s); m/z(FAB) 209 ($M + H^+$).

8.3.55 2-(3-(4-Methoxyphenyl)-1-propyl)-1,3-propanediamine (60)

2-(3-(4-Methoxyphenyl)-1-propyl)-1,3-propanediamide (**56**) (1.11 g, 4.43 x 10^{-3} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 34 mL, 3.40 x 10^{-2} mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-

evaporated with methanol (5 x 50 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **60** as a colourless oil (0.65 g, 66%); ν(film)/cm^{-1} 3368, 3294, 1611, 1584 and 1512; δ_H(300 MHz, $CDCl_3$) 1.31 (2 H, m, CH_2), 1.42 (1 H, sep, *J* 6.1, CH), 1.57 (6 H, m, CH_2, NH_2), 2.56 (2 H, t, *J* 7.4, CH_2), 2.67 (2 H, d of d, *J* 5.9, *J* 12.5, CH_2), 2.72 (2 H, d of d, *J* 5.2, *J* 12.5, CH_2), 3.78 (3 H, s, CH_3), 6.82 (2 H, d, *J* 8.8, CH) and 7.09 (2 H, d, *J* 8.1, CH); δ_C(75 MHz, $CDCl_3$) 29.2 (t), 29.4 (t), 35.4 (t), 43.7 (d), 43.8 (t), 55.3 (q), 113.8 (d), 129.3 (d), 134.6 (s) and 157.8 (s); m/z(ES+) 223 ($M + H^+$).

8.3.56 2-(3-(2-Methoxyphenyl)-1-propyl)-1,3-propanediamine (61)

2-(3-(2-Methoxyphenyl)-1-propyl)-1,3-propanediamide (**57**) (1.37 g, 5.47 x 10^{-3} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 43.8 mL, 4.38 x 10^{-2} mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-evaporated with methanol (5 x 50 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **61** as a colourless oil (1.05 g, 86%); ν(film)/cm^{-1} 3370, 3290, 1600 and 1587; δ_H(300 MHz, $CDCl_3$) 1.34 (2 H, m, CH_2), 1.44 (5 H, m, NH_2, CH), 1.60 (2 H, m, CH_2), 2.60 (2 H, t, *J* 7.4, CH_2), 2.67 (2 H, d of d, *J* 5.9, *J* 16.9, CH_2), 2.71 (2 H, d of d, *J* 5.9, *J* 16.9, CH_2), 3.80 (3 H, s, CH_3), 6.81-6.89 (2 H, m, Ar-H) and 7.10-7.19 (2 H, m, CH); δ_C(75 MHz, $CDCl_3$) 27.0 (t), 29.5 (t), 30.4 (t), 43.5 (d), 43.7 (t), 55.1 (q), 110.1 (d), 120.2 (d), 126.8 (d), 129.6 (d), 130.7 (s) and 157.2 (s); m/z(FAB) 223 ($M + H^+$).

8.3.57 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(4-methoxyphenyl)ethyl)-2,10-undecanedione (62)

To a suspension of K_2CO_3 (3.23 g, 2.30 x 10^{-2} mol) in dry DMF (10 mL) was added 2-(2-(4-Methoxyphenyl)ethyl)-1,3-propanediamine (**58**) (1.95 g, 9.36 x 10^{-3} mol) and 3-bromo-3-methyl-2-butanone (**29**) (3.86 g, 2.30 x 10^{-2} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (50 mL) was added. The mixture was filtered and the

solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **62** as a pale orange wax (2.07 g, 59%); ν(film)/cm^{-1} 3323, 1706, 1675, 1612, 1584 and 1513; δ_H(300 MHz, $CDCl_3$) 1.25 (12 H, s, CH_3), 1.58 (3 H, m, CH, CH_2), 1.97 (2 H, br s, NH), 2.18 (6 H, s, CH_3), 2.40 (2 H, m, CH_2), 2.53 (4 H, m, CH_2), 3.78 (3 H, s, CH_3), 6.82 (2 H, d, *J* 8.8, CH) and 7.08 (2 H, d, *J* 8.1, CH); δ_C(75 MHz, $CDCl_3$) 24.3 (q), 24.5 (q), 24.8 (q), 32.5 (t), 33.4 (t), 39.2 (d), 46.9 (t), 55.2 (q), 62.9 (s), 113.8 (d), 129.2 (d), 134.4 (s), 157.7 (s) and 213.4 (s); m/z(ES+) 377 ($M + H^+$).

8.3.58 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-methoxyphenyl)ethyl)-2,10-undecanedione (63)

To a suspension of K_2CO_3 (0.532 g, 3.85 x 10^{-3} mol) in dry DMF (2.5 mL) was added 2-(2-(2-Methoxyphenyl)ethyl)-1,3-propanediamine (**59**) (0.32 g, 1.54 x 10^{-3} mol) and 3-bromo-3-methyl-2-butanone (**29**) (0.635 g, 3.85 x 10^{-3} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (20 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **63** as a pale orange wax (0.20 g, 35%); ν(film)/cm^{-1} 3306, 1706, 1674, 1600 and 1588; δ_H(300 MHz, $CDCl_3$) 1.28 (12 H, m, CH_3), 1.50 (3 H, m, CH, CH_2), 2.18 (6 H, s, CH_3), 2.43-2.58 (6 H, m, CH_2), 3.80 (3 H, s, CH_3), 6.81-6.88 (2 H, m, CH) and 7.08-7.18 (2 H, m, CH); δ_C(75 MHz, $CDCl_3$) 24.2 (q), 24.6 (q), 24.9 (q), 27.6 (t), 31.4 (t), 39.8 (d), 47.0 (t), 55.1 (q), 63.0 (s), 110.1 (d), 120.3 (d), 127.0 (d), 129.6 (d), 130.4 (s), 157.2 (s) and 212.2 (s); m/z(ES+) 377 ($M + H^+$).

8.3.59 3,3,9,9-Tetramethyl-4,8-diaza-6-(3-(4-methoxyphenyl)-1-propyl)-2,10-undecanedione (64)

To a suspension of K_2CO_3 (1.01 g, 7.31 x 10^{-3} mol) in dry DMF (5 mL) was added 2-(3-(4-methoxyphenyl)-1-propyl)-1,3-propanediamine (**60**) (0.65 g, 2.92 x 10^{-3} mol) and 3-bromo-3-methyl-2-butanone (**29**) (1.21 g, 7.31 x 10^{-3} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (20 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **64** as a pale orange wax (0.63 g, 55%); ν(film)/cm^{-1} 3312, 1706, 1612, 1584 and 1512; δ_H(270

MHz, $CDCl_3$) 1.25 (14 H, m, CH_3, CH_2), 1.70 (3 H, m, CH, CH_2), 2.30 (6 H, s, CH_3), 2.44-2.70 (6 H, m, CH_2), 3.92 (3 H, s, CH_3), 6.94 (2 H, d, *J* 8.7, CH) and 7.20 (2 H, d, *J* 8.7, CH); δ_C(75 MHz, $CDCl_3$) 24.2 (q), 24.4 (q), 24.8 (q), 29.2 (t), 31.0 (t), 35.2 (t), 39.4 (d), 47.1 (t), 55.2 (q), 63.0 (s), 113.7 (d), 129.3 (d), 134.4 (s), 157.7 (s) and 213.3 (s); m/z(ES+) 390 ($M + H^+$).

8.3.60 3,3,9,9-Tetramethyl-4,8-diaza-6-(3-(2-methoxyphenyl)-1-propyl)-2,10-undecanedione (65)

To a suspension of K_2CO_3 (1.66 g, 1.22 x 10^{-2} mol) in dry DMF (10 mL) was added 2-(3-(2-methoxyphenyl)-1-propyl)-1,3-propanediamine (**61**) (1.05 g, 4.72 x 10^{-3} mol) and 3-bromo-3-methyl-2-butanone (**29**) (1.94 g, 1.20 x 10^{-2} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (50 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (95:5) on silica to give the title compound **65** as a pale orange wax (0.93 g, 50%); ν(film)/cm^{-1} 3400, 3318,1706, 1674, 1600 and 1588; δ_H(300 MHz, $CDCl_3$) 1.26 (12 H, m, CH_3), 1.33 (2 H, m, CH_2), 1.56 (2 H, m, CH_2), 1.64 (1 H, m, CH), 2.17 (6 H, s, CH_3), 2.47-2.60 (6 H, m, CH_2), 3.81 (3 H, s, CH_3), 6.82-6.89 (2 H, m, CH) and 7.09-7.19 (2 H, m, CH); δ_C(75 MHz, $CDCl_3$) 24.3 (q), 24.5 (q), 24.9 (q), 27.4 (t), 30.6 (t), 31.4 (t), 39.4 (d), 47.3 (t), 55.3 (q), 63.2 (s), 110.3 (d), 120.5 (d), 127.1 (d), 130.0 (d), 130.9 (s), 157.5 (s) and 213.5 (s); m/z(ES+) 391 ($M + H^+$).

8.3.61 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(4-methoxyphenyl)ethyl)-2,10-undecanedione dioxime (66)

Hydroxylamine hydrochloride (2.87 g, 4.12 x 10^{-2} mol) was added to NaOH (1.54 g, 3.85 x 10^{-2} mol) in methanol (40 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(4-methoxyphenyl)ethyl)-2,10-undecanedione (**62**) (2.07 g, 5.50 x 10^{-3} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from hot ethanol to give the title compound **66** as a shiny, colourless solid (0.89 g, 40%), mp 200-201 °C; ν(Nujol)/cm^{-1} 3356, 3300, 3194,1612, 1585 and 1513; δ_H(300 MHz, DMSO-d_6) 1.33 (12 H, s, CH_3), 1.53 (3 H, br s, CH, CH_2), 1.82 (6 H, s, CH_3), 2.42-2.67 (6 H, m, CH_2), 3.72 (3 H, s, CH_3), 5.95 (2 H, br s, NH), 6.84 (2 H, d, *J* 8.1, CH), 7.15 (2 H, d, *J*

8.1, CH) and 10.94 (2 H, s, OH); δ_C(75 MHz, DMSO-d_6) 9.7 (q), 23.9 (q), 31.5 (t), 32.7 (t), 46.0 (t), 55.0 (q), 59.3 (s), 113.7 (d), 129.2 (d), 133.8 (s) and 157.4 (s); m/z(ES+) 407 ($M + H^+$).

8.3.62 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-methoxyphenyl)ethyl)-2,10-undecanedione dioxime (67)

Hydroxylamine hydrochloride (0.37 g, 5.31 x 10^{-3} mol) was added to NaOH (0.20 g, 4.96 x 10^{-3} mol) in methanol (5 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-methoxyphenyl)ethyl)-2,10-undecanedione (**63**) (0.20 g, 5.31 x 10^{-4} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and precipitated from hot ethanol to give the title compound **67** as a colourless gum (0.50 g, 23%); δ_H(300 MHz, DMSO-d_6) 1.30 (12 H, s, CH_3), 1.42 (3 H, br s, CH, CH_2), 1.77 (6 H, s, CH_3), 2.58-2.65 (6 H, m, CH_2), 3.72 (3 H, s, CH_3), 3.74 (2 H, br s, NH), 6.79-6.90 (2 H, m, CH), 7.11-7.13 (2 H, m, CH) and 10.89 (2 H, s, OH); δ_C(75 MHz, DMSO-d_6)10.2 (q), 24.2 (q), 24.5 (q), 27.1 (t), 31.4 (t), 55.8 (q), 111.1 (d), 120.8 (d), 127.7 (d), 130.0 (d), 130.1 (s), 157.4 (s) and 221.5 (s); m/z(ES+) 407 ($M + H^+$).

8.3.63 3,3,9,9-Tetramethyl-4,8-diaza-6-(3-(4-methoxyphenyl)-1-propyl)-2,10-undecanedione dioxime (68)

Hydroxylamine hydrochloride (1.12 g, 1.61 x 10^{-2} mol) was added to NaOH (0.60 g, 1.51 x 10^{-2} mol) in methanol (15 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-tetramethyl-4,8-diaza-6-(3-(4-methoxyphenyl)-1-propyl)-2,10-undecanedione (**64**) (0.63 g, 1.61 x 10^{-3} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from hot ethanol to give the title compound **68** as a colourless solid (0.26 g, 38%, Found: C, 58.5; H, 9.0; N, 11.5%; $C_{23}H_{40}N_4O_3$ requires: C, 65.7; H, 9.6; N, 13.3%), mp 185 °C; ν(Nujol)/cm^{-1} 3216, 1612, and 1513; δ_H(300 MHz, DMSO-d_6) 1.32 (15 H, s, CH_3), 1.50 (3 H, br s, CH, CH_2), 1.80 (6 H, s, CH_3), 2.48-2.62 (6 H, m, CH_2), 3.73 (3 H, s, CH_3), 4.44 (2 H, br s, NH), 6.85 (2 H, d, *J* 6.6, CH), 7.11 (2 H, d, *J* 7.4, CH) and 10.89 (2 H, s, OH); δ_C(75 MHz, DMSO-d_6) 9.8 (q), 23.9 (q), 28.6 (t), 30.1 (t), 34.4 (t), 46.4 (t), 55.1 (q), 59.3

(s), 113.8 (d), 129.3 (d), 134.0 (s) and 157.5 (s); m/z(ES+) 421 ($M + H^+$).

8.3.64 3,3,9,9-Tetramethyl-4,8-diaza-6-(3-(2-methoxyphenyl)-1-propyl)-2,10-undecanedione dioxime (69)

Hydroxylamine hydrochloride (1.65 g, 2.38 x 10^{-2} mol) was added to NaOH (0.89 g, 2.22 x 10^{-2} mol) in methanol (15 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-tetramethyl-4,8-diaza-6-(3-(2-methoxyphenyl)-1-propyl)-2,10-undecanedione (**65**) (0.93 g, 2.38 x 10^{-3} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from hot ethanol to give the title compound **69** as shiny, colourless needles (0.39 g, 39%, Found: C, 59.8; H, 9.1; N, 12.3%; $C_{23}H_{40}N_4O_3$ requires: C, 65.7; H, 9.6; N, 13.3%), mp 198 °C; ν(Nujol)/cm^{-1} 3317, 3194, 1588 and 1492; δ_H(300 MHz, DMSO-d_6) 1.31 (15 H, s, CH_3), 1.49 (3 H, br s, CH, CH_2), 1.80 (6 H, s, CH_3), 2.56-2.61 (6 H, m, CH_2), 3.78 (3 H, s, CH_3), 4.48 (2 H, br s, NH), 6.84-6.96 (2 H, m, CH), 7.12-7.21 (2 H, m, CH) and 10.87 (2 H, s, OH); δ_C(75 MHz, DMSO-d_6) 10.2 (q), 24.4 (q), 27.1 (t), 30.2 (t), 30.8 (t), 46.8 (t), 55.7 (q), 59.7 (s), 111.1 (d), 120.7 (d), 127.6 (d), 130.1 (d), 130.3 (s) and 157.5 (s); m/z(ES+) 421 ($M + H^+$).

8.3.65 2-(2-Chloroethyl)pyridine[62] (70)

2-(2-Hydroxyethyl)pyridine (5.50 g, 4.50 x 10^{-2} mol) in $CHCl_3$ (10 mL) was treated dropwise with thionyl chloride (6.50 g, 5.50 x 10^{-2} mol) and heated for 2 hours at 65 °C. After removal of the solvent under reduced pressure, water was added and the mixture extracted twice with 10% HCl. The aqueous solution was neutralised with K_2CO_3 and the product extracted into DCM. After drying ($MgSO_4$) the solvent was removed under reduced pressure to give the title product **70** as a light brown oil (6.48 g, 100%), bp 88-90 °C @ 12 mmHg (lit.[62] 85-90 °C @ 10 mmHg); δ_H(300 MHz, $CDCl_3$) 3.23 (2 H, t, *J* 7.0, CH_2), 3.93 (2 H, t, *J* 6.8, CH_2), 7.17 (1 H, d of d, *J* 5.4, *J* 8.0, CH), 7.20 (1 H, d, *J* 8.5, CH), 7.63 (1 H, d of d, *J* 7.7, *J* 7.7, CH) and 8.56 (1 H, d, *J* 4.0, CH).

8.3.66 2-(3-Chloro-1-propyl)pyridine Hydrochloride[64] (71)

2-(3-Hydroxy-1-propyl)pyridine (9.33 g, 6.80 x 10^{-2} mol) in DCM (20 mL) was treated dropwise with thionyl chloride (13.00 g, 0.11 mol) and refluxed for 3 hours. After removal

of the solvent under reduced pressure, the dark brown oil was triturated with toluene and the resulting solid filtered and washed with pentane to give the title product **71** as a light brown powdery solid (13.19 g, 100%), mp 101-104 °C; δ_H(300 MHz, $CDCl_3$) 2.34 (2 H, m, CH_2), 3.35 (2 H, t, *J* 7.7, CH_2), 3.55 (2 H, t, *J* 7.8, CH_2), 7.77 (1 H, d, *J* 8.1, CH), 7.80 (1 H, t(app), *J* 6.6, CH), 8.36 (1 H, d of d, *J* 8.1, *J* 8.1, CH) and 8.64 (1 H, d, *J* 5.9, CH).

8.3.67 Diethyl 2-(2-(2-pyridinyl)ethyl)-1,3-propanedioate[67] (72)

Sodium metal (2.07 g, 9.00 x 10^{-2} mol) was dissolved in ethanol (50 mL). To the rapidly stirring solution was slowly added diethyl-1,3-propanedioate (45.70 g, 0.28 mol), stirring was continued for 30 minutes during which time a thick white precipitate formed. To this mixture was slowly 2-ethenylpyridine (20.0 g, 0.19 mol) which was then refluxed overnight. After sufficient further refluxing to neutralise the solution (moist litmus paper) the ethanol was removed at reduced pressure. The crude oil was diluted with water (100 mL) and concHCl (30 mL) and washed with diethyl ether. The aqueous phase was basified with 20% NaOH and the oily product extracted into diethyl ether. After washing with water the organic phase was dried ($MgSO_4$) and evaporated at reduced pressure. The crude oil was distilled at reduced pressure to give the title compound **72** as a yellow oil (22.74 g, 45%), bp 200-202 °C @ 13.5 mmHg (lit.[67] 130-134 °C @ 0.1 mmHg); δ_H(300 MHz, $CDCl_3$) 1.27 (6 H, t, *J* 7.0, CH_3), 2.35 (2 H, q(app), *J* 7.6, CH_2), 2.85 (2 H, t, *J* 7.7, CH_2), 3.40 (1 H, t, *J* 7.4, CH), 4.20 (4 H, q, *J* 6.9, CH_2), 7.13 (2 H, m, CH), 7.60 (1 H, d of d, *J* 7.7, *J* 7.7, CH) and 8.53 (1 H, d, *J* 4.4, CH).

8.3.68 2-(2-(2-Pyridinyl)ethyl)-1,3-propanediamide (73)

Diethyl 2-(2-(2-pyridinyl)ethyl)-1,3-propanedioate (**72**) (11.00 g, 4.10 x 10^{-2} mol) was dissolved in methanol (50 mL), treated with sodium methoxide (0.01 g, 2.55 x 10^{-4} mol) and saturated with ammonia gas at 0 °C. The mixture was left overnight at room temperature and was again saturated with ammonia gas and then placed in a freezer for 48 hours. The precipitated solid was filtered and the filtrate concentrated to yield more solid. The combined solid was recrystallised from hot ethanol to give the title compound **73** as colourless needless (6.54 g, 76%, Found: C, 58.3; H, 6.1; N, 20.4; $C_{10}H_{13}N_3O_2$ requires C, 58.0; H, 6.3; N, 20.3), mp 215-216 °C; ν(Nujol)/cm^{-1} 3383, 3168 and 1671; δ_H(300 MHz, DMSO-d_6) 2.06 (2 H, q(app), *J* 7.8, CH_2), 2.66 (2 H, t(app), *J* 7.7, CH_2), 3.03 (1 H, t, *J* 7.7, CH), 7.10 (2 H, br s, NH_2), 7.20 (2 H, m, CH), 7.30 (2 H, br s, NH_2), 7.70 (1 H, d of

d, *J* 7.7, *J* 7.4, CH) and 8.48 (1 H, d, *J* 5.1, CH); δ_C(75 MHz, DMSO-d_6) 29.5 (t), 35.2 (t), 52.5 (d), 121.2 (d), 122.7 (d), 136.4 (d), 148.9 (d), 160.7 (s) and 171.3 (s); m/z(ES+) 207 ($M + H^+$).

8.3.69 2-(2-(2-Pyridinyl)ethyl)-1,3-propanediamine (74)

2-(2-(2-Pyridinyl)ethyl)-1,3-propanediamide (**73**) (3.00 g, 1.40 x 10^{-2} mol) was added slowly, in portions to a solution of borane in THF (1 mol dm^{-3}, 100 mL, 0.10 mol). The mixture was refluxed for 24 hours, carefully acidified at 0 °C with concHCl to pH1 and concentrated by evaporation at reduced pressure. The residue was repeatedly co-evaporated with methanol (5 x 200 mL) and then neutralised with 10% NaOH solution. The aqueous solution was then saturated with salt and extracted with DCM. The combined organic phases were dried (Na_2SO_4) and evaporated at reduced pressure. The crude oil was distilled by kugelrohr at reduced pressure to give the title compound **74** as a yellow oil (1.35 g, 52%); ν(film)/cm^{-1} 3364, 3282, 1673, 1591 and 1568; δ_H(300 MHz, $CDCl_3$) 1.50 (1 H, sep, *J* 6.1, CH), 1.64 (4 H, br s, NH_2) 1.75 (2 H, m, CH_2), 2.80 (6 H, m, CH_2), 7.11 (1 H, d of d, *J* 5.5, *J* 7.0, CH), 7.17 (1 H, d, *J* 8.1, CH), 7.59 (1 H, d of d, *J* 7.4, *J* 7.7, CH) and 8.52 (1 H, d, *J* 4.0, CH); δ_C(75 MHz, $CDCl_3$) 29.9 (t), 35.7 (t), 43.3 (d), 43.7 (t), 121.1 (d), 122.7 (d), 136.4 (d), 149.2 (d) and 162.0 (s); m/z(ES+) 179 ($M + H^+$).

8.3.70 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)ethyl)-2,10-undecanedione (75)

To a suspension of K_2CO_3 (2.50 g, 1.90 x 10^{-2} mol) in dry DMF (10 mL) was added 2-(2-(2-pyridinyl)ethyl)-1,3-propanediamine (**74**) (1.35 g, 7.53 x 10^{-3} mol) and 3-bromo-3-methyl-2-butanone (**29**) (3.10 g, 1.90 x 10^{-2} mol). The mixture was stirred for 18 hours at 45 °C after which time DCM (50 mL) was added. The mixture was filtered and the solvent removed at reduced pressure. The product was loaded onto a silica pad and chromatographed with DCM/methanol (85:15) on silica to give the title compound **75** as a pale yellow wax (1.03 g, 39%); ν(film)/cm^{-1} 3304, 1705, 1668, 1592 and 1568; δ_H(300 MHz, $CDCl_3$) 1.32 (12 H, s, CH_3), 1.70 (2 H, m, CH_2), 1.83 (1 H, m, CH), 2.20 (6 H, s, CH_3), 2.46 (2 H, d of d, *J* 8.1, *J* 11.0, CH_2), 2.65 (2 H, d of d, *J* 3.7, *J* 11.0, CH_2), 2.80 (2 H, m, CH_2), 3.17 (2 H, br s, NH), 7.11 (1 H, d of d, *J* 5.5, *J* 7.0, CH), 7.16 (1 H, d, *J* 8.1, CH), 7.59 (1 H, d of d, *J* 7.7, *J* 7.7, CH) and 8.50 (1 H, d, *J* 3.7, CH); δ_C(75 MHz, $CDCl_3$) 23.8 (q), 24.2 (q), 24.7 (q), 31.5 (t), 35.7 (t), 38.2 (d), 47.3 (t), 63.3 (s), 121.1 (d), 122.9 (d), 136.5 (d), 138.6 (d) and 149.2 (s); m/z(ES+) 347 ($M + H^+$).

8.3.71 3,3,9,9-Tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)ethyl)-2,10-undecanedione dioxime (76)

Hydroxylamine hydrochloride (1.54 g, 2.22 x 10^{-2} mol) was added to NaOH (0.83 g, 2.07 x 10^{-2} mol) in methanol (22 mL) and stirred for 2 hours at 0 °C. The salt formed was filtered and to the free hydroxylamine solution was added 3,3,9,9-tetramethyl-4,8-diaza-6-(2-(2-pyridinyl)ethyl)-2,10-undecanedione (**75**) (1.03 g, 2.96 x 10^{-3} mol). The solution was stirred for 18 hours at room temperature after which time the solvent was removed at reduced pressure. The residue was triturated with a water and recrystallised from ethyl ethanoate to give the title compound **76** as a yellow, sticky solid (0.30 g, 27%), mp 49 °C; ν(film)/cm^{-1} 3168, 1644, 1594 and 1569; δ_H(300 MHz, $CDCl_3$) 1.21 (12 H, s, CH_3), 1.56 (1 H, m, CH), 1.68 (2 H, m, CH_2), 1.77 (6 H, s, CH_3), 2.38 (4 H, br s, CH_2), 2.72 (2 H, m, CH_2), 3.72 (2 H, br s, NH), 7.21 (1 H, d of d, *J* 5.1, *J* 6.6, CH), 7.28 (1 H, d, *J* 8.1, CH), 7.72 (1 H, d of d, *J* 7.4, *J* 8.1, CH), 8.49 (1 H, d, *J* 3.7, CH) and 10.59 (2 H, br s, OH); δ_C(75 MHz, $CDCl_3$) 9.3 (q), 25.1 (q), 30.5 (t), 34.9 (t), 39.7 (d), 45.6 (t), 121.1 (d), 122.6 (d), 136.4 (d), 148.8 (d) and 161.7 (s); m/z(ES+) 378 ($M + H^+$).

8.3.72 Diethyl 2-bromo-1,3-propanedioate[69] (77)

To a solution of diethyl 1,3-propanedioate (40.0 g, 0.24 mol) in CCl_4 (40 mL) was added bromine (41.1 g, 0.26 mol) dropwise. Initially a high power light was used to initiate the reaction (loss of colouration) after which time the bromine was added at a rate that kept the mixture bubbling gently. The mixture was then refluxed until HBr evolution ceased, washed thoroughly with sat. $NaHCO_3$ and evaporated at reduced pressure. The product was fractionally distilled at reduced pressure until pure to give the title compound **77** as a colourless oil (48.51 g, 81%), bp 109-120 °C @ 10 mmHg (lit.[69] 121-125 °C @ 16 mmHg); δ_H(300 MHz, $CDCl_3$) 1.32 (6 H, t, *J* 7.2, CH_3), 4.30 (4 H, q, *J* 7.1, CH_2) and 4.84 (1 H, s, CH).

8.3.73 1,1-Dimethylethyl *N*-(2-hydroxy-3-((((1,1-dimethylethyl)oxy)carbonyl)amino) propyl) carbamate[70] (78)

To a solution of 2-hydroxy-1,3-propanediamine (18.76 g, 0.208 mol) in water (75 mL), was added di-*t*-butyl dicarbonate (100.00 g, 0.458 mol) in dioxane (150 mL) followed by Na_2CO_3 (46.50 g, 0.525 mol) at 0 °C with stirring. After 2 hours the reaction was allowed to warm to room temperature and was then stirred overnight. After removal of the solvents

at reduced pressure the resulting paste was diluted with water (200 mL) and thoroughly extracted with ethyl ethanoate (5 x 100 mL). The combined organic phases were washed with water, brine and then dried (Na_2SO_4). After evaporation at reduced pressure the gummy residue was triturated with hexanes and then recrystallised from hexanes/diethyl ether to give the title compound **78** as a colourless solid (56.00 g, 93%), mp 99-100 °C (lit.[70] 99-101 °C); δ_H(300 MHz, $CDCl_3$) 1.43 (18 H, s, CH_3), 3.20 (4 H, m, CH_2), 3.72 (1 H, m, CH), 3.92 (1 H, br s, OH), 5.27 (2 H, br s, NH).

8.3.74 1,1-Dimethylethyl *N*-(2-methylsulphonyl-3-((((1,1-dimethylethyl)oxy)carbonyl) amino)propyl) carbamate[70] (79)

1,1-Dimethylethyl *N*-(2-hydroxy-3-((((1,1-dimethylethyl)oxy)carbonyl)amino)propyl) carbamate (**78**) (56.00 g, 0.193 mol) and triethylamine (30.55 g, 0.30 mol) were dissolved in DCM (250 mL) and stirred at 0 °C. Methylsulphonyl chloride (26.0 g, 0.23 mol) was added dropwise over 1 hour after which the solution was allowed to warm to room temperature and stirred overnight. The reaction mixture was diluted with water and the organic phase washed with water, dried (Na_2SO_4) and evaporated at reduced pressure. The crude product was recrystallised from DCM/diethyl ether to give the title compound **79** as a colourless, crystalline solid (61.58 g, 87%), mp 134-135 °C dec. (lit.[70] 136-138 °C); δ_H(300 MHz, $CDCl_3$) 1.44 (18 H, s, CH_3), 3.10 (3 H, s, CH_3), 3.27-3.54 (4 H, m, CH_2), 4.67 (1 H, m, CH), 5.21 (2 H, br s, NH).

8.3.75 *N,N',O*-Tris-(4-methylbenzenesulphonyl)-2-hydroxy-1,3-propanediamine (80)

2-Hydroxy-1,3-propanediamine (2.00 g, 2.20 x 10^{-2} mol) was dissolved in DCM (50 mL) and cooled to 0 °C. Pyridine (10.53 g, 0.133 mol) was added followed by 4-methylbenzenesulphonyl chloride (19.04 g, 0.10 mol) in portions. After overnight stirring the solvent was evaporated at reduced pressure and the resulting yellow oil triturated with water. The water was decanted and the residue dissolved in DCM which was dried (Na_2SO_4) and evaporated at reduced pressure. The crude product was chromatographed with DCM/ethyl ethanoate (1:1) on silica to give the title compound **80** as a colourless solid (5.04 g, 41%), mp 81 °C; ν(Nujol)/cm^{-1} 3272, 1598 and 1570; δ_H(300 MHz, $CDCl_3$) 2.41 (6 H, s, CH_3), 2.46 (3 H, s, CH_3), 3.15 (4 H, m, CH_2), 4.58 (1 H, quin, *J* 5.0, CH), 5.33 (2 H, t, *J* 6.8, NH), 7.27 (4 H, d, *J* 8.1, CH), 7.35 (2 H, d, *J* 7.7, CH), 7.64 (4 H, d, *J* 8.1, CH), 7.70 (2 H, d, *J* 8.4, CH); δ_C(75 MHz, $CDCl_3$) 21.7 (q), 21.9 (q), 42.5 (t), 78.5

(d), 127.1 (d), 128.2 (d), 130.0 (d), 130.3 (d), 132.6 (s), 136.4 (s), 143.9 (s) and 145.7 (s).

SECTION 4

Appendices

References

If you jump to the last chapter of a good book,
you will discover who did it.
If you jump to the last chapter of a good thesis,
you will discover who did it...first!

Paul Walker

9 Appendices

9.1 Extraction Experiment Details

The following relationships[43] were used to determine useful thermodynamic data from extraction experiment results. They were applied without derivation.

Extinction coefficient: $\varepsilon_{max} = A_{max} / C \times l$

Partition data: $$K_d = \frac{[M^{n+}(Oxonol^-)_n]_{org}}{[M^{n+}]_{aq}[Oxonol^-]^n_{aq}}$$

A measure of the solubility of a salt in an organic solvent in the presence of water.

Extraction data: $$K_e = \frac{[M^{n+}.HOST.(Oxonol^-)_n]_{org}}{[M^{n+}][Oxonol^-]^n_{aq}[HOST]_{org}}$$

A measure of the ability of an organically soluble ionophore to bind a guest salt from the aqueous phase.

Association data: $$K_a = K_e / K_d = \frac{[M^{n+}.HOST.(Oxonol^-)_n]_{org}}{[M^{n+}(Oxonol^-)_n]_{org}[HOST]_{org}}$$

A measure of the ability of an ionophore to bind a guest salt.

Thermodynamic data: $\Delta G_a = -RT\ln K_a$

The Gibbs' free energy of the association of an ionophore and its guest.

9.2 γ-Counter Error Analysis

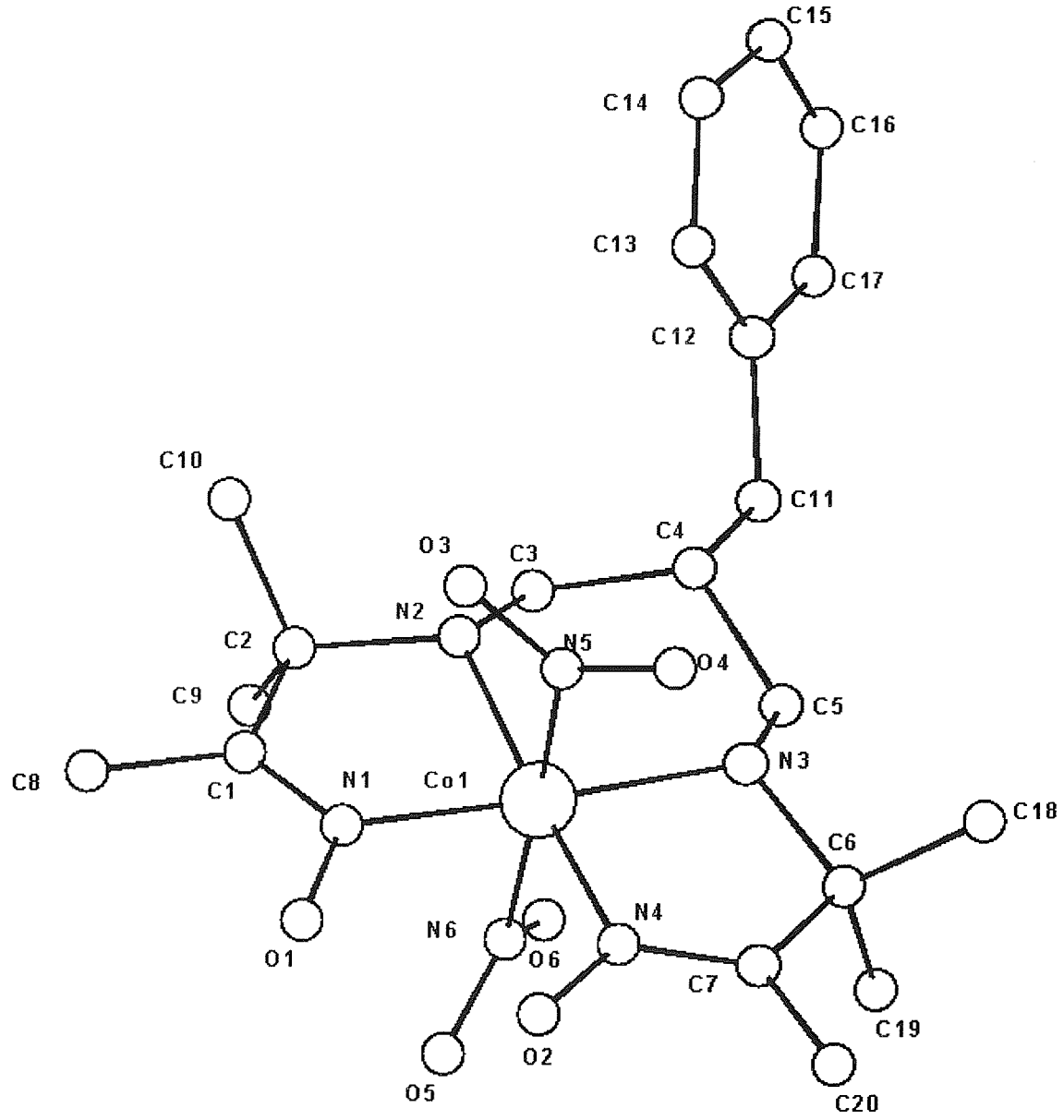
To determine the counting accuracy of the γ-counter used in this study the following expression was used:

$$\%Error = \frac{100 * 2 \text{ (standard deviations)}}{(\text{Number of decays})^{1/2}}$$

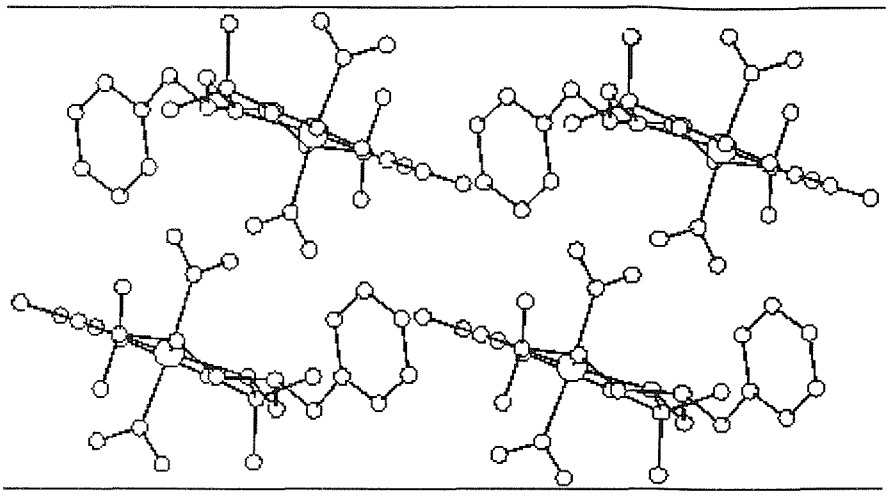
9.3 X-ray Structural and Collection Data

These reports were generated by the software used to solve the crystal structures.

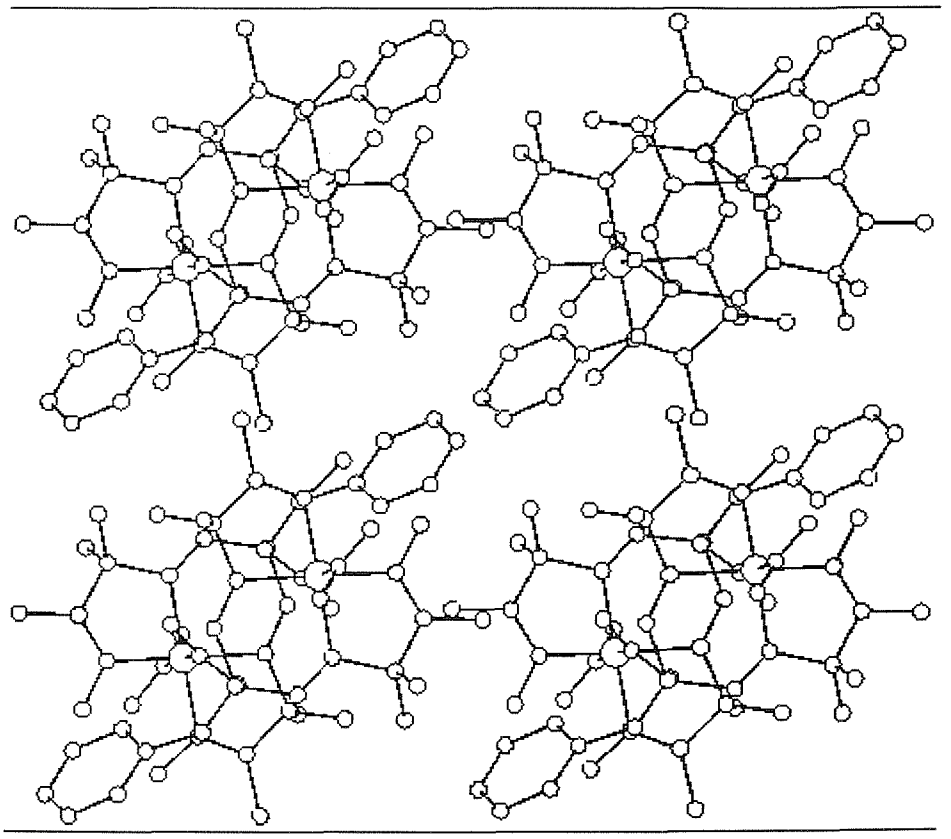
9.3.1 Co(III)(BnPnAO)$(NO_2)_2$



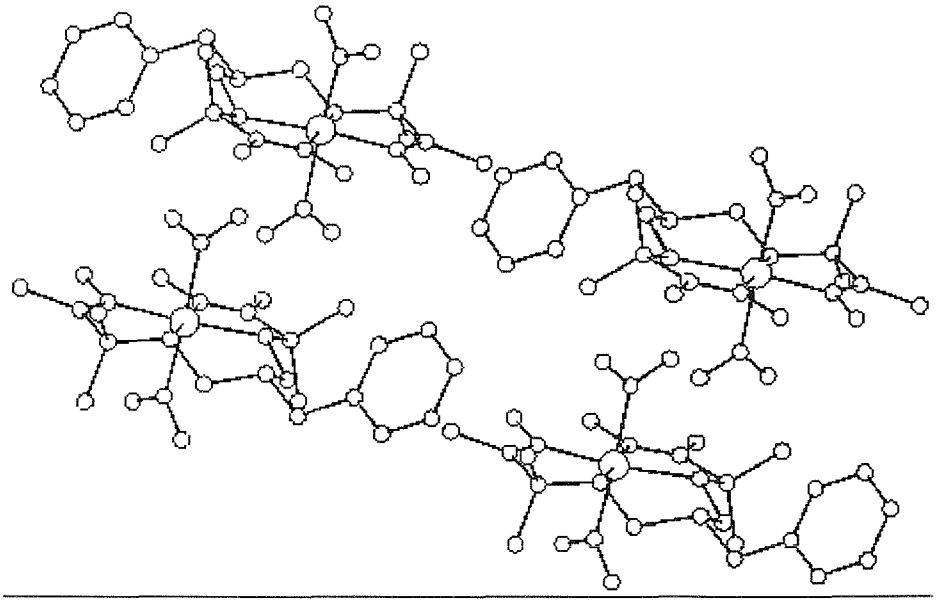
[Co(III)BnPnAO]$(NO_2)_2$



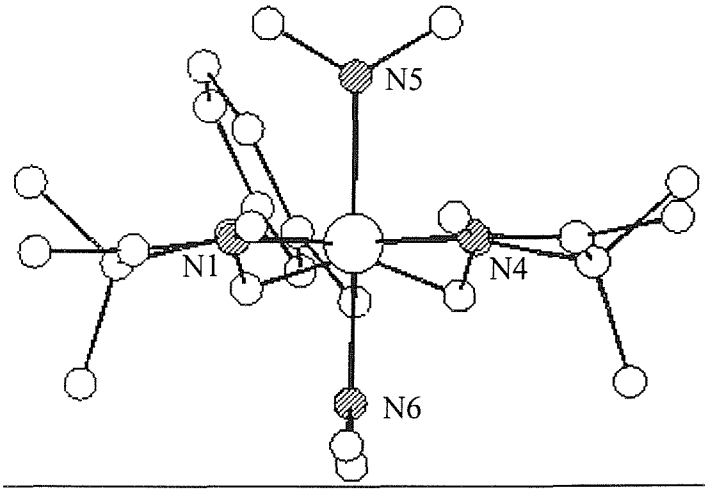
$[Co(III)BnPnAO](NO_2)_2$ View along A-axis



$[Co(III)BnPnAO](NO_2)_2$ View along B-axis



[Co(III)BnPnAO]$(NO_2)_2$ View along C-axis



[Co(III)BnPnAO]$(NO_2)_2$ View from oxime end along plane of ligand nitrogens

9.3.1.1 Data Collection

An orange slate crystal of $CoC_{20}H_{33}N_6O_6$ having approximate dimensions of 0.50 x 0.20 x 0.07 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully centred reflections in the range $19.01 < 2\theta < 22.35°$ corresponded to a primitive triclinic cell with dimensions:

a = 10.867(2) Å	α = 103.64(1)°
b = 12.248(2) Å	β = 93.66(2)°
c = 9.617(1) Å	γ = 71.47(1)°
V = 1179.3(4) Å^3	

For Z = 2 and F.W. = 512.45, the calculated density is 1.44 g cm^{-3}. Based on a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be $P\bar{1}$.

The data were collected at a temperature of 16 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.23° with a take-off angle of 6.0°. Scans of $(0.94 + 0.35 \tan \theta)°$ were made at a speed of 16.0° min^{-1} (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm. The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

9.3.1.2 Data Reduction

Of the 4388 reflections which were collected, 4149 were unique ($R_{int} = 0.044$). The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards decreased by 1.4%. A linear correction

factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Mo-Kα radiation is 7.8 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.82 to 1.00. The data were corrected for Lorentz and polarisation effects. A correction for secondary extinction was applied (coefficient = 1.52829e-07).

9.3.1.3 Structure Solution and Refinement Methods

The structure was solved by heavy-atom Patterson methods[99] and expanded using Fourier techniques[100]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[101] was based on 2143 observed reflections ($I > 3.00\sigma(I)$) and 299 variable parameters and converged (largest parameter shift was 0.01 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo| = 0.039$$

$$Rw = [(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w\, Fo^2)]^{1/2} = 0.038$$

The standard deviation of an observation of unit weight[102] was 1.37. The weighting scheme was based on counting statistics and included a factor ($p = 0.011$) to downweight the intense reflections. Plots of $\Sigma\omega(|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.31 and -0.25 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[103]. Anomalous dispersion effects were included in Fcalc[104]; the values for Δf' and Δf'' were those of Creagh and McAuley[105]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[106]. All calculations were performed using the teXsan[107] crystallographic software package of Molecular Structure Corporation.

9.3.1.4 Crystal Data

Empirical Formula	$CoC_{20}H_{33}N_6O_6$
Formula Weight	512.45
Crystal Colour, Habit	orange, slate
Crystal Dimensions	0.50 X 0.20 X 0.07 mm
Crystal System	triclinic
Lattice Type	Primitive
Cell Determination (2θ range)	20 (19.0 - 22.4°)
Omega Scan Peak Width at Half-height	0.23°
Lattice Parameters	a = 10.867(2)Å
	b = 12.248(2) Å
	c = 9.617(1) Å
	α = 103.64(1)°
	β = 93.66(2)°
	γ = 71.47(1)°
	V = 1179.3(4) $Å^3$
Space Group	$P\bar{1}$
Z value	2
D_{calc}	1.443 g cm^{-3}
F000	540.00
μ(MoKα)	7.76 cm^{-1}

9.3.1.5 Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Attenuator	Zr foil (factor = 8.59)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	16.9 °C
Scan Type	ω-2θ

Scan Rate	16.0° min^{-1} (in ω) (up to 4 scans)
Scan Width	(0.94 + 0.35 tan θ)°
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 4388
	Unique: 4149 (R_{int} = 0.044)
Corrections	Lorentz-polarisation Absorption
	(trans. factors: 0.8246 - 1.0000)
	Decay (1.37% decline)
	Secondary Extinction (coefficient: 1.52829e-07)

9.3.1.6 Structure Solution and Refinement

Structure Solution	Patterson Methods (DIRDIF92 PATTY)
Refinement	Full-matrix least-squares
Function Minimised	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4(Fo)^2/\sigma^2(Fo^2)$
p-factor	0.0110
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2143
No. Variables	299
Reflection/Parameter Ratio	7.17
Residuals: R; Rw	0.039; 0.038
Goodness of Fit Indicator	1.37
Max Shift/Error in Final Cycle	0.01
Maximum peak in Final Diff. Map	0.31 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.25 $e^-/Å^3$

9.3.1.7 Fractional Atomic co-ordinates and Biso/Beq

Atom	x	y	z	Beq
Co(1)	0.15627(7)	0.26381(6)	0.10241(8)	1.99(2)
O(1)	0.2109(4)	0.3357(3)	0.3968(4)	4.0(1)
O(2)	0.3891(3)	0.2905(3)	0.2304(4)	4.1(1)
O(3)	0.0313(4)	0.5089(3)	0.1704(4)	3.71(9)
O(4)	0.1843(4)	0.4610(3)	0.0180(4)	3.76(10)
O(5)	0.2739(4)	0.0727(3)	0.2205(4)	4.7(1)
O(6)	0.1597(4)	0.0281(3)	0.0434(4)	4.5(1)
N(1)	0.1201(4)	0.3133(3)	0.3018(4)	2.8(1)

N(2)	-0.0332(4)	0.2898(3)	0.0925(4)	2.16(10)
N(3)	0.1881(4)	0.2205(3)	-0.1062(4)	2.10(10)
N(4)	0.3341(4)	0.2528(4)	0.1080(5)	2.7(1)
N(5)	0.1191(4)	0.4320(3)	0.0966(4)	2.4(1)
N(6)	0.2007(4)	0.1029(4)	0.1234(5)	2.6(1)
C(1)	0.0083(6)	0.3247(4)	0.3482(6)	2.9(1)
C(2)	-0.0903(5)	0.2986(4)	0.2381(6)	2.9(1)
C(3)	-0.0839(5)	0.2173(4)	-0.0289(6)	2.6(1)
C(4)	-0.0353(5)	0.2158(4)	-0.1750(5)	2.4(1)
C(5)	0.1091(5)	0.1539(4)	-0.1988(5)	2.6(1)
C(6)	0.3332(5)	0.1740(5)	-0.1419(6)	3.0(1)
C(7)	0.3991(5)	0.2188(5)	-0.0088(7)	3.0(1)
C(8)	-0.0250(6)	0.3595(5)	0.5048(6)	4.7(2)
C(9)	-0.1109(6)	0.1826(5)	0.2480(6)	4.1(2)
C(10)	-0.2187(5)	0.3989(5)	0.2622(6)	4.6(2)
C(11)	-0.1099(5)	0.1527(4)	-0.2923(6)	3.4(1)
C(12)	-0.2399(5)	0.2264(4)	-0.3372(5)	2.5(1)
C(13)	-0.2951(5)	0.3462(5)	-0.2802(6)	3.3(1)
C(14)	-0.4105(5)	0.4098(5)	-0.3338(6)	3.8(1)
C(15)	-0.4714(5)	0.3538(6)	-0.4453(6)	4.0(2)
C(16)	-0.4190(5)	0.2355(5)	-0.5004(6)	3.7(1)
C(17)	-0.3042(5)	0.1722(5)	-0.4464(6)	3.1(1)
C(18)	0.3564(6)	0.2238(7)	-0.2665(7)	5.7(2)
C(19)	0.3844(5)	0.0400(5)	-0.1797(7)	4.9(2)
C(20)	0.5356(5)	0.2231(5)	-0.0136(7)	4.9(2)
H(1)	-0.0689	0.3697	0.0769	2.6034
H(2)	-0.0568	0.1387	-0.0151	3.0972
H(3)	-0.1758	0.2472	-0.0262	3.0972
H(4)	-0.0537	0.2953	-0.1832	2.8756
H(5)	0.1312	0.0781	-0.1781	3.0026
H(6)	0.1303	0.1451	-0.2966	3.0026
H(7)	0.1604	0.2967	-0.1327	2.5420
H(8)	0.2984	0.3228	0.3101	3.7067
H(9)	0.0306	0.3035	0.5527	5.5626
H(10)	-0.0154	0.4351	0.5436	5.5626
H(11)	-0.1127	0.3633	0.5168	5.5626
H(12)	-0.1429	0.1903	0.3403	4.8413
H(13)	-0.0312	0.1201	0.2302	4.8413
H(14)	-0.1726	0.1646	0.1780	4.8413
H(15)	-0.2787	0.3818	0.1914	5.4232
H(16)	-0.2521	0.4074	0.3544	5.4232
H(17)	-0.2038	0.4703	0.2569	5.4232
H(18)	-0.1236	0.0908	-0.2581	4.0470
H(19)	-0.0551	0.1199	-0.3748	4.0470
H(20)	-0.2537	0.3861	-0.2037	4.0571
H(21)	-0.4484	0.4923	-0.2931	4.5133
H(22)	-0.5497	0.3970	-0.4836	4.8442
H(23)	-0.4610	0.1964	-0.5764	4.4005
H(24)	-0.2686	0.0893	-0.4865	3.7152
H(25)	0.3072	0.1995	-0.3457	6.8413

H(26)	0.3304	0.3070	-0.2379	6.8413
H(27)	0.4460	0.1934	-0.2905	6.8413
H(28)	0.3432	0.0111	-0.2648	5.8028
H(29)	0.4752	0.0154	-0.1962	5.8028
H(30)	0.3659	0.0102	-0.1042	5.8028
H(31)	0.5668	0.1953	-0.1094	5.8018
H(32)	0.5354	0.3021	0.0214	5.8018
H(33)	0.5888	0.1743	0.0444	5.8018

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

9.3.1.8 Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Co(1)	0.0263(4)	0.0228(4)	0.0261(4)	-0.0074(3)	-0.0043(3)	0.0066(3)
O(1)	0.054(3)	0.065(3)	0.029(2)	-0.023(2)	-0.017(2)	0.005(2)
O(2)	0.040(2)	0.071(3)	0.046(3)	-0.026(2)	-0.019(2)	0.010(2)
O(3)	0.061(3)	0.023(2)	0.048(3)	-0.004(2)	0.004(2)	0.003(2)
O(4)	0.054(3)	0.038(2)	0.058(3)	-0.018(2)	0.000(2)	0.018(2)
O(5)	0.064(3)	0.044(2)	0.065(3)	-0.005(2)	-0.022(2)	0.027(2)
O(6)	0.063(3)	0.036(2)	0.072(3)	-0.020(2)	-0.015(2)	0.010(2)
N(1)	0.044(3)	0.030(3)	0.028(3)	-0.008(2)	-0.004(2)	0.004(2)
N(2)	0.026(2)	0.026(2)	0.030(3)	-0.007(2)	-0.002(2)	0.008(2)
N(3)	0.023(2)	0.030(2)	0.027(3)	-0.010(2)	-0.002(2)	0.005(2)
N(4)	0.033(3)	0.033(3)	0.040(3)	-0.019(2)	-0.013(2)	0.009(2)
N(5)	0.034(3)	0.028(2)	0.032(3)	-0.014(2)	-0.009(2)	0.009(2)
N(6)	0.035(3)	0.029(2)	0.036(3)	-0.010(2)	0.001(2)	0.010(2)
C(1)	0.052(4)	0.027(3)	0.027(3)	-0.005(3)	0.007(3)	0.009(2)
C(2)	0.034(3)	0.038(3)	0.036(4)	-0.006(3)	0.017(3)	0.008(3)
C(3)	0.029(3)	0.031(3)	0.043(4)	-0.015(2)	-0.006(3)	0.007(3)
C(4)	0.038(3)	0.028(3)	0.028(3)	-0.015(2)	-0.009(2)	0.006(2)
C(5)	0.038(3)	0.028(3)	0.031(3)	-0.012(2)	0.002(3)	-0.001(2)
C(6)	0.026(3)	0.044(3)	0.043(4)	-0.010(3)	0.011(3)	0.002(3)
C(7)	0.030(3)	0.034(3)	0.053(4)	-0.014(3)	-0.002(3)	0.010(3)
C(8)	0.082(5)	0.062(4)	0.033(4)	-0.021(4)	0.013(3)	0.005(3)
C(9)	0.063(4)	0.049(4)	0.053(4)	-0.025(3)	0.015(3)	0.012(3)
C(10)	0.044(4)	0.060(4)	0.059(4)	0.001(3)	0.018(3)	0.011(3)
C(11)	0.051(4)	0.033(3)	0.046(4)	-0.017(3)	-0.015(3)	0.005(3)
C(12)	0.029(3)	0.036(3)	0.032(3)	-0.009(3)	-0.004(2)	0.014(3)
C(13)	0.042(4)	0.036(3)	0.048(4)	-0.015(3)	-0.014(3)	0.009(3)
C(14)	0.045(4)	0.036(3)	0.058(4)	-0.008(3)	-0.010(3)	0.008(3)
C(15)	0.031(3)	0.066(4)	0.055(4)	-0.009(3)	-0.015(3)	0.026(3)
C(16)	0.041(4)	0.056(4)	0.037(4)	-0.013(3)	-0.013(3)	0.006(3)
C(17)	0.042(4)	0.039(3)	0.034(3)	-0.015(3)	-0.004(3)	0.000(3)
C(18)	0.051(4)	0.117(6)	0.055(5)	-0.031(4)	0.016(4)	0.021(4)
C(19)	0.035(4)	0.060(4)	0.074(5)	-0.008(3)	0.012(3)	-0.009(4)
C(20)	0.038(4)	0.065(4)	0.090(5)	-0.025(3)	0.002(4)	0.017(4)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

9.3.1.9 Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
Co(1)	N(1)	1.897(4)	Co(1)	N(2)	1.980(4)
Co(1)	N(3)	1.974(4)	Co(1)	N(4)	1.892(5)
Co(1)	N(5)	1.983(4)	Co(1)	N(6)	1.931(5)
O(1)	N(1)	1.349(6)	O(1)	H(8)	1.25
O(2)	N(4)	1.336(6)	O(2)	H(8)	1.19
O(3)	N(5)	1.225(5)	O(4)	N(5)	1.247(7)
O(5)	N(6)	1.234(6)	O(6)	N(6)	1.230(6)
N(1)	C(1)	1.276(8)	N(2)	C(2)	1.535(7)
N(2)	C(3)	1.482(6)	N(2)	H(1)	0.97
N(3)	C(5)	1.483(7)	N(3)	C(6)	1.528(6)
N(3)	H(7)	0.97	N(4)	C(7)	1.276(8)
C(1)	C(2)	1.512(8)	C(1)	C(8)	1.500(8)
C(2)	C(9)	1.531(9)	C(2)	C(10)	1.525(7)
C(3)	C(4)	1.526(8)	C(3)	H(2)	0.95
C(3)	H(3)	0.95	C(4)	C(5)	1.516(7)
C(4)	C(11)	1.548(7)	C(4)	H(4)	0.95
C(5)	H(5)	0.95	C(5)	H(6)	0.96
C(6)	C(7)	1.502(8)	C(6)	C(18)	1.53(1)
C(6)	C(19)	1.517(8)	C(7)	C(20)	1.505(9)
C(8)	H(9)	0.95	C(8)	H(10)	0.95
C(8)	H(11)	0.95	C(9)	H(12)	0.95
C(9)	H(13)	0.95	C(9)	H(14)	0.96
C(10)	H(15)	0.95	C(10)	H(16)	0.95
C(10)	H(17)	0.95	C(11)	C(12)	1.514(7)
C(11)	H(18)	0.95	C(11)	H(19)	0.95
C(12)	C(13)	1.384(7)	C(12)	C(17)	1.380(7)
C(13)	C(14)	1.390(7)	C(13)	H(20)	0.95
C(14)	C(15)	1.382(8)	C(14)	H(21)	0.95
C(15)	C(16)	1.362(8)	C(15)	H(22)	0.95
C(16)	C(17)	1.386(7)	C(16)	H(23)	0.95
C(17)	H(24)	0.96	C(18)	H(25)	0.95
C(18)	H(26)	0.94	C(18)	H(27)	0.95
C(19)	H(28)	0.96	C(19)	H(29)	0.95
C(19)	H(30)	0.94	C(20)	H(31)	0.95
C(20)	H(32)	0.95	C(20)	H(33)	0.95

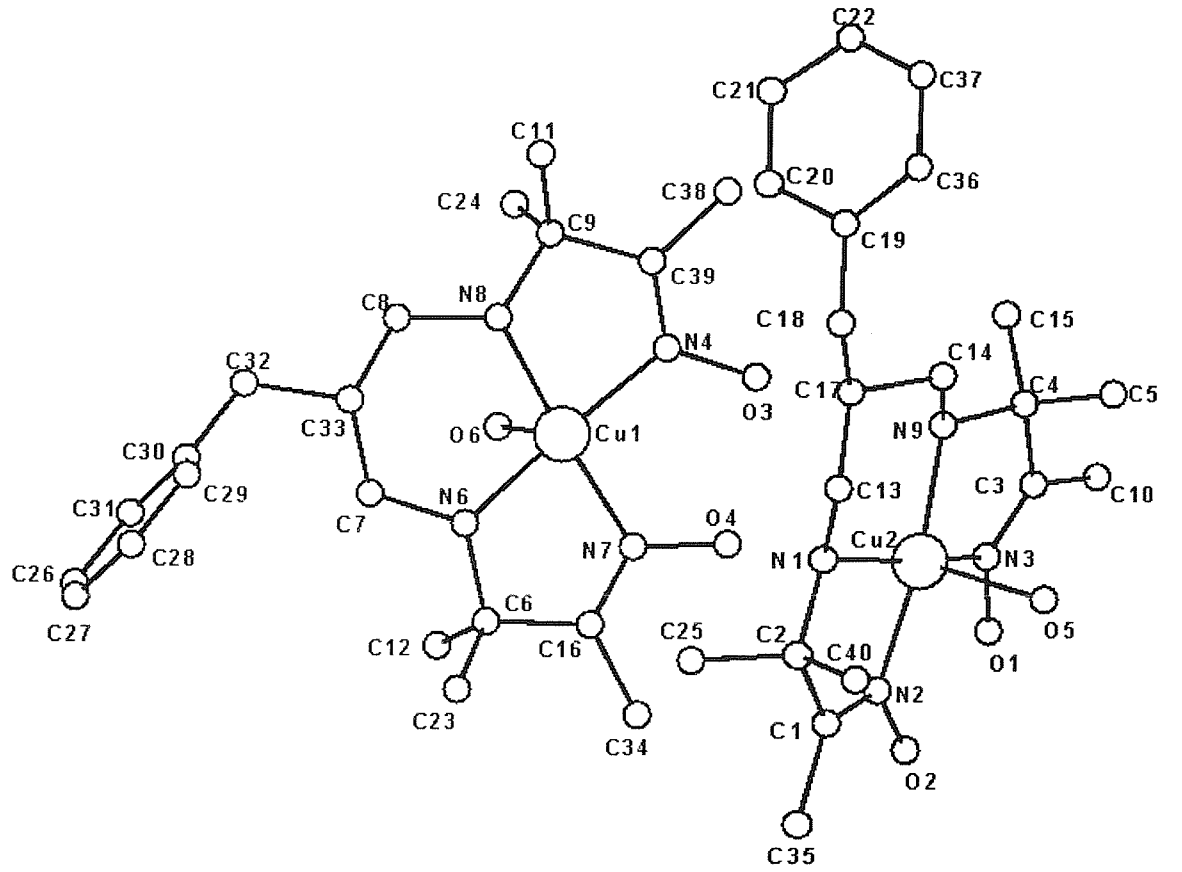
9.3.1.10 Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
N(1)	Co(1)	N(2)	82.3(2)	N(1)	Co(1)	N(3)	177.0(2)
N(1)	Co(1)	N(4)	98.5(2)	N(1)	Co(1)	N(5)	88.6(2)
N(1)	Co(1)	N(6)	87.7(2)	N(2)	Co(1)	N(3)	96.3(2)
N(2)	Co(1)	N(4)	174.7(2)	N(2)	Co(1)	N(5)	87.9(2)

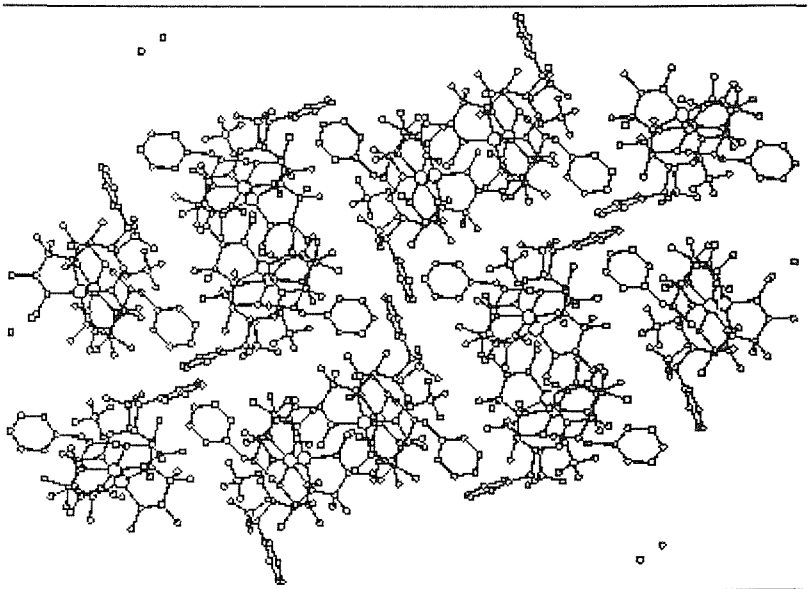
N(2)	Co(1)	N(6)	95.0(2)	N(3)	Co(1)	N(4)	82.6(2)
N(3)	Co(1)	N(5)	88.7(2)	N(3)	Co(1)	N(6)	95.1(2)
N(4)	Co(1)	N(5)	86.9(2)	N(4)	Co(1)	N(6)	90.2(2)
N(5)	Co(1)	N(6)	175.0(2)	N(1)	O(1)	H(8)	98.6
N(4)	O(2)	H(8)	100.0	Co(1)	N(1)	O(1)	121.4(4)
Co(1)	N(1)	C(1)	119.7(4)	O(1)	N(1)	C(1)	118.9(4)
Co(1)	N(2)	C(2)	111.7(3)	Co(1)	N(2)	C(3)	118.5(3)
Co(1)	N(2)	H(1)	103.7	C(2)	N(2)	C(3)	113.5(4)
C(2)	N(2)	H(1)	103.9	C(3)	N(2)	H(1)	103.5
Co(1)	N(3)	C(5)	118.4(3)	Co(1)	N(3)	C(6)	111.5(3)
Co(1)	N(3)	H(7)	103.3	C(5)	N(3)	C(6)	114.8(3)
C(5)	N(3)	H(7)	103.4	C(6)	N(3)	H(7)	103.0
Co(1)	N(4)	O(2)	120.9(3)	Co(1)	N(4)	C(7)	119.3(4)
O(2)	N(4)	C(7)	119.5(5)	Co(1)	N(5)	O(3)	120.2(4)
Co(1)	N(5)	O(4)	120.7(3)	O(3)	N(5)	O(4)	119.1(4)
Co(1)	N(6)	O(5)	119.1(4)	Co(1)	N(6)	O(6)	122.9(3)
O(5)	N(6)	O(6)	118.0(4)	N(1)	C(1)	C(2)	117.1(5)
N(1)	C(1)	C(8)	122.3(5)	C(2)	C(1)	C(8)	120.6(5)
N(2)	C(2)	C(1)	106.0(5)	N(2)	C(2)	C(9)	112.1(4)
N(2)	C(2)	C(10)	108.8(4)	C(1)	C(2)	C(9)	108.8(5)
C(1)	C(2)	C(10)	111.0(4)	C(9)	C(2)	C(10)	110.2(5)
N(2)	C(3)	C(4)	113.8(5)	N(2)	C(3)	H(2)	107.0
N(2)	C(3)	H(3)	108.5	C(4)	C(3)	H(2)	109.0
C(4)	C(3)	H(3)	109.0	H(2)	C(3)	H(3)	109.4
C(3)	C(4)	C(5)	113.5(4)	C(3)	C(4)	C(11)	108.5(5)
C(3)	C(4)	H(4)	108.4	C(5)	C(4)	C(11)	108.9(4)
C(5)	C(4)	H(4)	108.4	C(11)	C(4)	H(4)	108.9
N(3)	C(5)	C(4)	112.3(3)	N(3)	C(5)	H(5)	107.9
N(3)	C(5)	H(6)	108.8	C(4)	C(5)	H(5)	109.6
C(4)	C(5)	H(6)	109.0	H(5)	C(5)	H(6)	109.1
N(3)	C(6)	C(7)	105.8(4)	N(3)	C(6)	C(18)	108.4(4)
N(3)	C(6)	C(19)	112.3(5)	C(7)	C(6)	C(18)	111.1(5)
C(7)	C(6)	C(19)	108.7(4)	C(18)	C(6)	C(19)	110.4(5)
N(4)	C(7)	C(6)	116.9(5)	N(4)	C(7)	C(20)	121.8(5)
C(6)	C(7)	C(20)	121.3(5)	C(1)	C(8)	H(9)	110.3
C(1)	C(8)	H(10)	108.8	C(1)	C(8)	H(11)	109.2
H(9)	C(8)	H(10)	109.7	H(9)	C(8)	H(11)	109.4
H(10)	C(8)	H(11)	109.4	C(2)	C(9)	H(12)	109.7
C(2)	C(9)	H(13)	109.8	C(2)	C(9)	H(14)	109.6
H(12)	C(9)	H(13)	109.8	H(12)	C(9)	H(14)	109.1
H(13)	C(9)	H(14)	108.9	C(2)	C(10)	H(15)	109.8
C(2)	C(10)	H(16)	109.1	C(2)	C(10)	H(17)	109.1
H(15)	C(10)	H(16)	109.8	H(15)	C(10)	H(17)	109.7
H(16)	C(10)	H(17)	109.4	C(4)	C(11)	C(12)	117.6(4)
C(4)	C(11)	H(18)	107.1	C(4)	C(11)	H(19)	107.0
C(12)	C(11)	H(18)	107.8	C(12)	C(11)	H(19)	107.7
H(18)	C(11)	H(19)	109.4	C(11)	C(12)	C(13)	123.9(5)
C(11)	C(12)	C(17)	118.0(4)	C(13)	C(12)	C(17)	118.0(4)
C(12)	C(13)	C(14)	120.7(5)	C(12)	C(13)	H(20)	120.1
C(14)	C(13)	H(20)	119.2	C(13)	C(14)	C(15)	120.1(5)

C(13)	C(14)	H(21)	120.1	C(15)	C(14)	H(21)	119.8
C(14)	C(15)	C(16)	119.6(5)	C(14)	C(15)	H(22)	120.6
C(16)	C(15)	H(22)	119.8	C(15)	C(16)	C(17)	120.2(5)
C(15)	C(16)	H(23)	119.9	C(17)	C(16)	H(23)	119.9
C(12)	C(17)	C(16)	121.4(5)	C(12)	C(17)	H(24)	119.6
C(16)	C(17)	H(24)	119.1	C(6)	C(18)	H(25)	108.7
C(6)	C(18)	H(26)	109.0	C(6)	C(18)	H(27)	108.5
H(25)	C(18)	H(26)	110.3	H(25)	C(18)	H(27)	110.0
H(26)	C(18)	H(27)	110.3	C(6)	C(19)	H(28)	108.9
C(6)	C(19)	H(29)	109.3	C(6)	C(19)	H(30)	109.7
H(28)	C(19)	H(29)	109.2	H(28)	C(19)	H(30)	109.5
H(29)	C(19)	H(30)	110.2	C(7)	C(20)	H(31)	109.2
C(7)	C(20)	H(32)	108.9	C(7)	C(20)	H(33)	108.9
H(31)	C(20)	H(32)	110.0	H(31)	C(20)	H(33)	109.8
H(32)	C(20)	H(33)	110.0				

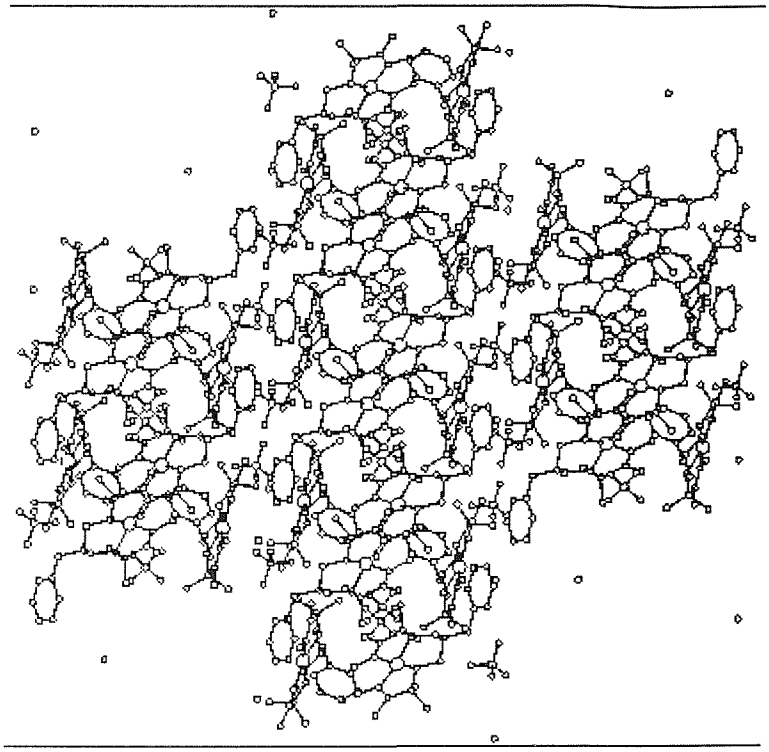
9.3.2 [Cu(II)(BnPnAO)(H_2O)]BF_4



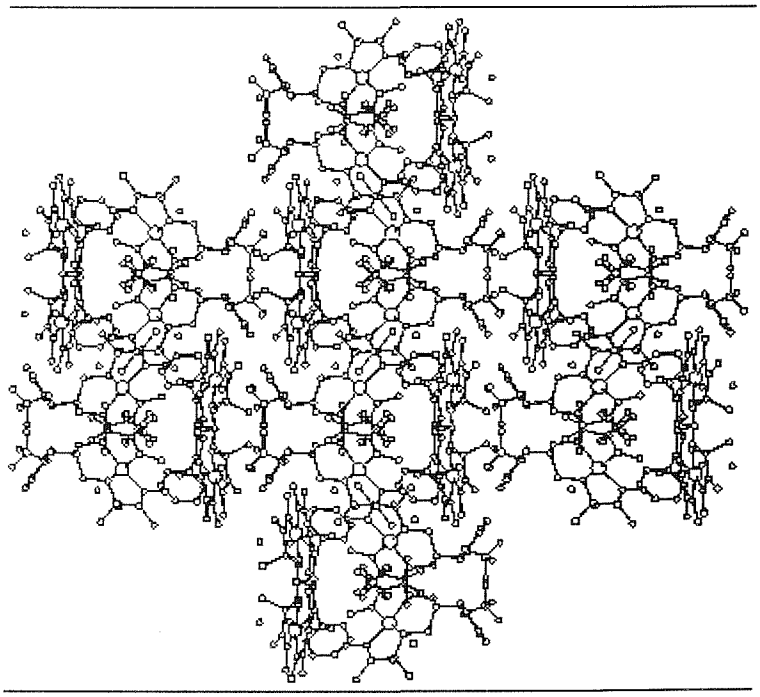
[Cu(II)BnPnAO(H_2O)]BF_4



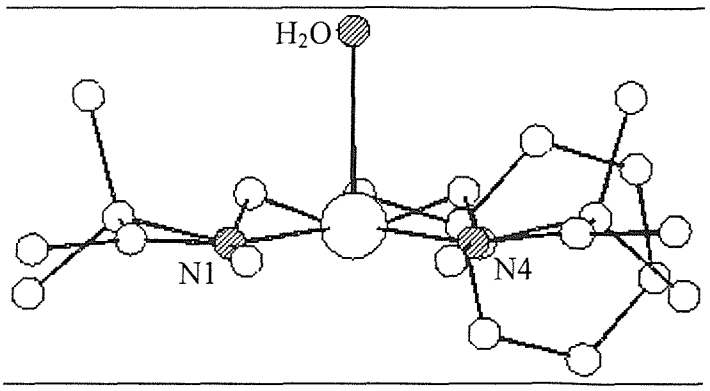
[Cu(II)BnPnAO(H_2O)]BF_4 View along A-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View along B-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View along C-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View from oxime end along plane of ligand nitrogens

9.3.2.1 Data Collection

A purple block crystal of $CuC_{20}H_{35}N_4O_3BF_4$ having approximate dimensions of 0.75 x 0.35 x 0.30 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centred reflections in the range $31.46 < 2\theta < 43.08°$ corresponded to a primitive triclinic cell with dimensions:

$a = 14.34(1)$ Å

$b = 18.44(2)$ Å $\qquad \beta = 99.52(5)°$

$c = 18.931(9)$ Å

$V = 4935(5)$ Å^3

For $Z = 8$ and F.W. = 529.87, the calculated density is 1.43 g cm^{-3}. The systematic absences of

$h0l: l \neq 2n$

$0k0: k \neq 2n$

uniquely determined the space group to be $P2_1/c$.

The data were collected at a temperature of -123 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 50.1°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.26° with a take-off angle of 6.0°.

Scans of $(1.31 + 0.35 \tan \theta)°$ were made at a speed of $16.0° \text{ min}^{-1}$ (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm. The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

9.3.2.2 Data Reduction

Of the 9360 reflections which were collected, 8981 were unique ($R_{int} = 0.041$). The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards decreased by 11.9%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Mo-Kα radiation is 9.4 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.93 to 1.00. The data were corrected for Lorentz and polarisation effects.

9.3.2.3 Structure Solution and Refinement Methods

The structure was solved by direct methods[108] and expanded using Fourier techniques[100]. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement[101] was based on 5906 observed reflections ($I > 2.50\sigma(I)$) and 595 variable parameters and converged (largest parameter shift was 0.39 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo| = 0.056$$

$$Rw = [(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w\, Fo^2)]^{1/2} = 0.076$$

The standard deviation of an observation of unit weight[102] was 2.64. The weighting scheme was based on counting statistics and included a factor ($p = 0.032$) to downweight the intense reflections. Plots of $\Sigma\omega(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum

and minimum peaks on the final difference Fourier map corresponded to 0.68 and -0.92 e^- /$Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[103]. Anomalous dispersion effects were included in Fcalc[104]; the values for Δf' and Δf'' were those of Creagh and McAuley[105]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[106]. All calculations were performed using the teXsan[107] crystallographic software package of Molecular Structure Corporation.

9.3.2.4 Crystal Data

Empirical Formula	$CuC_{20}H_{35}N_4O_3BF_4$
Formula Weight	529.87
Crystal Colour, Habit	purple, block
Crystal Dimensions	0.75 X 0.35 X 0.30 mm
Crystal System	monoclinic
Lattice Type	Primitive
Cell Determination (2θ range)	24 (31.5 - 43.1°)
Omega Scan Peak Width at Half-height	0.26°
Lattice Parameters	a = 14.34(1)Å
	b = 18.44(2) Å
	c = 18.931(5) Å
	β = 99.52(5)°
	V = 4936(5) $Å^3$
Space Group	$P2_1/c$
Z value	8
D_{calc}	1.426 g cm^{-3}
F000	2216.00
μ(MoKα)	9.43 cm^{-1}

9.3.2.5 Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated

Attenuator	Zr foil (factor = 8.59)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-123.1 °C
Scan Type	ω-2θ
Scan Rate	16.0° min^{-1} (in ω) (up to 4 scans)
Scan Width	(1.31 + 0.35 tan θ)°
$2\theta_{max}$	50.1°
No. of Reflections Measured	Total: 9360
	Unique: 8981 (R_{int} = 0.041)
Corrections	Lorentz-polarisation Absorption
	(trans. factors: 0.9275 - 1.0000)
	Decay (11.85% decline)

9.3.2.6 Structure Solution and Refinement

Structure Solution	Direct Methods (SHELXS86)
Refinement	Full-matrix least-squares
Function Minimised	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4(Fo)^2/\sigma^2(Fo^2)$
p-factor	0.0320
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	5906
No. Variables	595
Reflection/Parameter Ratio	9.93
Residuals: R; Rw	0.056; 0.076
Goodness of Fit Indicator	2.64
Max Shift/Error in Final Cycle	0.39
Maximum peak in Final Diff. Map	0.68 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.92 $e^-/Å^3$

9.3.2.7 Atomic co-ordinates and Biso/Beq

atom	x	y	z	Beq
Cu(1)	0.56631(5)	0.38205(4)	0.09947(3)	2.33(1)
Cu(2)	0.17304(5)	0.40702(4)	0.06268(3)	2.36(1)
F(1)	0.8790(3)	0.1440(2)	0.1348(3)	5.7(1)
F(2)	0.9687(3)	0.2377(2)	0.1123(2)	4.9(1)
F(3)	0.9973(4)	0.1822(3)	0.2188(2)	8.5(2)
F(4)	1.0277(3)	0.1240(3)	0.1216(3)	7.4(1)
F(5)	0.5499(3)	0.2028(2)	0.1946(2)	5.4(1)
F(6)	0.5582(3)	0.2929(2)	0.2772(2)	4.72(10)
F(7)	0.4317(2)	0.2162(2)	0.2593(2)	3.56(8)
F(8)	0.4533(2)	0.2996(2)	0.1748(2)	3.87(8)
O(1)	0.4020(3)	0.3531(2)	-0.0121(2)	2.93(9)
O(2)	0.3852(3)	0.4553(2)	0.0680(2)	2.87(9)
O(3)	0.1348(3)	0.5326(2)	-0.0316(2)	3.14(9)
O(4)	0.1587(3)	0.5612(2)	0.1015(2)	3.53(10)
O(5)	0.6684(3)	0.0487(2)	0.5395(2)	3.21(9)
O(6)	0.0195(3)	0.1195(2)	0.5831(2)	3.22(9)
N(1)	0.4923(3)	0.3319(3)	0.0179(2)	2.6(1)
N(2)	0.6479(3)	0.2942(3)	0.0976(2)	2.5(1)
N(3)	0.6255(3)	0.4204(2)	0.1953(2)	2.21(10)
N(4)	0.4717(3)	0.4540(2)	0.1119(2)	2.6(1)
N(5)	0.1407(3)	0.4583(2)	-0.0281(2)	2.6(1)
N(6)	0.1870(3)	0.3241(2)	-0.0031(2)	2.33(10)
N(7)	0.2406(3)	0.3609(2)	0.1527(2)	2.34(10)
N(8)	0.1825(3)	0.4917(3)	0.1263(2)	2.7(1)
C(1)	0.5280(4)	0.2771(3)	-0.0094(3)	2.6(1)
C(2)	0.6291(4)	0.2578(3)	0.0246(3)	2.7(1)
C(3)	0.7489(4)	0.3040(3)	0.1302(3)	2.8(1)
C(4)	0.7605(4)	0.3327(3)	0.2070(3)	2.7(1)
C(5)	0.7289(4)	0.4120(3)	0.2118(3)	2.9(1)
C(6)	0.5881(4)	0.4950(3)	0.2086(3)	2.5(1)
C(7)	0.4921(4)	0.5023(3)	0.1605(3)	2.7(1)
C(8)	0.4768(5)	0.2370(4)	-0.0725(3)	3.5(1)
C(9)	0.6403(4)	0.1747(3)	0.0358(3)	3.4(1)
C(10)	0.6950(5)	0.2855(4)	-0.0243(3)	3.7(2)
C(11)	0.5794(4)	0.5020(4)	0.2876(3)	3.5(1)
C(12)	0.6528(4)	0.5548(3)	0.1879(3)	3.2(1)
C(13)	0.4289(4)	0.5651(4)	0.1685(4)	3.8(2)
C(14)	0.8662(4)	0.3275(4)	0.2393(3)	3.5(1)
C(15)	0.8916(4)	0.3562(3)	0.3142(3)	2.9(1)
C(16)	0.9457(4)	0.4197(4)	0.3268(4)	3.8(2)
C(17)	0.9712(5)	0.4458(4)	0.3966(4)	4.6(2)
C(18)	0.9430(5)	0.4089(4)	0.4524(4)	4.1(2)
C(19)	0.8881(5)	0.3491(4)	0.4407(3)	4.1(2)
C(20)	0.8622(4)	0.3219(4)	0.3718(3)	3.4(1)
C(21)	0.1185(4)	0.4204(3)	-0.0851(3)	2.6(1)
C(22)	0.1308(4)	0.3380(3)	-0.0768(3)	2.6(1)
C(23)	0.1765(4)	0.2499(3)	0.0273(3)	2.5(1)
C(24)	0.2481(4)	0.2387(3)	0.0958(3)	2.4(1)

C(25)	0.2246(4)	0.2808(3)	0.1594(3)	2.7(1)
C(26)	0.2291(4)	0.4046(3)	0.2185(3)	2.9(1)
C(27)	0.2058(4)	0.4825(3)	0.1938(3)	3.1(1)
C(28)	0.0795(4)	0.4527(3)	-0.1564(3)	3.1(1)
C(29)	0.0320(4)	0.3029(3)	-0.0849(3)	3.5(1)
C(30)	0.1840(5)	0.3076(3)	-0.1326(3)	3.4(1)
C(31)	0.1475(5)	0.3772(4)	0.2534(3)	3.9(2)
C(32)	0.3219(5)	0.4017(4)	0.2715(3)	3.9(2)
C(33)	0.2054(5)	0.5440(4)	0.2459(3)	4.0(2)
C(34)	0.2539(4)	0.1572(3)	0.1166(3)	2.8(1)
C(35)	0.2833(4)	0.1079(3)	0.0606(3)	2.8(1)
C(36)	0.2206(4)	0.0591(4)	0.0230(4)	3.7(2)
C(37)	0.2479(5)	0.0133(4)	-0.0272(4)	4.2(2)
C(38)	0.3385(5)	0.0151(3)	-0.0408(3)	3.6(2)
C(39)	0.4022(4)	0.0641(4)	-0.0042(4)	3.6(2)
C(40)	0.3740(4)	0.1097(3)	0.0464(3)	3.2(1)
B(1)	0.9681(5)	0.1704(4)	0.1479(4)	3.2(2)
B(2)	0.4969(4)	0.2523(3)	0.2268(3)	2.3(1)
H(1)	0.4189	0.2188	-0.0616	3.9478
H(2)	0.4642	0.2690	-0.1123	3.9478
H(3)	0.5149	0.1979	-0.0838	3.9478
H(4)	0.6292	0.1511	-0.0094	3.9478
H(5)	0.5960	0.1580	0.0642	3.9478
H(6)	0.7027	0.1643	0.0593	3.9478
H(7)	0.6792	0.2636	-0.0700	3.9478
H(8)	0.7585	0.2738	-0.0043	3.9478
H(9)	0.6888	0.3367	-0.0288	3.9478
H(10)	0.7801	0.2584	0.1308	3.9478
H(11)	0.7773	0.3373	0.1021	3.9478
H(12)	0.7251	0.3030	0.2340	3.9478
H(13)	0.7566	0.4402	0.1788	3.9478
H(14)	0.7501	0.4291	0.2590	3.9478
H(15)	0.5553	0.5486	0.2959	3.9478
H(16)	0.5409	0.4632	0.3008	3.9478
H(17)	0.6402	0.4961	0.3160	3.9478
H(18)	0.6263	0.6009	0.1952	3.9478
H(19)	0.7134	0.5509	0.2168	3.9478
H(20)	0.6586	0.5497	0.1389	3.9478
H(21)	0.4209	0.5935	0.1263	3.9478
H(22)	0.3692	0.5475	0.1766	3.9478
H(23)	0.4565	0.5937	0.2083	3.9478
H(24)	0.8839	0.2779	0.2396	3.9478
H(25)	0.9008	0.3541	0.2094	3.9478
H(26)	0.9649	0.4448	0.2878	3.9478
H(27)	1.0079	0.4890	0.4053	3.9478
H(28)	0.9625	0.4259	0.5001	3.9478
H(29)	0.8672	0.3254	0.4800	3.9478
H(30)	0.8240	0.2796	0.3640	3.9478
H(31)	0.6230	0.2607	0.1352	3.9478
H(32)	0.5858	0.3846	0.2175	3.9478

H(33)	0.1238	0.4863	-0.1697	3.9478
H(34)	0.0219	0.4771	-0.1533	3.9478
H(35)	0.0681	0.4153	-0.1912	3.9478
H(36)	-0.0022	0.3132	-0.1310	3.9478
H(37)	-0.0011	0.3217	-0.0494	3.9478
H(38)	0.0386	0.2518	-0.0790	3.9478
H(39)	0.1488	0.3161	-0.1790	3.9478
H(40)	0.1927	0.2569	-0.1254	3.9478
H(41)	0.2438	0.3306	-0.1287	3.9478
H(42)	0.1144	0.2448	0.0380	3.9478
H(43)	0.1867	0.2145	-0.0070	3.9478
H(44)	0.3085	0.2538	0.0869	3.9478
H(45)	0.1602	0.2726	0.1631	3.9478
H(46)	0.2638	0.2639	0.2016	3.9478
H(47)	0.0908	0.3779	0.2193	3.9478
H(48)	0.1603	0.3289	0.2698	3.9478
H(49)	0.1405	0.4074	0.2927	3.9478
H(50)	0.3158	0.4291	0.3130	3.9478
H(51)	0.3715	0.4215	0.2498	3.9478
H(52)	0.3364	0.3528	0.2847	3.9478
H(53)	0.2261	0.5271	0.2932	3.9478
H(54)	0.2468	0.5813	0.2350	3.9478
H(55)	0.1431	0.5630	0.2422	3.9478
H(56)	0.2986	0.1521	0.1593	3.9478
H(57)	0.1934	0.1421	0.1251	3.9478
H(58)	0.1572	0.0573	0.0320	3.9478
H(59)	0.2034	-0.0198	-0.0524	3.9478
H(60)	0.3576	-0.0169	-0.0750	3.9478
H(61)	0.4650	0.0663	-0.0139	3.9478
H(62)	0.4182	0.1429	0.0715	3.9478
H(63)	0.2578	0.3307	0.0005	3.9478

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

9.3.2.8 Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cu(1)	0.0287(4)	0.0285(4)	0.0292(4)	0.0020(3)	-0.0019(3)	-0.0028(3)
Cu(2)	0.0345(4)	0.0268(4)	0.0267(4)	0.0016(3)	0.0000(3)	0.0005(3)
F(1)	0.046(2)	0.061(3)	0.109(4)	-0.006(2)	0.012(2)	0.030(3)
F(2)	0.072(3)	0.048(2)	0.070(3)	-0.015(2)	0.026(2)	0.002(2)
F(3)	0.163(5)	0.090(4)	0.052(3)	0.061(4)	-0.041(3)	-0.018(3)
F(4)	0.059(3)	0.079(3)	0.141(5)	0.018(3)	0.014(3)	-0.055(3)
F(5)	0.090(3)	0.047(2)	0.075(3)	0.013(2)	0.041(2)	0.007(2)
F(6)	0.057(2)	0.081(3)	0.039(2)	-0.025(2)	0.001(2)	0.002(2)
F(7)	0.047(2)	0.048(2)	0.039(2)	-0.008(2)	0.006(2)	0.010(2)
F(8)	0.046(2)	0.052(2)	0.048(2)	0.002(2)	0.003(2)	0.015(2)

O(1)	0.031(2)	0.039(2)	0.037(2)	-0.001(2)	-0.008(2)	0.001(2)
O(2)	0.027(2)	0.037(2)	0.041(2)	0.004(2)	-0.008(2)	0.001(2)
O(3)	0.045(2)	0.026(2)	0.044(2)	0.006(2)	-0.004(2)	0.000(2)
O(4)	0.056(3)	0.027(2)	0.049(3)	0.008(2)	0.003(2)	0.001(2)
O(5)	0.043(2)	0.034(2)	0.045(2)	0.003(2)	0.010(2)	-0.008(2)
O(6)	0.036(2)	0.035(2)	0.052(3)	-0.002(2)	0.009(2)	-0.008(2)
N(1)	0.028(3)	0.036(3)	0.032(3)	-0.001(2)	-0.004(2)	0.000(2)
N(2)	0.030(3)	0.037(3)	0.027(2)	-0.002(2)	-0.001(2)	-0.004(2)
N(3)	0.023(2)	0.025(2)	0.034(3)	0.000(2)	-0.001(2)	-0.001(2)
N(4)	0.027(2)	0.029(3)	0.037(3)	-0.004(2)	-0.005(2)	0.006(2)
N(5)	0.038(3)	0.024(3)	0.034(3)	0.004(2)	-0.002(2)	0.004(2)
N(6)	0.031(2)	0.027(2)	0.029(2)	-0.003(2)	-0.002(2)	0.005(2)
N(7)	0.035(3)	0.025(2)	0.027(2)	0.005(2)	0.002(2)	-0.003(2)
N(8)	0.035(3)	0.030(3)	0.036(3)	0.004(2)	0.003(2)	-0.002(2)
C(1)	0.038(3)	0.034(3)	0.028(3)	-0.003(3)	0.004(2)	0.000(3)
C(2)	0.035(3)	0.036(3)	0.031(3)	-0.002(3)	0.003(2)	-0.005(3)
C(3)	0.031(3)	0.033(3)	0.043(3)	0.006(3)	0.002(3)	0.001(3)
C(4)	0.030(3)	0.032(3)	0.038(3)	0.005(3)	0.000(2)	-0.002(3)
C(5)	0.031(3)	0.038(3)	0.038(3)	0.001(3)	-0.002(3)	-0.009(3)
C(6)	0.028(3)	0.029(3)	0.038(3)	0.003(2)	0.001(2)	-0.005(2)
C(7)	0.033(3)	0.025(3)	0.041(3)	-0.001(3)	-0.001(3)	-0.002(3)
C(8)	0.051(4)	0.045(4)	0.033(3)	0.001(3)	-0.004(3)	-0.005(3)
C(9)	0.043(4)	0.033(3)	0.050(4)	0.005(3)	0.000(3)	-0.009(3)
C(10)	0.047(4)	0.054(4)	0.041(4)	0.000(3)	0.014(3)	-0.004(3)
C(11)	0.044(4)	0.047(4)	0.039(3)	0.005(3)	-0.002(3)	-0.014(3)
C(12)	0.038(3)	0.031(3)	0.049(4)	-0.006(3)	-0.003(3)	-0.002(3)
C(13)	0.040(4)	0.037(4)	0.065(4)	0.008(3)	-0.002(3)	-0.015(3)
C(14)	0.032(3)	0.054(4)	0.044(4)	0.010(3)	0.003(3)	-0.007(3)
C(15)	0.031(3)	0.043(4)	0.034(3)	0.012(3)	-0.001(2)	-0.005(3)
C(16)	0.036(4)	0.056(4)	0.053(4)	0.003(3)	0.001(3)	0.003(3)
C(17)	0.049(4)	0.054(5)	0.069(5)	-0.010(4)	0.002(4)	-0.018(4)
C(18)	0.052(4)	0.060(5)	0.044(4)	0.003(4)	0.002(3)	-0.014(3)
C(19)	0.046(4)	0.066(5)	0.042(4)	0.006(4)	0.006(3)	0.000(3)
C(20)	0.037(3)	0.044(4)	0.046(4)	-0.003(3)	-0.002(3)	0.000(3)
C(21)	0.029(3)	0.035(3)	0.032(3)	0.000(3)	-0.004(2)	0.003(2)
C(22)	0.036(3)	0.031(3)	0.027(3)	-0.003(3)	-0.006(2)	0.006(2)
C(23)	0.037(3)	0.027(3)	0.031(3)	-0.001(3)	0.001(2)	0.007(2)
C(24)	0.030(3)	0.028(3)	0.032(3)	0.002(2)	0.000(2)	0.007(2)
C(25)	0.034(3)	0.036(3)	0.034(3)	0.005(3)	0.005(3)	0.007(3)
C(26)	0.042(3)	0.045(4)	0.024(3)	0.014(3)	0.002(2)	-0.001(3)
C(27)	0.034(3)	0.050(4)	0.032(3)	0.007(3)	0.002(3)	-0.005(3)
C(28)	0.046(4)	0.037(4)	0.032(3)	-0.005(3)	-0.007(3)	0.009(3)
C(29)	0.044(4)	0.040(4)	0.042(4)	-0.015(3)	-0.014(3)	0.009(3)
C(30)	0.064(4)	0.034(3)	0.029(3)	-0.003(3)	0.001(3)	-0.001(3)
C(31)	0.058(4)	0.057(4)	0.036(3)	0.008(4)	0.017(3)	0.001(3)
C(32)	0.052(4)	0.054(4)	0.038(3)	0.018(3)	-0.008(3)	-0.010(3)
C(33)	0.060(4)	0.049(4)	0.041(4)	0.013(3)	0.004(3)	-0.015(3)
C(34)	0.042(3)	0.027(3)	0.037(3)	0.002(3)	0.003(3)	0.010(2)
C(35)	0.040(3)	0.026(3)	0.037(3)	0.004(3)	-0.002(3)	0.008(2)
C(36)	0.039(4)	0.040(4)	0.058(4)	-0.002(3)	0.003(3)	-0.003(3)

C(37)	0.052(4)	0.041(4)	0.063(4)	-0.009(3)	-0.007(4)	-0.003(3)
C(38)	0.063(4)	0.032(4)	0.042(4)	0.009(3)	0.004(3)	-0.002(3)
C(39)	0.041(4)	0.040(4)	0.059(4)	0.005(3)	0.014(3)	0.004(3)
C(40)	0.035(3)	0.032(3)	0.053(4)	0.000(3)	0.001(3)	-0.001(3)
B(1)	0.035(4)	0.045(4)	0.040(4)	0.010(3)	-0.001(3)	-0.009(3)
B(2)	0.033(3)	0.026(3)	0.028(3)	-0.002(3)	0.008(3)	0.004(3)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

9.3.2.9 Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
Cu(1)	N(1)	1.956(4)	Cu(1)	N(2)	2.002(5)
Cu(1)	N(3)	2.001(4)	Cu(1)	N(4)	1.939(5)
Cu(2)	N(5)	1.949(4)	Cu(2)	N(6)	2.003(4)
Cu(2)	N(7)	2.004(4)	Cu(2)	N(8)	1.963(5)
F(1)	B(1)	1.351(8)	F(2)	B(1)	1.413(9)
F(3)	B(1)	1.355(8)	F(4)	B(1)	1.360(9)
F(5)	B(2)	1.392(8)	F(6)	B(2)	1.402(7)
F(7)	B(2)	1.374(8)	F(8)	B(2)	1.384(7)
O(1)	N(1)	1.380(6)	O(2)	N(4)	1.375(5)
O(3)	N(5)	1.375(6)	O(4)	N(8)	1.388(6)
N(1)	C(1)	1.280(8)	N(2)	C(2)	1.520(7)
N(2)	C(3)	1.487(7)	N(2)	H(31)	1.05
N(3)	C(5)	1.472(7)	N(3)	C(6)	1.513(7)
N(3)	H(32)	1.01	N(4)	C(7)	1.279(7)
N(5)	C(21)	1.281(7)	N(6)	C(22)	1.514(6)
N(6)	C(23)	1.501(7)	N(6)	H(63)	1.01
N(7)	C(25)	1.505(7)	N(7)	C(26)	1.515(7)
N(8)	C(27)	1.277(7)	C(1)	C(2)	1.527(8)
C(1)	C(8)	1.490(8)	C(2)	C(9)	1.551(8)
C(2)	C(10)	1.518(9)	C(3)	C(4)	1.530(8)
C(3)	H(10)	0.95	C(3)	H(11)	0.95
C(4)	C(5)	1.538(8)	C(4)	C(14)	1.540(8)
C(4)	H(12)	0.95	C(5)	H(13)	0.95
C(5)	H(14)	0.95	C(6)	C(7)	1.525(7)
C(6)	C(11)	1.527(9)	C(6)	C(12)	1.534(8)
C(7)	C(13)	1.492(9)	C(8)	H(1)	0.95
C(8)	H(2)	0.95	C(8)	H(3)	0.95
C(9)	H(4)	0.95	C(9)	H(5)	0.95
C(9)	H(6)	0.95	C(10)	H(7)	0.95
C(10)	H(8)	0.95	C(10)	H(9)	0.95
C(11)	H(15)	0.95	C(11)	H(16)	0.96
C(11)	H(17)	0.95	C(12)	H(18)	0.95
C(12)	H(19)	0.95	C(12)	H(20)	0.95
C(13)	H(21)	0.95	C(13)	H(22)	0.95
C(13)	H(23)	0.95	C(14)	C(15)	1.501(8)

C(14)	H(24)	0.95	C(14)	H(25)	0.95
C(15)	C(16)	1.402(9)	C(15)	C(20)	1.384(9)
C(16)	C(17)	1.40(1)	C(16)	H(26)	0.95
C(17)	C(18)	1.37(1)	C(17)	H(27)	0.95
C(18)	C(19)	1.35(1)	C(18)	H(28)	0.95
C(19)	C(20)	1.390(9)	C(19)	H(29)	0.95
C(20)	H(30)	0.95	C(21)	C(22)	1.536(8)
C(21)	C(28)	1.496(8)	C(22)	C(29)	1.541(9)
C(22)	C(30)	1.510(9)	C(23)	C(24)	1.529(7)
C(23)	H(42)	0.95	C(23)	H(43)	0.95
C(24)	C(25)	1.517(8)	C(24)	C(34)	1.553(8)
C(24)	H(44)	0.95	C(25)	H(45)	0.95
C(25)	H(46)	0.95	C(26)	C(27)	1.530(9)
C(26)	C(31)	1.523(10)	C(26)	C(32)	1.530(8)
C(27)	C(33)	1.504(9)	C(28)	H(33)	0.95
C(28)	H(34)	0.95	C(28)	H(35)	0.95
C(29)	H(36)	0.95	C(29)	H(37)	0.95
C(29)	H(38)	0.95	C(30)	H(39)	0.95
C(30)	H(40)	0.95	C(30)	H(41)	0.95
C(31)	H(47)	0.95	C(31)	H(48)	0.95
C(31)	H(49)	0.95	C(32)	H(50)	0.95
C(32)	H(51)	0.95	C(32)	H(52)	0.95
C(33)	H(53)	0.95	C(33)	H(54)	0.95
C(33)	H(55)	0.95	C(34)	C(35)	1.508(8)
C(34)	H(56)	0.95	C(34)	H(57)	0.95
C(35)	C(36)	1.384(8)	C(35)	C(40)	1.371(9)
C(36)	C(37)	1.38(1)	C(36)	H(58)	0.95
C(37)	C(38)	1.36(1)	C(37)	H(59)	0.95
C(38)	C(39)	1.385(9)	C(38)	H(60)	0.95
C(39)	C(40)	1.384(10)	C(39)	H(61)	0.95
C(40)	H(62)	0.95			

9.3.2.10 Bond Angles (°)

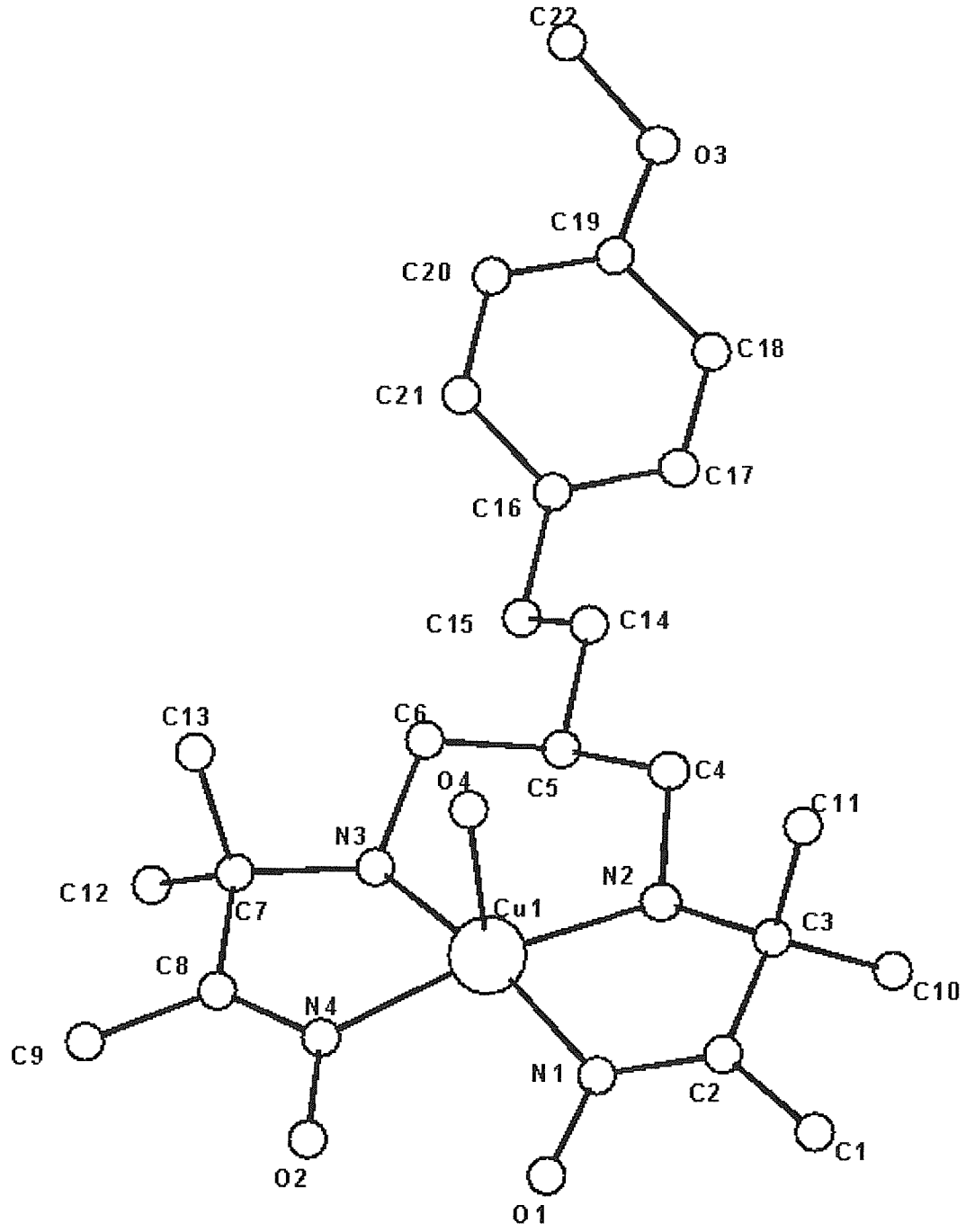
atom	atom	atom	angle	atom	atom	atom	angle
N(1)	Cu(1)	N(2)	81.2(2)	N(1)	Cu(1)	N(3)	167.6(2)
N(1)	Cu(1)	N(4)	96.9(2)	N(2)	Cu(1)	N(3)	98.1(2)
N(2)	Cu(1)	N(4)	168.0(2)	N(3)	Cu(1)	N(4)	81.3(2)
N(5)	Cu(2)	N(6)	81.7(2)	N(5)	Cu(2)	N(7)	165.1(2)
N(5)	Cu(2)	N(8)	97.9(2)	N(6)	Cu(2)	N(7)	96.9(2)
N(6)	Cu(2)	N(8)	170.1(2)	N(7)	Cu(2)	N(8)	80.9(2)
Cu(1)	N(1)	O(1)	122.7(3)	Cu(1)	N(1)	C(1)	119.4(4)
O(1)	N(1)	C(1)	117.9(4)	Cu(1)	N(2)	C(2)	110.9(3)
Cu(1)	N(2)	C(3)	115.3(3)	Cu(1)	N(2)	H(31)	101.5
C(2)	N(2)	C(3)	116.4(4)	C(2)	N(2)	H(31)	109.0
C(3)	N(2)	H(31)	102.0	Cu(1)	N(3)	C(5)	114.6(3)
Cu(1)	N(3)	C(6)	111.3(3)	Cu(1)	N(3)	H(32)	87.8
C(5)	N(3)	C(6)	115.6(4)	C(5)	N(3)	H(32)	117.4
C(6)	N(3)	H(32)	106.7	Cu(1)	N(4)	O(2)	121.2(3)
Cu(1)	N(4)	C(7)	118.9(4)	O(2)	N(4)	C(7)	119.9(5)

Cu(2)	N(5)	O(3)	122.0(3)	Cu(2)	N(5)	C(21)	118.0(4)
O(3)	N(5)	C(21)	119.9(4)	Cu(2)	N(6)	C(22)	110.5(3)
Cu(2)	N(6)	C(23)	115.5(3)	Cu(2)	N(6)	H(63)	93.9
C(22)	N(6)	C(23)	115.9(4)	C(22)	N(6)	H(63)	114.6
C(23)	N(6)	H(63)	104.3	Cu(2)	N(7)	C(25)	115.4(3)
Cu(2)	N(7)	C(26)	111.7(3)	C(25)	N(7)	C(26)	114.4(4)
Cu(2)	N(8)	O(4)	122.6(3)	Cu(2)	N(8)	C(27)	119.2(4)
O(4)	N(8)	C(27)	118.1(5)	N(1)	C(1)	C(2)	115.4(5)
N(1)	C(1)	C(8)	122.5(5)	C(2)	C(1)	C(8)	121.9(5)
N(2)	C(2)	C(1)	107.1(5)	N(2)	C(2)	C(9)	108.3(4)
N(2)	C(2)	C(10)	111.7(5)	C(1)	C(2)	C(9)	111.0(5)
C(1)	C(2)	C(10)	107.9(5)	C(9)	C(2)	C(10)	110.8(5)
N(2)	C(3)	C(4)	112.4(5)	N(2)	C(3)	H(10)	108.8
N(2)	C(3)	H(11)	108.9	C(4)	C(3)	H(10)	108.5
C(4)	C(3)	H(11)	108.6	H(10)	C(3)	H(11)	109.6
C(3)	C(4)	C(5)	113.5(5)	C(3)	C(4)	C(14)	107.5(5)
C(3)	C(4)	H(12)	109.1	C(5)	C(4)	C(14)	108.3(5)
C(5)	C(4)	H(12)	109.1	C(14)	C(4)	H(12)	109.2
N(3)	C(5)	C(4)	112.5(5)	N(3)	C(5)	H(13)	108.6
N(3)	C(5)	H(14)	108.5	C(4)	C(5)	H(13)	108.8
C(4)	C(5)	H(14)	108.8	H(13)	C(5)	H(14)	109.6
N(3)	C(6)	C(7)	106.9(4)	N(3)	C(6)	C(11)	109.1(4)
N(3)	C(6)	C(12)	111.5(5)	C(7)	C(6)	C(11)	111.5(5)
C(7)	C(6)	C(12)	107.9(5)	C(11)	C(6)	C(12)	109.9(5)
N(4)	C(7)	C(6)	116.3(5)	N(4)	C(7)	C(13)	122.9(5)
C(6)	C(7)	C(13)	120.7(5)	C(1)	C(8)	H(1)	109.6
C(1)	C(8)	H(2)	109.4	C(1)	C(8)	H(3)	109.4
H(1)	C(8)	H(2)	109.5	H(1)	C(8)	H(3)	109.6
H(2)	C(8)	H(3)	109.4	C(2)	C(9)	H(4)	109.3
C(2)	C(9)	H(5)	109.5	C(2)	C(9)	H(6)	109.4
H(4)	C(9)	H(5)	109.5	H(4)	C(9)	H(6)	109.4
H(5)	C(9)	H(6)	109.6	C(2)	C(10)	H(7)	109.5
C(2)	C(10)	H(8)	109.3	C(2)	C(10)	H(9)	109.3
H(7)	C(10)	H(8)	109.7	H(7)	C(10)	H(9)	109.6
H(8)	C(10)	H(9)	109.4	C(6)	C(11)	H(15)	109.2
C(6)	C(11)	H(16)	109.6	C(6)	C(11)	H(17)	109.2
H(15)	C(11)	H(16)	113.0	H(15)	C(11)	H(17)	109.4
H(16)	C(11)	H(17)	106.3	C(6)	C(12)	H(18)	109.4
C(6)	C(12)	H(19)	109.4	C(6)	C(12)	H(20)	109.4
H(18)	C(12)	H(19)	109.5	H(18)	C(12)	H(20)	109.5
H(19)	C(12)	H(20)	109.6	C(7)	C(13)	H(21)	109.5
C(7)	C(13)	H(22)	109.3	C(7)	C(13)	H(23)	109.4
H(21)	C(13)	H(22)	109.6	H(21)	C(13)	H(23)	109.7
H(22)	C(13)	H(23)	109.4	C(4)	C(14)	C(15)	115.1(5)
C(4)	C(14)	H(24)	107.9	C(4)	C(14)	H(25)	108.0
C(15)	C(14)	H(24)	108.1	C(15)	C(14)	H(25)	108.2
H(24)	C(14)	H(25)	109.6	C(14)	C(15)	C(16)	119.7(6)
C(14)	C(15)	C(20)	121.6(5)	C(16)	C(15)	C(20)	118.6(5)
C(15)	C(16)	C(17)	120.0(6)	C(15)	C(16)	H(26)	119.9
C(17)	C(16)	H(26)	120.2	C(16)	C(17)	C(18)	119.5(7)

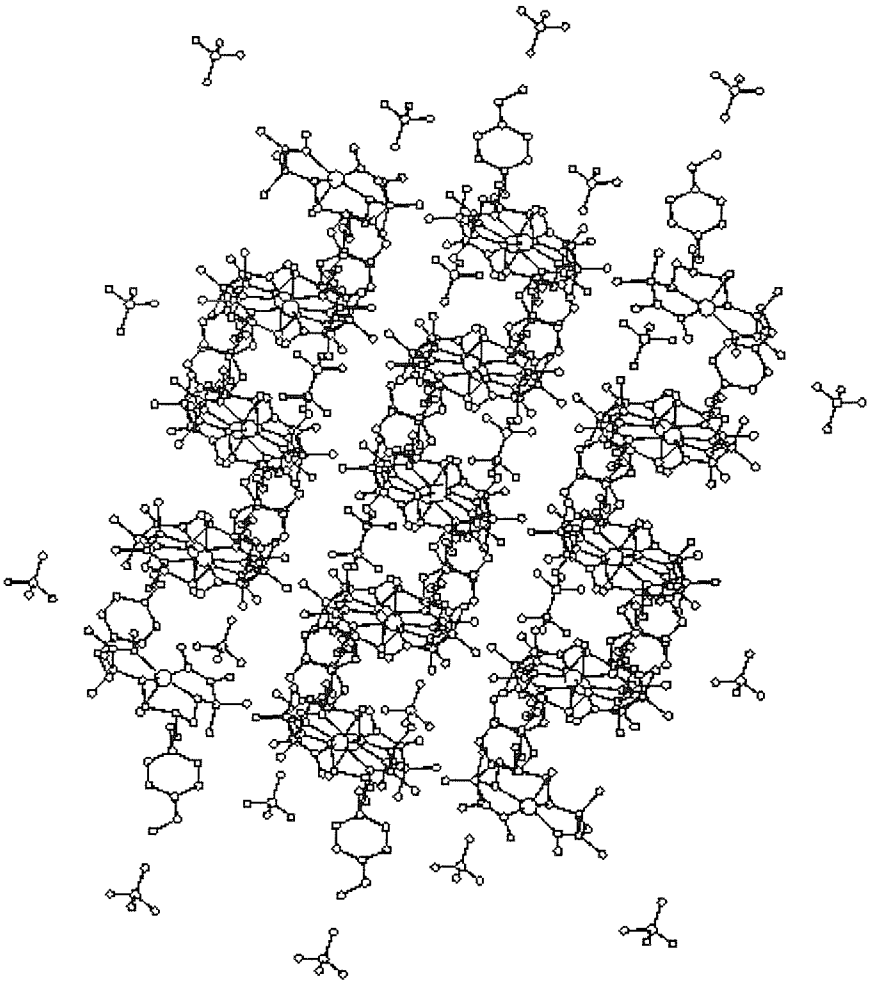
C(16)	C(17)	H(27)	120.2	C(18)	C(17)	H(27)	120.2
C(17)	C(18)	C(19)	121.0(6)	C(17)	C(18)	H(28)	119.3
C(19)	C(18)	H(28)	119.7	C(18)	C(19)	C(20)	120.4(6)
C(18)	C(19)	H(29)	119.7	C(20)	C(19)	H(29)	119.9
C(15)	C(20)	C(19)	120.4(6)	C(15)	C(20)	H(30)	119.7
C(19)	C(20)	H(30)	119.9	N(5)	C(21)	C(22)	116.4(5)
N(5)	C(21)	C(28)	123.2(5)	C(22)	C(21)	C(28)	120.4(5)
N(6)	C(22)	C(21)	107.3(4)	N(6)	C(22)	C(29)	111.1(5)
N(6)	C(22)	C(30)	109.2(4)	C(21)	C(22)	C(29)	108.6(5)
C(21)	C(22)	C(30)	111.0(5)	C(29)	C(22)	C(30)	109.6(5)
N(6)	C(23)	C(24)	110.7(4)	N(6)	C(23)	H(42)	109.2
N(6)	C(23)	H(43)	109.2	C(24)	C(23)	H(42)	109.2
C(24)	C(23)	H(43)	109.2	H(42)	C(23)	H(43)	109.5
C(23)	C(24)	C(25)	113.4(5)	C(23)	C(24)	C(34)	110.3(4)
C(23)	C(24)	H(44)	108.3	C(25)	C(24)	C(34)	107.7(5)
C(25)	C(24)	H(44)	108.6	C(34)	C(24)	H(44)	108.5
N(7)	C(25)	C(24)	112.3(5)	N(7)	C(25)	H(45)	109.1
N(7)	C(25)	H(46)	108.4	C(24)	C(25)	H(45)	108.9
C(24)	C(25)	H(46)	108.7	H(45)	C(25)	H(46)	109.4
N(7)	C(26)	C(27)	107.2(4)	N(7)	C(26)	C(31)	112.1(5)
N(7)	C(26)	C(32)	108.7(5)	C(27)	C(26)	C(31)	107.5(5)
C(27)	C(26)	C(32)	110.8(5)	C(31)	C(26)	C(32)	110.5(5)
N(8)	C(27)	C(26)	116.0(5)	N(8)	C(27)	C(33)	121.8(6)
C(26)	C(27)	C(33)	122.2(5)	C(21)	C(28)	H(33)	109.4
C(21)	C(28)	H(34)	109.5	C(21)	C(28)	H(35)	109.4
H(33)	C(28)	H(34)	109.5	H(33)	C(28)	H(35)	109.5
H(34)	C(28)	H(35)	109.6	C(22)	C(29)	H(36)	109.5
C(22)	C(29)	H(37)	109.5	C(22)	C(29)	H(38)	109.4
H(36)	C(29)	H(37)	109.6	H(36)	C(29)	H(38)	109.5
H(37)	C(29)	H(38)	109.3	C(22)	C(30)	H(39)	109.4
C(22)	C(30)	H(40)	109.5	C(22)	C(30)	H(41)	109.5
H(39)	C(30)	H(40)	109.5	H(39)	C(30)	H(41)	109.5
H(40)	C(30)	H(41)	109.5	C(26)	C(31)	H(47)	109.5
C(26)	C(31)	H(48)	109.4	C(26)	C(31)	H(49)	109.5
H(47)	C(31)	H(48)	109.4	H(47)	C(31)	H(49)	109.6
H(48)	C(31)	H(49)	109.5	C(26)	C(32)	H(50)	109.6
C(26)	C(32)	H(51)	109.4	C(26)	C(32)	H(52)	109.5
H(50)	C(32)	H(51)	109.4	H(50)	C(32)	H(52)	109.5
H(51)	C(32)	H(52)	109.4	C(27)	C(33)	H(53)	109.7
C(27)	C(33)	H(54)	109.5	C(27)	C(33)	H(55)	109.5
H(53)	C(33)	H(54)	109.4	H(53)	C(33)	H(55)	109.4
H(54)	C(33)	H(55)	109.3	C(24)	C(34)	C(35)	114.5(5)
C(24)	C(34)	H(56)	108.2	C(24)	C(34)	H(57)	108.2
C(35)	C(34)	H(56)	108.1	C(35)	C(34)	H(57)	108.2
H(56)	C(34)	H(57)	109.6	C(34)	C(35)	C(36)	121.3(6)
C(34)	C(35)	C(40)	120.5(5)	C(36)	C(35)	C(40)	118.1(6)
C(35)	C(36)	C(37)	121.3(6)	C(35)	C(36)	H(58)	119.3
C(37)	C(36)	H(58)	119.4	C(36)	C(37)	C(38)	120.2(6)
C(36)	C(37)	H(59)	119.7	C(38)	C(37)	H(59)	120.2
C(37)	C(38)	C(39)	119.4(6)	C(37)	C(38)	H(60)	120.2

C(39)	C(38)	H(60)	120.4	C(38)	C(39)	C(40)	119.9(6)
C(38)	C(39)	H(61)	119.9	C(40)	C(39)	H(61)	120.2
C(35)	C(40)	C(39)	121.1(5)	C(35)	C(40)	H(62)	119.4
C(39)	C(40)	H(62)	119.5	F(1)	B(1)	F(2)	107.9(5)
F(1)	B(1)	F(3)	111.5(6)	F(1)	B(1)	F(4)	109.8(6)
F(2)	B(1)	F(3)	107.8(6)	F(2)	B(1)	F(4)	108.9(6)
F(3)	B(1)	F(4)	110.8(6)	F(5)	B(2)	F(6)	108.7(5)
F(5)	B(2)	F(7)	109.8(5)	F(5)	B(2)	F(8)	108.5(5)
F(6)	B(2)	F(7)	110.5(5)	F(6)	B(2)	F(8)	107.8(5)
F(7)	B(2)	F(8)	111.3(5)				

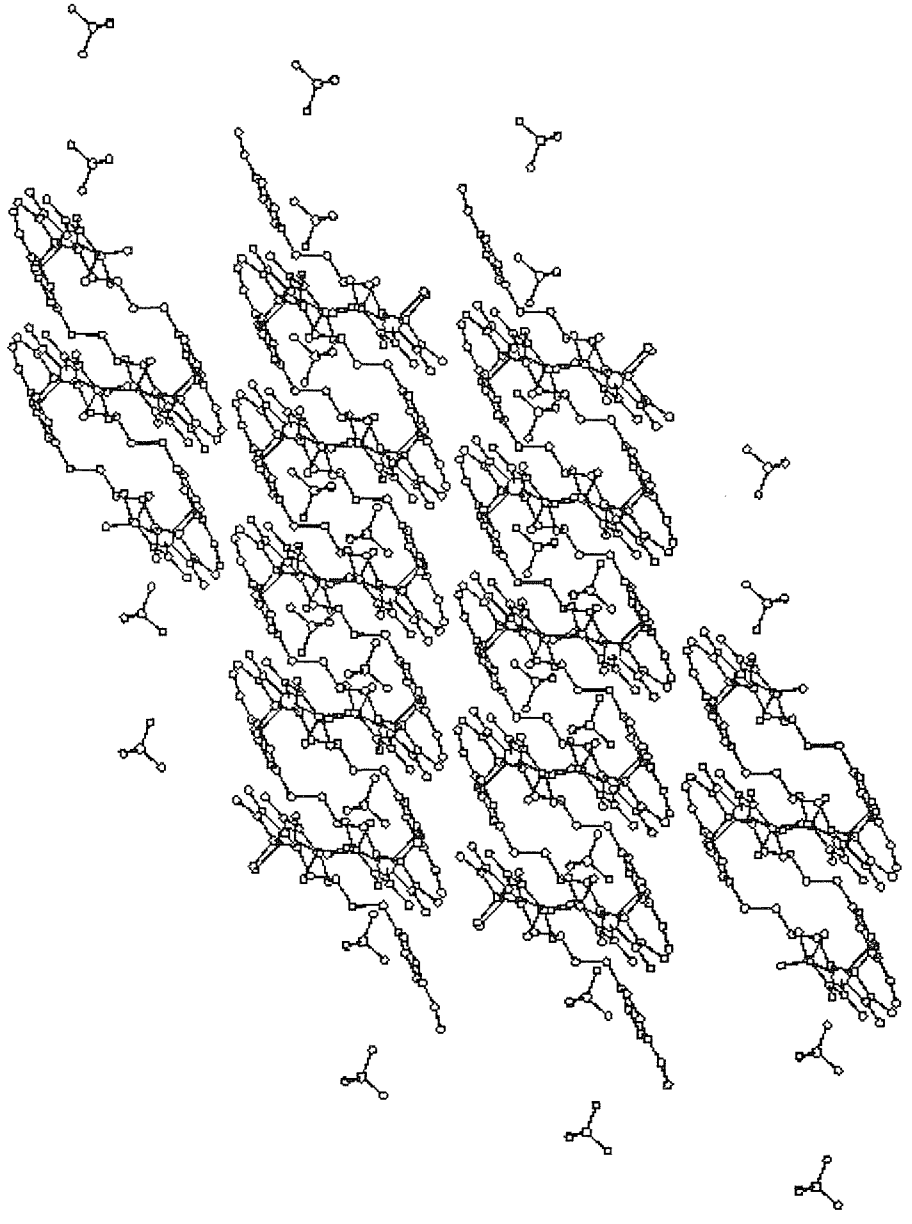
9.3.3 [Cu(II)(MeOBnPnAO)(H_2O)]BF_4



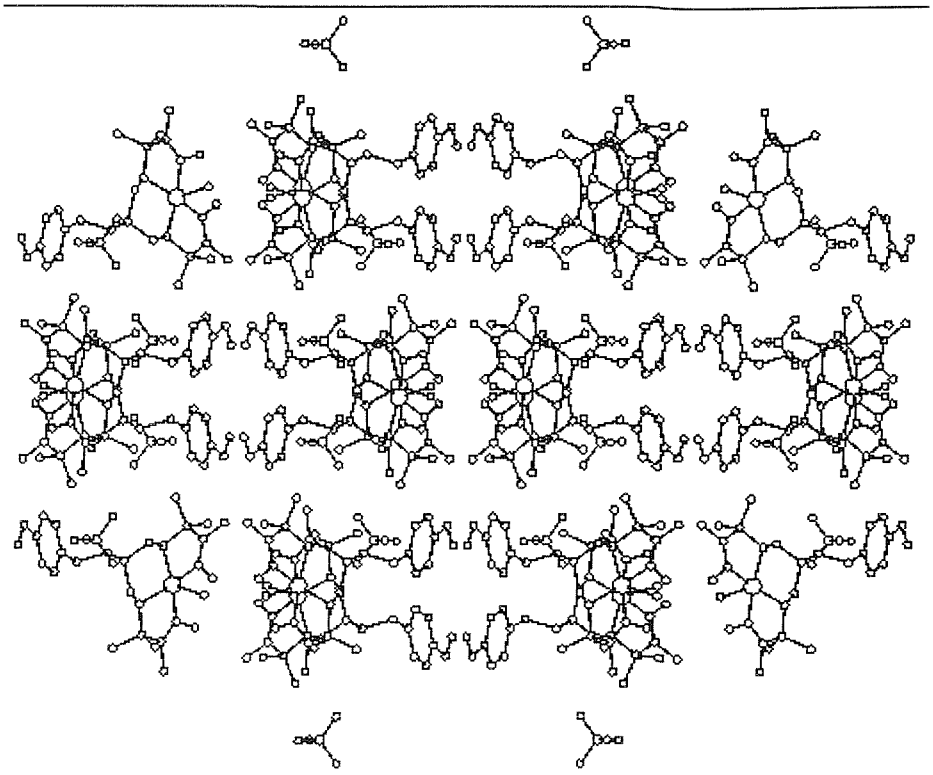
[Cu(II)BnPnAO(H_2O)]BF_4



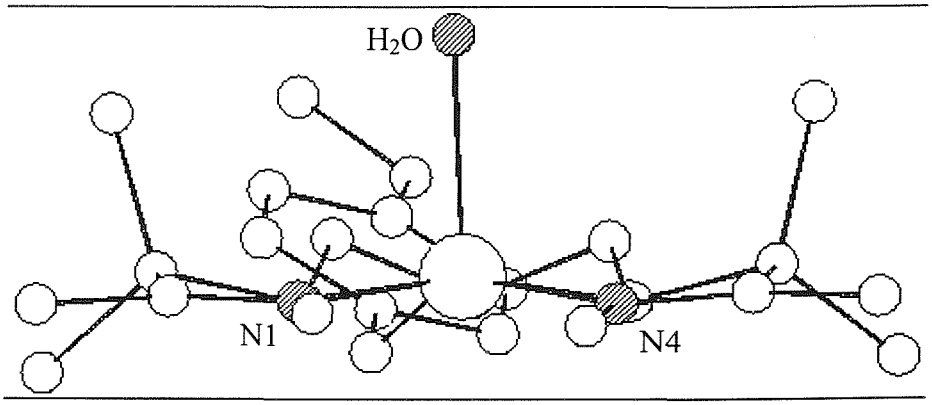
[Cu(II)BnPnAO(H_2O)]BF_4 View along A-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View along B-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View along C-axis



[Cu(II)BnPnAO(H_2O)]BF_4 View from oxime end along plane of ligand nitrogens

9.3.3.1 Data Collection

An purple column crystal of $CuC_{22}H_{39}N_4O_4BF_4$ having approximate dimensions of 0.65 x 0.15 x 0.15 mm was mounted on a glass fibre. All measurements were made on a Rigaku AFC7S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 20 carefully centred reflections in the range $19.11 < 2\theta < 21.98°$ corresponded to a primitive monoclinic cell with dimensions:

$a = 22.067(2)$ Å

$b = 19.047(2)$ Å $\quad \beta = 104.04(1)°$

$c = 12.928(4)$ Å

$V = 5271(1)$ Å^3

For Z = 8 and F.W. = 573.92, the calculated density is 1.45 g cm^{-3}. Based on the systematic absences of

hkl: $h+k \pm 2n$

h0l: $1 \pm 2n$

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be c2/c.

The data were collected at a temperature of -123 ± 1 °C using the ω-2θ scan technique to a maximum 2θ value of 50.0°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.25° with a take-off angle of 6.0°. Scans of (1.25 + 0.35 tan θ)° were made at a speed of 16.0° min^{-1} (in omega). The weak reflections ($I < 15.0\sigma(I)$) were rescanned (maximum of 4 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400 mm. The computer-controlled slits were set to 9.0 mm (horizontal) and 13.0 mm (vertical).

9.3.3.2 Data Reduction

Of the 4931 reflections which were collected, 4799 were unique ($R_{int} = 0.044$). The intensities of three representative reflections were measured after every 150 reflections. Over the course of data collection, the standards decreased by 1.4%. A linear correction factor was applied to the data to account for this phenomenon.

The linear absorption coefficient, μ, for Mo-Kα radiation is 8.9 cm^{-1}. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.93 to 1.00. The data were corrected for

Lorentz and polarisation effects.

9.3.3.3 Structure Solution and Refinement Methods

The structure was solved by heavy-atom Patterson methods[99] and expanded using Fourier techniques[100]. The non-hydrogen atoms were refined anisotropically. Some hydrogen atoms were refined isotropically, the rest were included in fixed positions. The final cycle of full-matrix least-squares refinement[101] was based on 2555 observed reflections ($I > 2.50\sigma(I)$) and 337 variable parameters and converged (largest parameter shift was 1.37 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma||Fo| - |Fc|| / \Sigma|Fo| = 0.038$$

$$Rw = [(\Sigma w(|Fo| - |Fc|)^2 / \Sigma w\, Fo^2)]^{1/2} = 0.038$$

The standard deviation of an observation of unit weight[102] was 1.39. The weighting scheme was based on counting statistics and included a factor ($p = 0.004$) to downweight the intense reflections. Plots of $\Sigma\omega(|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, $\sin\theta/\lambda$ and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.41 and -0.35 $e^-/Å^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[103]. Anomalous dispersion effects were included in Fcalc[104]; the values for $\Delta f'$ and $\Delta f''$ were those of Creagh and McAuley[105]. The values for the mass attenuation coefficients are those of Creagh and Hubbel[106]. All calculations were performed using the teXsan[107] crystallographic software package of Molecular Structure Corporation.

9.3.3.4 Crystal Data

Empirical Formula	$CuC_{22}H_{39}N_4O_4BF_4$
Formula Weight	573.92
Crystal Colour, Habit	purple, column
Crystal Dimensions	0.65 X 0.15 X 0.15 mm
Crystal System	monoclinic
Lattice Type	C-centred

Cell Determination (2θ range)	20 (19.1 - 22.0°)
Omega Scan Peak Width at Half-height	0.25°
Lattice Parameters	a = 22.067(2)Å
	b = 19.047(2) Å
	c = 12.928(4) Å
	β = 104.04(1)°
	V = 5271(1) $Å^3$
Space Group	C2/c
Z value	8
D_{calc}	1.446 g cm^{-3}
F000	2408.00
μ(MoKα)	8.92 cm^{-1}

9.3.3.5 Intensity Measurements

Diffractometer	Rigaku AFC7S
Radiation	MoKα (λ = 0.71069 Å)
	graphite monochromated
Attenuator	Zr foil (factor = 8.59)
Take-off Angle	6.0°
Detector Aperture	9.0 mm horizontal
	13.0 mm vertical
Crystal to Detector Distance	400 mm
Temperature	-123.1 °C
Scan Type	ω-2θ
Scan Rate	16.0° min^{-1} (in ω) (up to 4 scans)
Scan Width	(1.26 + 0.35 tan θ)°
$2\theta_{max}$	50.0°
No. of Reflections Measured	Total: 4391
	Unique: 4799 (R_{int} = 0.044)
Corrections	Lorentz-polarisation Absorption
	(trans. factors: 0.9262 - 1.0000)
	Decay (1.39% decline)

9.3.3.6 Structure Solution and Refinement

Structure Solution	Patterson Methods (DIRDIF92 PATTY)
Refinement	Full-matrix least-squares
Function Minimised	$\Sigma\omega(\|Fo\| - \|Fc\|)^2$
Least Squares Weights	$1/\sigma^2(Fo) = 4(Fo)^2/\sigma^2(Fo^2)$
p-factor	0.0040
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>3.00σ(I))	2555
No. Variables	337
Reflection/Parameter Ratio	7.58
Residuals: R; Rw	0.038; 0.038
Goodness of Fit Indicator	1.39
Max Shift/Error in Final Cycle	1.37
Maximum peak in Final Diff. Map	0.41 $e^-/Å^3$
Minimum peak in Final Diff. Map	-0.35 $e^-/Å^3$

9.3.3.7 Atomic co-ordinates and Biso/Beq

atom	x	y	z	Beq
Cu(1)	0.13954(3)	0.01373(3)	0.00908(5)	1.34(1)
F(1)	0.2286(1)	0.4327(2)	0.8353(2)	3.58(8)
F(2)	0.1425(1)	0.3743(2)	0.8557(3)	3.63(8)
F(3)	0.2278(2)	0.3147(2)	0.8399(3)	5.3(1)
F(4)	0.1681(1)	0.3724(2)	0.6978(2)	3.80(8)
O(1)	0.0516(1)	0.0309(2)	0.1425(2)	1.66(7)
O(2)	0.0892(2)	-0.0939(2)	0.1327(3)	1.91(8)
O(3)	0.4705(2)	0.1636(2)	-0.4806(3)	2.58(9)
O(4)	0.0692(2)	-0.0129(2)	-0.1417(3)	2.30(8)
N(1)	0.0830(2)	0.0639(2)	0.0774(3)	1.42(9)
N(2)	0.1618(2)	0.1117(2)	-0.0229(3)	1.43(9)
N(3)	0.2127(2)	-0.0346(2)	-0.0250(3)	1.23(8)
N(4)	0.1315(2)	-0.0790(2)	0.0719(3)	1.41(9)
C(1)	0.0255(2)	0.1700(3)	0.0949(4)	2.2(1)
C(2)	0.0729(2)	0.1287(3)	0.0554(4)	1.5(1)
C(3)	0.1087(2)	0.1615(2)	-0.0203(4)	1.5(1)
C(4)	0.1915(2)	0.1203(2)	-0.1143(4)	1.6(1)
C(5)	0.2486(2)	0.0738(2)	-0.1034(4)	1.6(1)
C(6)	0.2327(2)	-0.0048(2)	-0.1181(3)	1.7(1)
C(7)	0.2066(2)	-0.1132(2)	-0.0226(4)	1.5(1)
C(8)	0.1639(2)	-0.1300(2)	0.0509(4)	1.6(1)
C(9)	0.1578(3)	-0.2035(3)	0.0896(4)	2.6(1)
C(10)	0.1345(2)	0.2331(2)	0.0189(4)	2.2(1)

C(11)	0.0636(2)	0.1677(3)	-0.1318(4)	2.3(1)
C(12)	0.2713(2)	-0.1455(2)	0.0194(4)	2.1(1)
C(13)	0.1764(2)	-0.1428(3)	-0.1339(4)	2.0(1)
C(14)	0.2845(2)	0.0948(2)	-0.1867(4)	1.7(1)
C(15)	0.3529(2)	0.0716(3)	-0.1584(4)	2.5(1)
C(16)	0.3866(2)	0.0939(3)	-0.2430(4)	2.0(1)
C(17)	0.4002(2)	0.1642(3)	-0.2561(4)	2.0(1)
C(18)	0.4279(2)	0.1857(2)	-0.3358(4)	1.9(1)
C(19)	0.4428(2)	0.1368(3)	-0.4045(4)	2.0(1)
C(20)	0.4301(2)	0.0666(3)	-0.3935(4)	2.5(1)
C(21)	0.4026(2)	0.0458(3)	-0.3120(5)	2.7(1)
C(22)	0.4842(3)	0.1159(3)	-0.5562(4)	3.3(2)
B(1)	0.1910(3)	0.3732(4)	0.8064(5)	2.6(2)
H(1)	-0.0145	0.1500	0.0689	2.7048
H(2)	0.0360	0.1695	0.1710	2.7048
H(3)	0.0254	0.2173	0.0711	2.7048
H(4)	0.1947	0.1251	0.0390	1.7494
H(5)	0.2040	0.1680	-0.1173	2.0260
H(6)	0.1618	0.1084	-0.1773	2.0260
H(7)	0.2754	0.0804	-0.0342	1.9375
H(8)	0.2686	-0.0293	-0.1266	1.9985
H(9)	0.1996	-0.0105	-0.1791	1.9985
H(10)	0.2473	-0.0240	0.0356	1.4621
H(11)	0.1666	-0.2039	0.1653	3.1255
H(12)	0.1164	-0.2199	0.0611	3.1255
H(13)	0.1864	-0.2337	0.0668	3.1255
H(14)	0.1583	0.2513	-0.0273	2.7410
H(15)	0.1610	0.2288	0.0890	2.7410
H(16)	0.1014	0.2643	0.0207	2.7410
H(17)	0.0291	0.1963	-0.1274	2.8021
H(18)	0.0493	0.1224	-0.1568	2.8021
H(19)	0.0850	0.1885	-0.1798	2.8021
H(20)	0.2974	-0.1328	-0.0263	2.4785
H(21)	0.2890	-0.1286	0.0893	2.4785
H(22)	0.2676	-0.1951	0.0209	2.4785
H(23)	0.2023	-0.1326	-0.1808	2.3855
H(24)	0.1720	-0.1923	-0.1289	2.3855
H(25)	0.1366	-0.1221	-0.1598	2.3855
H(26)	0.2831	0.1446	-0.1932	2.0744
H(27)	0.2642	0.0742	-0.2529	2.0744
H(28)	0.3735	0.0922	-0.0923	2.9989
H(29)	0.3547	0.0220	-0.1523	2.9989
H(30)	0.3900	0.1985	-0.2094	2.4096
H(31)	0.4366	0.2341	-0.3433	2.2913
H(32)	0.4401	0.0329	-0.4408	2.9467
H(33)	0.3945	-0.0028	-0.3044	3.1696
H(34)	0.5036	0.1405	-0.6035	3.9626
H(35)	0.5116	0.0805	-0.5201	3.9626
H(36)	0.4466	0.0949	-0.5956	3.9626
H(37)	0.076(2)	-0.053(3)	0.135(4)	2.1(9)

H(38)	0.069(2)	-0.019(3)	-0.204(4)	3.8(10)
H(39)	0.030(2)	-0.019(3)	-0.143(4)	3.0(10)

$B_{eq} = 8/3\ \pi^2(U_{11}(aa^*)^2 + U_{22}(bb^*)^2 + U_{33}(cc^*)^2 + 2U_{12}(aa^*bb^*)\cos\gamma + 2U_{13}(aa^*cc^*)\cos\beta + 2U_{23}(bb^*cc^*)\cos\alpha)$

9.3.3.8 Anisotropic Displacement Parameters

atom	U_{11}	U_{22}	U_{33}	U_{12}	U_{13}	U_{23}
Cu(1)	0.0184(3)	0.0177(3)	0.0169(3)	0.0028(3)	0.0085(2)	0.0012(3)
F(1)	0.049(2)	0.058(2)	0.027(2)	-0.023(2)	0.005(2)	0.001(2)
F(2)	0.044(2)	0.053(2)	0.048(2)	-0.003(2)	0.025(2)	0.010(2)
F(3)	0.052(2)	0.058(3)	0.090(3)	0.022(2)	0.016(2)	0.024(2)
F(4)	0.050(2)	0.067(2)	0.026(2)	-0.020(2)	0.007(2)	-0.002(2)
O(1)	0.022(2)	0.027(2)	0.018(2)	0.001(1)	0.013(1)	0.001(1)
O(2)	0.027(2)	0.024(2)	0.028(2)	0.003(2)	0.021(2)	0.005(2)
O(3)	0.037(2)	0.032(2)	0.036(2)	-0.007(2)	0.023(2)	-0.006(2)
O(4)	0.018(2)	0.053(2)	0.015(2)	-0.003(2)	0.004(1)	-0.005(2)
N(1)	0.021(2)	0.021(2)	0.015(2)	0.003(2)	0.010(2)	0.005(2)
N(2)	0.019(2)	0.021(2)	0.016(2)	0.001(2)	0.007(2)	0.001(2)
N(3)	0.018(2)	0.014(2)	0.017(2)	0.002(2)	0.007(2)	-0.001(2)
N(4)	0.018(2)	0.020(2)	0.018(2)	0.001(2)	0.007(2)	0.002(2)
C(1)	0.027(3)	0.025(3)	0.036(3)	0.002(2)	0.013(2)	0.000(2)
C(2)	0.015(3)	0.027(3)	0.015(3)	0.001(2)	0.003(2)	-0.003(2)
C(3)	0.023(3)	0.018(3)	0.018(3)	0.007(2)	0.007(2)	0.003(2)
C(4)	0.024(3)	0.021(3)	0.020(3)	-0.001(2)	0.009(2)	0.003(2)
C(5)	0.020(3)	0.023(3)	0.019(3)	-0.005(2)	0.008(2)	-0.001(2)
C(6)	0.023(3)	0.023(3)	0.022(3)	0.001(2)	0.013(2)	0.000(2)
C(7)	0.021(3)	0.016(3)	0.024(3)	0.002(2)	0.011(2)	0.003(2)
C(8)	0.021(3)	0.018(3)	0.020(3)	0.002(2)	0.005(2)	0.000(2)
C(9)	0.044(4)	0.021(3)	0.041(3)	0.006(3)	0.023(3)	0.004(3)
C(10)	0.035(3)	0.022(3)	0.034(3)	0.004(3)	0.020(2)	-0.001(3)
C(11)	0.028(3)	0.036(3)	0.024(3)	0.015(2)	0.005(2)	0.006(2)
C(12)	0.025(3)	0.020(3)	0.035(3)	0.002(2)	0.010(2)	-0.001(2)
C(13)	0.027(3)	0.025(3)	0.029(3)	-0.004(2)	0.014(2)	-0.007(2)
C(14)	0.024(3)	0.023(3)	0.022(3)	-0.003(2)	0.010(2)	0.003(2)
C(15)	0.026(3)	0.039(3)	0.031(3)	0.003(3)	0.009(2)	0.008(3)
C(16)	0.014(3)	0.032(3)	0.031(3)	-0.002(2)	0.007(2)	0.007(2)
C(17)	0.017(3)	0.034(3)	0.028(3)	-0.004(2)	0.009(2)	-0.009(2)
C(18)	0.024(3)	0.018(3)	0.034(3)	-0.008(2)	0.012(2)	-0.006(2)
C(19)	0.019(3)	0.030(3)	0.028(3)	-0.005(2)	0.011(2)	-0.002(2)
C(20)	0.034(3)	0.027(3)	0.042(3)	0.002(3)	0.023(3)	-0.003(3)
C(21)	0.029(3)	0.023(3)	0.053(4)	0.006(2)	0.018(3)	0.003(3)
C(22)	0.040(4)	0.054(4)	0.039(4)	-0.002(3)	0.025(3)	-0.010(3)
B(1)	0.029(4)	0.043(4)	0.026(4)	-0.001(3)	0.005(3)	0.006(3)

The general temperature factor expression:

$\exp(-2\pi^2(a^{*2}U_{11}h^2 + b^{*2}U_{22}k^2 + c^{*2}U_{33}l^2 + 2a^*b^*U_{12}hk + 2a^*c^*U_{13}hl + 2b^*c^*U_{23}kl))$

9.3.3.9 Bond Lengths (Å)

atom	atom	distance	atom	atom	distance
Cu(1)	O(4)	2.235(3)	Cu(1)	N(1)	1.946(4)
Cu(1)	N(2)	1.998(4)	Cu(1)	N(3)	1.998(4)
Cu(1)	N(4)	1.969(4)	F(1)	B(1)	1.400(7)
F(2)	B(1)	1.372(7)	F(3)	B(1)	1.385(7)
F(4)	B(1)	1.371(6)	O(1)	N(1)	1.366(4)
O(2)	N(4)	1.388(4)	O(2)	H(37)	0.83(5)
O(3)	C(19)	1.376(5)	O(3)	C(22)	1.420(6)
O(4)	H(38)	0.81(5)	O(4)	H(39)	0.88(5)
N(1)	C(2)	1.274(6)	N(2)	C(3)	1.514(6)
N(2)	C(4)	1.492(6)	N(2)	H(4)	0.97
N(3)	C(6)	1.491(5)	N(3)	C(7)	1.505(6)
N(3)	H(10)	0.97	N(4)	C(8)	1.273(6)
C(1)	C(2)	1.494(6)	C(1)	H(1)	0.95
C(1)	H(2)	0.96	C(1)	H(3)	0.95
C(2)	C(3)	1.532(6)	C(3)	C(10)	1.517(7)
C(3)	C(11)	1.545(6)	C(4)	C(5)	1.518(6)
C(4)	H(5)	0.95	C(4)	H(6)	0.94
C(5)	C(6)	1.538(7)	C(5)	C(14)	1.535(6)
C(5)	H(7)	0.95	C(6)	H(8)	0.95
C(6)	H(9)	0.94	C(7)	C(8)	1.526(6)
C(7)	C(12)	1.528(6)	C(7)	C(13)	1.539(7)
C(8)	C(9)	1.503(7)	C(9)	H(11)	0.95
C(9)	H(12)	0.95	C(9)	H(13)	0.95
C(10)	H(14)	0.95	C(10)	H(15)	0.96
C(10)	H(16)	0.95	C(11)	H(17)	0.95
C(11)	H(18)	0.95	C(11)	H(19)	0.95
C(12)	H(20)	0.95	C(12)	H(21)	0.95
C(12)	H(22)	0.95	C(13)	H(23)	0.95
C(13)	H(24)	0.95	C(13)	H(25)	0.95
C(14)	C(15)	1.529(7)	C(14)	H(26)	0.95
C(14)	H(27)	0.95	C(15)	C(16)	1.525(7)
C(15)	H(28)	0.95	C(15)	H(29)	0.95
C(16)	C(17)	1.392(7)	C(16)	C(21)	1.384(7)
C(17)	C(18)	1.380(6)	C(17)	H(30)	0.95
C(18)	C(19)	1.382(6)	C(18)	H(31)	0.95
C(19)	C(20)	1.379(7)	C(20)	C(21)	1.395(7)
C(20)	H(32)	0.95	C(21)	H(33)	0.95
C(22)	H(34)	0.95	C(22)	H(35)	0.95
C(22)	H(36)	0.95			

9.3.3.10 Bond Angles (°)

atom	atom	atom	angle	atom	atom	atom	angle
O(4)	Cu(1)	N(1)	97.0(1)	O(4)	Cu(1)	N(2)	100.7(2)
O(4)	Cu(1)	N(3)	97.5(1)	O(4)	Cu(1)	N(4)	92.5(2)
N(1)	Cu(1)	N(2)	81.5(2)	N(1)	Cu(1)	N(3)	165.4(2)
N(1)	Cu(1)	N(4)	97.0(2)	N(2)	Cu(1)	N(3)	97.6(1)
N(2)	Cu(1)	N(4)	166.8(2)	N(3)	Cu(1)	N(4)	80.5(1)
N(4)	O(2)	H(37)	96(3)	C(19)	O(3)	C(22)	117.4(4)
Cu(1)	O(4)	H(38)	137(3)	Cu(1)	O(4)	H(39)	121(3)
H(38)	O(4)	H(39)	100(4)	Cu(1)	N(1)	O(1)	122.0(3)
Cu(1)	N(1)	C(2)	118.1(3)	O(1)	N(1)	C(2)	119.8(4)
Cu(1)	N(2)	C(3)	110.5(3)	Cu(1)	N(2)	C(4)	116.3(3)
Cu(1)	N(2)	H(4)	104.3	C(3)	N(2)	C(4)	116.0(3)
C(3)	N(2)	H(4)	104.1	C(4)	N(2)	H(4)	103.8
Cu(1)	N(3)	C(6)	114.5(3)	Cu(1)	N(3)	C(7)	111.9(3)
Cu(1)	N(3)	H(10)	104.2	C(6)	N(3)	C(7)	116.2(3)
C(6)	N(3)	H(10)	104.1	C(7)	N(3)	H(10)	104.2
Cu(1)	N(4)	O(2)	123.8(3)	Cu(1)	N(4)	C(8)	119.1(3)
O(2)	N(4)	C(8)	117.0(4)	C(2)	C(1)	H(1)	109.8
C(2)	C(1)	H(2)	109.4	C(2)	C(1)	H(3)	109.7
H(1)	C(1)	H(2)	109.4	H(1)	C(1)	H(3)	109.7
H(2)	C(1)	H(3)	108.9	N(1)	C(2)	C(1)	122.1(4)
N(1)	C(2)	C(3)	116.7(4)	C(1)	C(2)	C(3)	121.0(4)
N(2)	C(3)	C(2)	106.2(4)	N(2)	C(3)	C(10)	110.0(4)
N(2)	C(3)	C(11)	110.8(4)	C(2)	C(3)	C(10)	111.3(4)
C(2)	C(3)	C(11)	108.2(4)	C(10)	C(3)	C(11)	110.3(4)
N(2)	C(4)	C(5)	112.1(4)	N(2)	C(4)	H(5)	108.9
N(2)	C(4)	H(6)	108.2	C(5)	C(4)	H(5)	108.4
C(5)	C(4)	H(6)	109.1	H(5)	C(4)	H(6)	110.0
C(4)	C(5)	C(6)	113.3(4)	C(4)	C(5)	C(14)	109.9(4)
C(4)	C(5)	H(7)	108.8	C(6)	C(5)	C(14)	108.0(4)
C(6)	C(5)	H(7)	108.3	C(14)	C(5)	H(7)	108.4
N(3)	C(6)	C(5)	112.0(4)	N(3)	C(6)	H(8)	108.9
N(3)	C(6)	H(9)	108.1	C(5)	C(6)	H(8)	108.7
C(5)	C(6)	H(9)	108.9	H(8)	C(6)	H(9)	110.1
N(3)	C(7)	C(8)	107.1(4)	N(3)	C(7)	C(12)	109.1(4)
N(3)	C(7)	C(13)	111.5(4)	C(8)	C(7)	C(12)	111.1(4)
C(8)	C(7)	C(13)	108.2(4)	C(12)	C(7)	C(13)	109.9(4)
N(4)	C(8)	C(7)	115.8(4)	N(4)	C(8)	C(9)	122.7(4)
C(7)	C(8)	C(9)	121.4(4)	C(8)	C(9)	H(11)	109.7
C(8)	C(9)	H(12)	109.4	C(8)	C(9)	H(13)	109.9
H(11)	C(9)	H(12)	109.4	H(11)	C(9)	H(13)	109.2
H(12)	C(9)	H(13)	109.2	C(3)	C(10)	H(14)	109.8
C(3)	C(10)	H(15)	109.4	C(3)	C(10)	H(16)	110.0
H(14)	C(10)	H(15)	108.8	H(14)	C(10)	H(16)	109.6
H(15)	C(10)	H(16)	109.2	C(3)	C(11)	H(17)	109.5
C(3)	C(11)	H(18)	109.5	C(3)	C(11)	H(19)	109.4
H(17)	C(11)	H(18)	109.6	H(17)	C(11)	H(19)	109.4
H(18)	C(11)	H(19)	109.5	C(7)	C(12)	H(20)	109.4
C(7)	C(12)	H(21)	109.7	C(7)	C(12)	H(22)	109.3

H(20)	C(12)	H(21)	109.5	H(20)	C(12)	H(22)	109.4
H(21)	C(12)	H(22)	109.5	C(7)	C(13)	H(23)	109.3
C(7)	C(13)	H(24)	109.1	C(7)	C(13)	H(25)	109.4
H(23)	C(13)	H(24)	109.4	H(23)	C(13)	H(25)	109.9
H(24)	C(13)	H(25)	109.7	C(5)	C(14)	C(15)	113.8(4)
C(5)	C(14)	H(26)	108.1	C(5)	C(14)	H(27)	108.3
C(15)	C(14)	H(26)	108.5	C(15)	C(14)	H(27)	108.5
H(26)	C(14)	H(27)	109.5	C(14)	C(15)	C(16)	111.9(4)
C(14)	C(15)	H(28)	109.0	C(14)	C(15)	H(29)	109.1
C(16)	C(15)	H(28)	108.5	C(16)	C(15)	H(29)	108.7
H(28)	C(15)	H(29)	109.6	C(15)	C(16)	C(17)	120.9(5)
C(15)	C(16)	C(21)	121.5(5)	C(17)	C(16)	C(21)	117.5(5)
C(16)	C(17)	C(18)	121.6(5)	C(16)	C(17)	H(30)	119.4
C(18)	C(17)	H(30)	119.0	C(17)	C(18)	C(19)	119.8(4)
C(17)	C(18)	H(31)	120.0	C(19)	C(18)	H(31)	120.2
O(3)	C(19)	C(18)	115.2(4)	O(3)	C(19)	C(20)	124.8(5)
C(18)	C(19)	C(20)	120.0(4)	C(19)	C(20)	C(21)	119.4(5)
C(19)	C(20)	H(32)	120.2	C(21)	C(20)	H(32)	120.4
C(16)	C(21)	C(20)	121.6(5)	C(16)	C(21)	H(33)	119.5
C(20)	C(21)	H(33)	118.9	O(3)	C(22)	H(34)	109.4
O(3)	C(22)	H(35)	109.4	O(3)	C(22)	H(36)	109.6
H(34)	C(22)	H(35)	109.4	H(34)	C(22)	H(36)	109.4
H(35)	C(22)	H(36)	109.6	F(1)	B(1)	F(2)	110.0(5)
F(1)	B(1)	F(3)	107.7(5)	F(1)	B(1)	F(4)	109.2(5)
F(2)	B(1)	F(3)	109.2(5)	F(2)	B(1)	F(4)	109.9(5)
F(3)	B(1)	F(4)	110.8(5)				

10 References

1 D. Deutsch and K. Libson, *Comments Inorg. Chem.*, 1984, **3**(2-3), 83.

2 S. Jurisson, D. Berning, Wei Jia and Dangshe Ma, *Chem. Rev.*, 1993, **93**, 1137.

3 H. M. Chilton, S. W. Burchiel and N. E. Watson Jr., in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 564.

4 H. M. Chilton, S. W. Burchiel and N. E. Watson Jr., in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 330.

5 C. H. Taliaferro, R. J. Motekaitis and A. E. Martell, *Inorg. Chem.*, 1984, **23**, 1188.

6 J. A. Ponto, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 621.

7 D. P. Swanson, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 616.

8 E. K. John and M. A. Green, *J. Nucl. Med.*, 1990, **33**, 1764.

9 C. J. Jones in *Comprehensive Co-ordination Chemistry, Chapter 65, Applications in the Nuclear Fuel Cycle and Radiopharmacy*, eds., R. D. Gillard, J. A. McCleverty and G. Wilkinson, Pergamon Press, Oxford, 1987, Vol. 6, p. 881.

10 R. Edelman and S. Warach, *New Eng. J. Med.*, 1993, **328**, 708; R. B. Lauffer, *Chem. Rev.*, 1987, **87**, 901.

11 D. Parker, *Chem. Br.*, 1994, **30**, 818.

12 A. M. Verbruggen, *Eur. J. Nucl. Med.*, 1990, **17**, 346.

13 G. J. Hine and J. A. Sorenson, in *Instrumentation in Nuclear Medicine*, Academic Press, New York, 1974; R. N. Beck, in *Nuclear Medicine*, ed, H. Wagner, H-P Publishing, New York, 1975.

14 M. J. Clarke and L. Podbielski, *Coord. Chem. Rev.*, 1987, **78**, 253.

15 C. Perrier and E. Segrè, *Nature*, 1937, **140**, 193.

16 B. T. Kenna and P. K. Kuroda, *J. Inorg. Nucl. Chem. Lett.*, 1961, **23**, 142.

17 H. M. Chilton, and R. L. Witcofski, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 285.

18 E. A. Deutsch and S. Jurisson, in *Handbook on metals in clinical and analytical chemistry*, eds., H. G. Seiler, A. Sigel and H. Sigel, Marcel-Dekker, 1994, p. 587.

19 J. P. Leonard, D. P. Nowotnik and R. D. Neirinckx, *J. Nucl. Med.*, 1986, **27**, 1819; R. D. Neirinckx, L. R. Canning, I. M. Piper, D. P. Nowotnik, R. D. Pickett, R. A. Holmes, W. A. Volkert, A. M. Forster, P. S. Weisner, J. A. Marriot and S. B. Chaplin, *J. Nucl .Med.*, 1987, **28**, 191.

20 R. D. Neirinckx, J. F. Burke, R. C. Harrison, A. M. Forster, A. R. Andersen and N. A. Lassen, *J. Cereb. Blood Flow Metab.*, 1988, **8**(6), S4 - S12.

21 J. A. Ponto, H. M. Chilton and N. E. Watson Jr, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton, and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 510.

22 J. Singh, A. K. Powell, S. E. M. Clark and P. J. Blower, *J. Chem. Soc., Chem. Commun.*, 1991, 1115.

23 A. R. Fritzberg, S. Kasina, D. Eshima and D. L. Johnson, *J. Nucl. Med.*, 1986, **27**, 111.

24 L. D. Nosco, A. J. Tofe, T. J. Dunn, L. R. Lyle, R. G. Wolfangel, M. J. Bushmann, G. D. Grummon, D. E. Helling, M. E. Marmion, K. M. Miller, D. W. Pipes, T. W. Strubel and D. W. Wester, in *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*, eds., M. Nicolini, G. Bandoli and U. Mazzi, Cortina International, Verona, 1990, p. 381.

25 H. F. Kung, *Semin. Nucl. Med.*, 1990, **20**, 150.

26 A. J. Despopoulos, *Theor. Biol.*, 1965, **8**, 163.

27 H. M. Chilton and J. H. Thrall, in *Pharmaceuticals in Medical Imaging*, eds, D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 305.

28 W. C. Eckelman, G. Meinken and P. Richards, *J. Nucl. Med.*, 1972, **13**, 577.

29 S. C. Srivastava and P. Richards, in *Radiotracers for Medical Applications*, ed., G. V. S. Rayudu, CRC Series in Radiotracers in Biology and Medicine, CRC Press, Boca Raton, FL, 1983, p. 107.

30 S. Jurisson, *Drugs of the Future*, 1990, **15**, 1085.

31 E. H. Treher, L. F. Francesconi, M. F. Malley, J. Z. Gougoutas and A. D. Nunn, *Inorg. Chem.*, 1989, **28**, 3411.

32 S. S. Jurisson, W. Hirth, K. E. Linder, R. J. DiRocco, R. K. Narra, D. P. Nowotnik and A. D. Nunn, *Nucl. Med. Biol.*, 1991, **18**, 735.

33 E. Deutsch and W. Hirth, *J. Nucl. Med.*, 1987, **28**, 1491.

34 M. D. Loberg, M. Cooper, E. Harvey, P. S. Callery and W. Faith, *J. Nucl. Med.*, 1976, **17**, 633; M. D. Loberg and A. T. Fields, *Int. J. Appl. Radiat. Isot.*, 1977, **28**, 687.

35 A. G. Jones, M. J. Abrams and A. Davison, in *Technetium in Chemistry and Nuclear Medicine*, eds., E. Deutsch, M. Nicolini and H. N. Wagner Jr, Cortina International, Verona, 1983, p. 27; M. J. Abrams, A. Davison, A. G. Jones, C. E. Costello and H. Pang, *Inorg.Chem.*, 1983, **22**, 2798; R. Taillefer, L. Laflamme, G. Dupras, M. Picard, D. C. Phaneuf and J. Leveille, *Eur. J. Nucl. Med.*, 1988, **13**(10), 515.

36 D. Piwinca-Worms, J. F. Kronauge, B. L. Holman, J. Lister-James, A. Davison and A. G. Jones, *J. Nucl. Med.*, 1988, **29**, 55.

37 E. Deutsch, W. Bushong, K. A. Glavan, R. C. Elder, V. J. Sodd, K. L. Scholz, D. L. Fortman and S. J. Lukes, *Science*, 1981, **214**, 85.

38 B. L. Holman, A. G. Jones, J. Lister-James, A. Davison M. J. Abrams, J. M. Kirshenbaum, S. S. Tumeh and R. J. English, *J. Nucl. Med.*, 1984, **25**, 1350.

39 J. F. Kronauge, M. Kawamura, E. Lepisto, B. L. Holman, A. Davison, A. G. Jones, C. E. Costello and C. H. Zeng, in *Technetium and Rhenium in Chemistry and Nuclear Medicine 3*, eds., M. Nicolini, G. Bandoli and U. Mazzi, Cortina International, Verona, 1990, p. 677.

40 C. L. De Ligny, W. J. Gelsema, T. G. Tji, Y. M. Huigen and H. A. Vink, *Nucl. Med. Biol.*, 1990, **17**, 161; W. A. Volkert and E. Deutsch, in *Adv. Metals Med.*, eds., M. J. Abrams and B. Murrer, JAI Press Inc., Connecticut, 1992, Vol. 1; H. M. Chilton, R. J. Callahan and J. H. Thrall, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 419.

41 H. M. Chilton, M. D. Francis and J. H. Thrall, in *Pharmaceuticals in Medical Imaging*, eds., D. P. Swanson, H. M. Chilton and J. H. Thrall, Macmillan Publishing Co., New York, 1990, p. 537.

42 N. N. Greenwood and A. Earnshaw, in *Chemistry of the Elements*, Oxford, Pergamon Pres Plc, 1984.

43 S. S. Moore, T. L. Tarnowski, M. Newcomb, and D. J. Cram, *J. Am. Chem. Soc.*, 1977, **99**, 6398; K. E. Koenig, G. M. Lein, P. Stuckler, T. Koneda and D. J. Cram, *J. Am. Chem. Soc.*, 1979, **101**, 3553.

44 M. C. Grossel, D. J. Edwards, A. K. Cheetham, M. E. Eddy, O. Johnson and S. R. Postle, *J. Mater. Chem.*, 1991, **1**(2), 223.

45 D. J. Edwards, Ph.D. Thesis, Bedford College, University of London, 1987.

46 BP 1278621; BP 1521083; BP 1512863.

47 B. B. Corson, R. W. Scott and C. E. Vose, in *Organic Syntheses*, Eds. H. Gilman and A. H. Blatt, Wiley, New York, 1941, Coll. Vol. 1, 2nd Ed., p. 179.

48 J. M. Bobbitt and D. A. Scola, *J. Org. Chem.*, 1959, **25**, 560.

49 O. Silberrad and H. A. Phillips, *J. Chem. Soc.*, 1908, **93**, 474.

50 E. G. Vassian and R. K. Murmann, *Inorg. Chem.*, 1967, **6**, 2043.

51 K. Ramalingam, W. Zeng, P. Nanjappan and D. P. Nowotnik, *Synth. Commun.*, 1995, **25**(5), 743.

52 J. R. Morton and H. W. Wilcox, in *Inorganic Syntheses*, McGraw-Hill Book Co., New York, 1953, Vol. IV, p. 48.

53 W. Pritzkow and co-workers, *J. Prakt. Chem.*, 1965, **29**, 123; BP 1363066.

54 J. March in *Advanced Organic Chemistry*, Wiley, New York, 1985, 3rd Ed., p. 534.

55 P. Nanjappan, N. Raju, K. Ramalingam and D. P. Nowotnik, *Tetrahedron*, 1994, **50**(29), 8617.

56 W. Pfleiderer and H. Zondle, *Chem. Ber.*, 1966, **99**, 3008.

57 R. Adams and R. M. Kamm, in *Organic Syntheses*, Eds. H. Gilman and A. H. Blatt, Wiley, New York, 1941, Coll. Vol. 1, 2nd Ed., p. 250.

58 R. O. Hutchins and B. E. Marynoff, in *Organic Syntheses*, Ed. A. Brossi, Wiley, New York, 1973, Vol. 53 p. 21; S. Mahboobi and G. Grothus, *Arch. Pharm.(Weinheim, Ger.)*, 1994, **327**(6), 349; B. C. Whitmore and R. Eisenberg, *Inorg. Chem.*, 1983, **22**(1), 1.

59 Cache Molecular Modelling Suite, Tectronix.

60 S. Kim, J. I. Lee and Y. K. Kim, *J. Org. Chem.*, **50**(5), 560.

61 A. Caliezi, E. Lederer and H. Schinz, *Helv. Chim. Acta.*, 1951, **34**, 879.

62 S. Ohki and Y. Noike, *J. Pharm. Soc. Jap.*, 1952, **72**, 490.

63 G. W. Kabalka, M. Varma, S. V. Rajender, P. C. Srivastava and F.F. Knapp Jr, *J. Org. Chem.*, 1986, **51**(12), 2386.

64 J. J. Eisch, H. Gopal and D. A. Russo, *J. Org. Chem.*, 1974, **39**(21), 3110.

65 O. G. Lowe and L. C. King, *J. Org. Chem.*, 1959, **24**(9), 1200.

66 P. J. Hamrick Jr. and C. R. Hauser, *J. Am. Chem. Soc.*, 1961, **26**, 4199.

67 S. L. Shapiro, V. Bandurco and L. Freedman, *J. Am. Chem. Soc.*, 1962, **27**, 174.

68 S. Tanaka, *J. Am. Chem. Soc.*, 1951, **73**, 872.

69 C. S. Palmer and P. W. McWherter, in *Organic Syntheses*, Ed. F. C. Whitmore, Wiley, 1941, Coll. Vol. 4, 2nd Ed., p. 245.

70 K. Ramalingam, N. Raju, P. Nanjappan and D. P. Nowotnik, *Tetrahedron*, 1995, **51**(10), 2875.

71 R .M. Izatt, K. Pawlak and J. S. Bradshaw, *Chem. Rev.*, 1991, **91**(8), 1721.

72 F. Diomedi-Camassei, E. Nocchi, G. Sartori and A. W. Adamson, *Inorg. Chem.*, 1975, **14**(1), 25.

73 B. Bosnich, C. K. Poon and M. L. Tobe, *Inorg. Chem.*, 1965, **4**(8), 1102.

74 R. K. Murmann and E. O. Schempler, *Inorg. Chem.*, 1973, **12**(11), 2625.

75 T. Lee, Y. Chang, C. Chung and Y. Wang, *Acta Cryst.*, 1990, **C46**, 2360.

76 I. B. Liss and E. O. Schempler, *Inorg. Chem.*, 1975, **14**(12), 3035; E. O. Schempler, M. S. Hussain and R. K. Murmann, *Acta Cryst.*, 1981, **B37**, 234.

77 K. Matsuoka, T. Nogami and H. Mikawa, *Mol. Cryst. Liq. Cryst.*, 1982, **86**, 155.

78 D. D. Perrin and W. L. F. Armarego in *Purification of Laboratory Chemicals*, Pergamon Press Plc, Oxford, 1988.

79 J. S. Shukla and P. J. Bhatia, *J. Indian Chem. Soc.*, 1978, **55**, 281.

80 A. L. Cossey, R. L. N. Harris, J. L. Huppatz and J. N. Phillips, *Aust. J. Chem.*,1976, **29**, 1039.

81 B. M. Bhawal, S. P. Khanapure and E. R. Biehl, *Synth. Commun.*, 1990, **20**(20), 3235.

82 H. Oediger and F. Muller, *Liebigs Ann. Chem.*, 1976, 348.

83 P. Russell, *J. Am. Chem. Soc.*, 1950, **72**, 1853.

84 B. Newman, *J. Am. Chem. Soc.*,1950, **72**, 5163.

85 P. C. Belanger and C. S. Rooney, *J. Org. Chem.*, 1978, **43**(5), 906.

86 Campbell and Taylor, *J. Pharm. Pharmacol.*, 1950, **2**, 229.

87 J. Lockett and W. F. Short, *J. Chem. Soc.*, 1939, 787.

88 N. Kosui, M. Waki, T. Kato and N. Izumiya, *Bull. Chem. Soc. Jpn.*, 1982, **55**(3), 918.

89 H. Christol, A. Gaven, Y. Pietrasantra and J. L. Vernet, *Bull. Soc. Chim. Fr.*, 1971, 4150.

90 M. F. Semmelhack, P. Helquist, L. D. Jones, L. Keller, L. Mendelson, L. S. Ryono, J. G. Smith and R. D. Stauffer, *J. Am. Chem. Soc.*, 1981, **103**(21), 6460.

91 J. O. Knipe, P. J. Vasquez and J. K. Coward, *J. Am. Chem. Soc.*, 1982, **104**(11), 3202.

92 F. L. Schadt, C. J. Lancelot and P. V. R. Schleyer, *J. Am. Chem. Soc.*, 1978, **100**, 228.

93 G. Wittig and G. Kolb, *Chem. Ber.*, 1960, **93**, 1469.

94 S. E. N. Mohamed and D. A. Whiting, *J. Chem. Soc., Perkin Trans. 1*, 1983, **10**, 2577.

95 U. Siegel, R. Mues, R. Doenig and T. Eicher, *Phytochemistry*, 1991, **30**(11), 3643.

96 W. Tatewojsan, *Zh. Obshch. Khim.*, 1954, **24**, 1845.

97 J. F. Pallaud and R. Pallaud, *C. R. Seances Acad. Sci. Ser. C*, 1971, **273**, 711.

98 Kaldrikyan and Melik-Ogandzhanyan, *Arm. Khim. Zh.*,1967, **20**(1), 61.

99 PATTY:P. T. Beurskens, G. Admiraal, G. Beurskens, W. P. Bosman, S. Garcia-Granda, R. O. Gould, J. M. M. Smits and C. Smykella, in *The DIRDIF program system, Technical Report of the Crystallography Laboratory,* 1992, University of Nijmegen, The Netherlands.

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

101 Function minimised: $\Sigma\omega(|Fo| - |Fc|)^2$

where $\omega = 1/\sigma^2(Fo) = 4(Fo)^2/\sigma^2(Fo^2)$

$Fo^2 = S(C-RB)/Lp$

$\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$

S = Scan rate

C = Total integrated peak count

R = Ratio of scan time to background counting time

B = Total background count

Lp = Lorentz-polarisation factor

p = p-factor

102 Standard deviation of an observation of unit weight:

$$[\Sigma\omega(|Fo|-|Fc|)^2/(No-Nv)]^{1/2}$$

where No = number of observations

Nv = number of variables

103 D. T. Cromer and J. T. Waber, in *International Tables for X-ray Crystallography*, 1974, The Kynoch Press, Birmingham, England, Vol. IV, Table 2.2 A.

104 J. A. Ibers and W. C. Hamilton, *Acta Cryst.*, 1964, **17**, 781.

105 D. C. Creagh and W. J. McAuley, in *International Tables for Crystallography*, 1992, ed. A. J. C. Wilson, Kluwer Academic Publishers, Boston, Vol C, Table 4.2.6.8, pp 219-222.

106 D. C. Creagh and J. H. Hubbell, in *International Tables for Crystallography*, 1992, ed. A. J. C. Wilson, Kluwer Academic Publishers, Boston, Vol C, Table 4.2.4.3, pp 200-206.

107 teXsan: Crystal Structure Analysis Package, Molecular Structure Corporation (1985 and 1992).

108 SHELXS86: G. M. Sheldrick, in *Crystallographic Computing 3*, Eds. G. M. Sheldrick, C. Kruger and R. Goddard, 1985, Oxford University Press, pp 175-189.

"The Moving Finger writes; and, having writ,
Moves on: nor all thy Piety nor Wit
Shall lure it back to cancel half a Line,
No all thy Tears wash out a Word of it."

The Rubaiyat of Omar Khayyam