TOWARDS CHIRAL SENSORS

UNIVERSITY
of
GLASGOW

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Finally I would like to thank my supervisor Dr R. D. Peacock for all his effort and encouragement throughout this work and especially for his patience during the write up. I owe him a great deal.

To My Mother and Father

Summary

This research was based in the area of macrocycles and involved the synthesis, analysis and evaluation of novel chiral cyclophanes and crown ethers. The aim of this project was to use the knowledge from the disciplines of molecular recognition and molecular sensor technology to explore new directions in the developing field of molecular sensors for chiral molecules. The long term aim was to produce a general class of compounds that could be utilised as chiral sensors for a variety of guest molecules.

The mode of detection is an essential part of the design of all sensors and in this work we attempted to use fluorescence (and electrochemical) signal transduction methods.
One of the original ideas of this project and a main theme throughout, was to incorporate the chiral unit with the fluorescent transducer. This may be achieved by the use of chiral bi-aryl based compounds as building blocks.

The incorporation of bi-aryls into the structure of the sensors cavity should increase the chirality of the cavity and amplify any chiral-chiral interaction. The incorporation of the signal transducer into the chiral building block should allow a direct relationship with any chiral interaction. The use of bi-aryls also allows the sensor to have C_2 symmetry, or higher, which helps to simplify any host-guest interactions.

In this work novel prototype compounds (sensors) were designed and their synthesis, as single enantiomers, attempted. The apparent ease of resolution of binaphthol made this molecule an ideal building block from which to start. Several binaphthyl based heteraphanes were synthesised enantiomerically pure. Although these compounds were found to be unsuitable for complexation studies they led to the synthesis of functionalised heteraphanes suitable for further study. The syntheses of some of these compounds were unsuccessful due to metal complexation of their acyclic intermediates leading to steric and electronic hindrance. This work led to the development of routes to key synthetic intermediates and to the development of a more systematic methodology for the design and synthesis of potential chiral sensors.

CHAPTER ONE

INTRODUCTION

If all on earth acknowledge the beautiful as beautiful
then thereby the ugly is already positioned.
If all on earth acknowledge the good as good
then thereby the non-good is already positioned.
For existence and non-existence generate each other.
Heavy and light complete each other.
Long and short shape each other.
High and deep convert each other.
Before and after follow each other.
Lao Tzu 'Tao Te Ching', I Dao 2

1.1 Preamble

The study of inclusion phenomena had been underway long before the discovery of crown ethers by Pederson in the 1960's. Naturally occurring hosts such as cyclodextrins (Schardinger's dextrin[1]) had been recognised and studied since their first isolation in 1891[1b]. The insoluble complexes/inclusion compounds of cyclodextrins had been effectively used in the separation and purification of the individual dextrins, α, β and γ, since 1911[1c]. The inclusion phenomena of clathrate formation had also been known since the turn of the century[2] (1890's), however the term clathrate only appeared in 1949. It was not just naturally occurring inclusion hosts that were studied, indeed cyclophanes[3], which were first synthesised in the 1930's, were known, by the 1950's, to interact with neutral guests forming intermolecular charge transfer complexes in solution.

The discovery of crown ethers did however seed the imagination of many and gave rise to the synthetic strategy for a whole new chemistry. The nature of this new Host-Guest chemistry, with the reversible formation and interaction of complexed ions/molecules, has always been (albeit unknown) at the very heart of life and science and is now recognised as a vast and truly interdisciplinary field.

1.2 Roots

Charles J. Pederson[4] discovered the first crown ether, 1 in figure 1, in the 1960's, as a small quantity of unknown product from the synthesis of the multidentate phenolic ligand (see 2 in figure 1). He named this new class of compound 'crown ethers' and gave them a systematic nomenclature, for example; Dibenzo[18]crown-6 for 1, which is still in use today. He went on to make around 60 crown ethers of varying size and binding capability, studying their complex formation and stability with alkali metals. Thus he was able to define the most effective crown ethers as

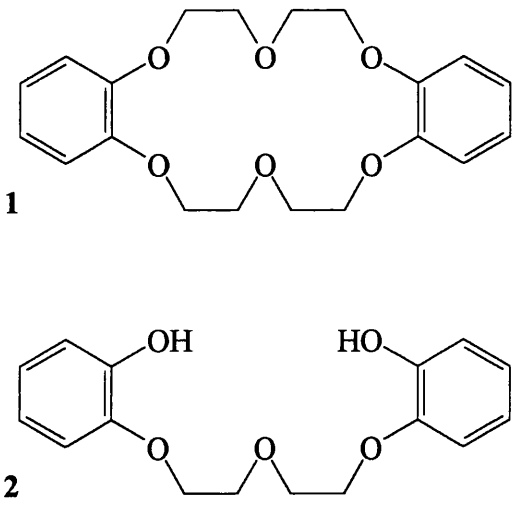


Fig.1; The first synthetic crown ether, compound 1 was obtained from the synthesis of compound 2

those containing 5-10 oxygen atoms in the ring, each separated from the next by 2 carbon atoms. He realised, from the yields obtained from a minority of starting material, that an element of pre-organisation/self-organisation must be involved and concluded that the ring closure step, either by a second molecule of bis(2-chloroethyl) ether or catechol, was facilitated by the sodium ion acting as some form of template.

Jean-Marie Lehn[5], who was interested in the transport and distribution of alkali metals in nerve cells, at the time, perceived that the cation binding properties of the macrocyclic polyethers reported by Pederson, in 1967, combined the complexing ability and chemical stability that he was looking for to investigate biological processes. He then began work synthesising compounds containing a three dimensional, spherical cavity, which would surround entirely the bound ion reasoning that this should form stronger complexes than the "rather flat" macrocycles. Thus in 1969, he along with J.P. Sauvage and B. Dietrich, published the design, synthesis and binding properties of the macrobicyclic ligands, the cryptates, which were capable of spherical recognition by size complementarity. Cryptates were synthesised for the complexation of cations and for the complexation of anions (by protonated polyamine cryptates); the ion-macrocycle complexes being known as cryptands. He went on to look at anion co-ordination and recognition, coreceptor molecules and multiple recognition, Supramolecular reactivity and catalysis, transport processes and carrier design and has gone from supermolecules to polymolecular assemblies.

Donald J. Cram[6] started off in the area of cyclophanes in the 1950's, which had been known under different names since the 1930's. In 1951 Cram and Steinberg reported the synthesis of [2,2]-paracyclophane. In the late 50's he was inspired by nature and believed it possible to design, prepare and study synthetic systems that might mimic aspects of evolutionary biological systems, specifically the binding of organic entities. By the late 1960's the technology was available to allow the study of Host-Guest complexation studies. CPK models became available, and proved to be invaluable. After Pederson published the first crown ether papers in 1967, Cram realised that this would be an excellent entry point into the field of complexation, which was further demonstrated by the first cryptand papers of Lehn et al in 1969. In the early 1970's Cram et al started to work on the synthesis of chiral crown ethers and in 1973 they published their first papers[6a,b] on the synthesis, complexation and binding properties of

crown ethers containing homochiral binaphthol (The first published synthesis of a chiral crown compound was in 1972 by F. Wudl and F. Gaeta[7], see figure 2).

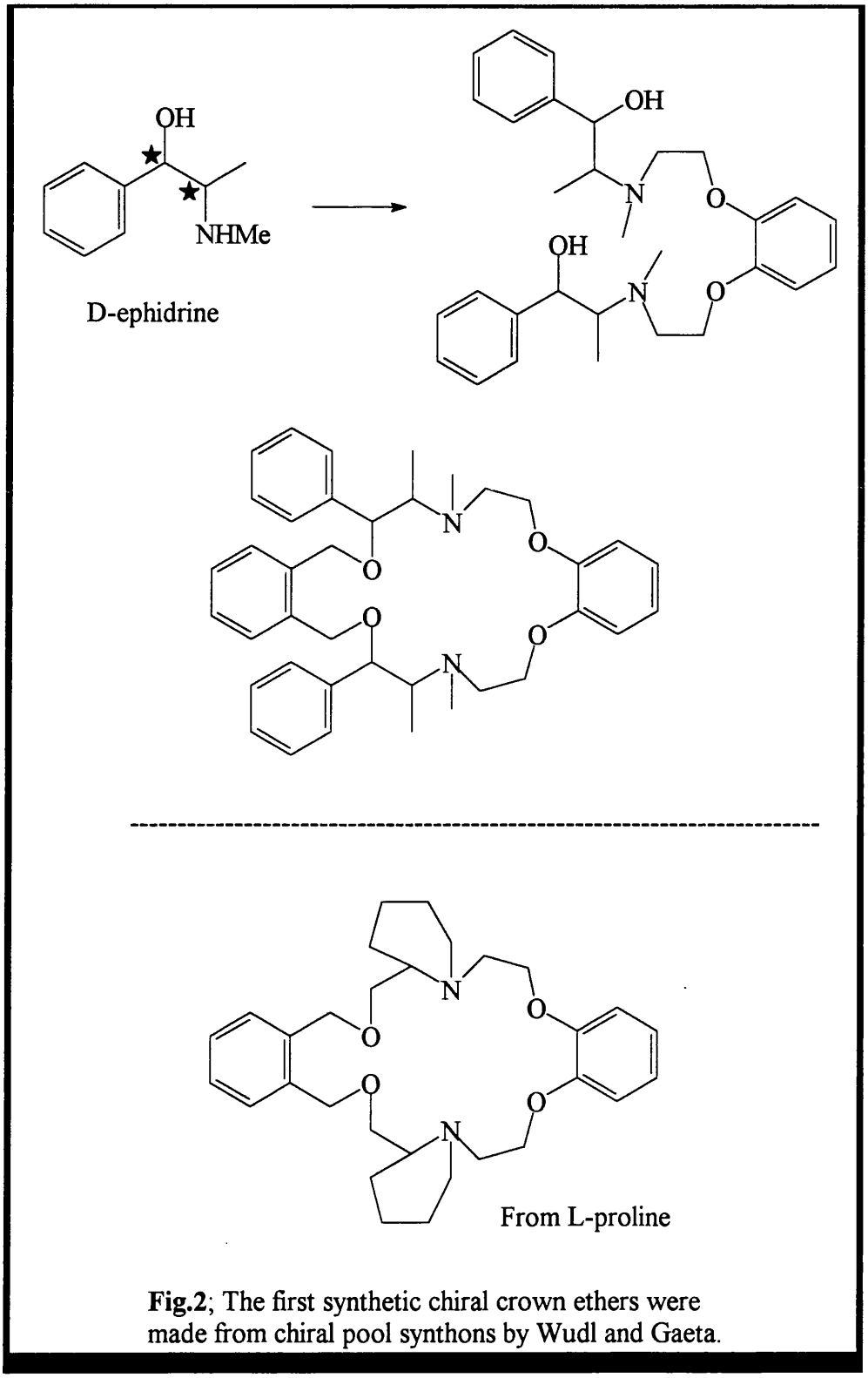


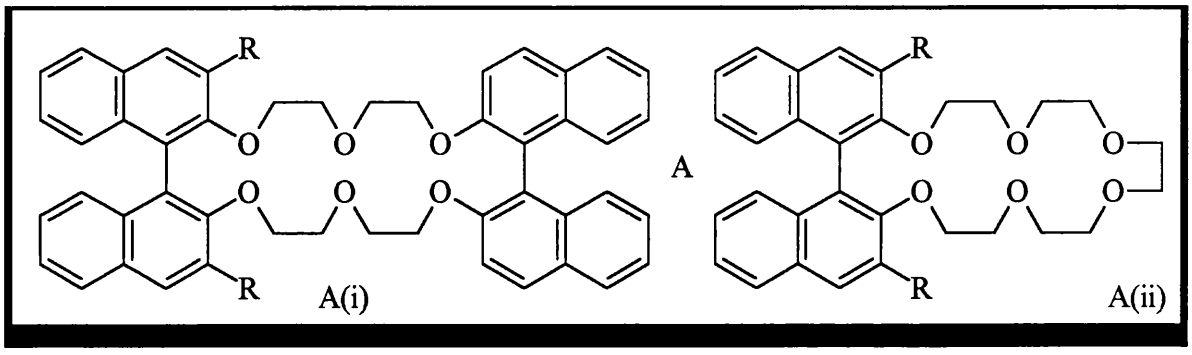
Fig.2; The first synthetic chiral crown ethers were made from chiral pool synthons by Wudl and Gaeta.

Cram et al went on to look at the design and synthesis of enzyme-mimicking host compounds and other more rigidly pre-organised crown compounds. Some of their conclusions were :

1. Corey - Pauling - Koltan molecular models of potential complexes can be used as a rough means of evaluating potentially complementary host- guest relationships.
2. Host compounds that have their binding sites positioned prior to complexation (pre-positioned) have higher binding energies than those which have repositioning imposed during guest complexation. In other words, pre-organisation is a central determinant of binding power.
3. Matching of sizes, shapes, and electronic properties of binding portions of hosts and guests is a necessary requisite to structural recognition. In other words, complementarity is the central determinant of structural recognition.

In 1987 Pederson, Lehn and Cram received the Noble Prize for chemistry, for the discovery and pioneering studies on crown ether synthesis and host-guest complexation chemistry.

1.3 Chiral Recognition and Transportation



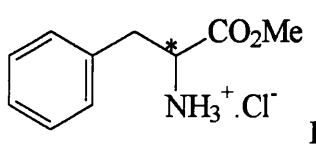
In 1976 Cram et al published a paper entitled "Host- Guest Complexation. 1. Concept and Illustration"[8] in which they describe, in detail, the design, syntheses and complexation studies of structured molecular complexes between macrocyclic polyethers and open chain analogues, as hosts, with a series of onium salts (organic amine salts) as guests. In this they detail, amongst others, the synthesis of A(ii), 2,2`-binaptho[20]crown6, a compound which along with its analogues, was to become one of the cornerstones of his chiral recognition studies. This compound had previously been synthesised by Cram[7] as a homochiral compound. These were the first papers in a series which became focused on the synthesis, complexation and enantiomer recognition/ transportation of analogues of A(i) and A(ii) towards chiral amine salts.

Compounds A(i), A(ii) and their analogues have amongst the highest enantiomer selectivities shown for chiral ammonium ions[9a,b,c].

After synthesising homochiral A(i), A(ii) and derivatives, Cram et al. went on to study them, first of all by testing their abilities to dissolve, by complexation, crystalline organic ammonium and hydronium cations at ambient temperature, into deuteriochloroform for NMR studies[10]. Solubilisation (lipophilization) is very likely due to complexation through a tripod arrangement of $^{+}NH---OR_2$ or $^{+}OH---OR_2$ hydrogen bonds, as was found in the solid state by several crystal structures. They went on to look at chiral recognition in solution using amino acid salts, such as valine hydrochloride[11], then to chiral recognition in transport, at first using hosts that were covalently bound to polystyrene resin, in studies aimed at chromatographic resolution of chiral amino acid and ester salts[12]. Later they used bulk liquid membranes[13], through which chiral amines and amino-acid ester salts were transported via solubilisation by complexation. At first transport experiments were carried out in U-tubes to find which host enantiomer preferred which guest enantiomer, then in W-tubes to try and effect resolution of racemic mixtures. The U-tube experiments, which involved several racemic guest species with transportation times of 12-182 hours, gave transport of 8-12% in 74-82% optical purity. The W-tube experiments were designed for continuous and simultaneous removal of each enantiomer from a central reservoir of racemate through two separate bulk liquid membranes (chloroform pools) containing opposite enantiomers of host.

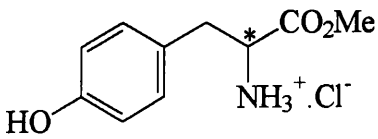
The guests used were Phenyl alanine methyl ester hydrochloride (H-G1), Tyrosine methyl ester hydrochloride (H-G2) and Phenyl ethyl amine hydrochloride (H-G6), and depending on experimental details the L-phenyl alanine methyl ester was transported by the S,S host in optical purity ranging from 70 to 86% and the D-ester was transported by the R,R host in optical purities ranging from 77 to 90%.

Host Guests for Transportation



H-G1

Phenyl-alanine methyl ester Hydrochloride

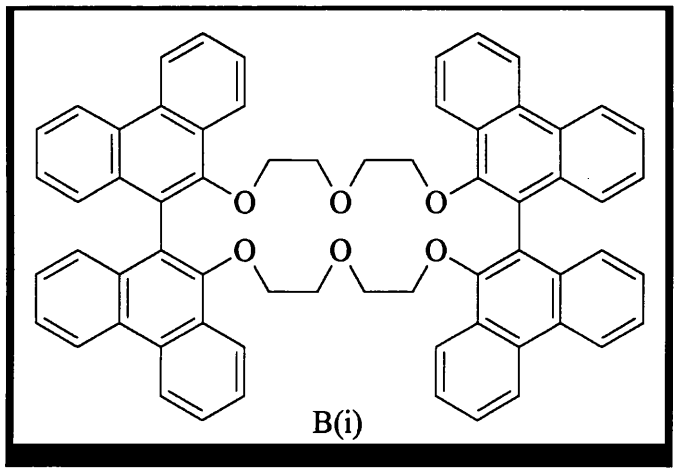


H-G2

Tyrosine methyl ester Hydrochloride

Cram et al went on to calculate the $\Delta(\Delta G)$ values for the differential complexation of various amino acid ester enantiomers with different derivatives of A(i) and A(ii).

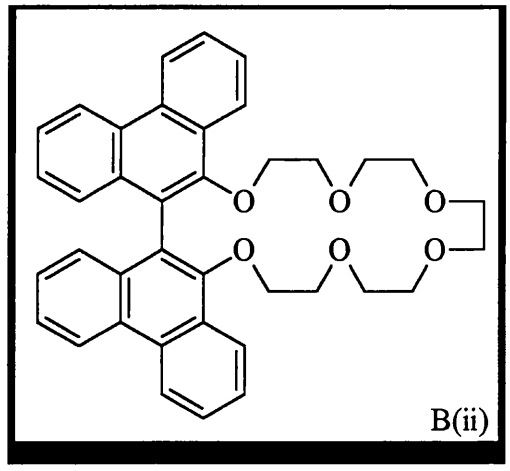
1.3.2



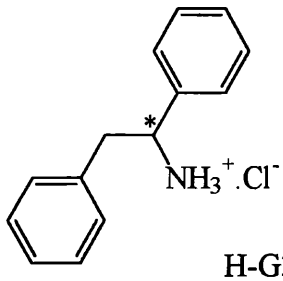
B(i)

Koji Yamamoto et al. synthesised optically pure crown ether compounds of type B[14], and examined their chiral recognition behaviour under transportation conditions. They tested their hosts B(i) + B(ii), by transportation of enantiomeric guest molecules (H-G1,3 and 4) through bulk liquid membranes, and found very high enantiomer selectivity for 1,2-diphenyl ethyl amine(H-G3).

Compound B(i) appeared to have a faster transportation rate over B(ii), with typically around 3% guest transported in 0.5 hrs by B(i) compared to 12 hrs by B(ii). It was also noted that (-)-(R,R)-B(ii) had opposite enantiomer selectivity to (-)-(S)-B(i). The results also indicated that higher optical purity (up to 78%) was achieved at low temperature (-5°C) compared with the same experiments conducted at room temperature (19°C).

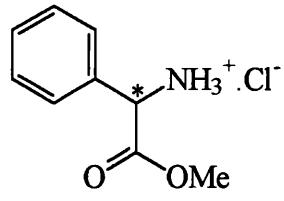


B(ii)



H-G3

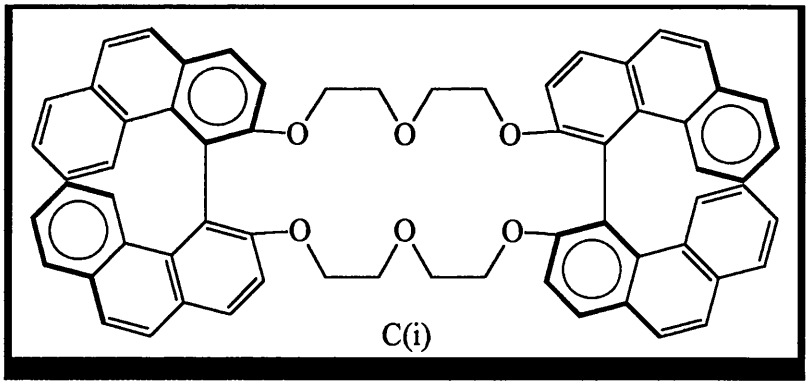
1,2-Diphenylethylamine Hydrochloride



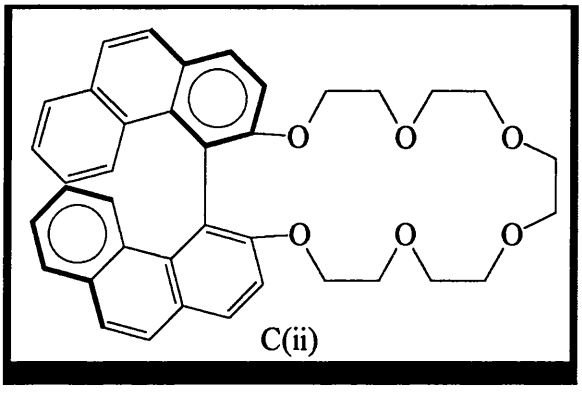
H-G4

Methyl-phenylglycinate Hydrochloride

As an expansion to the work described above, Yamamoto et al synthesised optically pure compounds C(i) and C(ii)[15] and examined their recognition properties, under similar bulk liquid membrane conditions. These novel hosts were tested with guests H-G3, 4 and 5.

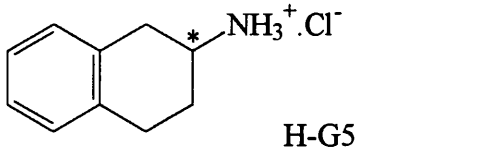


C(i)



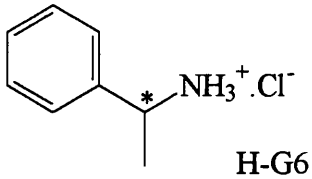
C(ii)

Similarly to the compounds of B, C(i) showed faster transportation rates over C(ii) and higher optical purities (66% for H-G3 over ½ hr with 1.6% transported) and 74% optical purity for H-G5 over 0.5 hrs, with 2.5% transported compared to 42% purity for same time and 2.1% for C(ii). (+)-(S)-C(i) shows a high selectivity for 1,2-diphenyl ethyl amine hydrochloride (H-G3) and 2-aminotetralin hydrochloride. (H-G5).



H-G5

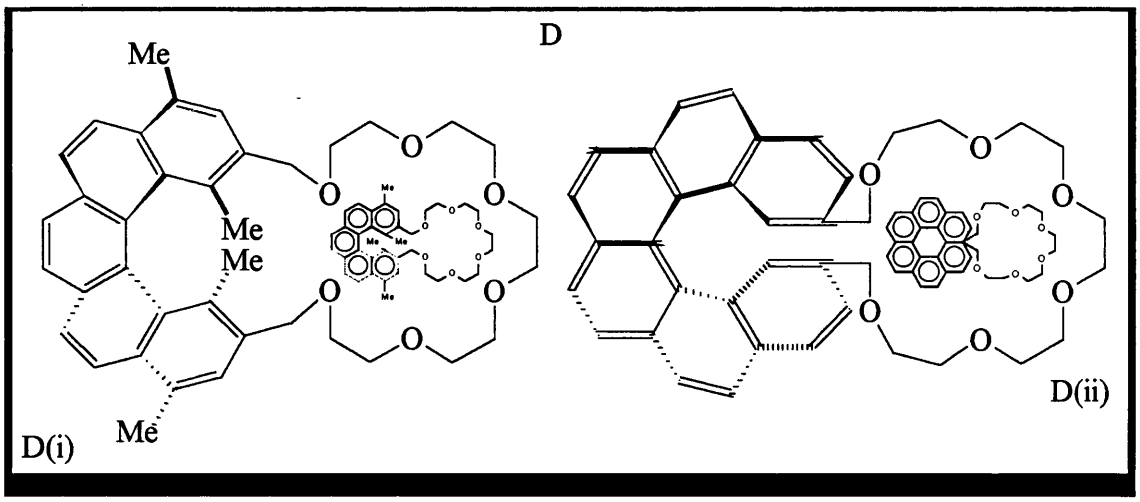
1,2,3,4-Tetrahydro-2-naphthylamine Hydrochloride [2-Aminotetralin]



H-G6

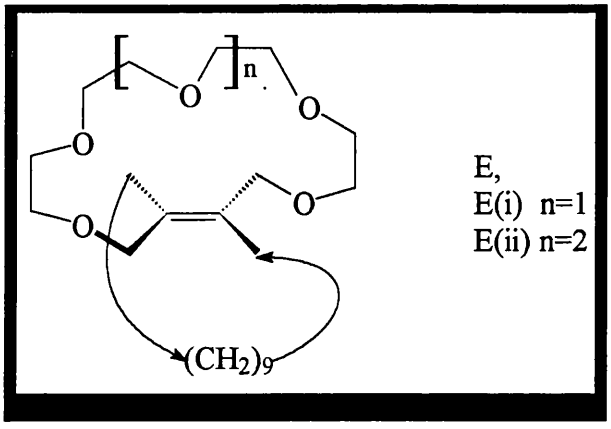
1-Phenylethylamine Hydrochloride

Yamamoto, Okamoto et al. synthesised optically pure D(i) and D(ii)[16], prior to the synthesis of B(i)+(ii) and C(i)+(ii). In this case optical resolution of D(i) and D(ii) was achieved by HPLC.



They tested them for the differential transport of enantiomeric methyl-phenyl glycinate hydrochloride and phenyl ethyl amine hydrochloride, through bulk liquid membranes. In these chiral recognition tests, the results appear more variable with transportation times from 4-6 hrs, percentages transported from 2-12% and purities from 18-77%. The best recognition behaviour was shown by the tetramethylpentahelicene D(i), towards methyl-phenyl glycinate hydrochloride (H-G4), with a transportation time of 6 hrs, 6% was transported in optical purity of up to 77%.

Yamamoto and Okamoto et al. continued their interest in chiral twisted π-electron systems by synthesising trans-doubly-bridged ethylene framed crown ethers in 1985[17], compounds E. Again resolution of their compounds was achieved by HPLC.

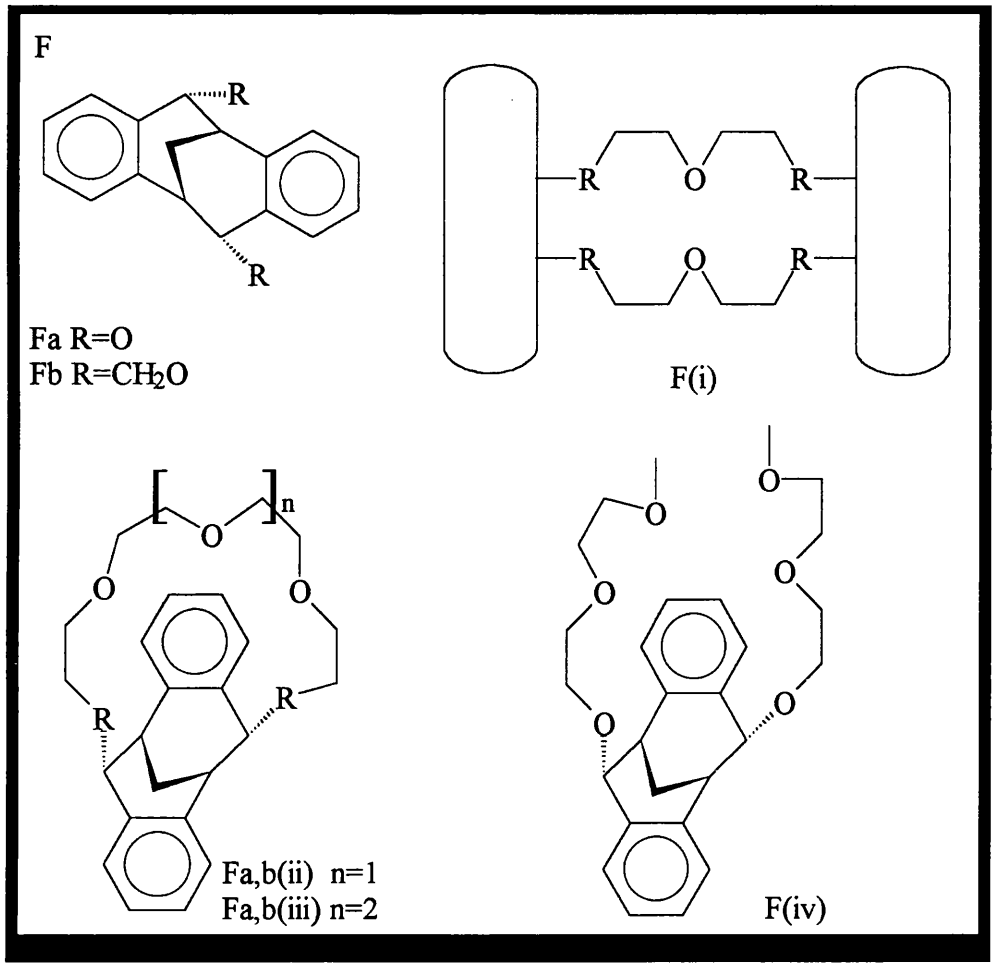


They tested these crown ethers in transportation experiments using racemic 1-Phenyl ethyl amine hydrochloride (H-G6) and racemic Methyl-phenyl glycinate hydrochloride (H-G4). They found that at 20°C with transportation times of 1.0-1.5 hrs they transported 4.5-6.1% of the guest with 24-61% enantiomeric excess. Their results indicated that E(i) -[(5 oxygens)-crown15] had a higher enantiomer selectivity than E(ii), towards both substrates (where methyl phenyl glycinate had the high of 61% e.e. with 6.1% transported in 1.0 hrs.).

The differential transport experiments carried out by Yamamoto-Okamoto were performed using apparatus equivalent to the U-tube experiments of Cram et al.. These

appear to have suffered from a flaw in the design of the apparatus. This consisted of an outer cylindrical glass vessel containing aqueous and chlorinated solvents with an inner central glass tube, which penetrated the boundary between the solvents. The liquid layer through which the host-guest complex moved contained lithium hexafluorophosphate in order for the guest to be transported as the hexafluorophosphate salt. Ion exchange occurs at the liquid-liquid interface where the organic analyte and the lithium transfer across [$LiPF_{6\ org}$ + GCl_{aq} --> $LiCl_{aq}$ + $GPF_{6\ org}$]. This is partly driven by the 'softer' analyte and PF_6 ions greater solubility/affinity for organic solvents combined with the 'harder' lithium and chloride ions greater solubility/affinity for water. With such experimental design it should be noted that, as Cram pointed out[18], the racemic solution loses is racemate status at the same rate of transportation of one hand - creating a concentration gradient - which in turn can affect the recognition ability as it becomes more likely that the "wrong" hand is transported.

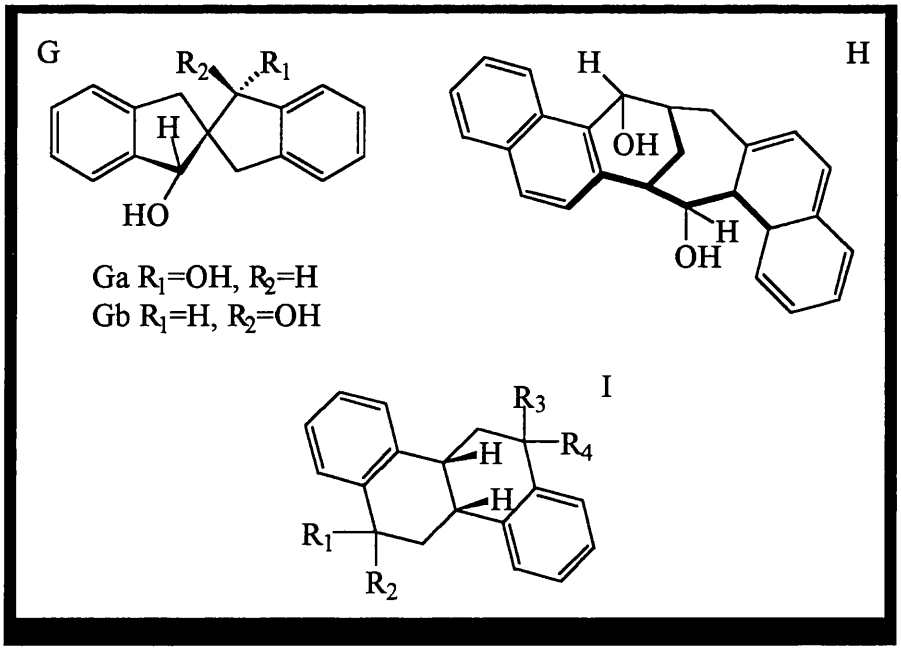
In 1985, Koichiro Naemura et al. published the synthesis and enantiomer recognition abilities of some novel crown ethers[19], containing the 5,6,11,12-Tetrahydro-5,11-methanodibenzo[a,e] cyclo-octane subunit (Fa and Fb). In this paper the synthesis of the subunit and several cyclic and open chain polyethers were described.



The enantiomer recognition abilities of these polyethers were tested in transport experiments, using conventional apparatus[20] transporting 1,2-diphenyl ethyl amine hydrochloride (H-G3) and methyl-phenyl glycinate hydrochloride (H-G4). Their results showed that all the crown ethers containing the methanodibenzo[a,e]cyclo-octane subunit had a higher enantiomer selectivity and faster transport rate towards the 1,2-diphenyl ethyl amine. Also and importantly, they show that the selectivity of the open chain polyether [F(iv)] is comparable to that of the actual crown ethers [Fa,b(i), (ii), and (iii)]. With transportation time of 1.5 hrs and 11% transported the open chain polyether gave 84% optical purity which compares well with the macrocyclic Fb(iii), which with time of 2.5 hours gave 15% transported in an optical purity of 80%.

Shortly after the publication of these results, Naemura et al. published the synthesis and chiral recognition properties of similar novel chiral crown ethers based on the chiral sub-units [trans, trans-(Ga) and cis, trans-(Gb)]-2,2'-spirobiindan-1,1'-diol[21] (G), (-)-(5S,6R,13S,14R)-5,6,13,14-tetrahydro-5,13-methanocycloocta[1,2-a;5,6-a']-dinaphthalene-6,14-diol[22] (H) and cis-4,b,5,6,10b,11,12-hexahydrochrysene[23] (I).

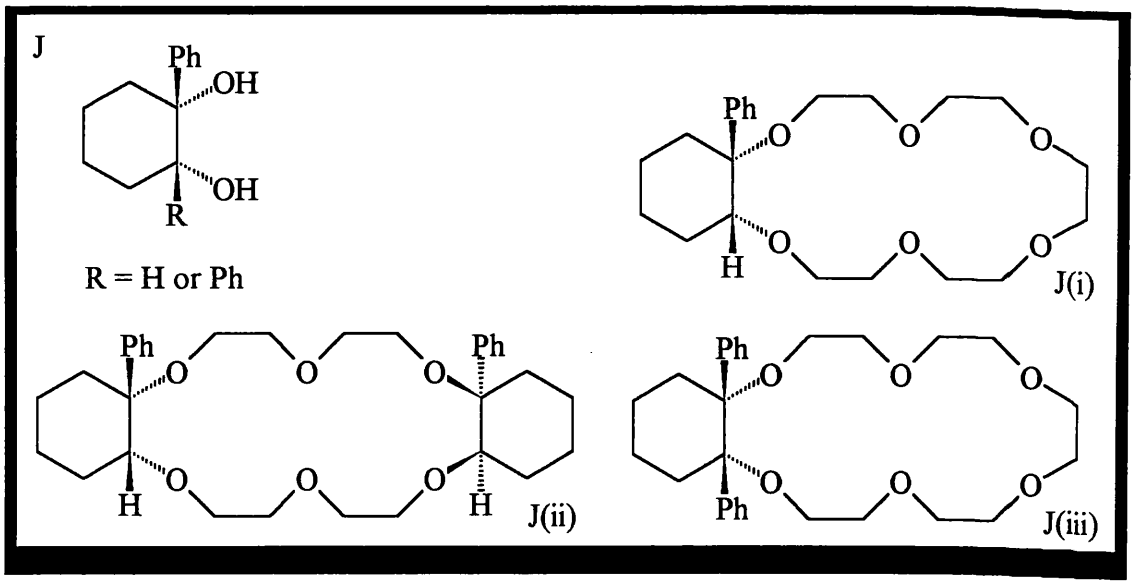
Fractional crystallisation methods and chiral column HPLC methods were used to purify these chiral subunits.



They used the same transportation experiments with the same guest amine salts (H-G3 and 4) as well as 2-aminotetralin hydrochloride (H-G5). The results of these experiments showed matching transportation rates with poorer optical purities. These experiments led them to comment that host molecules possessing a conformationally rigid chiral subunit have a higher enantiomer selectivity than those with less rigidity, towards these three guest substrates.

" The results appear to suggest that a conformationally flexible chiral subunit reduces the enantiomer selectivity of crown ethers of this type "[21].

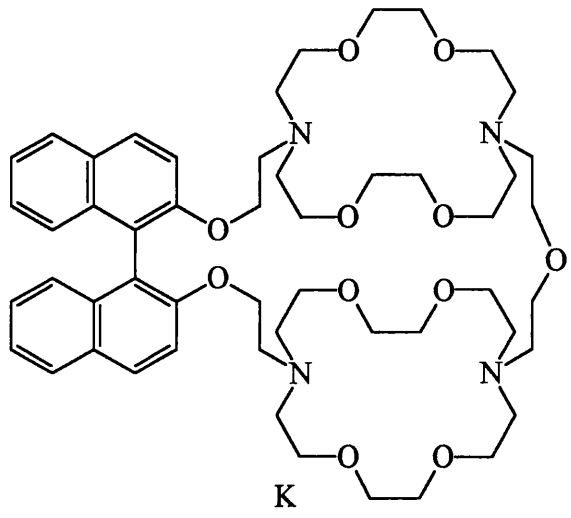
In 1993 they used a Pig liver esterase mediated hydrolysis to prepare chiral 1,2-diol subunits in high yield and optical purity, (J(i)), with these subunits they synthesised a number of crown ethers [J(ii), J(iii)] and used these in differential enantiomer transportation experiments of chiral amine salts[24] (H-G3 and H-G4). Although these enzyme-catalysed resolutions (by enantioselective hydrolysis of racemic acetates) only gave a maximum of 91% e.e. the optical purity was "easily" improved by recrystallisation and by chiral column HPLC.



The enantiomer recognition experiments for these crown compounds showed preferential optical purity for the transportation of 1,2-diphenylethyl amine hydrochloride where the (R,R) crown compound preferred the (S) enantiomer of both guests. They also went on to give a reasonable explanation for the observed chiral recognition behaviour on the basis of the structures of the diastereoisomeric complexes, using CPK molecular models.

To date it must be Cram who has given the most in-depth chiral recognition and transportation studies of crown ethers with his 1,1'-binapthyl-2,2'-diol-crown compounds.

Lehn also used the 1,1-binaphthyl sub-unit to impart chirality to a novel cryptate (K) which he synthesised for the synergic transport of a cation-anion pair (as such co-transport has dual binding it should also have dual selectivity).



Lehn's homochiral cryptand with double selection synergic transport possibilities

1.4 Sensor Technology

The requirement to probe chemical systems, biotic and abiotic, for the presence of specific ions/molecules forms the basis (driving force behind) of the development of sensors and sensor technology.

A sensor can be defined, simply, as a device that interacts with matter or energy and yields a measurable signal in response. Therefore for a sensor to operate it must contain a site/element of recognition and a transducer, which can be separate or integral, specific or non-specific, to convert the recognition energy into the desired energy of detection. A transducer is defined as a device for converting energy from one form to another. Recognition of a substrate (guest) by a sensor (host), by its very nature, energetically distinguishes between the complexes formed by a host with different guest substrates. This energy difference can be measured in many ways through signal transduction. The method of signal transduction can be split into two main categories, those of electrochemical and spectroscopic (optical), which can themselves be further broken down. Electrochemical techniques of interest involve voltammetric/amperometric measurements and potentiometric measurements. Optical techniques of interest involve absorbance measurements, reflectance measurements, fluorescence/phosphorescence measurements and scattering measurements.

1.4.1 Chiral Sensors

Chirality in industry[25] is of growing importance especially in the pharmaceutical market. The chirality of a molecule is as important as its structure or charge, especially in its interaction with biological systems. As early as 1910, the stereoselectivity of drug action had been realised. It is now known that pharmacologically less active or inactive stereoisomers may well contribute to the toxicity or adverse affects of drugs[26]. Guidelines have been issued to regulate the production and use of chiral medicinal products, such that now the stereoisomer of interest must be identified and full justification must be given for its use over its stereoisomers. There has been an increasing emergence of new single enantiomer drugs, as well as the re-examination of existing racemates. Although the advantages of enantiomerically pure drugs have been demonstrated the approval of racemates can be fully justified on several grounds, including "*in vitro*" / "*in vivo*" racemisation, and their production and use will continue.

The current methods of enantiomer identification are essentially spectroscopic and time consuming. As such the development of a reliable system that will provide sensitive and rapid enantiomer identification is of considerable interest, especially one which could be used in vivo, either in solution (intracellular possibilities) or bound to an optical fibre.

The incorporation of the signal transducer into the recognition site (chemical recognition molecule) results in the class distinction between micro/macro-scopic sensors and molecular sensors. This distinction leads to the following definitions[44]. A *Chemical Sensor* is a micro- or macro-scopic device that interacts reversibly with a chemical analyte with signal transduction. A *Chemosensor* is a molecule of synthetic origin that signals the presence of matter or energy. A *Biological Sensor*: a micro- or macro-scopic device which interacts reversibly with a biological analyte with signal transduction. A *Biosensor* is a of molecule of biotic origin that signals the presence of matter or energy.

For a chemosensor to operate there must be;

1- Reversible interaction between the sensor and analyte (complexation)

2- Recognition of guest by host (selectivity)

3- Transduction of recognition into a detectable differentiating signal

4- Most importantly the chemosensor must have suitable acronyms associated with it.

1.4.2 Electrochemical Techniques

In 1992 David Parker published a paper[27], in which he derivatised an α-cyclodextrin and used this as the chiral recognition species in a potentiometric ion selective electrode, to form a chiral sensor. This work continued and in 1994 he published further results[28] on the enantioselectivity of derivatised cyclodextrins used in potentiomeric chiral sensors. These electrodes showed a cell electrode potential difference, between enantiomers, of up to 29mV for ephedrinium ions.

Previous work on enantiomeric discrimination by potentiomeric electrodes had utilised chiral ionophores to form complexes with chiral primary ammonium salts. Simon et al.[29] used open chain chiral ionophores and obtained a potential difference of 2mV between the enantiomers of phenylethylamine hydrochloride ($PEAH^+$). Lehn et al.[30] used chiral crown ethers and found a potential difference of up to 25mV, between the enantiomers of phenylethylamine hydrochloride ($PEAH^+$). Other early attempts are summarised in a review article by Prelog in 1978[31]. In the presence of alkali/alkaline earth metal cations these sensors suffer from much reduced limits of detection and sensitivity. Parker's sensors do not suffer from this problem as they rely on the inclusion of the hydrophobic parts of guests. They are also able to complex secondary and tertiary ammonium salts.

Sensors based on electrochemical transduction techniques have substantial technological foundation and are of much interest. They also have the advantages of having a very large working concentration range, are generally robust and reusable (making them well suited to industrial applications). They have the disadvantages of their working sensitivity being limited by background noise and they require physical waveguides (wires) to link the sensor with the amplifier / recorder (which limits biological applications). The basic principles behind any working sensor are the same and as such should be transferable between any transducer mechanism - or at the very least the regulations / restrictions governing a sensor with one transduction mechanism should be transferable, thus the design of another sensor with different signalling mechanism should be greatly eased.

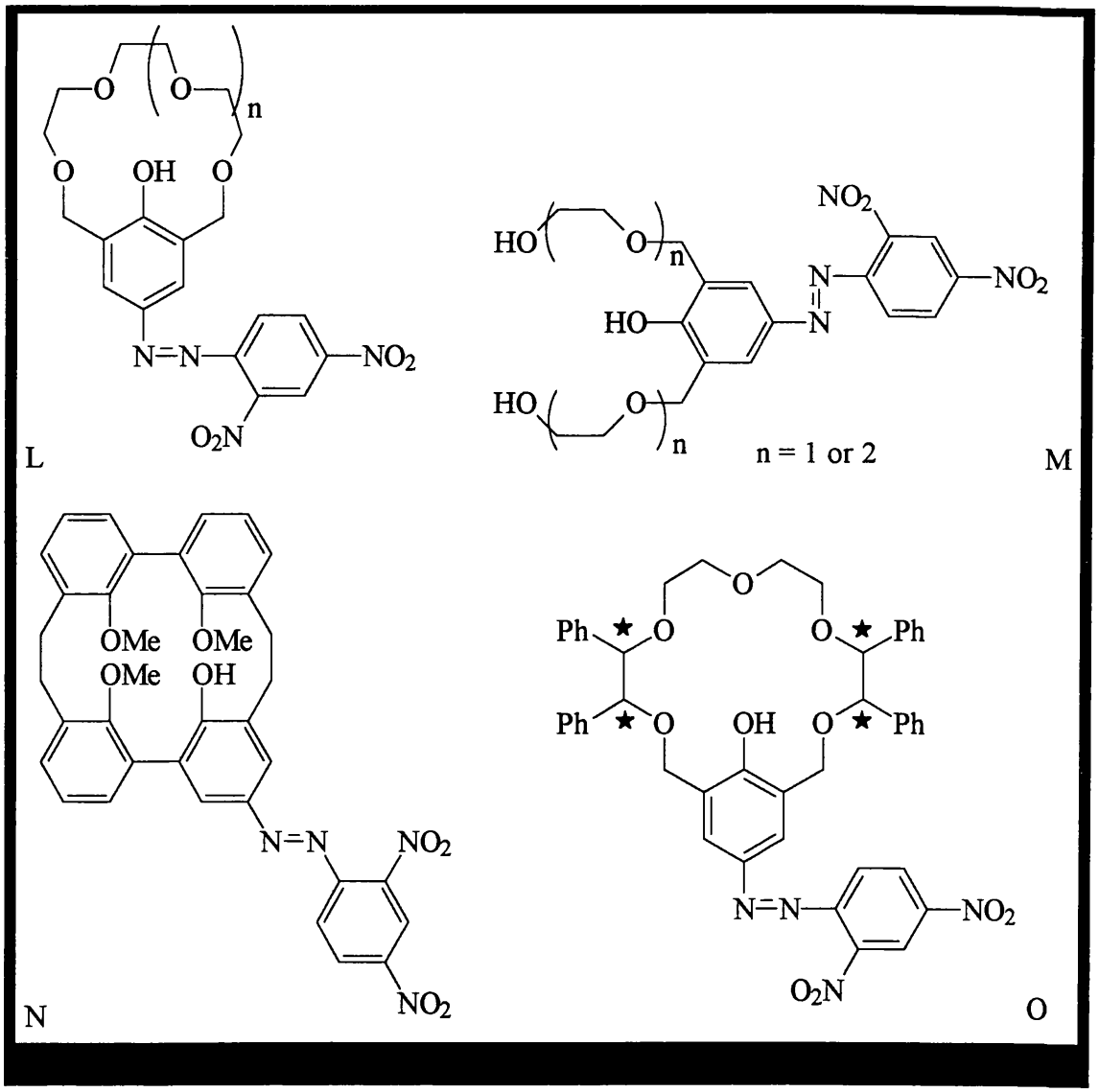
1.4.3 Optical Techniques

The two main areas of research in optical transduction that have been developed are based on chromophoric host ligands (crown compounds) and cholesteric liquid crystals.

Some of the techniques that have been developed for optical sensors are discussed by de Silva and McCoy in a short review of switchable photonic molecules[32].

UV-Visible Chromophoric Host compounds

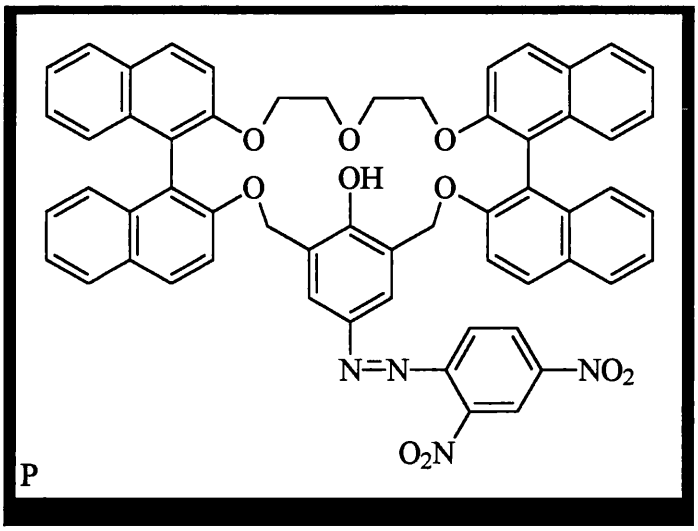
In 1992 Koji Yamamoto joined with Takahiro Kaneda and others in a project to synthesise optically active azophenolic acerands that would show enantioselective colouration upon binding of chiral amines[33]. Kaneda had already reported (with S. Misumi) amine-selective and enantiomer-selective complexation-colouration with azophenol crown ether compounds[34,35] and acyclic relatives, compounds L, M, N and O.



In these compounds the guest is 'electronically linked' to the host's signalling mechanism and as such they are very sensitive to environmental and electronic change.

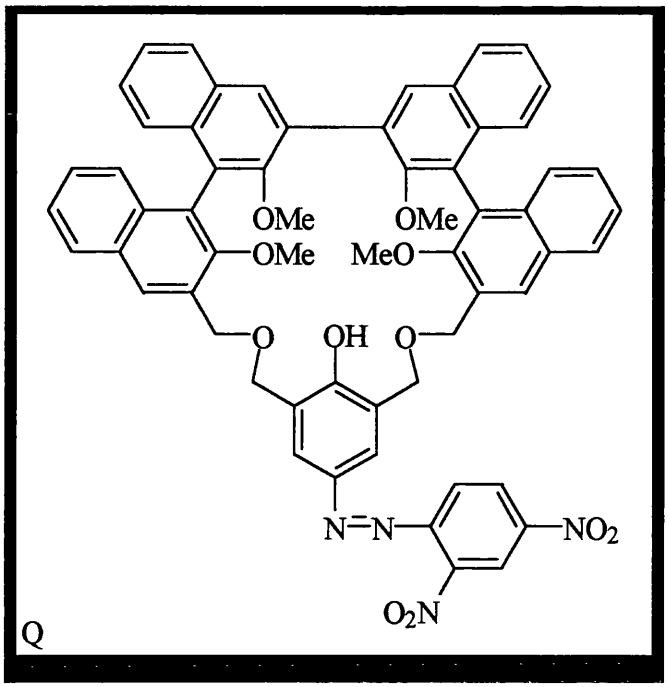
Importantly with these compounds the primary amine free base can and should be used. The amine, upon complexation with the host reacts with the phenolic part to form what the author calls a saltex. As the phenol is an integral part of the dye its deprotonation causes an electronic change resulting in a colour change. The difference in absorption maxima for some of the amines tested range from 4nm to 8nm with L and 3nm to 17nm with O. In the non-chiral azophenolic studies Kaneda used many amines, primary, secondary and tertiary, including ethylamine, ethanolamine, diethylamine, triethanolamine, di-isopropylamine, t-butylamine, 22,66-tetramethyl-piperadine and piperazine. They found that for some amines there was a blue shift and for others there was a red shift. In the chiral azophenolic studies for enantioselective colouration, which was their major aim, they used several chiral amines [both monoalkyl and ethanolamines] including nor-pseudoephedrine, phenylethylamine (PEA) and naphthylethylamine (NEA). With (R)-PEA they found that the RRRR host gave a lower λ_{max} (567.9 by 4nm) and a larger absorbance (by 41%) compared with the SSSS host. With (S)-PEA an almost equal and opposite result is found (as may be expected), with the SSSS host having a lower λ_{max} (567.0 by 4.9nm) and a larger absorbance (by 46%). In the complexation studies involving NEA an analogous trend was found. With (R)-NEA the RRRR host gave a lower λ_{max} (566.9 by 3nm) and a larger absorbance (by 65%) over the SSSS host. Again the reverse effect is seen with (S)-NEA, where the SSSS host gave a lower λ_{max} (566.9 by 5.1nm) and a larger absorbance (by 80%) over the RRRR host.

Yamamoto, Kaneda et al. synthesised crown compounds P and Q[33], containing an azophenolic unit to act as signal transducer and two 1,1'-binapthyl units to act as the chiral recognition source. In their enantioselective colouration experiments three amines were used, 2-aminopropan-1-ol, 1-(1-napthyl)ethylamine and 1-phenylethylamine.



P

Again it is important to note that the free amine guest is used, which forms a salt complex (saltex) with the phenol. The absorption maxima for these phenolates appeared in the long wavelength region and varied from 561nm to 587nm, purple region of the visible spectrum. Over the range of guests used, which were (S)-2-aminopropan-1-ol, (S)-naphthylethylamine and (S)-phenylethylanine, there were differences in λ_{max} of 3nm to 8nm between the saltexes of the (R,R) and (S,S) hosts. From their results they showed that the more rigid host (Q), with a tetranaphthyl sequence, had a higher enantiomer selective colouration, than the less rigid host (P), with the two separated binaphthyl sequences exhibiting a difference of up to 8nm in λ_{max} values between diastereomeric sets of the hosts towards sterically bulky amines, at 0°C. It was noted that this observation was compatible with host Q showing better complementarity, based on steric grounds, than the opposite isomer, as shown by three point models. Hydrogen bonding between the phenolic oxygen of the host and an NH^+ hydrogen stabilises the energy of the polar ground state leading to a blue shifted enantiomer specific colouration.

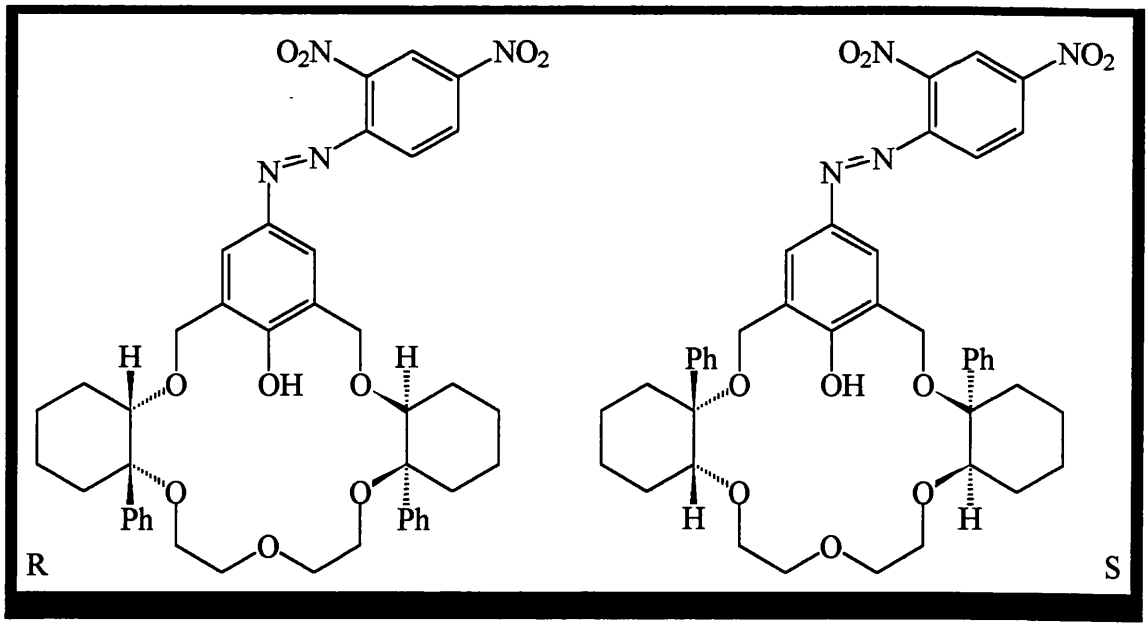


Q

It should be noted that there is no mention of any fluorescence study of these compounds and complexes having been or about to be investigated. However they do say that "the attractive properties of the 1,1'-binapthyl moiety, characterised by the presence of a powerful inherently chiral chromophore", directed their continuing efforts in this field.

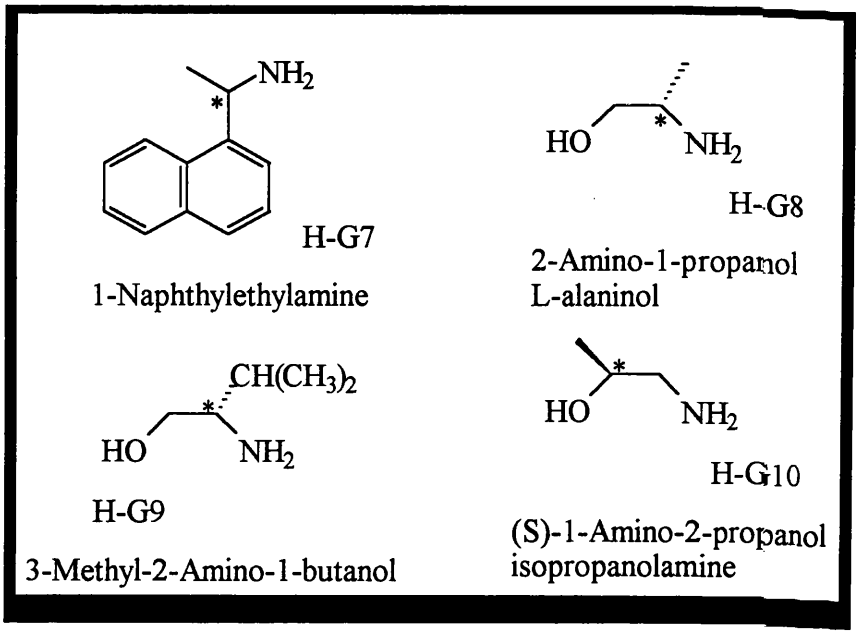
Kaneda has written a chapter detailing the principles and applications of amine-selective colour complexation with chromogenic acerands in which he focuses on various organic cations as guests for particular indicators[36].

Recently Naemura and Kaneda have combined their efforts on the preparation of chiral azophenolic crown ethers[37] [as sensors] based on Naemura's chiral diol (G), which they report can now be kinetically resolved by lipase mediated acylation. This gives a more practical route for large quantities of the required chiral subunit to be prepared. [This arises as a result of the greater ease with which enzymic reactions are carried out in organic solvents as opposed to aqueous media]. Both their chiral crown ethers (R and S) showed an absorption maximum at 418nm in their respective UV-visible spectra. The absorption maxima of the complexes of these crown ethers with the amines tested (chiral and achiral) appeared in the region of 574-600nm.



In these experiments they used both RRRR and SSSS enantiomers of each compound and looked at their interactions with one enantiomer of selected amines ((S)-phenylethylamine and (S)-naphthylethylamine). For host R with (S)-PEA the SSSS enantiomer had a lower λ_{max} (585 by 3nm) but a higher association constant, with the relative ratio of K_a-values being 2.01 for the SSSS compared with 1 for the RRRR. For host S with (S)-PEA an analogous but opposite effect is seen with the SSSS enantiomer still having a lower λ_{max} but also a lower association constant, with the relative ratio of K_a-values being 1.89 for the RRRR host. A similar effect was seen when the (S)-1-naphthylethylamine was used as the guest amine. With crown compound R the SSSS host again has lower λ_{max} (584 by 2nm) and larger association constant with the relative ratio of K_a-values being 1.95. With S the RRRR host has a lower λ_{max} (595 by 3nm) and a higher association constant with the relative ratio of K_a-values being 1.38 for RRRR. This trend was similarly upheld when other chiral amines (H-G9,10 and 11) were used. With (S)-(H-G8) host 1 the SSSS enantiomer had a relative ratio of K_a-values of 1.13, with host 2 the RRRR enantiomer had the larger relative K_a-value of 1.40. With guest (S)-H-G9 both SSSS hosts have the larger K_a-value, where host 1 has the very marginal value of 1.04 and host 2 has the value of 1.15. With guest H-G10 the SSSS host 1 has the expected larger relative ratio K_a-value of 1.37 and the RRRR host 2 also has the larger value of 1.17.

The trends observed in the association constants for the diastereoisomeric complexes of R and S with these chiral amines can be rationally interpreted in terms of steric interaction between the chiral host and chiral guest. They used CPK molecular models to examine the complexes formed with the assumption that the phenolate oxygen atom participates in a three point binding system with the protonated guest. They also used the assumption that the smallest group of the amine shall occupy the most hindered area of the host-guest complex. The experimental results obtained from these amines fit well with the steric interactions of the models used. They also performed experiments with achiral primary and secondary amines, finding that host R bound primary amines more weakly than host S. CPK models suggest that this difference is due to the cyclohexane donor oxygen atoms being covered (sterically restricted) by the axial hydrogen atoms of the cyclohexane, thus weakening a (Cram's) three point binding. CPK models also suggest that host S does not encounter the same steric restraint hence is expected to have a larger binding constant.



In this work by using a phenolate ion interaction to fix the three point binding it was shown that by changing the position of the binding site relative to the chiral barriers, a reversal in the enantiomer selectivity could be achieved.

Fluorescent Chromophoric Compounds

Chiral recognition/discrimination has previously been studied using fluorescence in the excited state associations between 2,2'-dihydroxy-1,1'-binaphthalene and amines[38] and in the exciplex quenching of a 2,2'-dimethyl-1,1'-bianthryl-N,N'-dimethyl-aniline system by chiral electron donating and accepting molecules[39]. [See also "Chiral discrimination in fluorescence quenching of (R)-(-)-1,1'-binaphthyls by chiral amines" by Irie et al.[40,41]].

Iwanek and Mattay[38] determined the stability constants of complexes, in the ground state, of optically active binaphthol with several amines in a series of solvents. Fluorescence quenching in the presence of chiral amines was studied in some solvents, with distinct differences only being found in acetonitrile. A weak fluorescence of the excited ion pair with hydrogen bonding was observed for all investigated systems in all the solvents used. They noted that in the excited state, proton transfer leading to an ion pair may explain the chiral discrimination in acetonitrile.

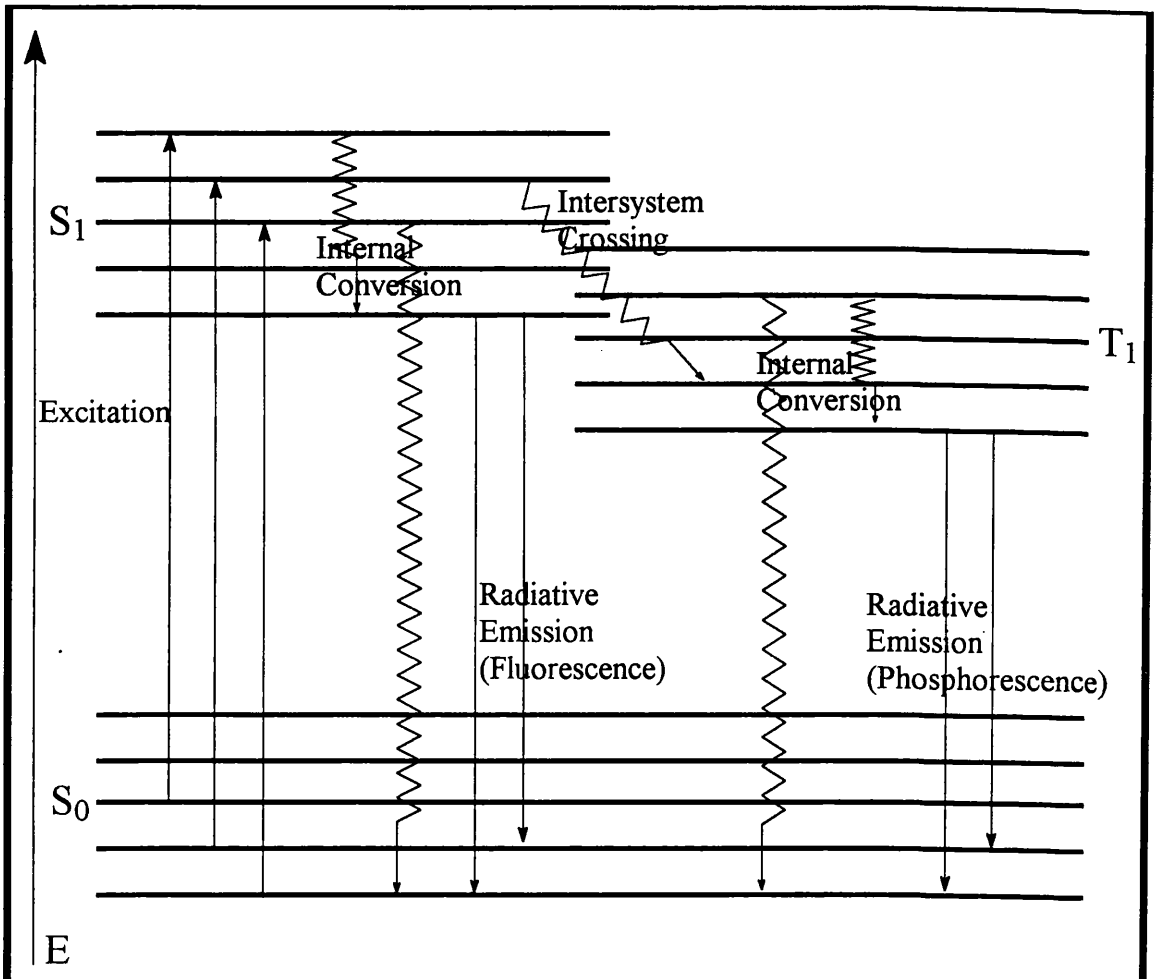
Mizuno et al.[39] reported that the rates of fluorescence quenching depended on the structure and the chirality of the quenchers. They also reported that the quenching rate of the exciplex emission of these systems show an intermediate value between those of the optically active systems. This strongly suggests that chiral quenchers interact with optically active exciplexes in an enantioselective manner. It was also noted that the enantioselectivity in quenching of the exciplex emission decreased with increasing solvent polarity.

1.5 Fluorescence

Fluorescence/Luminescence[42] is one of the oldest and most established analytical techniques still used today. Nicolas Monardes, a Spanish botanist, was the first person to record an observation of fluorescence, in 1565, of an aqueous extract of Lignium Nephiticiem (reference given to this in refs. 43 & 44). In 1845 the first crude emission spectrum was obtained for quinine by John Herschel. George Stokes, in 1852, was the first to determine and report that fluorescence emission was at a longer wavelength than the excitation. He also noted that the fluorescence intensity of a sample was quenched by itself at higher concentrations (auto quenching) and could also be quenched by the presence of other additional non-fluorescent molecules or impurities. These observations led him to propose that fluorescence should be used for the detection of organic substances. The first analytical use of fluorescence was in 1867, by F. Goppelsroder, who developed a method for the determination of aluminium (III) ions.

Fluorescence is a process in which radiation is emitted by molecules or atoms that have been excited by the absorption of radiation. The molecule before excitation is usually in the singlet ground electronic state S_0, to which it returns, often to a vibrationally excited form, as a result of the emission from the electronic excited state S_1 (generally

vibrational ground electronic excited state). Emission from an electronic excited state is called fluorescence only when the states from which emission originates and terminates have the same multiplicity. If the states differ the emission is known as phosphorescence, with the states of principal concern being the lowest excited triplet state, T_1, and the ground singlet state, S_0. Phosphorescence emissions have relatively long lifetimes (10^{-3} to 10 sec.) compared to the relatively short lifetimes of fluorescence (10^{-7} to 10^{-10} sec.) due to the probability of transition being large only when the multiplicity does not change through transition. In addition to the radiative processes that can occur to an excited molecule/atom there are radiationless processes through which energy can be lost. These are the result of conversion of electronic energy into vibrational energy and the energy loss is known as internal conversion except when the process occurs between the first excited singlet state and the lowest excited triplet state where it is known as intersystem crossing.



Schematic electronic state energy level diagram, including vibrational levels, describing the processes of Fluorescence and Phosphorescence.
Where S_0 is the ground state.

Figure F1

Within the area of optical transducers, fluorescence has been said to be the optimal signal transduction mechanism for a potential sensor, especially within the area of biological systems.

a- Fluorescence is easily and sensitively detected. Very low concentrations can be detected to the extent that molecular fluorescence has allowed single molecule detection for some time. [As a consequence little perturbation or damage is incurred to a host if used in a living system]. With a good choice of fluorophore (for the specified environment) the emission signal can be read against zero/near-zero background, hence very low concentrations of sensor can be used.

b- Fluorescence is a molecular phenomenon, hence fluorescence methods possess a microenviromental sensing capability with spatial resolution approaching molecular (nanometer) dimensions. [The wavelength of light imposes a higher limit to spatial visualisation.]

c- Excited state lifetimes are short so fluorescence methods have high temporal resolution thus they have the possibility of real time assay. However, the excited state is long enough to allow interaction with its environment [without being chemically reactive - photochemical reactivity]. The rates of complexation/decomplexation would be determining in real assay time. "A logical sensor design strategy would optimally trade off strong binding (high stability constants, hence low detection limits) with high complexation-decomplexation rate constants."[44]

d- Fluorescence is usually non-destructive [causes no damage to host systems]. Single molecules could infiltrate systems of cellular dimensions with little perturbation or damage to the host.

e- Monitoring of both excitation and emission spectra; where emission can be observed as Intensity, Intensity Ratio or Lifetime measurements.

f- Fluorescent sensors communicate via photons, thus remote communication becomes feasible without the need for physical waveguides. However with the advent of fibre optics and laser technology, the immobilisation of a fluorescent sensor onto an optical fibre is possible. The advantages that would be gained, for example with the ease of use of such a robust probe, are traded off against the loss of microenviromental sensing and cellular infiltration capabilities.

Some of the difficulties encompassed with the development and use of molecular fluorescent sensors are;

a- This can be more expensive as they require two independent experimental variables, excitation and emission wavelengths (however this increases the analytical sensitivity).

b- In host systems the fluorescent signal can be distorted by quenchers other than the desired analyte. This can be minimised by selection of sensor and transduction technique for any given application.

c- The short excited state lifetime can prevent the complete attainment of sensor analyte equilibrium and thereby give rise to non-thermodynamic information about the sensor environment. This can then be misleading in interpretation.

d- Biological systems, because of auto-fluorescence of protein residues, require the development of long wavelength (near IR) fluorophores (or other mechanisms such as phosphors) to avoid distorting background fluorescence (noise).

e- Fluorescent chemosensors have a very limited working concentration range (compared with that of electrochemical systems) due to auto-quenching and emission distortion at higher concentrations.

1.5.1 Methods/Mechanisms of Fluorescent Signal Transduction

There are many methods by which fluorescence signal transduction may be effected. These can be put into categories of Intensity measurements, Intensity Ratio measurements and Lifetime measurements.

Intensity measurement is the most common method, used to date, for distinguishing between signals. This method has been used for the detection of analytes by collision and complexation (methods for halide ions and molecular oxygen rely on quenching by collision). The fluorescence spectrum of the free, unbound sensor is compared with the spectrum of the sensor in the presence of analyte. The difference between spectra, which appears as an increase or a decrease in the fluorescence intensity, at a single wavelength, is taken as the analyte responsive signal. Sensors that use the complexation of analytes to give an intensity change can undergo either an increase (chelation-enhanced fluorescence, CHEF) or a decrease (chelation-enhanced quenching, CHEQ) in fluorescence intensity (in their respective intensities). The resultant decrease or increase is generally a consequence of whether the analyte is or is not inherently quenching. Sensors that rely on collision, only show a decrease in intensity (quenching).

In the area of intensity measurements a more rigorous strategy has developed in the use of intra-molecular Photo-Electron Transfer (PET), in the excited state of the molecular sensor, to effect the possibility of a signalling on-off switch. This is brought about by the incorporation of a ligating/quenching unit at a fixed distance from the fluorophore. With good choice of ligator/quencher the excited state of the fluorophore is quenched by electron transfer from the ligator unit. Thus in the free state the molecular sensor

exhibits no/little fluorescence. Upon binding of an analyte the ligating unit of the sensor has electron density tied up and the energy requirement for electron transfer (oxidation of the ligating unit) is too great, thus the molecular sensor fluoresces. PET systems have been used extensively in fluorescent molecular sensors, their design and use have been outlined by De Silva[44,46] and others[45,47].

Whenever intensity measurements are used, the concentration of sensor must be known accurately in order that the fluorescence intensity can be interpreted correctly. This requirement becomes one of the major drawbacks to this type of signalling for reasons such as the decomposition/degradation of fluorophore due to 'photo-bleaching' or dispersion through living systems and changes in the immediate environment. The problem of photo-bleaching is paramount when the sensor is bound to an optical fibre, as this would require constant recalibration in extreme cases and gives rise to the required development of fluorophores with substantially better photo-stability.

If the binding of an analyte causes a spectral shift, the use of Intensity Ratio measurements can, when correctly calibrated, provide a solution to the problem of concentration certainty. This can be achieved by the monitoring of multiple excitation/emission wavelengths for the decrease of signal intensity, of the free unbound sensor, in one area and the emergence and increase of a new signal, due to the analyte-sensor complex, at another wavelength, over an analyte concentration range. As it is the intensity ratio of signals that is being looked at the sensors' working ability becomes independent of its own concentration, as long as it is operating within its concentration range and the analyte is in excess.

Other mechanisms that can utilise Intensity Ratio measurements are those involving excimers. Fluorescence emission is known to change with concentration and temperature, increasing the concentration of fluorophore causes a new emission signal to be formed in a red shifted position due to excimer formation. Excimer formation arises from an energy transfer from the excited state of one fluorophore to the initial ground state of another fluorophore of the same or different species resulting in an emission of a different wavelength. Excimers can be formed at much lower than anticipated concentrations by the use of intramolecular bichromophores, where the ratio of monomer to excimer fluorescence intensity is governed by the flexibility of the spacer employed between the two chromophores, conformational mobility is generally far

greater in the free ligand and as such the monomer usually dominates. Excimer formation and stability is dependant on the degree of overlap of the π-orbitals on both components. The excimer emission spectra is also dependant on the distance between chromophores, which can be drastically different in unbound and bound states. Also this must clearly change with changes in bound guest (analyte). Exciplex formation is also possible, where an exciplex is an excimer consisting of two different chromophores/fluorophores. The conformational effects of linked anthracene excimers have been studied by Ferguson et al[48]. Such anthracene excimers and other exciplexes have been successfully used by H. Bous-Laurent et al[49], among others[50,51], in spatial and metal recognition studies.

Another signal transduction mechanism that can be exploited in intensity ratio experiments is the use of energy transfer from a chromophore, in an excited state, to an inter/intra-molecular acceptor, in a ground state, via charge transfer. Non-radiative relaxation, such as this, from the excited state can be effected by Fluorescence Resonance Energy Transfer (FRET). Such relaxation could act as a fluorescence dimmer switch or as a secondary transducer, as the energy of the initial excited state could be quenched to an extent, by charge transfer, determined by the distance and overlap, both spatial and energetic, of the inter/intra-molecular acceptor. The acceptor, in turn, is put into an excited state which could decay back to its ground state by non-radiative means or via a radiative emission. The use of such charge transfer mechanisms in fluorescent chemosensors is described by B Valeur et al and to a lesser extent by L Sousa et al, in their respective works[52]. The dependence of cation induced charge transfer absorption on distance, orientation (overlap) and mutual fixation of donor and acceptor components of (m,n) paracyclophanes has also been studied by Staab et al[53].

With recent advances in the technology of fluorescence lifetime measurement, the proposition of such lifetime-based measurements has offered new opportunities and advantages over existing intensity based technologies. The advantages include sensor concentration independence such that the exact sensor concentration, which is affected by variables such as photo-bleaching, dispersal and washout, is not required. As a consequence the recalibration of sensors mounted on physical waveguides such as optical fibres, would no longer be required. Many of these advantages can also be associated with Intensity Ratio measurements.

Lifetime sensing can be affected by collisional quenching, a dynamic quenching event which is not easily detected by any other mechanism. Collisional quenchers include oxygen, chlorinated hydrocarbons, halides and sulphur dioxide amongst others. The sensitivity toward one analyte over others arises only from highly specific indicators. These sensors still require to be photostable, on the grounds of probe durability and robustness, although the lifetime is, within reason, independent of dye concentration. Fluorescence lifetime can be related to concentration in the same manner as intensity, using the Stern-Volmer equation;

$I_0/I = 1+K_{sv}[A]$, where I_0 is the original intensity and K_{sv} is the intensity constant for the sensors interaction with analyte A.

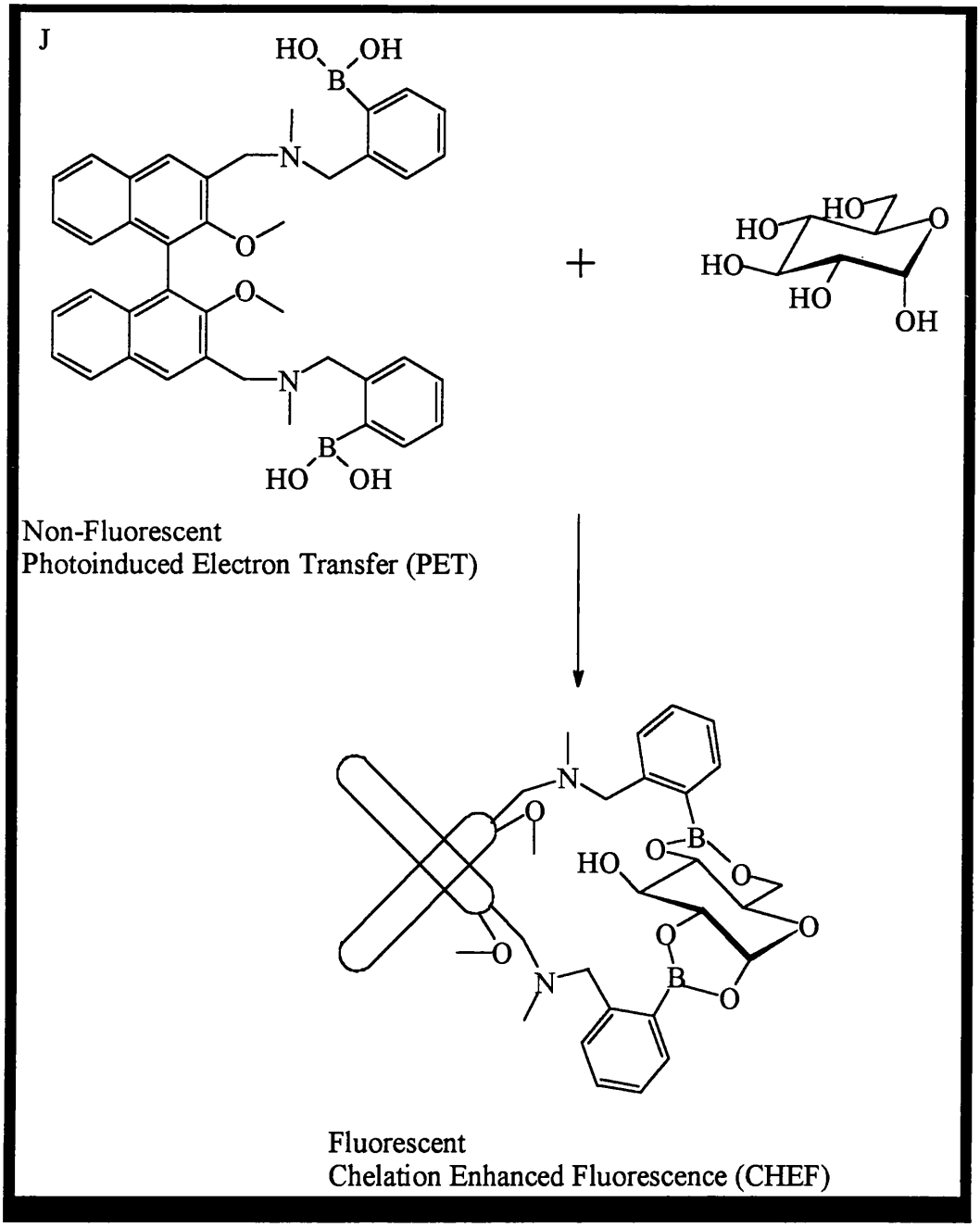
$\tau_0/\tau = 1+K_{sv}[A]$, where τ_0 is the original lifetime and K_{sv} is the lifetime constant for the sensors interaction with analyte A.

Lifetime based sensing can also be achieved for systems employing analyte binding, using intrinsic/conjugate probes or donor-acceptor pairs. The donor-acceptor pairs can be inter or intra-molecular, however the intra-molecular pairs are superior as they do not suffer from possible changes in donor-acceptor ratio. A conjugate probe is one in which the fluorophore is covalently linked to the analyte receptor via an inert spacer. An intrinsic probe is one in which the analyte sensitive region is built into the fluorophore. Existing fluorescent probes based on intensity or intensity ratio mechanisms appear to be easily translated into lifetime based techniques.

Fluorescence excitation and emission can be affected by environmental factors such as solvents, acidity and cations present. These affects can be seen as changes in the absorption/emission maxima, the fluorescence quantum yield in intensities, intensity ratios and lifetimes. Although the synthesis of fluorescent chiral sensors may be long, difficult and low yielding the production of a few milligrams may be enough for thousands of analyses.

1.5.2 Fluorescent Chiral Sensors

The first fluorescent chiral sensor was made by Seiji Shinkai et al.[54] as part of their ongoing chemorecognics project (A commentary on the significance of this landmark discovery was given by A.P. deSilva[55]). Shinkai reported the chiral discrimination of D- and L- monosaccharides using a designed receptor molecule that acts as a sensor by virtue of its fluorescent response to binding of the guest species.



Upon binding of each enantiomer of monosaccharide the fluorescence intensity is altered to different degrees, by the changes caused to the photo-electron transfer (PET)

processes in operation (which when unbound, quench the sensors fluorescence). This discovery follows on from their previous success in molecular recognition using similar PET systems. Their experiments showed that both steric and electronic factors were involved in the chiral recognition. Sensor (J) shows a selectivity for fructose over other monosaccharides and a selectivity for one optical isomer, dependant on its own chirality. They proposed that this sensor is a bimodal chiral probe were both the fluorescence intensity and the stability of the 1:1 saccharide complex reflect the chirality of the bound saccharide. This work by Shinkai has arisen from his long running Chemorecognics programme (for molecules with analyte recognition properties), with more recent publications charting the continued effort in the development and study of this and some other of his sensors[56,57,58].

1.6 Sensor System Requirements

The requirements for an operational sensor system put forward here range from the very basic absolute requirements to some of the more advanced and desirable capabilities. At this stage in their development any working sensor will only have a few of these capabilities, however the desire to make a sensor with all these and more is in the foreground of all new sensor design and syntheses.

It is desired that a sensor has;

A- Selectivity;

1-Towards one enantiomer

2-Towards one guest

If it does not have this it must have the ability to bind both enantiomers to similar degrees with large differences in the signal outcome in order that the ratio is easily detectable. Must have large differential signal tolerances towards enantiomers. This also applies to different guests as ultimately sensors may be required to be used in environments where there are mixtures of compounds (guests) - for example within living systems. A mixture of the above is the most likely.

B- Real time reversible complexation (association/dissociation)

C- Signal transduction

D- Sensitivity towards very low concentrations and towards real time changes in concentrations

E- Internal calibration preferred

F- Chemical and Photochemical stability

G- Signal stability, i.e. low dependence on environmental factors such as pH, temperature, Solvent polarity etc.

H- Excitation to be possible by a cheap portable source

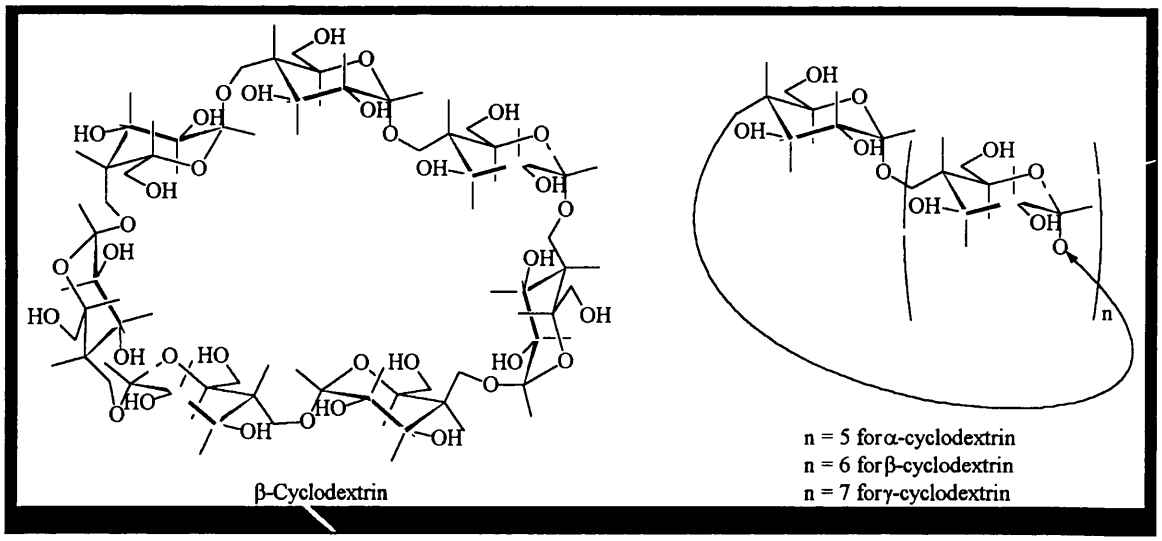
I- Detection to be possible by a simple, cheap, portable detector, preferably with no interference from background or adventitious fluorescence

J- Ideally would like to keep all of the above criteria whilst immobilising and using as an indicator stick or in conjunction with optical fibre technology

1.7 Important Classes of Host

1.7.1 Cyclodextrins

Cyclodextrins are cyclic polysaccharides (oligo-saccharides) of variable size, made up from glucose units, all in classical C1 chair conformation, linked by α-1,4-bonds. They have an overall shape of a truncated cone with the wider side formed by the secondary hydroxyl groups. The smallest cyclodextrin is α-cyclodextrin, composed of six glucose units. In 1992, the largest cyclodextrin that had been isolated was composed of nine glucose units, although the higher analogues are believed to consist of up to thirteen glucose units. The cavity is relatively hydrophobic while the external faces are hydrophilic.



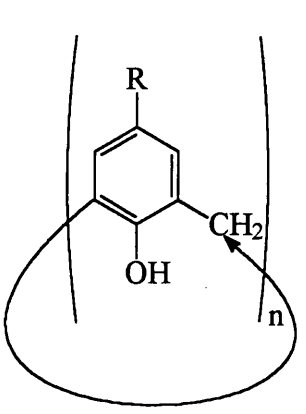
Cyclodextrins have a powerful, inherently chiral cavity, which is capable of complexing neutral guests well and some are relatively cheap. However, they are CD/UV/Visible/Fluorescent silent and as such require derivatisation before possible use as optical sensors. Also, they only exist as one enantiomer, which is unfortunate as the availability of both hands of any particular molecular sensor is a particular advantage as concomitant detection by two probes is possible.

Cyclodextrins and their derivatives have shown enantioselectivity in the complexation of and the reactions involving chiral molecules[59,60,61,62]. Chromophoric derivatives of cyclodextrins have shown guest responsive colour changes[63], including changes in fluorescence[64,65,66]. Chromophoric enantioselectivity has been investigated using fluorescent derivatives of cyclodextrins[67,68], however no appreciable chiral discrimination was observed.

1.7.2 Calixarenes[69,70]

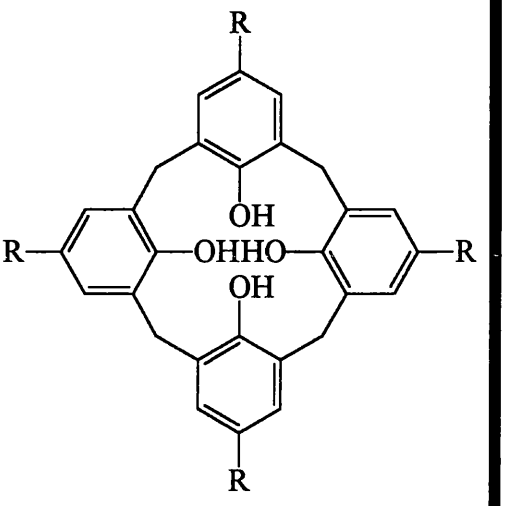
Another important class of host compounds are the calixarenes, these synthetic hosts are bowl shaped molecules, their name originating from the Greek word *calix*, meaning vase. Calixarenes have been known for a long time, however it is only recently that interest in these compounds has gained a new enthusiasm with a great increase in the number of papers being published. This revival can be attributed to reasons such as the synthesis of these macrocycles can now be accomplished on a large scale and in good yield, also the ease and selectivity with which calixarenes can be functionalised. This gives rise to a class of compounds which can be synthesised to orders of size and

conformational mobility and used as basic building blocks. Calixarenes can have several basic conformations, depending on the direction each unit faces. For a calix[4]arene these are the cone formation, where the oxygen of each unit points downward, (to what would be the bottom of the bowl), giving a uniform cavity without breaks, the partial cone , where one of the units points in the opposite direction and the 1,3-alternate, where the units immediately next to each other are sitting in opposite directions. This gives rise to cavities with a variety of interesting shapes and sizes.



n = 4 - 8
R = alkyl

General calixarene structure



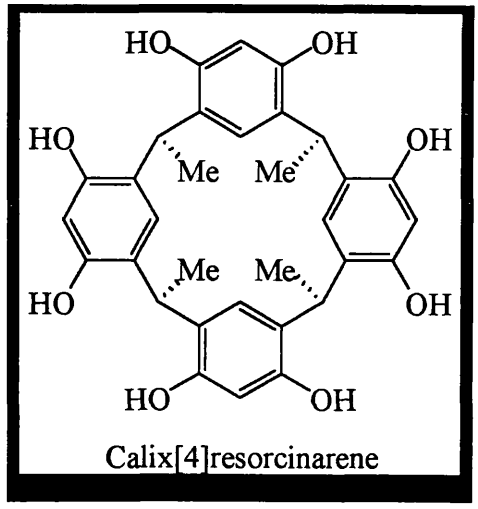
p-tert-butylcalix[4]arene

The work done on the derivatisation of calixarenes has in the main been on their development and use as ion receptors and carriers which has resulted in many compounds with high selectivity and great efficiency. Calixarenes have been derivatised with, amongst other functionality, crown ethers of various sizes to enhance their binding and selection abilities[71]. They have also been joined together to form bis-calixarenes and used in metal ion transportation studies where they were used to eliminate inter-molecular metal hopping. Calixarenes have also been used to synthesise prototype sensors such as the fluorescent calix[4]arene made by Takashi Jin et al., which acted as an intra-molecular excimer forming Na^+ sensor in non aqueous solution[72]. This was achieved by the modification of the basic p-tert-butyl-calix[4]arene unit with two pyrene arms on the 1,3-oxygens. The excimer : monomer fluorescence intensity ratio of this calix[4]arene was shown to change with the complexation of sodium ions, this change is induced by the re-orientation of the molecule's configuration upon binding. It was suggested that the distance between the two pyrene units is expanding upon binding and

as such there is an increase in the monomer emission and a subsequent decrease in the excimer emission.

The inclusion of neutral guests into the cavity of calixarenes, which is hydrophobic (apolar) in the cone formation, is also of growing interest. Most of the larger calixarenes are known to form clathrate inclusion complexes with neutral molecules, with the guest most often occupying inter-molecular gaps. Calix[8]arene has however been used in the purification of the buckminster-fullerene C_{60}, where simple fractional precipitation techniques have been employed to increase the purity of C_{60} up to 98.8%. The inclusion complexes of the smaller calix[4]arenes generally differ in that they often form intra-molecular complexes in the solid state. These complexes have been shown to have high levels of quite fine shape selective discrimination. Complex formation in solution is less well documented, with studies that have shown such complex formation, the driving force has most likely been electrostatic interactions.

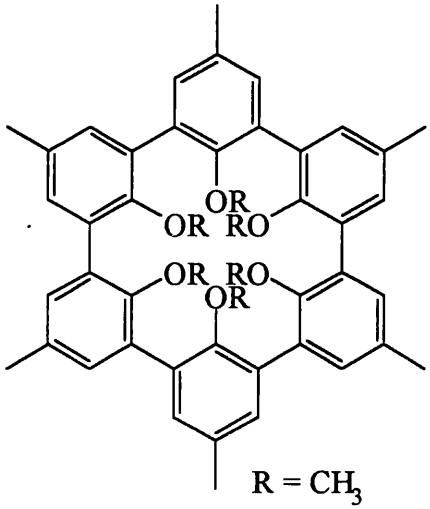
A closely related class of compounds to calixarenes are the calix-resorcinarenes which have the same basic bowl shape and are synthesised in a similar manner. Calixarenes are synthesised from the base catalysed condensation of phenols with formaldehyde while calix-resorcinarenes are formed from acid catalysed condensations of resorcinol with aldehydes. Another important difference between calix-resorcinarenes and calixarenes is that the phenol functionality of the calix-resorcinarenes points upwards, out of the cavity.



Calix[4]resorcinarene

Cram[73] designed and studied many calix-resorcinarenes, which have also been called cavitands, with a view to their use as synthetic molecular cavities. The structure and conformational mobility of the archetype calix[4]resorcinarene had already been established[74]. It was found, as expected, that these compounds only crystallise as solvates as they are so rigid that they are unable to fill their voids either inter-molecularly or intra-molecularly. The cavity size of these systems could be modified by the derivatisation with various groups of different flexibility. A further class of compounds was created by taking two calix-resorcinarenes and joining them together to produce a closed surface host which Cram named carcerands. The synthesis of the first carcerand

was brought about with the view to completely imprison guests cutting them off from other chemical interactions. By imprisoning guests in this way he found that their chemistry could be controlled in ways which had previously not been possible. The imprisoned guests could undergo photochemical reactions and as there were no other guests with which to interact, highly reactive products could be synthesised and kept in a stable environment. In this way Cram was able to synthesise cyclobutadiene which was shown to be stable in its isolated environment.

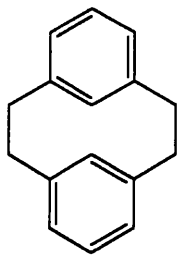


Spherand

He also synthesised another similar class of compounds, the spherands, via the reductive coupling of phenols, which were used to study the effects of pre-organisation on binding constants, along with their acyclic counterparts, the podands. The spherands and podands radically differ in their conformational structures and solvation states. The spherands posses a single conformation, with each unit alternately pointing up and down and each of its oxygens remain unsolvated whereas the podands have many possible conformations and all of their oxygens are solvated.

1.7.3 Cyclophanes[3,75]

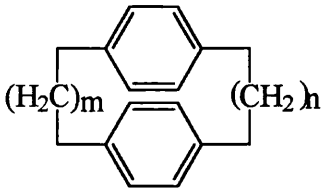
Another important class of host compounds are the cyclophanes. Cyclophanes (phanes) refer to macrocycles constructed purely of carbon bridged aromatic (benzene) units.


[2,2]metacyclophane the first cyclophane synthesised in 1899[76]

Heterophanes refer to phanes that contain hetero-atoms in any of the aromatic rings that make up the phane. Heteraphanes refer to phanes that contain hetero-atoms in the bridging units between the aromatic rings. With this definition it is clear that this class of host compounds could easily encompass any macrocycle containing an aromatic unit.

The initial (real) interest in cyclophanes started with small rigid molecules and the view to using them as models to answer

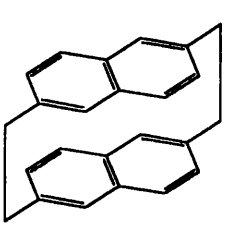
questions about intra-molecular electronic interactions and influences arising from the face to face positioning of aromatic rings. Intra-molecular charge transfer complexes and strain energies of such small molecules was also of interest.



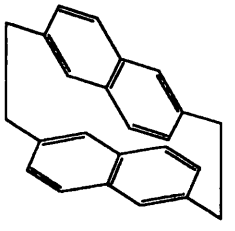
m=2 n=2; m=3 n=2; m=4, n=2
[2,2]- [3,2]- [4,2]-paracyclophane

Their subsequent growth and development to molecules that are capable of forming complexes with a diverse range of guests in a variety of conditions and acting with such purpose as transportation accelerators and enzyme mimicking catalysts is a testament to their range of abilities. The understanding of molecular interactions and influences has been greatly enhanced by the study of small cyclophane systems, giving an increased knowledge of non-covalent influences in ground and excited states.

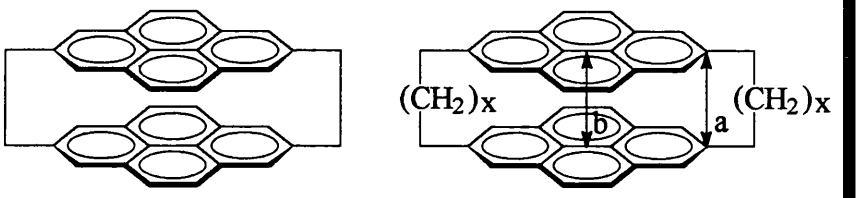
Small cyclophanes have been used to show and project (map) the dependence on distance, overlap and strain of intra-molecular chromophores, in their consequent excimer and exciplex spectra. The many in-depth studies into small rigid cyclophanes and their many structural isomers have been the foundation for much of the work on their larger cousins. When the same trends are seen in larger, more flexible molecules, models and information of organisation by primary binding in other parts of the molecule, can be drawn from comparison of spectra to give distances and overlap geometry. However a problem with the study of small cyclophane is that in some of the smaller phanes the aromatic units are severely distorted from planar. This type of distortion does not occur in inter-molecular complexes. The degree of distortion also affects the exact distance between the two chromophores as well as disrupting the π-electrons such that the spectra obtained can not give a direct relationship to the distance between the chromophores. Such distortion is high energy and as such the probability of a larger less rigid molecule taking up a similar conformation is very unlikely.



[2,2](2,6)naphthalenophane
achiral



[2,2](2,6)naphthalenophane
chiral

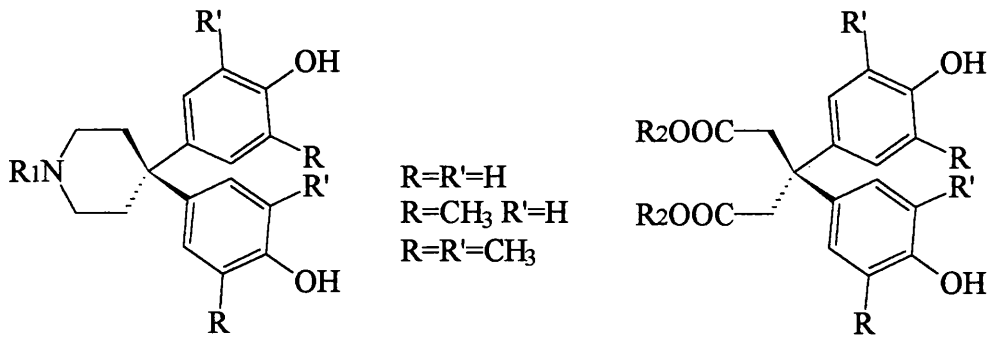


[2,2](2,7)pyrenophane

when x changes from 2 to 4 then distance a changes from 2.79 to 3.68A and distance b changes from 3.76 to 3.48A
Also λ max goes from 18,000 to 21,300cm

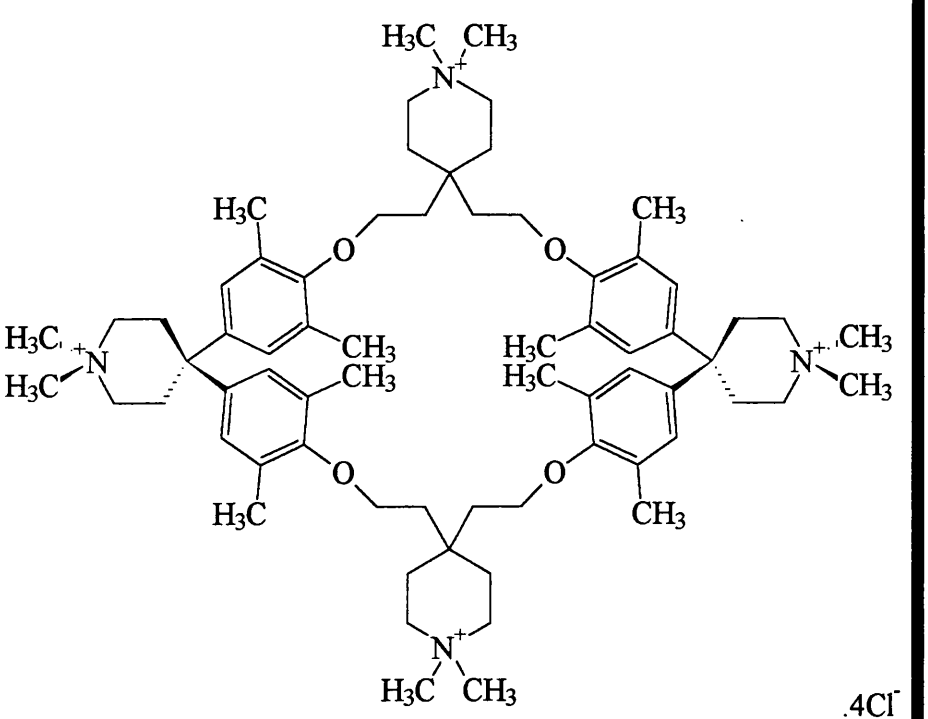
A man who has become a great exponent of the virtues of cyclophanes is François Diederich[77]. He entered the area of cyclophanes originally with an interest in the development of water soluble hosts that would have cavities with prominent hydrophobic binding properties. Research into the synthesis of host systems with the ability to bind neutral (apolar) guests was probably first approached by the work of Stetter and Roos in 1955[78]. However the first true cavity inclusion of a neutral guest by a cyclophane host was reported in 1980 by Koga et al.[79], who found inclusion in both the solid state and in aqueous media.

Diederich was very interested in studying the hydrophobic effect as it was believed to be 'the specific driving force for the association of apolar binding partners in aqueous solution'. He was effectively interested in making synthetic hosts with similar properties to those of cyclodextrins. Synthetic hosts have the advantage that simple modifications can change the cavity size, rigidity and binding properties allowing a designer fit for guest molecules. Synthetic hosts can also be synthesised in both/all enantiomeric forms, which is where naturally occurring hosts lose out. For their initial studies on water-soluble cyclophane hosts they utilised diphenyl spiro carbons as building blocks which gave them both the required rigidity of shape (in the desired spatial arrangement) and functionality (locants) for water solubility, remote from the binding cavity (in order that this functionality does not preferentially influence the mode of binding).



Spiro diphenylmethane spacers as used by Diederich for water soluble cyclophane hosts.

These aromatic building blocks were bridged with alkyl chains, via the phenolic oxygen, which varied in length varying the cavity size and binding ability. The rigidity of the host cavity could be changed by employing less flexible bridges and the water solubility could also be changed in a similar manner. To increase both the rigidity and the water solubility of these hosts spiro piperidinium rings were employed in the bridges. Further to this, by employing a bicyclic system, as with Lehn's cryptands, greater rigidity, solubility and a more complete encapsulation of guests, could be achieved.



A cyclophane for guest complexation in aqueous solution, with four spiro piperidinium rings for rigidity and water solubility.

The studies of the complexation behaviour of these compounds in aqueous solution were mostly done by NMR spectroscopy and were at concentrations below those which lead to non-stoichiometric aggregates being formed between the host and guest. These can give very misleading results as the aggregation is driven by the same forces that were to drive the inclusion of guest by host, thus this behaviour had to be studied before the complexation. With the complexation of neutral compounds in aqueous solution they found that they could extract from organic solutions and use this to preferentially accelerate the transportation of arenes through aqueous solution. With the success in complexation in aqueous solution they went on to investigate the complexation behaviour of similar non-ionic cyclophanes in organic solution. The driving force for the complexation of analytes in organic solution is predominantly enthalpic in nature for the initial non-functionalised cyclophanes. The binding strength was found to be very dependant on the nature of the solvent being used, such that solvation phenomena must be responsible for the differences. Competition by solvent for inclusion can also play a major role in the binding strengths, especially for solvents like benzene and carbon disulphide. Another complexation driving force that has become very important in cyclophane host-guest complexes is that of electron donor-acceptor interactions. The major elements of electron donor-acceptor behaviour can be explained as electrostatic, polarisation and charge-transfer interactions, although charge transfer is generally only seen in specifically designed complexes. Electron donor-acceptor interactions act to increase the stability of the formed complexes thus giving extra recognition possibilities. Cyclophanes have also been used for chiral recognition[80,81] in diastereomeric host-guest complexes in aqueous solution as well as enzyme mimics for catalysis.

An interesting chiral cyclophane, with high symmetry, which, during the early stages of this project, became influential (directional) in the design of prototype sensors had been synthesised by Dougherty et al.[82]. This cyclophane was built up from ethenoanthracene units, which could be synthesised enantiomerically pure using a highly selective asymmetric Diels-Alder reaction. It encompassed a variety of spacer units which were used to affect the molecules rigidity and thus its selectivity. They found that these hosts displayed a strong and fairly general attraction for quaternary ammonium guests and neutral guests with electron-deficient π-systems, with preliminary studies also finding some enantioselective binding. This was ascribed to donor-acceptor interactions between

the guests and the electron rich π-systems of the hosts. The greatest influence was in their design specification, in which they sought to create an inherently chiral cavity and binding site as opposed to a chirally perturbed, inherently achiral cavity and binding site. This design specification was brought about from the anticipation that such an intrinsically chiral cavity (host) would posses a greater "degree of chirality" over any chirally perturbed cavity (host). This qualitative argument of feeling and intuition and its consequences, in the "fuzzifications" of the term chirality, is fully dissected in a paper by Mislow and Bickart[83].

This is in no way a full account of all of the work that has been done and that is going on in this area of chemistry. It is merely, what is hoped to be, an interesting selection of some of the work of some of the researchers in some of the relevant areas.
For other chiral crown ethers that have been used successfully in optical resolution and asymmetric reaction systems see the further reading section in the reference section.

CHAPTER TWO

EXPERIMENTAL

Thirty spokes surround the hub:
In their nothingness consists the carriage's effectiveness.
One hollows the clay and shapes it into pots:
In its nothingness consists the pot's effectiveness.
One cuts out doors and windows to make the chamber:
In their nothingness consists the chamber's effectiveness.
Therefore: what exists serves for possession.
What does not exist serves for effectiveness.
Lao Tzu 'Tao Te Ching', I Dao,11

(2.1) INSTRUMENTATION

(2.1.1) General

UV spectra were obtained using a Perkin-Elmer Lambda 9 spectrophotometer. Reference and sample spectra were obtained in a TSL 1 cm semi-micro far-U.V. quartz cuvette. Corrected spectra were produced by sample-reference subtraction using the Perkin-Elmer PECSS suite of programs.

One and two dimensional NMR spectra were obtained on Bruker AM 200 and WP 200 spectrometers (200 MHz, FT-NMR) using the Bruker Aspect 3000 suite of programs. All samples are referenced internally to solvent resonance. Deuterated solvents were purified by freeze-thaw degassing and stored under a nitrogen atmosphere, over 4Å molecular sieves where necessary, otherwise they were used as bought.

FT-infra-red spectra were obtained on a Philips FTIR spectrometer. All solid samples were prepared as 8 mm diameter KBr discs using 300 mg of KBr and a press force of 8 tons, all liquid samples were run as thin films on NaCl plates. Melting points were recorded in air using a Gallenkamp melting point apparatus and were uncorrected. Thin layer Chromatography was carried out on Merck Kieselgel G (silica) plates of 0.25mm thickness. Column chromatography was carried out using Sorbsil C60 40/60 A silica gel. Optical rotations were carried using an Optical Activity Limited AA10 polarimeter operating at 589nm with 1 and 5ml cells having a path length of 10cm (1dm).

Elemental analyses were carried out using a Carlo-Erba 1106 elemental analyser with a Hewlett Packard 3394 integrator.

Fluorescence spectra were obtained with a SPEX Fluoromax instrument using DM3000 software.

(2.1.2) Mass Spectroscopy

Low resolution mass spectra were obtained with an AEI 12 mass spectrometer and high resolution mass spectra were obtained using a VG updated 902 mass spectrometer.

FAB Mass Spectrometry (LSIMS)

The low resolution Fast Atom Bombardment (LSIMS) mass spectra were obtained from the EPSRC Mass Spectrometry Service Centre at Swansea. The spectra were run on their VG Autospec instrument using Caesium ion bombardment at 25kV energy on to the sample dissolved in a matrix liquid, 3-nitrobenzyl alcohol (NOBA). Each spectrum

contains matrix ions which prevent useful spectra being obtained at low mass. The computer software used to produce the spectra does not allow the subtraction of matrix ions in a normalised fashion such that ^{13}C containing matrix ions are not removed from the spectrum.

A few samples were run on a selection of spectrometers, as a test of each spectrometer's ability, including an autospecOATOF electrospray unit which operated as positive ion generating using a mobile phase of acetonitrile + 1% acetic acid with a flow-rate of 40μl/min and a source temperature of 100°C. An autospecQ CI mass spectrometer using a negative ionisation mode and an autospecQ FAB mass spectrometer using a positive ionisation mode were also used.

(2.1.3) X-Ray Crystallographic Data Collection

Crystallographic data was obtained by Dr Louis Farrugia; crystals were mounted on a glass fibre and data collected at ambient temperature on an Enraf-Nonius CAD4F automated diffractometer in the $\theta/2\theta$ scan mode, using graphite monochromated X-radiation ($\lambda = 0.71069$Å).

Unit cell dimensions were determined using the SET 4 routine by refinement of the setting angles ($11 < \theta < 13$) averaging angles from four diffracting positions. All calculations were performed on a MICROVAX 3600 computer using the Glasgow GX suite of programs.

(2.2) MATERIALS AND SOLVENTS

Chemicals, their suppliers and purity used in preparative work are listed in table 2.2.1. Solvents and purification methods are listed in table 2.2.2.

Table 2.2.1 Chemicals and suppliers.

Aluminium Chloride	(Aldrich)	97%+
Ammonium hexafluorophosphate	(Fluka)	98%+
1,2-Bis(2-chloroethoxy)ethane	(Lancaster)	98%+
Bovine Pancreas Acetone Powder	(Aldrich)	----
Bromine	(Aldrich)	99.5%+
Bromodiphenylmethane	(Aldrich)	95%

Bromomethyl-methyl-ether	(Aldrich)	Technical Grade 90%
2-Chloroethanol	(Aldrich)	99%
2-(2-Chloroethoxy)ethanol	(Lancaster)	99%
2-Chloroethylmethyl sulphide	(Aldrich)	97%
1,8-Di(bromomethyl)naphthalene	(Aldrich)	97%
α,α'-Dibromo-m-xylene	(Aldrich)	97%
α,α'-Dibromo-p-xylene	(Aldrich)	97%
2,3-Dihydropyran	(Lancaster)	97%
3,5-Dinitro-benzoylchloride	(Aldrich)	97%
Ethylene oxide	(BDH)	98%
Ethylene sulphide	(Aldrich)	98%
2-Hydroxynaphthalene	(Fluka)	98%
Iron (III) Chloride Hexahydrate	(Aldrich)	98%
Pentanoyl Chloride	(Aldrich)	98%
(R) & (S)-Phenyl alanine	(Aldrich)	99%
(R) & (S)-1-Phenylethylamine	(Aldrich)	98%
Potassium tert-Butoxide	(Lancaster)	98%
Potassium hydroxide	(BDH)	85%+
Sodium in liquid paraffin	(Fisons)	99%+
Sodium carbonate	(BDH)	99.9%
Sodium chloride	(Koch Light)	99%+
Sodium hydride	(BDH)	60% dispersion in mineral oil
Sodium hydrogen carbonate	(Prolabo)	99%
Sodium hydroxide	(BDH)	97%+
Sodium metabisulphite	(Aldrich)	97%+
Sodium phosphate dibasic dodecahydrate	(Janssen)	98%
Sodium sulphate	(Aldrich)	99%
Sodium Taurocholate	(Fluka)	Technical Grade
Tetraethyleneglycol	(Aldrich)	99%
Thionyl chloride	(Aldrich)	99%+
Triethylamine	(Prolabo)	99%
(R) & (S)-Tyrosine	(Aldrich)	98%

Table 2.2.2 Solvents and purification methods.

Absolute Ethanol	Twice distilled from magnesium turnings and iodine, under N_2; stored over 4Å sieves.
Acetonitrile	Distilled from calcium hydride under N_2.
Cyclohexane	Distilled from sodium metal under N_2
Dichloromethane	Distilled from calcium hydride under N_2.
Diethyl ether	Distilled from sodium benzophenone under N_2.
Dimethyl formamide	Distilled from calcium hydride under vacuum. Stored over 4Å sieves.
Methanol	Stored over activated 3Å sieves.
40-60°C Petroleum Ether	Distilled under N_2 from sodium/potassium alloy.
Pyridine	Distilled from potassium hydroxide
Tetrahydrofuran	Distilled under N_2 from sodium benzophenone.

Toluene	Distilled from sodium under N_2 and stored over 4Å molecular sieves.

All other solvents used were of technical grade and no further purification was carried out.

(2.3) ABBREVIATIONS

abs	absorbance
bpt	boiling point
bm	broad multiplet
bs	broad singlet
d	doublet
δ = ppm	parts per million
Δ	difference
DCM	Dichloromethane
DMF	Dimethyl formamide
DMSO	Dimethyl sulphoxide
EI	Electron Ionisation
EtOAc	Ethyl Acetate
equiv.	equivalents
FAB	Fast Atom Bombardment
IR	Infra-red
LSIMS	Liquid Secondary Ion Mass Spectrometry
m	multiplet
MeCN	Acetonitrile
MHz	Megahertz
mmol	millimoles
mpt	melting point
MS	Mass Spectrometry
NMR	Nuclear Magnetic Resonance
NOBA	Nitrobenzyl alcohol
Petrol	Petroleum ether (40/60)

PPL	Plane Polarised Light
pyr.	pyridinium
q	quartet
s	singlet
t	triplet
tBuOK	Potassium tert-Butoxide
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
UV	ultra-violet

Structural diagrams of the targeted and synthesised molecules can be found in the experimental appendix with their corresponding quick reference numbers.

Three dimensional molecular models were generated using Alchemy™ (version two) and Hyperchem™ (release 4.5 for windows) computational molecular modelling programmes. When the Hyperchem® molecular modelling system was used the molecular mechanics optimisation was generally performed using the Polak-Ribiere (conjugate gradient) algorithm option, with termination at RMS gradient of 1×10^{-5} kcal/(Åmol) or after ~2000 cycles. The molecular mechanics optimisation (minimisation) was run at least twice for each model and the molecular dynamics calculation was often used (with various settings) between each minimisation in an attempt to find the global minimum energy of each molecule. These models were used to give an indication of possible/likely shapes of targeted molecules and to assess their potential as sensors.

Many of the following reactions gave very crude mixtures. Yields are generally only given where these mixtures were successfully purified (yield after purification) and often only an aliquot of mixture has been purified. Where little or no information of yield is given it can be assumed that the yield was low or indistinguishable from analysis.

(2.4) SYNTHESIS

BINAPHTHOL SYNTHESIS AND RESOLUTION

Racemic 2,2'-Dihydroxy-1,1'-binaphthol

The binaphthol used in the resolution was synthesised using the method given in Vogel[84] which is essentially the same as the original method of Rudolf Pummerer et al. which was published in 1926. The reaction was done on a 110-130g β-Naphthol (0.76-0.903 moles) scale, with the reaction solvent (5-6 litres of distilled water) being recycled up to 5 times, (the best yields and highest quality was achieved when the solvent was recycled only once.)

2-Naphthol (110-130g, 0.76-0.9 moles) was heated to incipient reflux in distilled water (6 litres) until it had all dissolved or oiled out. To this vigorously stirred solution/suspension was slowly added a solution of iron (III) chloride hexahydrate (220-248g, 1.02-1.06 equivalents, 0.81-0.92 moles) in water (~500ml), in one portion. The oily solution of 2-naphthol reacts quickly with the iron(III) chloride (forming iron (II) chloride, the blue tinge seen during reaction) and the desired binaphthol precipitates out. The mixture is left heating (~90°C) for 15 minutes after the addition of the iron (III) chloride, before being allowed to cool to ~65C and filtered through a warm Buchner filter funnel. The filter cake was then washed with two portions of hot water (~400ml @ ~80-90C) and partially dried under suction. The filter cake was then dried in a vacuum oven before being recrystallised twice from toluene to give the 2,2'-Dihydroxy-1,1'-Binaphthol in 60-65% yield, mpt 218-220°C.

2-Naphthol (10-20% of original amount) can be reclaimed from the hot filtrate by precipitation & filtration upon cooling.

^{1}H NMR d_6-Acetone

ArH (d) 7.94 Δ=0.02093δ = 4.19Hz; ArH (d) 7.885 Δ=0.03809δ = 7.62Hz; ArH (d) 7.38 Δ=0.04444δ = 8.89Hz; ArH (d of d) 7.325 Δ=1.56Hz, Δ=0.145δ = 29Hz, 7.18 Δ=1.55Hz; ArH (d) 7.29 Δ=7.65x$10^{-3}\delta$ = 1.53Hz; ArH (d) 7.255 Δ=9.88x$10^{-3}\delta$ = 1.98Hz; ArH (d) 7.21 Δ=7.59x$10^{-3}\delta$ = 1.52Hz; ArH (m) 7.115; ArH (m) 7.08

These are too many signals to be a simple spectrum. It obviously contains secondary splitting.

^{13}C NMR

ArH 119.38, 123.62, 125.35, 127.015, 128.84, 130.54; ArR 114.83, 129.89, 135.41, 154.38

2,2'-Dihydroxy-1,1'-binaphthalene (Binaphthol) was resolved using the method of R.J. Kazluskas[85].

Racemic 1,1'-Binapthyl-2,2'-dipentanoate

To a stirred solution of racemic binaphthol (203.1g, 0.71mol. 1 equivalent) and triethylamine (215ml, 1.52moles, 2.17 equivalent) in diethyl ether (2 litres) was added cautiously, pentanoyl chloride (185 ml, 1.56 mol., 2.20 equiv.) over a period of about 30 minutes. The resultant mixture was left for a further 2 hours at room temperature, to ensure complete reaction, before being washed with two 2 litre portions of 1M sodium bicarbonate solution and one 2 litre portion of water. The resultant clear yellow solution was not purified further before being used in the next step of the resolution.

A sample of the ether solution was evaporated to dryness to give a thick sticky oil which did not show hydroxyl peaks (3500-3400 cm^{-1}), which would have been characteristic of binaphthol, in it's infra-red spectrum. This showed that the esterification reaction had gone to completion.

$C_{30}H_{30}O_4$ MW 454

EIMS M^+= 454

^1H NMR $CDCl_3$

CH_3 (t) 0.47; CH_2 (m) 0.775; CH_2 (m) 1.00; CH_2 (t) 1.97; ArH (m) 7.11; ArH 7.28; ArH (d) 7.81, 7.74

^{13}C NMR

CH_3 13.56; CH_2 21.73, 26.53, 35.76; ArH 121.96, 125.65, 126.18, 126.69, 127.92, 129.40; ArR 123.6, 131.55, 133.37, 146.81; CO 171.89

IR

No -OH stretch seen, CH stretch at 3050 cm^{-1}, CH_2,CH_3 stretch at 2880, 2910, 2950 cm^{-1}, C=O at 1760 cm^{-1}, C=C aromatic at 1600, 1625 cm^{-1}

(S)-(-)-1,1'-Bi-2-naphthol [1A]

The above ether solution was split into two equal portions and each used separately in the next stage. Each aliquot of ether solution was diluted to two litres and two litres of 0.1M phosphate buffer (pH 7.5) was added to each with stirring. Crude sodium taurocholate (30g) was added which caused an opaque emulsion to form. Bovine pancreas acetone powder (50g) which contains cholesterol esterase as the active enzyme was added and the mixture stirred for 3 days at room temperature. The stirring speed was held as slow as possible whilst retaining a good emulsion - enzymes can be destroyed by shear forces. The pH of the reaction mixture was monitored carefully and kept at pH 7.2 ± 0.3 by the addition of 1M sodium hydroxide. The first eight hours of the reaction require the most pH monitoring and readjustment. There is sometimes a lag period in the start of consumption of base, presumably for the enzyme to become hydrated. The base consumption also depends on the activity of the bovine pancreas acetone powder and the relative amount of (S)-binaphthol dipentanoate.

The consumption of base virtually ceases after the first 24 hours, however the pH was monitored for 3-4 days and the reaction stopped when the pH becomes constant.

The stirring was stopped and ethanol (200ml) was added to break the emulsion, the mixture was allowed to settle (several hours) and the ether layer was decanted from the aqueous and emulsion layers. The aqueous layer was discarded and the unbroken emulsion layer was separated by the addition of 80g of magnesium sulphate. The combined organic portions from each resolution pot were dried over magnesium sulphate before being filtered and evaporated to ~300ml before toluene (~500ml) was added and the resultant solution cooled, to 4°C, overnight to crystallise out the S-binaphthol. The crystalline material obtained was washed with toluene and dried under suction. The filtrate was reconcentrated and a further, small amount of crystals were obtained after cooling. Recrystallisation of the combined crystals yielded 53-57.6g, (S)-(-)-binaphthol as colourless crystals with mpt 210°C and optical rotation $[\alpha]_{589}^{18} = -36.9$ (THF). This gives a corrected yield of 52.2-56.7% which compares with the corrected literature yield of 64-67%, where the yield is corrected to the amount of this enantiomer initially present (50%).

Comparison of yields with the literature suggests that the hydrolysis was not complete as the literature states that 'isolation of binaphthol and diester by crystallisation is substantially more difficult and less efficient from reaction mixtures containing <40 mole % binaphthol. This was possibly due to low cholesterol esterase activity and a cooler room temperature.

Binaphthol

$C_{20}H_{14}O_2$ MW 286

EIMS M^+=286

^{1}H NMR d_6 acetone

ArH (m) 7.905 (7.86-7.95) ArH (d) 7.38 (7.40, 7.36); ArH (d) 7.18; ArH (m) 7.12; ArH (m) 7.08

$CDCl_3$ OH (s) 6.65

^{13}C NMR

ArH 119.38, 123.62, 125.35, 127.02, 128.84, 130.54 ; ArR 114.83, 130.54, 135.40, 154.38

IR

OH stretch, symmetric 3500 cm^{-1}, asymmetric 3400 cm^{-1}, CH stretch, 3050 cm^{-1}, CC aromatic stretch, 1600 and 1625 cm^{-1}

UV

The UV was run as a 6.99×10^{-5} M solution in DCM giving a spectrum from which six peaks were picked.

peak 1 at 353.70nm, abs 0.044, ε = 629; peak 2 at 332.80nm, abs 0.268, ε = 3832;
peak 3 at 319.30nm, abs 0.202, ε = 2888; peak 4 at 289.7nm, abs 0.325,ε = 4647;
peak 5 at 278.10nm, abs 0.352, ε = 5033; peak 6 at 266.9nm, abs 0.319, ε = 4561

(R)-(+)-1,1'-Binaphthyl-2,2'-dipentanoate [1B]

^{1}H NMR $CDCl_3$

ArH (d) 7.81 Δ=0.04447δ = 8.90Hz; ArH (d) 7.74 Δ=0.04076δ = 8.16Hz; ArH (m) 7.27 (7.31-7.23); ArH (d) 7.26 Δ=0.04401 = 8.81Hz; ArH (m) 7.11 (7.16-7.06); CH_2 (t) 1.93 Δ_1=0.03727δ = 7.46Hz, Δ_2=0.03695δ = 7.395Hz; CH_2 (m) 0.99 (1.06-0.92); CH_2 (m) 0.775 (0.90-0.65); CH_3 (t) 0.47 Δ_1=0.03417δ = 6.84Hz, Δ_2=0.03642δ = 7.28Hz

^{13}C NMR

CH_3 13.56; CH_2 21.73, 26.53, 33.76; ArH 121.96, 125.65, 126.18, 126.69, 127.925, 129.395; ArR 123.605, 131.545, 133.67, 146.815, 171.895

IR

showed no sign of hydroxyl groups and showed CH_3, CH_2, CH stretches at ~ 3000 cm^{-1} and C=C vibrations at ~ 1620 and 1600 cm^{-1}.

(R)-(+)-1,1'-Binaphthol

The filtrate from the (S)-(-)binaphthol crystallisation was evaporated to dryness and the resultant liquor taken up into methanol (~500ml). This solution was cooled overnight to give (R)-1,1'-binaphthol-2,2'-dipentanoate in ~90-95g yield, mpt 63.5°C (27.9-29.5% yield) [100% yield of R dipentanoate, from 203g racemate (101.5g R) would be 161.12g, hence 55.9-59% corrected yield].

The recrystallised dipentanoate was then dissolved in dry methanol (1 litre) and sodium methoxide (up to two equivalents) was added, the mixture was then left to stir at room temperature for 4-5 hours. The reaction mixture was then neutralised (pH test papers) using concentrated hydrochloric acid (35%), diluted with 0.1M phosphate buffer (pH 7), and extracted with a 2:1 mixture of diethyl ether and toluene. The organic extract was then washed with one portion of water, one portion of saturated brine and dried over magnesium sulphate before being concentrated (to ~300ml) and cooled overnight (4°C) to crystallise. The crystalline material obtained was filtered and washed with toluene to give 48.5 - 52.9g with mpt 210°C (47.8-52.1% yield from starting binaphthol) and optical rotation $[\alpha]_{589}^{10.5}$= +36.73 (THF).

All of the following reactions were carried out using homochiral starting materials.

Mono-protection of Binaphthol

The first synthesis of mono-protected binaphthol was attempted using the method of Cram et al[86].

Synthesis of 2-Benzhydryloxy-2'-hydroxy-1,1'-binaphthyl [1C]

To a solution of (S)-(-)-Binaphthol (28.03g, 0.098mols) in THF (300ml) was added Potassium-tert-Butoxide (12.15g, 98%, 0.1mols) as a solid, in one portion. The mixture was stirred , under nitrogen, for 15 minutes at ambient temperature. A solution of bromodiphenylmethane (benzhydrylbromide) (27.2g, 0.11mol, 95%) in THF (200ml) was added in one portion and the mixture was then heated at reflux for 27 hours. The mixture was allowed to cool before being evaporated to dryness, under vacuum. The residue was then taken up into DCM (300ml) and washed with two portions of sodium hydroxide (2 × 200ml), one portion of water (200ml) and one portion of saturated brine solution (250ml) before being dried over magnesium sulphate. The DCM solution was then filtered and evaporated to dryness under vacuum to give a dark brown tarry oil. This oil did not crystallise as a solvate of diethyl ether, however slow crystallisation from diethyl ether : 40-60 petroleum ether (~75:25) did give 3.7g (8.2%) yield of crude mono-protected product (binaphthol). A further 2.5g (5.5%) yield of crude mono-protected product was obtained from a chilled mixture of the crude oil in diethyl ether : cyclohexane mixture.

2-Benzhydryloxy-2'-hydroxy-1,1'-binaphthyl [1C]

$C_{33}H_{24}O_2$

M^+=452, fragments 285, 167

^{1}H NMR, d_6 Acetone

Ar_2-C<u>H</u>-OAr (s) 6.53; Ar<u>H</u> (m) 7.10; Ar<u>H</u> (m) 7.47; Ar<u>H</u> (m) 7.80; O<u>H?</u> (s) 3.05

Diethyl ether

C<u>H_2</u> (q) 3.407; C<u>H_3</u> (t) 1.124

^{13}C NMR

$Ar_2\underline{C}HOAr$ 81.69; $\underline{Ar}H$ 117.315, 119.16, 123.483, 124.41, 125.74, 125.86, 126.70, 127.04, 127.32, 127.89, 128.04, 128.75, 128.79, 128.91; $\underline{Ar}R$ 116.44, 120.40, 129.70, 130.02, 130.07, 130.235, 135.25, 142.85, 143.01, 153.81, 154.45

Diethyl Ether

$\underline{C}H_2$ 66.04; $\underline{C}H_3$ 15.57

IR similar to that of binaphthol except now only a single OH stretch ~ 3400 cm^{-1}

Bromodiphenylmethane (Ph_2CHBr) starting material

^1H NMR $CDCl_3$

$C\underline{H}$ (s) 6.37; $Ar\underline{H}$ (m) 7.35, 7.56

Mono protection of (S)-(-)-Binaphthol using Bromodiphenylmethane (other attempts)

A solution of binaphthol in THF (varied dilution from 1.0g per 50ml to 1.0g per 10 ml) was stirred with tBuOK (~1.05-1.1 equivalents) for 30 min under nitrogen. A dilute solution of bromodiphenylmethane (Ph_2CHBr) in THF was then added (~1g per 5ml to ~1g per 30ml) and the mixture was then heated at reflux over night before being allowed to cool and worked up.

These attempts gave mixtures of starting material, mono-protected and di-protected compounds. Small quantities of a highly fluorescent colourless compound were also obtained, which were thought to be degradation compounds of the protection group. This compound was also obtained from the first fractions of the columns that were run in the attempted purifications.

TLC analysis showed;

20% EtOAc, binaphthol R_f=0.235, mono-protected R_f=0.39, Δ=0.155

30% EtOAc, binaphthol R_f=0.425, mono-protected R_f=0.53, Δ= 0.105

Attempts at column chromatography using eluent regimes as above were not successful in purification of the mixtures of products and starting materials. As a result of this, partially impure mono-protected binaphthol was used in subsequent reactions.

Monoprotection of binaphthol using Bromo-Methyl-methoxy ether (BrMOM)

Synthesis of 2-Methoxymethyl-2'-hydroxy-1,1'-binaphthyl [1D]

One of the first attempts at mono-protection using BrMOM gave a worked up solution which when analysed by TLC and IR suggested the presence of a large amount of binaphthol. Investigation into the reasons for why this may have come about revealed that the saturated brine solution was residually acidic. This may have been acidic enough to allow the mono-protected species to deprotect. This may also have caused similar effects in the mono-protection attempts using bromo-diphenylmethane. From this observation reactions were worked up in the same manner as before except that a slightly basified brine solution was used.

To a stirred slurry of potassium-tert-butoxide (2.14g, 98%, 0.017moles) in THF (45ml) under nitrogen, was added a solution of (S)-binaphthol (5.21g, 0.0182moles) in THF (95ml) in one portion. A precipitate was seen to appear and disappear during the course of the addition (precipitation of mono/di salt then dissolution of said salt). The mixture was then left to stir under nitrogen at ambient temperature for twenty-five minutes. A solution of bromo-methyl-methoxy ether (2.43g, 95%, 0.0184moles) in THF (35ml) was then added in one portion and a colourless precipitate formed immediately (potassium bromide). The mixture was then left to stir at ambient temperature for a further three hours to ensure complete reaction. The mixture was then concentrated to dryness under vacuum before being taken up into DCM (150ml). The mixture was then washed with one portion of water (200ml), two portions of saturated sodium carbonate (2 × 150ml), another portion of water and a portion of saturated brine (200ml) before being dried over magnesium sulphate. The organic solution was then filtered and evaporated to dryness under vacuum. The resultant solid would not crystallise from diethyl ether and TLC analysis showed it to be a mixture of binaphthol, mono-protected binaphthol and di-protected binaphthol. (NMR analysis showed a quantitatively unresolved mixture of the said components). No further analysis was done before further purification was attempted. Purification of the mixture was done using column chromatography on silica gel with eluent of 90% DCM : 10% 40-60 Petroleum ether. TLC analysis had shown that one of the best separations of these components was achieved using this solvent system with the diprotected having an R_f value of ~0.61 and the mono-protected having

an R_f value of ~0.47 (Δ R_f = 0.14). This gave an amount of pure, semi pure mono-protected binaphthol and the di-protected species.

After the work up the DCM solutions usually gave thick oils which did not crystallise from diethyl ether and often formed a solid foam under high vacuum. These foams generally appeared as mixtures of the mono- and di-protected species, with various compositions (with ratios ranging from ~40:60 to ~60:40 respectively) from TLC, MS and NMR analysis. As the diprotected species could play no part in base catalysed SN2 reactions, these oil/foams were often used without further purification with the hope that purification of later steps would be far easier due to what should be large differences in physical characteristics.

Mono-protection, higher dilution attempt

To a solution of (S)-(-)-binaphthol (11.36g, 39.72mmol) in THF (~400ml), was added potassium-tert-butoxide (4.54g, 40.53mmol) in THF (~300ml), in one portion. This mixture was left to stir for 20 minutes, under nitrogen at ambient temperature. A solution of bromomethyl methyl ether (4.97g, mmol) in THF (~100ml) was added and the mixture allowed to stir overnight at ~40°C. The mixture was then evaporated to dryness, taken up into DCM and worked up in the usual manner. This gave a solid that formed a crystalline precipitate from diethyl ether. This precipitate was filtered and dried under vacuum to give 6.19g of a colourless solid which was shown to be the desired mono-protected binaphthol, by TLC, MS, mpt (143°C) and NMR analysis. Binaphthol (~1.95g) was reclaimed from acidification of the basic washes. The increase in mono-yield and its crystallisation was probably due to the increase in dilution, however it appears to have been a one off.

2-Methoxymethyl-2'-hydroxy-1,1'-binaphthyl [1D]

EIMS M^+=330

^{1}H NMR $CDCl_3$

Ar<u>H</u> (m)7.93; O<u>C</u>H_2OAr (m) 5.06 (A,A' system, d,d), close unresolved d,d; O<u>C</u>H_3 (s) 3.18

^{13}C NMR

<u>C</u>H_3 56.101; <u>C</u>H_2 94.94; <u>Ar</u>H 117.065, 117.49, 123.26, 124.70, 124.79, 125.08, 126.42, 127.23, 128.04, 128.11, 129.79, 130.90 ; <u>Ar</u>R 129.045, 130.15, 133.9, 153.59

Synthesis of 1,17-Bisbenzhydryl-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-1,6,9,12,17-pentaoxy-heptadecyl-2,4,13,15-tetraene [2A]

Reaction of mono-protected binaphthol with Diethylene glycol ditosylate

To a mixture of crude mono-protected binaphthol (11.01g) in THF (~500ml), was added potassium hydroxide (3.45g) in distilled water (50ml). This mixture was heated at reflux for one hour, under nitrogen before a solution of diethylene glycol-ditosylate (9.56g, moles) in THF (~100ml) was added in one portion. This mixture was heated at reflux for a further 65 hours before being allowed to cool and worked up. The worked up mixture was purified further by column chromatography on silica gel, using ethyl acetate : petroleum ether as eluent. The first fraction appeared to be a decomposition product of the protecting group. This product was also obtained from purification attempts of the mono-protected binaphthol. Its ^{13}C NMR spectrum showed 7 signals, 6 tertiary and one quaternary, its mass spec. showed a M^+=167, =Ph_2CH fragment. Possibly a dimer or is an anion with counter-ion.

1,17-Bis-benzhydryl ether [2A]

MW 947, not seen in EIMS, fragment too heavy for mass spectrometer used.

Ph_2CH fragment seen, M^+=167

no $TsOCH_2CH_2OCH_2CH_2OTs$ fragments seen

^1H NMR

ArH (m) 7.89, ArH (m) 7.67, ArH (m) 7.31, ArH (m) 7.25, ArH (m) 7.0; CH (s) 6.18; CH_2 (m) 3.845 (3.92-3.77); CH_2 (m/t) 3.465 (3.49-3.44); CH_2 (m/t) 3.24 (3.26-3.22); CH_2 (m) 2.78 (2.89-2.67)

^{13}C NMR

OCH_2 68.52, 69.77 (69.335); OCH 82.15; ArH 114.855, 116.88, 123.825, 125.565, 125.83, 126.42, 126.53, 126.63, 127.40, 127.51, 127.88, 127.99, 128.25, 128.50, 129.00, 129.54, 129.79; ArR 120.215, 121.35, 129.28, 129.46, 134.23, 141.76, 144.67, 154.15, 153.26

Synthesis of 1,17-Bis(methoxymethyl)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-1,6,9,12,17-pentaoxy-heptadecyl-2,4,13,15-tetraene

To a solution of the mono-protected binaphthol (6.03g, 18.27mmol, FW330) in THF (~700ml), under nitrogen, was added a solution of potassium hydroxide (2.04g, 36.43mmol) in water (~60ml). This solution was left to stir for 20 minutes before diethylene glycol ditosylate (5.07g, 12.25mmol, FW414) was added in one portion as a solid. The mixture was then heated at reflux overnight, for ~18 hours, before being allowed to cool and evaporated to dryness under vacuum to give a solid. This was taken up into DCM (~250ml) and washed with water (2 × 200ml), saturated sodium carbonate solution (2 × 200ml) and saturated brine (250ml) before being dried over magnesium sulphate. The DCM solution was then evaporated to dryness to give an oil which was shown to be a mixture by TLC. This mixture was further purified by column chromatography, on neutral alumina, using a graduated mixture of ethyl acetate : 40-60 petroleum ether.

Mixtures of the mono- and di-protected species were also used in an attempt to synthesis the desired compound.

$C_{48}H_{42}O_7$ MW 730

EIMS M^+=730 (3.0%), 731 (2.0%)

^{1}H NMR $CDCl_3$

ArH (m) 7.76 (7.85-7.67); ArH (m) 7.48 (7.30-7.09); OCH_2O (m) 4.91; CH_2 (m/d) 3.91; CH_2 (m/d) 3.67; CH_2 (m/t) 3.60; CH_2 (m/t) 3.28; CH_2 (m) 2.98 (3.01-2.95); CH_3 (s) 3.03

Synthesis of 1,15-Dihydroxy-4,8,11-trioxa-1,2:3,4:12,13:14,15-tetra(1,2-naphtho)-pentadeca-1,3,12,14-tetraene [2B]

A general method of deprotection was used for the removal of the acid sensitive protecting groups employed in these syntheses.

The protected compound was taken up into THF/propanol or other suitable solvent with hydrochloric acid (~15%) and stirred overnight at ambient temperature. The mixture was then evaporated to near dryness and taken up into DCM. The DCM solution was then washed twice with saturated sodium carbonate, then water then saturated brine before being dried over magnesium sulphate. The DCM solution was then filtered and

evaporated to dryness under high vacuum. The mixture was analysed by IR for the presence of OH stretches, TLC for the presence of protected and partially deprotected compound and by EIMS.

$C_{44}H_{34}O_5$ MW=642

EIMS M^+= 642 (10.9%), 643 (6.3%) [^{13}C / M^++H]

Synthesis of N-Tosyl-4,9,12,15,20-pentaoxy5,6:7,8:16,17:18,19-tetra(1,2-naphtho)-docosa-5,7,16,18-tetraene (Attempted) [2D]

To a stirred mixture of compound 2B (2.7g, 4.2mmol, 1.015equiv., 642MW) and bis(2-tosyloxyethyl)-N-tosylamine (2.42g, 4.27mmol, 567MW) [diethanolamine-tritosylate] in THF (~70ml) was added potassium hydroxide (0.93g, 16.9mmol, 4equiv.) in water (~8ml). This mixture was then refluxed overnight for ~16 hours before being allowed to cool and concentrated to ~20ml. Dichloromethane (50ml) was then added and the resulting mixture was washed with sodium hydroxide (2 × 40ml, 2M), water (50ml) and saturated brine (40ml) before being evaporated to dryness under vacuum. TLC analysis showed a number of compounds including the starting material. Purification was attempted using column chromatography on silica gel, however the desired product was not unequivocally isolated.

This reaction was attempted several times whilst varying the kind and amount of base[10.4mmol diol with 7.83g 13.8mmol, 1.3equiv. tritosylate with 1.55g KOH (in ~20ml water)], the length of reaction and with starting material of varied quality. The desired product was shown to be present (by EIMS) on a number of occasions, however it was always elusive in purification attempts by fractional crystallisation and column chromatography. A number of other compounds were isolated in varying purity from these purification attempts.

$C_{55}H_{47}NO_7S$ MW 865

EIMS M^+=865 (7.7%)

Other attempts gave results including;

A: EIMS M^+=865 (2.0%)

B: EIMS M^+=711 (0.4%), possibly Bis(binaphtho)-22-crown-6

C: EIMS M^+=356 (100%), 357 (25.9%), this may be a cyclic 1:1 binaphthol : C_4H_8O adduct, peak at 509 (0.8%) seen, however no Ts peak at 155

^{1}H NMR $CDCl_3$

Ar<u>H</u> (d) 7.965 Δ=0.04488δ = 8.98Hz; Ar<u>H</u> (d) 7.875 Δ=0.03846δ = 7.70Hz; Ar<u>H</u> (d) 7.40 Δ=0.0453 = 9.06Hz; Ar<u>H</u> (m) 7.27 (7.36-7.18); Ar<u>H</u> (d) 7.135 Δ=6.56x10^{-3}δ = 1.31Hz; Ar<u>H</u> (d) 7.09 Δ=2.66x10^{-3}δ = 0.5Hz; C<u>H</u>$_2$ (d,d) 4.535 Δ=0.01095δ = 2.19Hz, Δ=0.03126δ = 6.25Hz, 4.50 Δ=0.01131δ = 2.26Hz; C<u>H</u>$_2$ (d,d) 4.47 Δ=0.01062δ = 2.125Hz, Δ=0.0316δ = 6.325Hz, 4.40 Δ=0.01064δ = 2.13Hz; C<u>H</u>$_2$ (d,d) 4.255 Δ=0.01105δ = 2.21Hz, Δ=0.02668δ = 5.34Hz, 4.225 Δ=0.01095δ = 2.19Hz; C<u>H</u>$_2$ (d,d) 4.19 Δ=0.01146δ = 2.29Hz, Δ=0.02613δ = 5.23Hz, 4.165 Δ=0.01098δ = 2.20Hz; C<u>H</u>$_2$ (m,d) 3.695 (3.80-3.59)

^{13}C NMR

O<u>C</u>H$_2$ 70.08, 71.45; <u>Ar</u>H 115.85, 123.74, 125.435, 126.515, 127.97, 129.30; <u>Ar</u>R 120.74, 129.35, 134.315, 153.585

D: EIMS No peak at 865, however peak at 509 (41.7%), 510 (14.7%) which may be a cyclic 1:1 binaphthol : C_4H_8NTs product

Microanalysis	C	H	N	
(Theory)	73.1	5.3	2.7	for cyclic 1:1 binaphthol:C_4H_8NTs
(Theory)	76.30	5.43	1.62	for what wanted - M^+=865
Result	72.57	5.76	1.87	

^{1}H NMR $CDCl_3$

Ar<u>H</u> (d,d) 7.96 Δ=0.01227δ = 2.45Hz, Δ=0.045δ = 9.00Hz, 7.915Δ=0.01245δ = 2.49Hz; Ar<u>H</u> (d) 7.855 Δ=0.03963δ = 7.93Hz; Tosyl Ar<u>H</u> (d,d) 7.64 Δ0.04134δ = 8.27Hz, Δ=0.32018δ = 64.08Hz, 7.32 Δ=0.04234δ = 8.47; Ar<u>H</u> (d) 7.38 Δ=0.04531δ = 9.0Hz; Ar<u>H</u> (m) 7.20 (7.32-7.08); C<u>H</u>$_2$ (m) 4.575 (4.59-4.56); C<u>H</u>$_2$ (m) 4.45 (4.50-4.40); C<u>H</u>$_2$ (m) 4.165 (4.22-4.11); C<u>H</u>$_2$ (m) 3.57 (3.74-3.40); C<u>H</u>$_2$ (m) 3.225 (2.275-2.175); C<u>H</u>$_3$ (s) 2.385

^{13}C NMR

Ts<u>C</u>H$_3$ 21.46; N<u>C</u>H$_2$ 2.02; H$_2$ 9.89, 70.04, 71.41; H 13.725, 115.88, 123.53, 123.71, 125.425, 125.53, 126.50, 127.165, 127.165, 127.975, 128.08, 129.10, 129.28, 129.425, 129.853; <u>Ar</u>R 119.34, 120.91, 133.96, 134.31, 135.51, 143.73, 152.87, 153.615

The integration ratio for ArH to CH_2 is correct, however the integration for ArH, CH_2 to CH_3 is suspiciously low. This may be a mixture of mono adducts [1:1 Binaphthyl : Ditosylate ($TsOCH_2CH_2OCH_2CH_2OTs$ and $TsOCH_2CH_2NTsCH_2CH_2OTs$)].

E: $C_{48}H_{40}O_6$ MW=712 Bis(binaphtho)-22-crown-6 [2C]

EIMS M^+=712 (6.8%), 713 (3.4%), 714 (1.1%), Tosyl fragment seen M^+=155

Accurate EIMS does not show M^+ anywhere near 712, however it was probably not capable of determining accurate masses this high.

Microanalysis	C	H
Theory	80.9	5.7
Result	74.19	5.32

^{1}H NMR $CDCl_3$

ArH (m) 7.925 (two doublets, with impurity); ArH (m) 7.1-7.4; CH_2OAr (dm) 4.46, 4.19; CH_2OR (bm) 3.70 (dm close together)

^{13}C NMR

CH_2O 70.07, 71.43; ArH 115.89, 123.75, 125.47, 126.51, 127.99, 129.31; ArR 120.78, 134.36, 153.63

NMR spectrum impure with other ether signals, most likely non cyclic precursors of the product

Synthesis of 2-(2'-chloroethoxy)ethyl-2''tetrahydropyranyl ether [3A]

The synthesis of 2-(2'-chloroethoxy)ethyl-2''tetrahydropyranyl ether was carried out using the method given by Cram et al[87].

To a stirred mixture of 2-(2'-chloroethoxy)ethanol (25.12g, 0.202moles) and 2,3-dihydropyran (23.1g, 0.275moles) under nitrogen, was added one drop of concentrated hydrochloric acid (35%). The mixture was stirred at ambient temperature for one hour before being basified to approximately pH 7.0 with tribenzylamine. The mixture was then distilled under vacuum (lit. bpt 87-88°C at 0.5mm) to give 41.5g of a clear liquid (99% yield), from which a small amount of solid dropped out upon standing for a day. This left 40.3g of a clear liquid (96% yield) which appeared to be pure by NMR analysis (at least 95%+) and did not contain any characteristic hydroxyl peaks of the starting alcohol.

$C_9H_{17}ClO_3$ MW 163.5

EIMS M^+=163 (36.4%), 165 (11.2%)

^{1}H NMR $CDCl_3$

$C\underline{H}_2$ (m) 3.495 (3.565-3.425); $CH/C\underline{H}_2$ (m) 3.375 (3.425-3.325); $C\underline{H}_2$ (m) 1.48 (1.55-1.41); $C\underline{H}_2$ (m) 1.27 (1.37-1.17)

Synthesis of 2,2'-Bis(5-tetrahydropyranyl-ether-3-oxa-1-oxy-pentyl)-1,1'-binaphthyl [3B]

The synthesis of 2-(2'-oxaethoxy)ethyl-2''tetrahydropyranyl ether-1,1'-binaphthyl was attempted using several methods all based on Cram et al[86].

A solution of (R)-(+)-binaphthol (5.00g, 17.5mmol) in n-butanol (~90ml) was refluxed with sodium hydroxide (1.77g, 44.25mmol) under nitrogen, for one hour. A solution of 2-(2'-chloroethoxy)ethyl-2''tetrahydropyranyl ether (10.01g, 48mmol) in n-butanol (5ml) was then added in one portion and the mixture refluxed for 19 hours. A further portion of the chloro-ether (5g, 24mmol) was then added with sodium hydroxide (0.5g, 12.5mmol) and the mixture refluxed for a further 7 hours. A final portion of the chloro-ether (2g, 9.59mmol) and sodium hydroxide (0.2g, 5mmol) was then added and the mixture was refluxed for a further 11 hours. The mixture was allowed to cool before being filtered. The filtrate was not purified any further before the alcohol was deprotected.

$C_{38}H_{46}O_8$ MW 630

EIMS M^+=630 (3.9%), M^++H=631 (1.7%)

Fragments M^+-protecting group, M^+-2 × protecting group

^{1}H NMR $CDCl_3$

Ar$\underline{H}$ (d) 7.90 (7.923, 7.878); Ar$\underline{H}$ (d) 7.825 (7.84, 7.81); Ar$\underline{H}$ (d) 7.32 (7.34, 7.30); Ar$\underline{H}$ (m) 7.245 (7.31-7.18); Ar$\underline{H}$ (m) 7.10; Ar$\underline{H}$ (m) 7.06; C$\underline{H}$ (s) 4.58; $C\underline{H}_2$ (m) 3.81 (3.87-3.75); $C\underline{H}_2$ (m) 3.595 (3.74-3.45); $C\underline{H}_2$ (m) 1.80 (1.86-1.74); $C\underline{H}_2$ (m) 1.57 (1.71-1.43)

^{13}C NMR

protecting $\underline{C}H_2$ 19.37, 25.325, 30.46, 42.64; protecting $\underline{C}H$ 98.865; $O\underline{C}H_2$ 62.13, 66.55, 70.53, 71.255; $\underline{Ar}H$ 117.875, 123.72, 124.27, 127.14, 128.22, 130.965; $\underline{Ar}R$ 129.27, 133.545, 152.70

Synthesis of 2,2'-Bis(5-hydroxy-3-oxa-1-pentyloxy)-1,1'-binaphthyl [3C]

Deprotection of 2-(2'-oxaethoxy)ethyl-2''tetrahydropyranyl ether-1,1'-binaphthyl

The deprotection was carried out by acidification of the above filtrate with hydrochloric acid (~10%) and refluxing for 1-2 hours. The mixture was allowed to cool before being evaporated to dryness to give a dark oil which contained a mixture of products and starting materials amongst other things. This mixture was placed in a warm bath (~70-80°C) under a high vacuum in an attempt to take off starting alcohol, which has a bpt of 79-81°C @ 5mm. An alternative deprotection method that may be used is that of Bier and Mundy[88], using activated ion exchange resins.

The synthesis of 2,2'-bis(5-hydroxy-3oxa-1-pentyloxy)-1,1'-binaphthyl was also carried out directly in a reaction between binaphthol and 2-(2-chloroethoxy)ethanol.

(S)-Binaphthol (5.0g, 17.48mmol), potassium carbonate (25g, 181mmol, 10.34equiv., MW138) and 2-chloroethoxy ethanol (6.0g, 48.2mmol, 2.75equiv.) in THF (~180ml) was held at reflux overnight for 16 hours during which time the reaction mixture turned green. TLC analysis showed several spots including a large amount of binaphthol starting material. The mixture was held at reflux for a further 10 days during which time further portions of 2-chloroethoxy ethanol were added (3g, 24mmol, 1.37equiv. in total). The final analysis by TLC showed little binaphthol and a large amount of what was thought to be the desired di-armed product (from comparison with authentic), some mono-armed product and some polymer or degradation product.

This mixture was purified by column chromatography on silica gel using a gradient of THF starting from 40% going up to 75%. This gave 300mgs of the pure di-armed product from 1g of the crude mixture. The desired di-armed binaphthyl had an R_f value of 0.41 using 75% THF : petrol as eluent, also an R_f of 0.053 using 40% THF.

This reaction was attempted several times whilst varying the kind and amount of base, the reaction length and the work up procedure.

$C_{28}H_{30}O_6$ MW 462

EIMS M^+=462 (6.0%), M^++H=463 (1.8%)

Calculated exact mass, M=462.204238

EIMS Accurate mass M^+=462.2028

^{1}H NMR $CDCl_3$

ArH (d) 7.93 (7.949, 7.904); ArH (d) 7.84 (7.86, 7.82); ArH (d) 7.407 (7.43, 7.385); ArH (m) 7.255 (7.35-7.16); ArH (m) 7.12; CH_2 (d,m) 4.125, 4.015 (4.16-4.09, 4.07-3.96); CH_2 (m) 3.73 (3.76-3.70); CH_2 (m) 3.425 (3.50-3.35); CH_2 (m) 3.14 (3.16-3.12); OH (bs) 2.88

^{13}C NMR

OCH_2 61.40, 69.45, 69.76, 72.41; ArH 115.87, 123.39, 125.39, 126.33, 127.91, 129.39; ArR 120.50, 129.535, 134.02, 154.26

Synthesis of Dinaphtho[2,1-b:2',3'-d]furan-8,13-(8H,13H)-dione [3E]

A small amount of this naphthofuranoquinone was serendipitously obtained in low yield (10's of milligrams) from the reaction of 2-(2'-chloroethoxy)ethyl-2''tetrahydropyranyl ether with (R)-1,1'-binaphthol, following exactly the method of Cram et al. Where the deprotection was carried out at high temperature (~150 °C) under vacuum in the presence of pyridine hydrochloride acting as the acid catalyst. The structure of this compound was elucidated using x-ray crystallography.

This compound has previously been synthesised by Ishikawa et al.[89] in order to help in the characterisation of organic pollutants released from coal and to asses their health effects. It was synthesised by the condensation of phenols with2,3-dichloro-1,4-naphthoquinone in pyridine.

$C_{20}H_{10}O_3$ MW 298

^{1}H NMR $CDCl_3$

ArH (d/m) 9.68 (9.70, 9.66); ArH (d of m) 8.285, 8.21 (8.31-8.26, 8.23-8.19); ArH (t/m) 7.94 (7.98, 7.94, 7.90); ArH (m) 7.35 (7.77-7.70); ArH (s) 7.19

Synthesis of 2,2'-Bis(5-chloro-3-oxa-1-pentyloxy)-1,1'-binaphthyl [3F]

To a solution of the diol [3C] (~5g, 0.011moles) in toluene (100ml), under nitrogen, was added thionyl chloride (10ml) and the mixture was heated, at 75°C, for 26 hours. The mixture was allowed to cool and poured onto ice-water (~150g), to destroy any excess thionyl chloride. The toluene solution was then washed with water (100ml), then with saturated brine solution (100ml) before being dried over magnesium sulphate. The

toluene solution was then evaporated to dryness under high vacuum to give a light brown oil (bis(2-chloroethyl)ether has a boiling point of 65.67°C @ 15mmHg). This oil was purified by column chromatography, on neutral alumina, using a gradient of ethyl acetate : 40-60 petroleum ether as eluent. The dichloro- product had an R_f value of 0.27 using 30% EtOAc : Petrol.

$C_{28}H_{28}Cl_2O_4$ MW 499

EIMS M^+=498 (52.7%), 500 (39.6%), 502 (11.4%)

M^++H=499 (39.1%), 501 (25.8%)

^{1}H NMR $CDCl_3$

ArH (d) 7.96 (7.98, 7.94); ArH (d) 7.88 (7.90, 7.86); ArH (d) 7.435 (7.46, 7.41); ArH (m) 7.34 (7.39-7.29); ArH (m) 7.225 (7.25-7.20); CH_2 (m) 4.125 (4.21-4.04); CH_2 (t) 3.50; CH_2 (m) 3.13

^{13}C NMR

$ClCH_2$ 42.875; OCH_2 69.56, 69.975, 71.15; ArH 115.42, 123.82, 125.43, 126.41, 127.92, 129.41; ArR 120.41, 134.41, 154.13, 154.18

Synthesis of 2,3:4,5:14,15:16,17-Tetra(1,2-naphtho)-8,9,10,11:20,21,22,23-di(1,4-phenyl)-1,6,13,18-tetraoxy-tetraicosaheteraphane [4A]

1st Attempt

A slurry of (R)-binaphthol (2.01g, 7.03 mmol) and potassium carbonate (3.7g, 26.8mmol, ~4 equivalents) in butan-1-ol (~250ml) was refluxed under nitrogen for 30minutes. This visibly gave a bright yellow colour possibly due to the formation of the phenoxide ion (potassium counter-ion). A solution of α,α'-dibromo-p-xylene (4.01g, 15.2mmol, 2.16 equiv.) in butan-1-ol (~20ml) was then added in one portion to the refluxing mixture. The yellow phenoxide colour was noted to depreciate rapidly, with an equivalent rate of formation of a white precipitate assumed to be KBr. The solution was refluxed for another hour, until the yellow colouration was no longer visible, after which it was filtered and worked up. Typically the reaction mixture was evaporated under vacuum to dryness before being taken up into dichloromethane (~100-150ml). The DCM solution was then washed with portions (~100ml) of dilute acid, water and

saturated brine, dried over magnesium sulphate and evaporated to dryness under vacuum. The resulting mixture gave three main spots by TLC corresponding to unreacted binaphthol, a binaphthol-xylene-butanol adduct and a xylene-butanol adduct. The mixture was purified by column chromatography, using a silica column packing with an elution system of 20% ethyl acetate : petrol (40/60) and a dry-column flash chromatography type method.

The major product obtained by chromatography was 2,2'-bis(α'-oxybutyl-α-oxy-p-xylyl)-1,1'-binaphthyl

$C_{44}H_{46}O_4$ MW 638

^{1}H NMR $CDCl_3$

ArH (t) 7.79 (7.835, 7.79, 7.745); ArH (d) 7.302 (7.325, 7.28); ArH (m) 7.22 (7.25-7.19); ArH (d) 7.11 (7.12, 7.10); xylyl α ArH (d) 6.978 (6.998, 6.958) Δ=0.04018δ = 8.04Hz; xylyl β ArH (d) 6.834 (6.854, 6.814) Δ=0.03974δ = 7.95Hz, Δ α/β = 0.1039δ = 20.79Hz; $ArCH_2$ (s) 4.93; $ArCH_2$ (s) 4.28; OCH_2 (t) 3.305 (3.34, 3.305, 3.27); CH_2 (m) 1.47 (1.54-1.40); CH_2 (m) 1.305 (1.36-1.25); CH_2 (m) 1.165 (1.21-1.12)

^{13}C NMR

CH_3 13.94; CH_2 19.35, 31.80; OCH_2 70.15, 70.94, 72.545; ArH 115.97, 123.69, 125.53, 126.28, 126.75, 127.44, 127.88, 129.24; ArR 120.70, 129.415, 134.145, 136.78, 137.71, 154.05

2nd Attempt

(R)-Binaphthol (2.07g, 7.24 mmol) was refluxed for 30minutes under nitrogen in THF (~150ml) with potassium-tert-butoxide (1.695g, 15.1mmol, 2.09equivalents). A solution of α,α'-dibromo-p-xylene (2.17g, 8.22 mmol) in THF (~60ml) was added to this mixture in one portion and the reaction mixture was refluxed overnight. This gave a bright yellow (fluorescent) precipitate and solution. The solution was filtered evaporated to dryness, taking the resultant solid up into DCM (~60ml). The DCM solution was then washed with portions (~70ml) of dilute (~2M) sodium hydroxide solution, water and saturated brine, finally drying over magnesium sulphate before being evaporated to dryness.

TLC of the crude mixture (using 20% EtOAc) gave three main spots R_f 0.23 (dibromoxylene), 0.14 (probably binaphthol) and the baseline (which upon further investigation was seen to contain more than one product that were THF elutable). Attempts at purifying the mixture by fractional crystallisation were unsuccessful.

Crude mixture of oligomers

^{1}H NMR $CDCl_3$

ArH (m) 7.86 (7.91-7.81); ArH (m) 7.252 (7.31-7.195); ArH (m) 6.655 (6.84-6.47); CH_2 4 distinct peaks; (d,d) 4.485 (4.97, 4.00) dimer; CH_2 (d) 4.915 (4.92, 4.91) trimer; CH_2 (s) 4.84 tetramer ?; 4.73 (4.74-4.72) higher oligomer or polymer

^{13}C NMR

This shows a broad CH_2 peak at 70.69 (more than one type) and the other signals are also broad or split.

3rd Attempt

A solution of (S)-binaphthol (0.5g, 1.75mmol) in THF (~100ml), was refluxed under nitrogen for 30min, with potassium carbonate (0.91g, 6.59mmol, ~1:8 ratio binaphthol : carbonate). A solution of α,α'-dibromo-p-xylene (0.923g, 3.496mmol, ~2equivalents) in THF (20ml) was added to this mixture and the reaction was allowed to reflux for a further 1-2 hours. A further portion of binaphthol (0.50g, 1.75mmol) was then added in THF (~40ml) and the mixture allowed to continue at reflux overnight. The reaction was allowed to cool and was worked in a typical manner. The resultant colourless solid was shown, by TLC (THF : petrol eluent), to be a mixture of products. This mixture was purified by dry column flash chromatography using a 20% THF : petrol(40/60) eluent. This method was not very successful, however it did give an amount of pure di-oligomer, pure tri-oligomer and a mixture of what was thought to be higher oligomers.

Further purification of the higher oligomers was not undertaken as they were present in very small quantities and they were not thought to be of great interest to the specific goal of this project.

Di-oligomer [4A]

$C_{56}H_{40}O_4$ MW 776

EIMS M^+=776 (30.4%), M^++H=777 (17.8%) or M^+ with 1 ^{13}C

FAB (LSIMS) MS M^+=776, M^++H=777, M^++Na=799, M^++K=815, peak max. = 776

Element	C	H
Theory	86.59	5.15
Result	86.56	5.16

UV

The UV was run as a 2.01×10^{-5} M solution in DCM giving a spectrum from which five peaks were picked.

peak 1 at 337.40nm, abs 0.319, ε = 15870; peak 2 at 324.20nm, abs 0.278, ε = 13830; peak 3 at 293.90nm, abs 0.437, ε = 21741; peak 4 at 282.70nm, abs 0.506, ε = 25174; peak 5 at 272.30nm, abs 0.487, ε = 24228

Optical rotation for (S) was $[\alpha]_{589}^{15}$ = -132.7 (THF)

^1H NMR $CDCl_3$

ArH (d) 7.87 (7.88, 7.86); ArH (d) 7.837 (7.84, 7.815); ArH (m) 7.33 (7.38-7.28); ArH (s) 7.235; ArH (d) 7.197 (7.205, 7.19); ArH (s) 7.16; xylyl ArH (s) 6.69; CH_2 (d,d) 4.985 (5.02, 4.95) Δ=0.06394δ = 12.79Hz, (4.92, 4.86) Δ=0.06375δ = 12.76Hz, Δ α/β = 0.0289 = 5.78 Hz

^{13}C NMR

CH_2 70.80; ArH 115.885, 123.58, 125.395, 126.29, 126.64, 127.94, 129.125; ArR 120.29, 129.305, 134.14, 136.48, 154.135

Di-oligomer [4A] from other isolation

^1H NMR $CDCl_3$

ArH (s) 7.875; ArH (d) 7.84 (7.85, 7.83); ArH (m) 7.32 (7.37-7.27); ArH (m) 7.24 (7.25-7.23); ArH (d) 7.19 (7.20, 7.18); ArH (s) 7.14; xylyl ArH (s) 6.69; CH_2 (d,d) 5.007 (5.04, 4.975) Δ=0.06356δ = 12.72Hz, 4.907 (4.94, 4.875) Δ=0.06347δ = 12.70Hz, Δ d/d = 0.03282δ = 6.57Hz

^{13}C NMR

O<u>C</u>H_2 70.86; <u>Ar</u>H 115.94, 123.555, 125.38, 126.245, 126.66, 127.88, 129.075; <u>Ar</u>R 120.355, 129.29, 134.11, 136.475, 154.11 - expect to see 7 <u>Ar</u>H and 5 <u>Ar</u>R

IR

No OH stretches, CH, CH_2 stretch at 3066, 3015, 2940 and 2877 cm^{-1}, C=C stretch at 1631, 1596

A 2-Dimensional NMR spectrum (proton-carbon) was recorded of the para-heteraphane dimer, which gave the following results:

Carbon at shift (ppm)	corresponds to	Proton at shift (ppm)	
Binaphthyl			
ArH	115.95	7.227	(m)
ArH	123.6	7.338	(m)
ArH	125.35	7.17	(d)
ArH	126.2	7.235	(m)
ArH	128.9	7.87	(d)
ArH	129.1	7.85	(d)
Xylyl			
ArH	126.6	6.69	(s)
CH_2	70.9	4.92, 4.99	(d,d)

Tri-oligomer [4B] 2,3:4,5:14,15:26,27:28,29-Hexa(1,2-naphtho)-8,9,10,11:20,21,22,23:32,33,34,35-tri(1,4-phenyl)-1,6,13,18,25,30-hexaoxy-hexatriaconta-heteraphane

$C_{84}H_{60}O_6$ MW 1092

EIMS does not go high enough however does show peaks up to 776

FAB (LSIMS) MS M^+=1165 ($1^{13}C$), M^++H= 1166, M^++ Na = 1188

(mpt below 172)

^{1}H NMR $CDCl_3$

ArH (s) 7.895; ArH (s) 7.87; ArH (m) 7.307 (7.38-7.245); ArH (s) 7.215; ArH (s) 7.21; ArH (s) 7.175; xylyl ArH (s) 6.735; CH_2 (d,d) 4.927 (4.96, 4.895) Δ=0.06543δ = 13.10Hz, 4.84 (4.88, 4.82) Δ=0.06531δ = 13.07Hz

^{13}C NMR

OCH_2 70.72; ArH 115.88, 123.66, 125.44, 126.39, 126.685, 127.885, 129.175; ArR 120.53, 129.33, 134.16, 136.64, 154.02

Tri-oligomer [4B], other isolation

^{1}H NMR $CDCl_3$ Far weaker solution than above

ArH (s) 7.855; ArH (s) 7.81; ArH (m) 7.257 (7.34-7.175); ArH (d) 7.262 (7.27, 7.255); ArH (d) 7.217 (7.225, 7.21); xylyl ArH (s) 6.075; CH_2 (s) 4.86

The oligomeric products would only form a microcrystalline solid, all attempts at co-crystallising the dimer with electron deficient aromatic species such as nitrobenzene, dinitrobenzene, dinitrophenol and homochiral N-(3,5-dinitrobenzoyl)-α-methylbenzylamine were also unsuccessful, yielding a similar microcrystalline solid.

Attempted synthesis of p-heteraphane dimer molybdenum tricarbonyl complex

This reaction was done in an attempt at synthesising a crystalline derivative that would be suitable for X-ray crystallography. A solution of the heteraphane dimer was refluxed in DCM with molybdenum hexacarbonyl (~1.07 equiv.), with a nitrogen flushed vent, for ten days. A sample of this solution was taken and its infra-red spectrum recorded. The solution was then flushed through with nitrogen before being evaporated to dryness under slightly reduced pressure. A sample of the resultant solid was taken up into $CDCl_3$ under nitrogen and its NMR spectrum recorded.

^{1}H NMR $CDCl_3$

ArH (d) 7.885; ArH (d) 7.84; ArH (d) 7.385; ArH (t) 7.35; ArH (d) 7.315; ArH (d) 7.285; ArH (s) 7.24; ArH (m) 7.23; xylyl ArH (s) 6.69; CH_2 (d,d) 5.00 Δ=0.06387δ = 12.78Hz, 4.91 Δ=0.06361δ = 12.73Hz

^{13}C NMR

O<u>C</u>H_2 70.86; <u>Ar</u>H 115.93, 123.575, 125.395, 126.27, 126.66, 127.91, 129.11; <u>Ar</u>R 120.34, 129.30, 134.13, 136.49, 154.125

IR

Looking at the carbonyl region there is a single dominating peak at 1980 cm^{-1}, this correspond to the asymmetric stretch of $Mo(CO)_6$. There is possibly a very slight shoulder on this peak at 2015 cm^{-1} which has an accompanying peak at 2050 cm^{-1}, these are very definitely overwhelmed by the starting material.

This reaction was attempted once more using a much more reactive molybdenum compound, $Mo(CO)_3(MeCN)_3$. The reaction was left refluxing for 14 days, under nitrogen, before being evaporated to dryness. The NMR spectrum of this solid was also identical to the starting dimer.

NMR experiment involving p-heteraphane dimer with a single enantiomer chiral shift reagent, N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine

In an attempt to establish whether or not the heteraphane dimer would interact, enantiospecifically or otherwise, with an electron deficient guest, the dimer was taken up into $CDCl_3$ and aliquots of N-(3,5-dinitrobenzoyl)-α-methylbenzylamine (DNP) were added and the mixture's NMR spectrum taken. Each mixture was thoroughly mixed and left to stand for at least an hour before their NMR spectra were recorded. The final mixtures were also rerun after being allowed to sit for one week.

4A sample pre-addition of guest

A representative NMR spectrum of the heteraphane dimer was taken as a reference and purity test before the dimer sample was split in two and mixed with (L) and (D)-N-(3,5-dinitrobenzoyl)-α-methylbenzylamine respectively.

^{1}H NMR $CDCl_3$

Ar<u>H</u> (s) 7.88; Ar<u>H</u> (d) 7.84 Δ=0.01389δ = 2.80Hz; Ar<u>H</u> (m) 7.32 (7.37-7.27); Ar<u>H</u> (m) 7.20 (7.25-7.15); xylyl Ar<u>H</u> (s) 6.69; C<u>H_2</u> (d,d) 5.00 Δ=0.06365δ = 12.74Hz, Δ=0.03354δ = 6.71Hz, 4.91 Δ=0.06351δ = 12.71Hz

^{13}C NMR

O<u>C</u>H_2 70.88; <u>Ar</u>H 115.95, 123.56, 125.385, 126.245, 126.67, 127.88, 129.08; <u>Ar</u>R 120.38, 129.305, 134.93, 136.48, 154.11

4A with (D)-N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine [7B] (ratio 1:1)

^{1}H NMR $CDCl_3$

Dimer

Ar<u>H</u> (s) 7.875; Ar<u>H</u> (d) 7.835 Δ=0.01432δ = 2.865Hz; Ar<u>H</u> (m) 7.325 (7.38-7.27); Ar<u>H</u> (m) 7.195 (7.25-7.14); xylyl Ar<u>H</u> (s) 6.685; C<u>H_2</u> (d,d) 5.005 Δ=0.06357δ = 12.72Hz, Δ=0.03324δ = 6.65Hz, 4.907 Δ=0.06344δ = 12.695Hz

DNP [7B]

Ar<u>H</u> (t) 9.13; Ar<u>H</u> (d) 8.97; C<u>H</u> (m) 5.335 Δ = ~7Hz; [Δ_1 =0.03509δ = 7.02Hz, Δ_2 =0.03587δ = 7.18Hz, Δ_3 =0.03599δ = 7.20Hz, Δ_4 =0.03516δ = 7.04Hz] C<u>H</u> (m) is possibly a d of q (quintets); C<u>H_3</u> (d) 1.66 Δ=0.03457δ = 6.92Hz

^{13}C NMR

Dimer [4A]

O<u>C</u>H_2 70.88; <u>Ar</u>H 115.97, 123.565, 125.38, 126.25, 126.685, 127.89, 129.085; <u>Ar</u>R 120.38, 129.305, 134.133, 136.47, 154.11

DNP [7B]

<u>C</u>H_3 21.37; <u>C</u>H 50.28; <u>Ar</u>H 121.02, 126.30, 127.18; <u>Ar</u>R 128.90, 137.78, 141.92, 148.52, 161.855

4A with (L)-N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine [7B[(ratio 1:0.75)

^{1}H NMR $CDCl_3$

Dimer [4A]

Ar<u>H</u> (s) 7.875; Ar<u>H</u> (d) 7.837 Δ=0.01454δ = 2.9Hz; Ar<u>H</u> (m) 7.33 (7.39-7.27); Ar<u>H</u> (m) 7.195 (7.25-7.14); xylyl Ar<u>H</u> (s) 6.685; C<u>H_2</u> (d,d) 5.005 Δ=0.06361δ =12.73Hz, Δ=0.03343δ =6.69Hz, 4.91 Δ=0.06347δ =12.70Hz

DNP [7B]

ArH (t) 9.14; ArH (d) 8.97; CH (t) 5.34 Δ_1=0.03569δ = 7.14Hz, Δ_2=0.03599δ = 7.20Hz; CH_3 (d) 1.665 Δ=0.03358δ = 6.72Hz

Lower concentrations of each enantiomer of N-(3,5-dinitrobenzoyl)-α-methylbenzylamine were also used and their respective NMR spectra also showed no apparent shifts.

Synthesis of 2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10:19,20,21-di(1,3-benzyl)-1,6,12,17-tetraoxy-docosa-heteraphane [4C]

(S)-Binaphthol (0.50g, 1.75mmol) in THF (~30ml) was refluxed under nitrogen with oven dried potassium carbonate (2.3g, 16.66mmol, 9.5equivalents) for 30min. A solution of α,α'-dibromo-meta-xylene in THF (~10ml) was then added and the reaction allowed to reflux for 1-2 hours. A second portion of (S)-binaphthol (0.51g, 1.78mmol) was then added and the mixture continued to reflux overnight. The mixture was left to cool and worked up to give a mixture of products as a colourless solid, similar to the analogous para-compound, plus a very small amount of what was thought to be monomer.

The mixture was purified by column chromatography with gradient elution using THF : Petrol 40/60, which gave an amount of pure dimer some pure trimer and some more impure products which are thought to possibly contain higher oligomers, but have not been investigated further.

Monomer

$C_{28}H_{20}O_2$ MW 388

Only a small amount of the monomer was obtained, which was impure with eluent residue. The THF used in the column eluent gave very good separation however it tended to give residues which were not very volatile, no matter how rigorously purified beforehand.

^{1}H NMR $CDCl_3$

ArH (d) 7.80 (7.82, 7.78); ArH (d) 7.72 (7.74, 7.70); ArH (d) 7.3475 (7.37, 7.325); ArH (m) 7.24; ArH (m) 7.17; ArH (m) 6.85; CH_2 (d,d) 5.20 (5.23, 5.17) Δ=0.06224δ = 12.45Hz, 4.98 (5.01, 4.95) Δ=0.06250δ = 12.50Hz, Δ d/d = 0.15490δ = 31.00Hz

Di-oligomer [4C]

$C_{56}H_{40}O_4$ MW 776

EIMS M^+=776

FAB (LSIMS) MS M^+=776, M^++H=777, M^++Na=799

Electrospray MS M^+=776, M^++Na=799, M^++K=815

No higher oligomers were found

Microanalysis	C	H
Theory	86.56	5.16
Results	86.59	5.15

UV

The UV was run as a 1.75×10^{-5} M solution in DCM giving a spectrum from which five peaks were picked.

peak 1 at 360.60nm, abs 0.043, ε = 2457; peak 2 at 336.8nm, abs 0.261, ε = 14914; peak 3 at 326.50nm, abs 0.239, ε = 13657; peak 4 at 282.60nm, abs 0.440, ε = 25142; peak 5 at 273.00nm, abs 0.417, ε = 23828

Optical rotation of (S) was $[\alpha]_{589}^{15}$ = -126.45 (THF)

^{1}H NMR $CDCl_3$

ArH (d) 7.973 (7.995, 7.95); ArH (d) 7.92 (7.94, 7.90); ArH (m) 7.30 (7.40-7.20); ArH (m) 6.855 (6.91-6.80); ArH (d) 6.697 (6.715, 6.68); ArH (s) 6.52; CH_2 (d,d) 4.76 (4.79, 4.73) Δ=0.06203δ = 12.41Hz, 4.63 (4.66, 4.60) Δ=0.07032δ = 12.39Hz, Δ d/d = 0.07032δ = 14.07Hz

^{13}C NMR

O<u>C</u>H_2 71.31; <u>Ar</u>H 116.41, 123.795, 125.48, 125.58, 125.815, 126.35, 127.86, 129.23; <u>Ar</u>R 121.06, 129.49, 134.17, 137.46, 154.30

^{1}H NMR d_6-benzene

Ar<u>H</u> (d) 7.81 (7.82, 7.80); Ar<u>H</u> (d) 7.77 (7.78, 7.76); Ar<u>H</u> (d) 7.317 (7.338, 7.297); Ar<u>H</u> (m) 7.21 (7.25-7.17); Ar<u>H</u> (m) 7.09 (7.13-7.05); Ar<u>H</u> (m) 6.61 (6.72-6.50); C<u>H_2</u> (d,d) 4.58 (4.61, 4.55) Δ=0.06181δ = 12.37Hz, 4.50 (4.53, 4.47) Δ=0.06229δ = 12.47Hz, Δ d/d = 0.029311δ = 5.865Hz

Tri-oligomer [4D] 2,3:4,5:13,14:15,16:24,25:26,27-Hexa(1,2-naphtho)-8,9,10:19,20,21:30,31,32-tri(1.3-phenyl)-1,6,12,17,23,28-hexaoxy-tristriaconta-heteraphane

$C_{84}H_{60}O_6$ MW 1164

EIMS does not go high enough however do see peaks up to 776

FAB (LSIMS) MS M^++H=1165 (or M^+ with 1 ^{13}C), M^++Na=1187/1188

No higher oligomers were found

^{1}H NMR $CDCl_3$

Ar<u>H</u> (d) 7.875 (7.895, 7.855); Ar<u>H</u> (m) 7.35 (7.39-7.31); Ar<u>H</u> (m) 7.22 (7.25-7.19); Ar<u>H</u> (s) 6.71; Ar<u>H</u> (m) 6.64 (6.66-6.62); Ar<u>H</u> (s) 6.38; C<u>H_2</u> (s) 4.60

^{13}C NMR

O<u>C</u>H_2 70.72; <u>Ar</u>H 115.92, 123.72, 124.95, 125.455, 126.35, 127.875, 129.16; <u>Ar</u>R 120.70, 129.37, 134.145, 137.23, 154.045

Tetra-oligomer

$C_{112}H_{80}O_8$ MW 1552

^{1}H NMR $CDCl_3$

Ar<u>H</u> (d) 7.82 (7.84, 7.80); Ar<u>H</u> (d) 7.765 (7.77, 7.76); Ar<u>H</u> (m) 7.21 (7.19-7.08); Ar<u>H</u> (m) 7.17 (7.19-7.15); Ar<u>H</u> (m) 6.555 (6.59-6.52); Ar<u>H</u> (s) 6.26; C<u>H_2</u> (s) 4.49

Synthesis of 2,2'-Bis(α'-bromo-α-oxy-para-xylyl)-1,1'-binaphthyl [5A]

Crude reclaimed (R)-binaphthol (1.025g, 3.58mmol) was refluxed with potassium carbonate (2.46g, 17.8mmol) under nitrogen for ~1hr in a mixture of THF (~50ml) and acetonitrile (~25ml, in an attempt to increase the solubility of the di-phenolate salt). α,α'-Dibromo-p-xylene (2.01g, 7.61mmol) was then added in one portion and this mixture was refluxed overnight. The mixture was allowed to cool and worked up in a typical manner. It was shown (by TLC) to contain many products, however, it was also shown to contain the target compound by mass spectrometry. The mixture was not purified further as the mixture appeared to be very difficult to separate (using TLC).

EIMS M^+=650, 652, 654

2nd Attempt

(R)-Binaphthol (1.01g, 3.53mmol) in THF (~100ml) was very slowly (over 1-2hrs) added to a solution of 60% sodium hydride (0.41g, 10.25mmol) and α,α'-dibromo-p-xylene, refluxing in dry THF (~150ml) under nitrogen. The mixture was refluxed for ~15hrs, allowed to cool and worked up to give a white solid. The majority of the excess α,α'-dibromo-p-xylene was fractionally crystallised out and the remaining mixture was purified using gravimetric column chromatography on silica using 30% THF : petrol 40/60. This gave the sought after dibromo-binaphthyl compound in 47% yield (1.09g) as a white powder after purification.

TLC analysis showed several spots using 30% THF eluent with the stating material dibromo compound with R_f 0.74, the dibromo product with R_f 0.40 (main product), trace binaphthol with R_f 0.36 and traces of other products.

Other synthesis for DiBr used binaphthol (3.1g, 10.8mmol), α,α'-dibromo-p-xylene (27.5g, 104.16mmol, 9.64equiv.), sodium hydride (1.22g, 60%, 30.5mmol, 2.82equiv.) in ~500ml THF. R_f 0.61 10%THF/EtOAc v similar

$C_{34}H_{28}Br_2O_2$ MW 652

EIMS M^+=650 (1.3%), 652 (2.8%), 654 (1.5%)

also see fragments for M^+-bromoxylene, no DiBr starting material fragments were seen

Microanalysis	C	H
Theory	66.46	4.34
Result	66.52	4.345

^{1}H NMR $CDCl_3$

ArH (t/d,d)7.94 (7.99, 7.94, 7.89); ArH (d) 7.42 (7.44, 7.40); ArH (m) 7.38 (7.415-7.35); xylyl α ArH (d) 7.105 (7.125, 7.085) Δ=0.04071δ = 8.14 Hz; xylyl β ArH (d) 6.905 (6.925, 6.885) Δ=0.04055δ = 8.12 Hz; Δ α/β = 0.15909δ = 31.84 Hz; CH_2 (t) 5.035 (5.10, 5.035, 4.97); CH_2 (s) 4.39

^{13}C NMR

$BrCH_2$ 33.39; OCH_2 70.63; ArH 115.79, 123.84, 125.49, 126.43, 127.02, 127.955, 128.86, 129.395; ArR 120.68, 129.47, 134.15, 136.72, 137.855, 153.905

Isolation from other synthesis

^{1}H NMR $CDCl_3$

ArH (d/m) 7.94 (7.96, 7.92); ArH (d/m) 7.88 (7.90, 7.86); ArH (m) 7.40 (7.42-7.38); ArH (m) 7.23 (7.27-7.19); xylene ArH (d,d) 7.08, 6.88 (7.105, 7.065; 6.90, 6.86) (AA'BB'); OCH_2 (t) 5.02 (AA'); $BrCH_2$ (s) 4.38

Synthesis of 1,6,13,16,19,22,25-Heptaoxy-2,3:4,5-di(1,2-naphtho)-8,11,27,30-di(1,4-benzyl)-hentriaconta-heteraphane [5B]

To a stirred solution of 2,2'-bis(α'-bromo-α-oxy-p-xylyl)-1,1'binaphthyl (0.25g, 0.38mmol) in THF (90ml) with sodium hydride (0.043g, 60%, 1.075mmol, 2.83equiv.) was added tetra-ethylene glycol (0.076g, 0.39mmol, 1.03equiv.). The mixture was then heated at reflux overnight for 14 hours, allowed to cool and evaporated to dryness under vacuum. TLC analysis using 30% THF : petrol showed two spots one with R_f 0.05 and the other on the baseline (just above). This mixture was purified by column chromatography on silica gel using an increasing gradient of THF.

Monomer [5B]

$C_{44}H_{44}O_7$ MW 684

EIMS M^+=684 (7.2%), M+H=685 (3.4%)

FAB (LSIMS) M+H=685 (or M^+ with 1 ^{13}C), M+Na=707

Also see a trace at 860 which is possibly due to G051+NOBA+Na = 684+153+23=860

Also a trace at 883, possibly due to G051+NOBA+2xNa = 684+153+2x23 = 883

UV

The UV was run as a 2.485×10^{-5} M solution in DCM giving a spectrum from which three peaks were picked.

peak 1 at 337.00nm, abs 0.219, ε = 8812.9; peak 2 at 324.50m, abs 0.211, ε = 8490.9 peak 3 at 280.70nm, abs 0.468, ε = 18832

^1H NMR $CDCl_3$

ArH (t) 7.89 (7.935, 7.89, 7.845); ArH (d) 7.367 (7.39, 7.345); ArH (m) 7.315 (7.37-7.26); ArH (d) 7.225 (7.215, 7.235); xylyl α ArH (d) 7.03 (7.05, 7.01) Δ=0.04172δ = 8.35Hz; xylyl β ArH (d) 6.965 (6.985, 9.945) Δ=0.04164 = 8.33Hz, Δ α/β = 0.02327 = 4.66Hz; $ArOCH_2Ar$ (d,d) 5.067 (5.10, 5.035) Δ=0.0648δ = 12.98Hz, 4.47 (5.00, 4.94) Δ=0.06479δ = 12.97Hz; $ArCH_2$ (t) 4.45 (4.51, 4.45, 4.39) Δ_1=0.06203δ = 12.41Hz Δ_2=0.06161δ = 12.33Hz; OCH_2 (s/m) 3.68; OCH_2 (m) 3.56 (3.58-3.54)

^{13}C NMR

OCH_2 69.50, 70.655, 70.71, 70.84, 72.925; ArH 115.80, 123.635, 125.40, 126.305, 126.59, 127.535, 127.89, 129.23; ArR 120.485, 129.335, 134.20, 136.90, 137.30, 154.015

Di-oligomer

$C_{88}H_{88}O_{14}$ MW 1368

EIMS does not go high enough, however do see peaks up to ½ size of M (684)

FAB (LSIMS) M+Na=1392 M^+=1368 (1369 if 1 C^{13})

Also see a trace at 1568 which is possibly due to G052 + NOBA + Na +Na = 1368 (1369) + 153 +23 +23 = 1568 (1569)

^{1}H NMR $CDCl_3$

ArH (t) 7.795 (7.84, 7.795, 7.75); ArH (d) 7.29 (7.31, 7.27); ArH (m) 7.245 (7.285-7.205); ArH (s) 7.186; ArH (m) 7.13 (7.14-7.12); xylyl α ArH (d) 6.969 (6.989, 6.949) Δ0.04035δ = 8.075Hz; xylyl β ArH (d) 6.827 (6.847, 6.807) Δ=0.04044δ =8.09Hz, Δ α/β = 0.10199 = 20.41Hz; $ArOCH_2Ar$ (s) 4.91; $ROCH_2Ar$ (s) 4.33; OCH_2 (s) 3.535; OCH_2 (m) 3.47 (3.52-3.425)

^{13}C NMR weak

OCH_2 69.33, 70.57, 70.86, 72.84; ArH 125.45, 126.25, 126.64, 127.50, 127.84

Synthesis of 2,2'-Bis(α'-N-triazacyclononane-α-oxy-p-xylyl)-1,1'binaphthyl [5C]

To a solution of capped TACN (triazacyclononane-N,N,N-monomethylamide) (106.6mg, 0.767mmol) in acetonitrile/THF solution (~2:1) was added dropwise, over 30 minutes, a solution of 2,2'-bis-(α-oxy-α'-bromo-p-xylene)-1,1'-binaphthyl (250mg, 0.383mmol) in THF/acetonitrile mixture (~2:1). The mixture was allowed to stir overnight (~14 hours) at room temperature during which time a colourless precipitate dropped out. The mixture was filtered and the filter cake washed with two portions of THF/acetonitrile mixture (~1:1), before being dried under suction.

The precipitate was not purified further before being decapped. The precipitate was refluxed with sodium hydroxide solution (100ml, 2M) overnight (~14 hours). The reaction mixture was then allowed to cool before being extracted with three portions of chloroform (3x100ml). The combined organics were then washed with water before being evaporated to dryness to give a solid which foamed under high vacuum.

(capped TACN FW 139, DiBr FW 652)

$C_{48}H_{56}N_6O_2$ MW 748

EIMS M^+=748 not seen, M^+ - TACN = 620 seen, no starting dibromide seen

^{1}H NMR $CDCl_3$

ArH (d) 7.915 (7.94, 7.89); ArH (d) 7.81 (7.84, 7.78); ArH (d) 7.405 (7.43, 7.38); ArH (m) 7.27; ArH (m) 7.22 (7.25-7.19); xylene ArH (d,d) 7.04, 6.89 (7.06-7.02; 6.91-6.87)

(AA'BB'); OC$\underline{H}_2$ (s) 5.00; ArC$\underline{H}_2$N (s) 3.58; C$\underline{H}_2$N (s) 2.74; C$\underline{H}_2$N (m) 2.555 (2.57-2.54); N$\underline{H}$ (bs) 2.34

^{13}C NMR too weak

Synthesis of 1,8,15,22-tetra-aza-29,34-dioxy-10, 13:24, 27:36, 39-tri(1,4-phenyl)-1, 8:15, 22-N,N,N,N-di(4,4'-bipyridinium)-30,31:32,33-di(1,2-naphtho)-tetraconta-heteraphane Tetrakis-hexafluorophosphate [5D]

A solution of 2,2'-bis-(α-oxy-α'-bromo-p-xylene)-1,1'-binaphthyl (200mg, 0.307mmol, MW 652), 1,1'-[1,4-phenylene-bis(methylene)]-bis-4,4'-bipyridinium bis-hexafluorophosphate (217.2mg, 0.3076mmol, MW 416+290=706) and 1,4-bis-8-(di-t-butyl)-methylsilyl-3,6-dioxy-1-oxa)-benzene in acetonitrile (100ml) was stirred at ambient temperature for one week, during which time a light brown precipitate dropped out. The reaction mixture was filtered and the filter cake washed with three portions of chloroform (50ml) [to remove any residual template] and dried under suction. The dried precipitate (398mg, 95.5% yield, MW1358) was analysed by NMR, which appeared to show two compounds, presumably mono- and di- oligomeric products. The precipitate was purified by column chromatography on silica gel using a methanol, ammonium chloride (2.11M), nitromethane (7:2:1) eluent. The collected fractions were analysed by TLC using the same eluent and the pure fractions were combined and carefully evaporated to dryness using a high vacuum oil pump and a warm water bath (~35°C). The solid was then taken up into water and the product precipitated out by the addition of potassium hexafluorophosphate. The precipitate was then filtered off and dried under high vacuum.

The mono-adduct product had an R_f value of 0.245 in the said eluent. The assumed di-adduct product had an R_f value of 0.1091. There was also an amount of unknown compound seen to be left on the baseline, possibly a polymeric or decomposition compound. There was no sign of either of the starting materials by TLC and NMR analysis.

Attempts at crystallising the mono-adduct from acetone water mixture resulted in its apparent decomposition.

The reaction was also carried out using the same conditions except without the use of a template. This resulted in very similar quantities of initial precipitate which gave a slightly smaller amount of the purified mono-product.

Product MW 1358 as di Br, di PF_6, MW 1488 as tetraPF_6

Crude 5D - Tetra PF_6

^{1}H NMR d_6 DMSO

pyridinium ArH (m) 9.45; pyridinium ArH (m) 8.71; ArH (m) 8.05; ArH (s) 7.715; ArH (s) 7.65; ArH (m) 7.435; ArH (m) 7.28; ArH (m) 7.085; ArH (m) 7.02; CH_2 (s) 5.96; CH_2 (s) 5.85; CH_2 (s) 5.20

Impurities

pyridinium ArH (m) 9.365 and 8.915; ArH (m) 7.80; ArH (m) 7.36

^{13}C NMR

CH_2 63.05, 63.055, 69.367; ArH 115.477, 122.07, 123.74, 126.03, 126.55, 127.31, 127.58, 128.17, 128.99, 129.50, 129.88, 145.72, 145.86 ; ArR 119.35, 133.26, 133.46, 135.33, 138.95, 149.27, 149.49, 151.13, 153.54

5D, expect to see 13 equivalent ArH and 9 equivalent ArR

Purified 5D

$C_{64}H_{52}N_4O_2.PF_6$ MW 908 + 580 = 1488

FAB Mass Spec. (LSIMS) NOBA matrix

M^++H 1489, M^++H-PF_6 1344, M^++H-2PF_6 1199

^{1}H NMR d_6-DMSO

pyr.α ArH (m) 9.53 (9.57-9.49); pyr.β ArH (m) 8.72 (8.77-8.67); ArH (m) 8.045 (8.12-7.97); ArH (d/m) 7.76 (7.77, 7.75); ArH (d/m) 7.67 (7.69, 7.65); ArH (d/m) 7.475 (7.49, 7.46); ArH (d/m) 7.37 (7.39, 7.35); ArH (t/m) 7.275; ArH (d) 7.09 (7.11, 7.07); ArH (d) 6.99 (7.01, 6.97)

^{1}H NMR d_6-Acetone

pyr.α ArH (m) 9.16 (9.19-9.13); pyr.β ArH (m) 8.61; ArH (m) 7.88 (8.08-7.68); ArH (m) 7.225 (7.44-7.01); CH_2 (s) 6.03 and 5.86; CH_2 (t) 5.17 (5.24, 5.17, 5.10); H_2O 3.96

Acetone 2.25

^{1}H NMR CD_3CN @ 313K

pyr.α ArH (m) 8.21; pyr.β ArH (m) 7.85; ArH (s) 7.41 and 7.37; ArH (m) 7.26; ArH (s) 6.96 and 6.91; ArH (m) 6.625 (6.72-6.53); ArH (m) 6.41 (6.43-6.39); CH_2 (s) 5.15 and 5.00; CH_2 (d,d) 4.43

^{13}C NMR

CH_2 65.98, 72.09; ArH 117.56, 125.66, 126.44, 128.44, 128.99, 129.07, 129.38, 130.98, 131.29, 132.29, 146.91; ArR 133.69, 135.47, 136.46, 141.25, 151.705, 155.735

(5D) Di-oligomer

$C_{128}H_{104}N_8O_4 \cdot 8PF_6$ MW 1816 + 1160 = 2978

FAB MS, (LSIMS) very weak sample which gave weak ions to 2978 M^+ in an NOBA matrix.

^{1}H NMR d_6-DMSO, very weak sample

pyr.α ArH (m) 9.475 (9.51-9.44); pyr.β ArH (m) 8.95 (8.97-8.93); ArH (m) 8.59 (8.70-8.48); ArH (m) 8.165 (8.22-8.11); ArH (m) 7.84 (7.86-7.82); ArH (m) 7.655 (7.675-7.635); CH_2 (s) 6.28, 6.05, 5.72

also two large broad peaks at 8.53 and 3.49 ppm, water and NH_4

^{1}H NMR unknown solvent

pyr.α ArH (m) 8.25; pyr.β ArH (m) 7.695; ArH (m) 7.34, 6.925, 6.565, 6.40; CH_2 (s) 5.21, 5.04, 4.46

peak @ 1.3 d-solvent

Synthesis of 2,3:4,5-Di(1,2-naphtho)-8,9,10-(1,8-naphthyl)-1,6-dioxy-undeco-heteraphane [6A]

Reaction of 2,2'-Dihydroxy-1,1'-binapthalene with α,α'-Bis-1,8-(bromomethyl)-naphthalene

To a stirred solution of (R)-binaphthol (0.452g, 1.58 mmol) in THF (50ml) was added potassium tert-butoxide (0.345g, 3.08 mmol, 1.95 equiv.). The mixture was warmed to

40°C for 30 minutes before being evaporated to dryness under vacuum to give a bright yellow solid (presumably bis-potassium dinaphthoxide). A solution of α,α'-bis-1,8-(bromomethyl)-naphthalene (1.0g, 3.18mmol in 10ml THF) was added to this solid in one portion. The mixture was then heated to reflux for one and a half hours until the yellow colouration had all but disappeared. The mixture was allowed to cool from reflux before potassium carbonate (1.81g, 13.1mmol) and (R)-binaphthol (0.465g, 1.63mmol) were added, the mixture was then heated at reflux, under nitrogen, overnight (~14hours) before being allowed to cool and evaporated to dryness under vacuum. This solid was then taken up into dichloromethane and stirred with water (~150ml) until all of the inorganics had dissolved (~30minutes). The mixture was then separated and the dichloromethane solution washed sequentially with one portion of water (100ml) and one potion of saturated brine solution (100ml) before being dried over magnesium sulphate. This solution was then filtered and evaporated to dryness to give a slightly yellow solid, which was seen to be a mixture by TLC. Purification was attempted using column chromatography, on silica gel, (with a 20% THF : petrol 40/60 eluent and 75ml fractions - main spots came off very quickly) which afforded a small quantity (~0.1g) of the bis(bromomethyl)-naphthalene starting material and a larger, slightly impure, quantity of what was later shown to be the monomeric adduct, which was recrystallised from diethyl-ether.

Fraction 8

EIMS showed no sign of anything higher than M^+=438

The FAB MS, LSIMS spectrum of powdered fraction from column (Fraction 8) was not possible to obtain as the sample formed a solid mass when mixed with NOBA matrix and introduced into a vacuum.

^{1}H NMR $CDCl_3$

ArH (s) 7.85; ArH (s) 7.81; ArH (bs/m) 7.76; ArH (t/m) 7.43 (7.47, 7.43, 7.39); ArH (m) 7.225 (7.26-7.19); CH_2 (vbd) 5.83, 5.65 (5.74)

^{13}C NMR

broad CH_2 72.88, 76.03; ArH 123.92, 125.10, 126.35, 128.12, 131.76, 133.89; ArR 119.45, 136.23, 132.00

F8 sample diluted by ~75%

^{1}H NMR $CDCl_3$

ArH (s) 7.79; ArH (s) 7.75; ArH (t) 7.38 (7.42, 7.38, 7.34); ArH (s) 7.16; ArH (bs) 7.04; CH_2 (bs) 5.735

Starting DiBr material, ^{1}H NMR $CDCl_3$ CH_2 (s) 5.19ppm, ^{13}C NMR CH_2 37.26ppm

Fraction 20

^{1}H NMR ($CDCl_3$) spectrum was quite dirty with eluent impurities, however it did appear to contain an amount of what may have been higher oligomer. Attempts at further purification were unsuccessful.

^{1}H NMR $CDCl_3$

ArH (m) 7.675 (7.81-7.54); ArH (m)7.27 (7.34-7.20); ArH (m) 7.07 (7.19-6.95); CH_2 (m/A,A') 5.49 (5.50, 5.48)

Recrystallised mono-oligomer (F8)

$C_{32}H_{22}O_2$ MW 438

EIMS M=438 (25.8%), no starting di-bromo compound seen, no Br compounds seen.

Microanalysis	C	H
Theory	87.67	5.02
Result	87.65	5.12

^{1}H NMR $CDCl_3$, of single crystal chip

ArH (d) 7.88; ArH (bs) 7.84; ArH (m) 7.83; ArH (t) 7.47 (7.51, 7.47, 7.43); ArH (s) 7.25 ($CDCl_3$?); ArH (m) 7.255; ArH (bs) 7.15; CH_2 (vbs) 5.80

^{13}C NMR too weak

Synthesis of 1,17-Bis(methoxymethyl)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho)-7,8,9-(1,8-naphthyl)-1,6,12,17-tetraoxy-heptadecane [6B]

Reaction of 2-hydroxy-2'-methoxymethyl-1,1'-binapthyl with α,α'-bis-1,8-(bromomethyl)-naphthalene

To a stirred slurry of sodium hydride (60% dispersion in mineral oil, 0.45g, 11.25mmol) in THF (45ml), under nitrogen, was added dropwise, a solution of the 2-hydroxy-2'-methoxymethyl-1,1'-binapthyl (1.073g, 3.25mmol) compound, in THF (50ml). Hydrogen gas was evolved and the mixture was left to stir for 25 minutes under nitrogen at ambient temperature. The mixture was noted to turn bright yellow, possibly due to phenoxide ion association complexes being formed or due to impurities. Bis-1,8-(bromomethyl)naphthalene (0.512g, 1.63mmol) was then added to the mixture in one portion as a solution in THF (30ml). The reaction mixture was then heated to mild reflux and left overnight for about 19 hours at this temperature.

The reaction mixture lost its colour during this time and an amount of white precipitate (sodium bromide) dropped out of solution. Analysis by TLC on silica plates showed that only a trace amount of the mono-hydroxy compound was left. The excess sodium hydride was then destroyed by careful addition of methanol (~10ml) then water (~3ml). The resultant mixture was concentrated under vacuum to give a thick oil which was taken up into DCM and washed sequentially with 1 portion of sodium hydroxide (2M, 100ml), water (~100ml), saturated brine (~100ml) before being dried over magnesium sulphate. The DCM solution was then filtered and the filtrate concentrated under vacuum to give a solid glass which formed a foam under high vacuum (1-5 mm Hg). This glass/foam was not purified any further before being used in the next stage - the deprotection of the naphthol.

Synthesis of 1,15-Dihydroxy-5,10-dioxy-1,2:3,4:12,13:14,15-tetra(1,2-naphtho)-7,8,9-(1,8-naphthyl)-pentadecane [6C]

Deprotection of Bis-binaphthyl-methyl-naphthalene compound [6B]

A general deprotection method was used to deprotect the methoxy methyl ethers to form the desired naphthol compound.

A few drops of concentrated hydrochloric acid (35%) were added to a stirred solution of the bis-binaphthyl-methylnaphthalene compound in propan-2-ol, THF 1:1 mixture. The mixture was left stirring for 16 hours at room temperature (13-18 ^{0}C) before being concentrated under vacuum to give a thick oil, wet with solvent. This oil was then taken up into dichloromethane and washed sequentially with one portion of 0.1 molar hydrochloric acid, two portions of 2M sodium hydroxide, one portion of water, one portion of saturated brine before being dried over magnesium sulphate. the dichloromethane solution was then filtered and concentrated under vacuum to give a solid glass. This material was purified by column chromatography on silica gel, using 90-95% DCM with 40-60 petroleum ether, to give 0.70g of product diol, 61% yield from the starting mono-protected binaphthol.

$C_{52}H_{36}O_4$ MW 724

EIMS M^+=724 (0.1%, Real peak, persistent over 10 scans)

M^+-binaphthol seen, 438, no bromine compounds seen

FAB MS M^+=724, M^++Na=747

Electrospray MS M^+=724 (723.5), M^++Na=747 (747.5), M^++K=763 (763.5)

also see peaks at; 1471.9 which could be for 2M + Na (with $1^{13}C$ / H^+)

1487.9 which could be for 2M + K (with 1 ^{13}C / H^+)

CI MS, with negative ionisation M=724, M+K=763

Microanalysis	C	H
Theory	86.19	4.97
Result	81.33	4.87

^{1}H NMR $CDCl_3$

Ar<u>H</u> (m) 7.87 (7.91-7.84) Ar<u>H</u> (m) 7.72 (7.75-7.68); Ar<u>H</u> (m) 7.54; Ar<u>H</u> (m) 7.28 (7.35-7.21); Ar<u>H</u> (m) 7.04 (7.13-6.95); Ar<u>H</u> (d) 6.79 (6.81, 6.77); C<u>H</u>$_2$ (t/d,d) 5.04 (5.11, 5.04, 4.97); O<u>H</u> (s) 4.59 (disappears with D_2O)

^{13}C NMR

O<u>C</u>H_2 72.07; <u>Ar</u>H 117.21, 117.295, 123.05, 124.335, 124.44, 124.747, 125.114, 126.125, 127.06, 127.75, 128.08, 129.47, 130.59, 131.49; <u>Ar</u>R 115.21, 117.88, 128.77, 129.75, 131.35, 133.61, 133.88, 135.28, 151.06, 154.312

Synthesis of 2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10:19,20,21-bis(1,8-naphthyl)-1,6,12,17-tetraoxy-docosa-heteraphane [6D]

Reaction of α,α'-Bis(2-oxy-2'-hydroxy-1,1'-binapthyl)-1,8-dimethyl naphthalene [6C] with 1,8-Bis(bromomethyl) naphthalene

To a stirred slurry of sodium hydride (0.07g, 60%, 17.5mmol) in THF (50ml) was added dropwise, a solution of the bis-binaphthyl-methylnaphthalene compound (0.30g, 0.414mmol), in THF (72ml), under nitrogen. The mixture was warmed to 45°C and left to stir for 20 minutes, to fully deprotonate the naphthol. A solution of α,α',-1,8-bis(bromomethyl)-naphthalene (0.133g, 0.4235mmol) in THF (60ml), was then added in one portion. The mixture was heated at reflux for 21 hours before being allowed to cool to room temperature after which the excess sodium hydride was destroyed by the careful addition of methanol then water. The reaction mixture was then evaporated to dryness under vacuum and taken up into DCM (~35ml). The DCM was then washed with one portion of sodium hydroxide (2M, ~30ml), two portions of water (2 × 30ml) and one portion of saturated brine (~40ml) before being dried over magnesium sulphate. The DCM solution was then filtered and evaporated to dryness under vacuum to give a light yellow glass. This material appeared to run very close to, yet always slightly in front of, the starting diol by TLC analysis. The glass was further purified by column chromatography on silica gel, using 95-100% chloroform, with petroleum ether, as eluent. This gave 0.278g of what appeared, by NMR analysis, to be slightly impure starting diol. This recovered starting material was then used in a second reaction with α,α'-1,8-bis(bromomethyl)-naphthalene, in a further attempt at cyclisation.

Second Cyclisation Attempt

The recovered bis-binaphthol starting material was made up to 0.315g (0.387mmol) with pure compound and added, under nitrogen to a stirred solution of potassium hydroxide in water/THF mixture (7ml:95ml). This mixture was then heated at reflux for 98 hours,

during which time it was monitored by TLC, which showed that the reaction did not appear to proceed. A small amount of colourless precipitate dropped out of solution during the course of the reaction, it was collected and shown to be sparingly soluble in water, DCM, $CDCl_3$ and acetone. This was thought to be hydrolysed 1,8-bis-(bromomethyl)-naphthalene or a hydrolysed polymeric product of this starting material. The reaction mixture was allowed to cool and worked up in a similar manner to that used previously to give the starting bis-binaphthyl compound. The reaction was analysed by NMR and TLC analysis, which proved that the reaction had not proceeded. Almost all of the starting bis-binaphthyl compound was recovered slightly impure.

^1H NMR $CDCl_3$

ArH (m) 7.87; ArH (m) 7.70; ArH (m) 7.54; ArH (m) 7.35; ArH (m) 7.27; ArH (m) 6.996; ArH (d) 6.77; CH_2 (d,d) 5.07, 4.98 (AA'); OH (s) 4.53 (disappears with addition of D_2O)

^{13}C NMR

OCH_2 72.05; ArH 117.21, 117.25, 123.02, 124.31, 124.42, 124.72, 125.09, 126.09, 127.03, 127.714, 128.045, 129.43, 130.54, 121.47; ArR 115.07, 117.85, 128.74, 129.72, 131.265, 131.325, 133.57, 133.84, 135.27, 151.02, 154.29

Synthesis of 1,20-Bis(methoxymethyl)-2,3:4,5:16,17:18,19-tetra(1,2-naphtho)-1,6,12,15,20-hexaoxy-icosa-2,4,16,18-tetraene [2E]

A mixture of 2-(methoxymethyl)-2'-hydroxy-1,1'-binaphthol (3.0g, 9.09mmol) and sodium hydride (0.44g, 60%, 11mmol, 1.21equiv.) was heated at reflux in THF (70ml) under nitrogen for ½ an hour. 1,2-bis(2-chloroethoxy)ethane (0.98g, 5.24mmol, 0.576equiv.) was added to this mixture which was held at reflux for a further 36 hours. Analysis by TLC showed an amount of starting naphthol that had not yet reacted. A further portion of 1,2-bis(2-chloroethoxy)ethane (0.6g, 3.2mmol, 0.35equiv.) was added with sodium hydride (0.175g, 60%, 4.37mmol, 0.48equiv.) and the mixture held at reflux for 16 more hours. The mixture was allowed to cool before being evaporated to dryness and taken up into DCM 80ml). The DCM solution was then washed with water (~80ml), sodium hydroxide (2 × 70ml, 2M), saturated brine (~70ml), dried over magnesium sulphate and evaporated to dryness to give a thick oil, which was slightly yellow in colour. This oil was purified by column chromatography on silica gel using a

30% THF : petrol eluent which gave 1.0g of the desired product (28.4% yield after purification). This product formed a glass when evaporated to dryness, which 'foamed' under high vacuum and had a melting point below 90°C. The desired product had an R_f of 0.189 using this solvent system, the 1:1 adduct with single binaphthyl unit and chloro arm had an R_f value of 0.435. There was also a small amount of the starting naphthol recovered.

The NMR spectrum of the 1:1 adduct appears clean however as the molecule is non symmetric and chiral it appears complex.

The deprotection step was carried out as standard, where the protected compound was taken up into THF/propanol mixture and stirred with hydrochloric acid (15%) overnight before being evaporated to dryness, taken up into DCM and washed and dried.

An alternative deprotection method that is used for the deprotection of tetrahydro-pyranyl ethers[88] may be employed in the deprotection of these acetals.

$C_{50}H_{46}O_8$ MW 774

EIMS M^+=774

^{1}H NMR $CDCl_3$

ArH (m) 7.78-7.96; ArH (d) 7.53; ArH (d) 7.42; ArH (bm) 7.30-7.15; OCH_2O (A,A', d,d) 4.94, 5.06; OCH_2R (bm) 3.97, 4.09; RCH_2O (t) 3.34; OCH_3 (s) 3.15; OCH_2 (t) 2.83

^{13}C NMR

OCH_3 55.79; OCH_2 69.35, 69.50, 70.25, 95.245; ArH 115.63, 117.34, 123.70, 123.94, 125.41, 125.55, 126.18, 126.295, 127.78, 127.85, 129.35; ArR (120.28, 121.39)?, 129.82, 133.99, 152.70, 154.23

Mono-arm precursor to 1,21-above

$C_{28}H_{29}ClO_5$ MW 480.5

EIMS M^+=480 (19.4%), 482 (7.6%)

^{1}H NMR $CDCl_3$

ArH (m) 7.84-7.98; ArH (d) 7.56; ArH (d) 7.43; ArH (m) 7.16-7.35; CH_2 (A,A', d,d) 5.07, 4.97; OCH_2 (bm) 4.10; OCH_2 (m) 3.52; OCH_3 (s) 3.16; OCH_2 (m) 3.11

^{13}C NMR

O<u>C</u>H_2 42.57; O<u>C</u>H_3 55.81; O<u>C</u>H_2 69.57, 69.84, 70.35, 70.44, 71.04, 95.25; <u>Ar</u>H 115.38, 117.39, 123.97, 125.38, 125.575, 126.21, 126.33, 127.76, 127.85, 129.14, 129.40; <u>Ar</u>R 120.21, 123.72, 134.025, 152.67, 154.155

Synthesis of 1,18-Dihydroxy-1,2:3,4:15,16:17,18-tetra(1,2-naphtho)-5,8,11,14-tetraoxy-octadeca-1,3,15,17-tetraene [2F]

This was synthesised from the above 1,20-bis(methoxymethyl)-2,3:4,5:16,17:18,19-tetra(1,2-naphtho)-1,6,12,15,20-hexaoxy-icosa-2,4,16,18-tetraene using the general deprotection method used previously.

^{1}H NMR $CDCl_3$

Ar<u>H</u> (bm) 7.82-7.97; Ar<u>H</u> (bm) 7.06-7.39; O<u>H</u> (bs) 5.59; C<u>H</u>$_2$ (bm) 4.00 (3.90-4.10); C<u>H</u>$_2$ (t) 3.28; C<u>H</u>$_2$(t) 2.90

^{13}C NMR

O<u>C</u>H_2 69.02, 69.495, 70.17; <u>Ar</u>H 115.57, 118.02, 123.16, 124.185, 124.98, 125.15, 126.34, 127.08, 128.00, 128.12, 129.55, 130.50; <u>Ar</u>R 116.90, 129.03, 133.94, 134.04, 151.53, 155.21

Synthesis of 1-Aza-4,9,12,15,18,23-hexaoxy-5,6:7,8:19,20:21,22-tetra(1,2-naphtho)-N-Tosyl-pentaicosa-5,7,19,21-tetraene (attempted) [2H]

To a solution of (SS) 2F (100mg, MW654, 0.153mmol) and sodium hydride (0.029g, 60%, 0.725mmol,4.74equiv.) in THF (60ml) was added bis(2-tosyloxyethyl)-N-tosylamine (92.3mg, 0.163mmol, 1.065 equiv.). The mixture was held at reflux for 48 hours under nitrogen before being allowed to cool and evaporated to dryness. The resulting solid was taken up into DCM (70ml) and washed with water (2 × 70ml), saturated sodium bicarbonate (50ml), saturated brine (50ml) and dried over magnesium sulphate. The DCM solution was then evaporated to dryness to give a solid mixture of what analysed to be starting materials by TLC and EIMS.

The reaction was repeated using potassium tert-butoxide as base and 1,4-dioxane as solvent. Again held at reflux for 48 hours to give the same result.

Synthesis of 2,2'-Bis-(2-hydroxy-1-oxy-ethyl)-1,1'binaphthyl [3G]

Reaction of binaphthol with ethylene oxide[92]

To a stirred mixture of powdered (S)-binaphthol (5.0g, 17.5mmol) and dried potassium carbonate (5.1g, 36.95mmol) held at -70°C under nitrogen, was added an excess of liquid ethylene oxide (~10ml) - which had also been held at the same temperature. The resulting slurry was then left stirring under nitrogen and allowed to warm to 0°C, where it was held at for ~ one hour before being allowed to warm to ~10°C - at which point it appeared thinner and had a slight yellow tint. The mixture was then heated to ~40-50°C where it was held for 2-3 hours during which time all the excess/unreacted ethylene oxide was driven off. The reaction mixture was then allowed to cool before being stirred over a mixture of DCM and water (~30:30ml), dissolving all of the reactants. The DCM solution was then diluted (~30ml DCM) and washed with sodium hydroxide (3× 40ml, 4M) then water and saturated brine before being dried over magnesium sulphate. The DCM solution was then filtered and evaporated to dryness, it was shown to contain both the di-armed and mono-armed products by TLC. The combined aqueous washings were extracted with DCM after acidification. These extracts were shown to contain both the mono-armed product and unreacted binaphthol. The mono- and di armed products were purified by column chromatography, on silica gel using a THF : petrol or DCM : petrol eluent.

This reaction was attempted a number of times with slight variations in the temperatures and times that the mixture was held, however these reaction mixtures were not heated above room temperature. The reaction was also attempted using different bases including caesium carbonate, all of which gave similar yields of each product. Purification attempts of the mixture of mono- and di-armed binaphthyl were made by fractional crystallisation. However all attempts still gave mixtures with mpt ~200°C and NMR spectra where the mono-armed appeared to be in excess ~7mono:5.7di.

On more than one occasion, after washing with saturated brine solution (slightly basified) a precipitate dropped out of solution which did not re-dissolve upon the addition of more dichloromethane or water. This precipitate was then filtered off and the dichloromethane solution evaporated to dryness under vacuum. Analysis of the dried organic solution showed a mixture of the starting material (binaphthol), the mono (armed) substituted binaphthol and the di-substituted binaphthol whilst the precipitate

appeared to be pure mono armed binaphthol. The precipitate appeared to be soluble in THF and after evaporation to dryness, appeared to be soluble in DCM and other solvents. The precipitate appeared to give a green fluorescence as compared with the characteristic blue fluorescence of binaphthyl compounds. Initially the THF solution of the precipitate also showed a green fluorescence, which changed to a more characteristic blue fluorescence over a period of a few hours.

2,2'-Bis-(2-hydroxy-1-oxy-ethyl)-1,1'binaphthyl [3G]

$C_{24}H_{22}O_4$ MW 374

EIMS M^+=374 (100%), 375 (26.5%)

Accurate EIMS M^+=374.1503 calc.=374.151809 MH^+=375.1547 calc.=375.159634 or is $^{12}C_{23}{}^{13}C^1H_{22}{}^{16}O_4$

^{1}H NMR $CDCl_3$

ArH (m/d,d) 7.87-8.00; ArH (m) 7.06-7.46; CH_2 (dm) 3.96-4.054, 4.16-4.255; CH_2 (bm/s) 3.555; OH (s) 2.51

^{13}C NMR

OCH_2 61.15, 71.63; ArH 115.90, 124.145, 125.20, 126.75, 128.165, 129.83; ArR 120.26, 129.62, 133.805, 153.53

Mono-arm [3H] and mono-arm salt

$C_{22}H_{18}O_3$ MW 330

M^+=330 (100%), 331 (24%), binaphthol fragment 286 (81.7%)

Salt M^+=330 (93.8%), 331 (22.9%), binaphthol fragment 286 (100%)

^{1}H NMR $CDCl_3$

ArH (m) 7.85-7.99; ArH (m) 7.23-7.39; ArH (s) 7.11, 7.07; ArOH (bs) 6.18; CH_2 (m) 4.04; CH_2 (bm) 3.49; OH (bs) 2.43

^{13}C NMR

OCH_2 61.02, 70.75; ArH 115.28, 117.82, 123.39, 124.34, 124.70, 125.18, 126.615, 127.18, 128.17, 128.25,129.85, 130.625; ArR 117.33, 129.11, 129.62, 133.76, 133.92, 151.17, 154.515

Synthesis of 2,2'-oxy-ethanethiol-1,1'-binaphthyl

A slurry of (S)-binaphthol (1.03g, 3.6mmol) and lithium hydride (0.10g, 12.5mmol) in THF (20ml), was stirred at ambient temperature under nitrogen. To this slurry was added freshly filtered ethylene sulphide (0.48g, 8.0mmol) and the mixture was then warmed to ~40°C where it was held for two hours (during which time a colourless precipitate was seen to be formed). The mixture was allowed to cool to ambient temperature before being filtered and evaporated to dryness under vacuum. TLC analysis showed only one compound corresponding to unreacted binaphthol. The melting point of the final solid was identical to that of authentic binaphthol (209-210°C). This reaction was repeated using a variety of bases of different strengths and concentrations and without any base at a number of different temperatures. All of these attempts resulted in the same colourless precipitate (presumably polyethylenesulphide) and unreacted binaphthol.

Synthesis of 2,2'-Bis(2-methylsulphide-1-oxyethyl)-1,1'-binaphthyl [3I]

A mixture of binaphthol (1.27g, 4.44mmol), chloroethyl-2-methylsulphide (1.04g, 9.41mmol, 2.12equiv.) and potassium hydroxide (0.65g, MW56, 11.6mmol2.61equiv.) in THF (~80ml) and water (~8ml) was held at reflux overnight for ~19 hours, under nitrogen. The mixture was left to cool before being evaporated to dryness under vacuum to give a light yellow oil. TLC analysis showed that this oil was a mixture of compounds, the di- and mono-armed product and starting binaphthol. This oil was then taken up into DCM (40ml) and washed with water (50ml), sodium hydroxide (2 × 40ml, 2M), saturated brine and dried over sodium sulphate before being evaporated to dryness. The oil was further purified by column chromatography on silica using a gradient of EtOAc, starting from 10%, with petrol as eluent.

2,2'-Bis(2-methylsulphide-1-oxyethyl)-1,1'-binaphthyl [3I]

$C_{26}H_{26}O_2S_2$ MW 434

M^+=434, 435

IR, run as a thin film on NaCl plates

No OH stretch seen, CH stretches ~3000 cm^{-1}, aromatic CC bonds stretches at ~1600 and 1620 cm^{-1}.

^{1}H NMR $CDCl_3$

ArH (d) 7.84; ArH (d) 7.76; ArH (d) 7.31; ArH (m) 7.04-7.27; $C\underline{H}_2O$ (bm) 4.037; CH_2S (t) 2.35; $C\underline{H}_3$ (s) 1.576

^{13}C NMR $CDCl_3$

$\underline{C}H_3S$ 15.832; $\underline{C}H_2S$ 33.039; $\underline{C}H_2O$ 70.179; $\underline{Ar}H$ 115.69, 123.78, 125.38, 126.335, 127.84, 129.38; $\underline{Ar}R$ 120.63, 129.49, 134.05, 154.03

Mono-arm [3J]

$C_{23}H_{20}O_2S$ MW 360

EIMS M=360

Synthesis of 6,6'-Dibromo-2,2'-dihydroxy-1,1'-binaphthyl [7A]

This reaction was attempted using two methods, firstly the method of Pradellok et al.[90] and secondly the method of Cram[91].

(R)-Binaphthol (5.0g, 17.5mmol) was dissolved in hot glacial acetic acid (55ml, 100°C) and cooled to ~70°C (below 70°C came out of solution). Bromine (5.6g, 35mmol, 2equiv.) was added dropwise over 20 minutes and the mixture allowed to cool slowly to ambient temperature (over ~2 hours). Water was added (~20ml) and this mixture was evaporated to dryness to give an oil which was taken up into DCM (40ml) and stirred over aqueous sodium metabisulphite (~30ml, 10%) until decolourised (until all the Br_2 was destroyed). The DCM solution was then washed with water (40ml), saturated sodium carbonate (30ml), saturated brine (40ml) and dried over magnesium sulphate before being evaporated to dryness. TLC analysis showed a mixture of products including a strong spot corresponding to binaphthol. EIMS analysis of the crude mixture showed no mass higher than that of the mono-substituted bromine, the largest signal being for binaphthol.

There was no precipitate after cooling or after the addition of water, as was claimed in the paper.

A solution of (R)-binaphthol (2.06g, 7.20mmol) in DCM (55ml) was cooled to -75°C and bromine (1ml, 3.102g, 19.375mmol, 2.7equiv.) was added over 10 minutes with

stirring. The mixture was then allowed to warm up to ambient temperature, over ~3-4 hours. The excess bromine was then destroyed by stirring the mixture with sodium bisulphite solution (50ml, 10%) for ~1 hour during which time the solution went from a red-brown to a light yellow colour. The DCM solution was then washed with water (2 × 50ml), saturated brine (50ml) and dried over sodium sulphate. The DCM solution was then evaporated to dryness to give a solid which analysed by TLC and EIMS as a mixture of the desired dibromide and mono-bromide.

$C_{20}H_{12}Br_2O_2$ MW 444

EIMS M^+=444 (100%), 446 (45%), 448 (2.0%)

M^++H=445 (34.5%), 447 (10.7%)

^{1}H NMR $CDCl_3$

ArH (s/m) 8.00; ArH (d) 7.76 (7.74, 7.78); ArH (m) 7.30 (7.37-7.23); ArH (d) 6.94 (6.96, 6.92); OH (s) 5.16

^{13}C NMR

ArH 118.94, 125.924, 130.38, 130.49, 130.67; ArR 110.5, 117.99, 131.91, 152.18

Was ~ 10% impure

EIMS M^+=366 (2.3%)

Synthesis of (S) and (R)- N-(3,5-Dinitrobenzoyl)-α-methylbenzylamine [7B]

A solution of (R)-1-phenylethylamine (10.5g, 86.8mmol) in THF (~140ml) and triethylamine (9.68g, 95.8mmol) was stirred at 0°C under nitrogen. To this was added a solution of 3,5-dinitrobenzoylchloride (21.57g, 93.6mmol) in THF (~50ml) at such a rate that the reaction temperature did not rise above 10°C. The mixture was allowed to warm up to ambient temperature and was stirred for a further two hours before being evaporated down to ~50ml. A mixture of chloroform (~250ml) and water (~150ml) was then added and the mixture allowed to stir for ~ ½ an hour until all was solubilised. The chloroform solution was then separated and washed with water (2 × 150ml) then saturated brine (~150ml) before being dried over magnesium sulphate. The chloroform solution was then filtered and concentrated to ~75ml before being left to chill (4°C) overnight. The crystals that had formed were then filtered off and washed with

chloroform (2 × 20ml) before being recrystallised from chloroform. This gave a final amount of crystalline material of 24.4g, 89% yield with melting point of 160-161°C(lit. 160-161). MW 315

$[\alpha]_{589}^{15}$ = +12.6 :(lit = +46.2 20°C in acetone),(-46 18°C in acetone)

^{1}H NMR $CDCl_3$

ArH (m) 8.99; ArH (d) 8.10 Δ=0.03788δ = 7.58Hz; ArH (m) 7.205 (7.35-7.06); CH (d of q) 5.17 (5.245, 5.21, 5.17, 5.14, 5.105), Δ_1=0.03436 = 6.876Hz, Δ_2=0.03576δ = 7.157Hz, Δ_3=0.0357δ = 7.14Hz, Δ_4=0.03469δ = 6.94Hz; CH_3 (d) 1.565 Δ=0.03472δ = 6.95Hz

^{13}C NMR

CH_3 21.60; CH 50.38; ArH 120.97, 126.10, 127.52, 128.54; ArR 137.49, 142.355, 148.32, 152.275

Synthesis of Methyl esters of D and L Tyrosine [7C] AND D and L Phenyl alanine [7D] as their Hydrochloride Salts

General method for amino acid methyl esters

A solution of (L)-tyrosine (15.0g, 82.87mmol) and thionyl chloride (15ml, 24.4g, 205mmol, 2.48equiv.) in dry methanol (~200ml) was held at reflux overnight for 14 hours. The mixture was evaporated to dryness under vacuum and the solid was recrystallised from EtOAc or MeOH or a mixture of both. This gave the required methyl ester as hydrochloride salt in ~95% yield.

(L)-Tyrosine Me ester .HCl had a mpt of 191d (lit. 192d), D-t mpt 191d

(L)-Phenyl alanine Me ester .HCl had mpt 156-7, D-p mpt 157-8 (literature mpt 158)

The natural enantiomers were used on a 10 g scale whilst the synthetic enantiomers were used on a 1g scale.

L-Tyrosine Methyl Ester Hydrochloride [7C] (Methyl Tyrosinate)

^{1}H NMR $CDCl_3$ with d_4 MeOH (~30%)

ArH AA'BB'(d,d), 6.68, Δ=0.04278δ = 8.56Hz, Δ=0.24687δ = 49.40Hz, 6.61, Δ=0.04272δ = 8.55Hz; CH_2 (t) 3.96, Δ_1=0.03249δ = 6.50Hz, Δ_2=0.03119 = 6.24Hz; CH (s) 3.595; CH_3 (d) 2.98, Δ=0.03371δ = 6.75Hz; NH_3 (bs) 4.195

^{13}C NMR

$\underline{C}H_2$ 34.95; $\underline{C}H_3$ 52.595; $\underline{C}H$ 53.825; $\underline{Ar}H$ 115.575, 130.07; $\underline{Ar}R$ 123.68, 156.33, 168.755

D-Tyrosine Methyl Ester Hydrochloride [7C] (Methyl Tyrosinate)

^1H NMR $CDCl_3$ with d_4 MeOH (~30%)

Ar$\underline{H}$ AA'BB' (d,d) 6.84, Δ=0.04281δ = 8.57Hz, Δ=0.245415δ = 49.11Hz, 6.595 Δ=0.04292δ = 8.59Hz; $N\underline{H}_3$ (bs) 4.25; $C\underline{H}$ (t) 3.93, Δ_1=0.03291δ = 6.585Hz, Δ_2=0.03092δ = 6.19Hz; $C\underline{H}_3$ (s) 3.595; $C\underline{H}_2$ (d) 2.96 Δ=0.0319δ = 6.385Hz

L-Phenyl Alanine Methyl Ester Hydrochloride [7D] (Methyl Phenylalanate)

^1H NMR $CDCl_3$ with ~ 30% d_4 MeOH

Ar$\underline{H}$ (m) 7.17 (7.26-7.08); $C\underline{H}$ (t) 4.09, Δ_1=0.03249δ = 6.50Hz, Δ_2=0.03221δ = 6.45Hz; $N\underline{H}_3$ (bs) 4.01; $C\underline{H}_3$ (s) 3.64; $C\underline{H}_2$ (d) 3.15 Δ=0.03238δ = 6.48Hz

^{13}C NMR

$\underline{C}H_2$ 35.91; $\underline{C}H_3$ 52.79; $\underline{C}H$ 53.79; $\underline{Ar}H$ 127.71, 128.855m 129.15; $\underline{Ar}R$ 133.37, 168.83

D-Phenyl Alanine Methyl Ester Hydrochloride [7D] (Methyl Phenylalanate)

^1H NMR $CDCl_3$ with ~ 30% d_4 MeOH

Ar$\underline{H}$ (m) 7.155, (7.25-7.06); $C\underline{H}$ (t) 4.07, Δ=0.03265δ = 6.53Hz, Δ=0.03236δ = 6.48Hz; $N\underline{H}_3$ (bs) 4.00; $C\underline{H}_3$ (s) 3.62; $C\underline{H}_2$ (d) 3.12 Δ0.03253δ = 6.51Hz

General Synthesis of the Hydrochloride salts of selected chiral amines

The hydrochloride salts of amines were synthesised using one of two generalised methods.

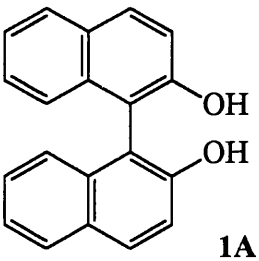
Method 1: The required amine was dissolved in a suitable solvent, most commonly chloroform, with stirring under nitrogen and placed in an ice-bath. An excess of concentrated hydrochloric acid (of analytical grade) was then added dropwise and the resulting mixture left to stir at 0°C for ½ an hour. The mixture was then filtered and the filter cake was washed with 2 portions of warm chloroform before being dried under high vacuum at ~ 25°C.

Method 2: The required amine was dissolved in a suitable dry solvent, most commonly chloroform, with stirring under nitrogen and was cooled to °C. An excess of hydrogen chloride gas was then slowly bubbled through the solution at a rate which did not allow

the internal temperature to rise above 25°C. The mixture was then left to stir, at ambient temperature, with nitrogen being flushed through the system for ~1/2 an hour. The mixture was then filtered and the filter cake washed with two portions of warm chloroform before being dried under vacuum at ambient temperature.

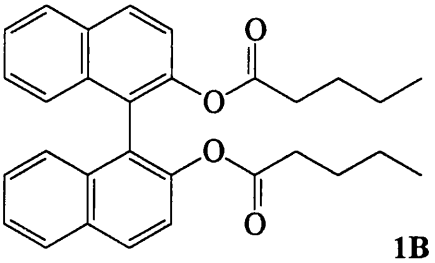
In both methods the original chloroform solution was made dilute enough to allow the intermediate and final mixture to be stirred easily in order that the product was obtained in high yield and purity.

EXPERIMENTAL APPENDIX



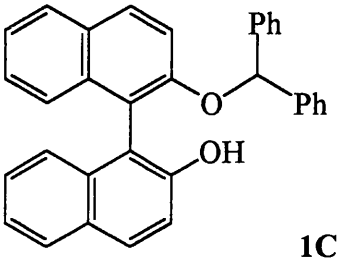
1A

2,2'-Dihydroxy-1,1'-binaphthyl



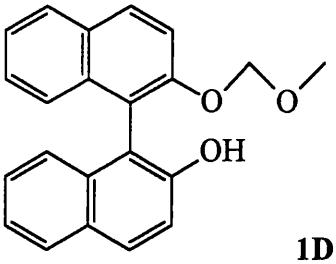
1B

1,1'-Binaphthyl-2,2'-dipentanoate



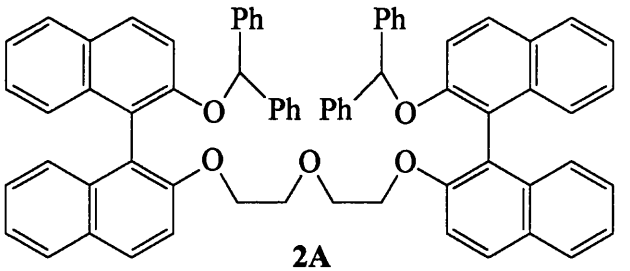
1C

2-Benzhydryloxy-2'-hydroxy-1,1'-binaphthyl
[Diprotected] 2,2'-Bis(benzhydryloxy)-1,1'-binaphthy



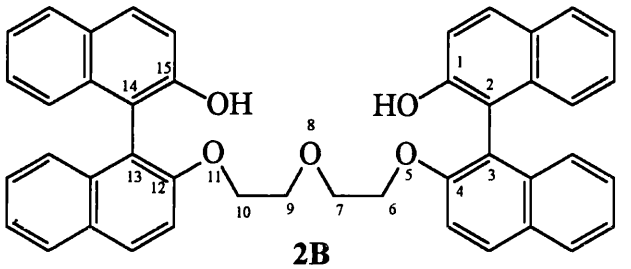
1D

2-Methoxymethylether-2'-hydroxy-1,1'-binaphthyl
[diprotected] 2,2'-Bis(methoxymethylether)-1,1'-binaphthyl



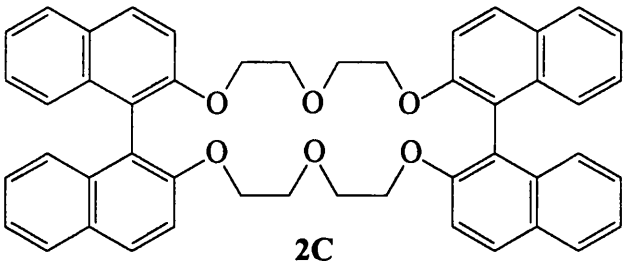
2A

1,17-Bisbenzhydryl-2,3:4,5:13,14:15,16-tetra-(1,2-naphtho)-
1,6,9,12,17-pentaoxaheptadecyl-2,4,13,15-tetraene



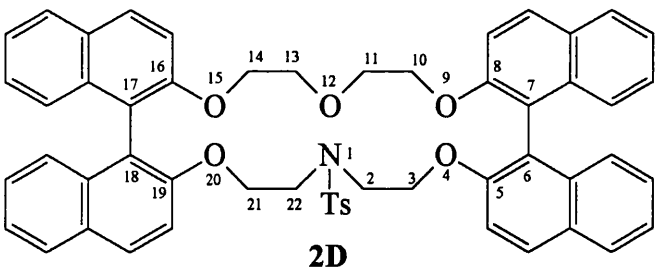
2B

1,15-Dihydroxy-4,8,11-trioxy-1,2:3,4;12,13:14,15-tetra-
(1,2-naphtho)-1,3,12,14-tetraene-pentadecane



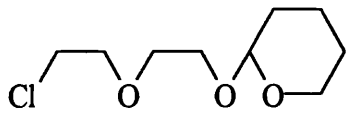
2C

Bis-(binaphtho)-22-crown-6 /
1,6,9,12,17,20-Hexaoxy-2,3:4,5:13,14:15,16-tetra-(1,2-naphtho)-docosane



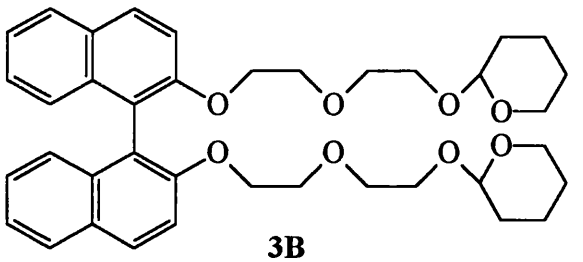
2D

N-Tosyl-4,9,12,15,20-pentaoxy-1-aza-5,6:7,8:16,17:18,19-
tetra-(1,2-naphtho)-cyclodocosa-5,7,16,18-tetraene



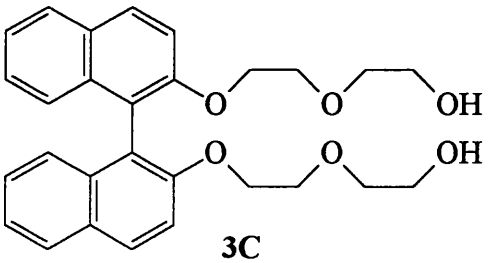
3A

2-(2'-Chloroethoxy)ethyl-2"-tetrahydropyranyl ether



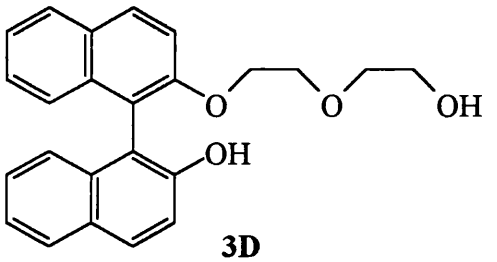
3B

2,2'-Bis-(5-oxytetrahydropyranylether
-3oxa-1-pentyloxy)-1,1'-binaphthyl



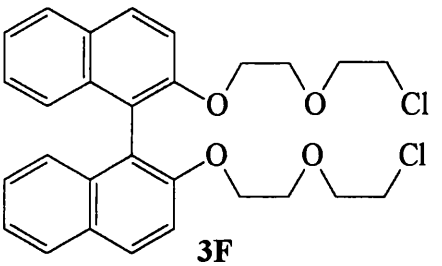
3C

2,2'-Bis-(5-hydroxy-3oxa-1-pentyloxy)-1,1'-binaphthyl



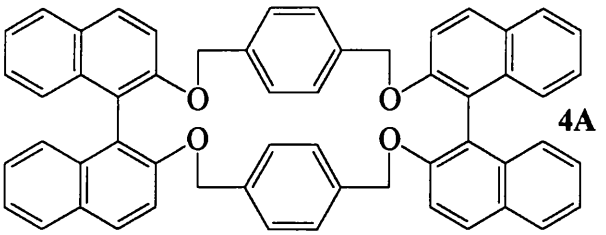
3D

2'-(5-oxa-ethoxyethanol)-2-hydroxy-1,1'-binaphthol



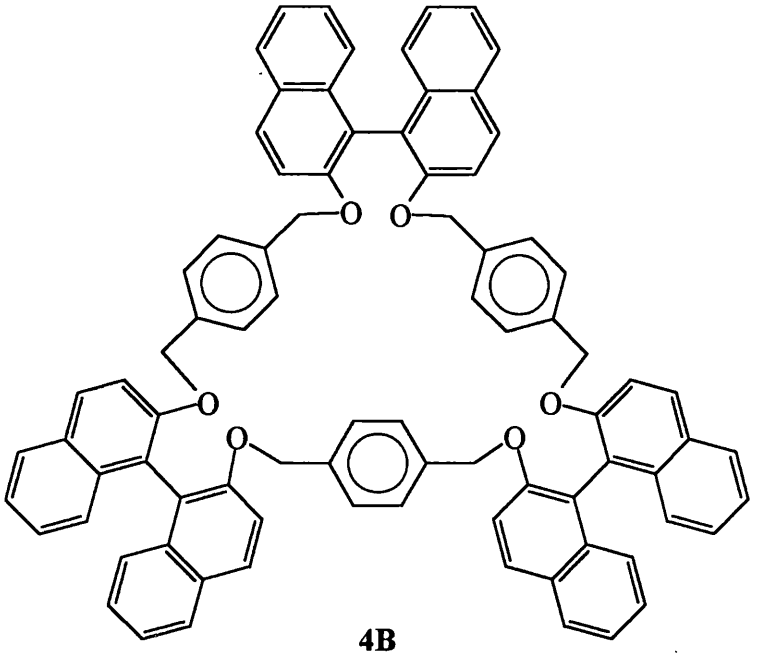
3F

2,2'-Bis-(5-chloro-3oxa-1-pentyloxy)-1,1'-binaphthyl



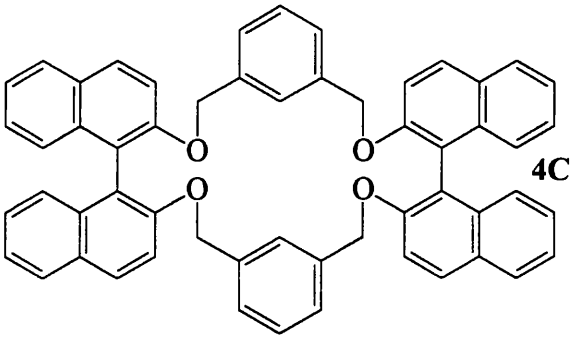
4A

2,3:4,5:14,15:16,17-Tetra-(1,2-naphtho)-8,9,10,11:20,21,22,23
-di(1,4-phenyl)-1,6,13,18-tetraoxy-tetraicosa-heteraphane



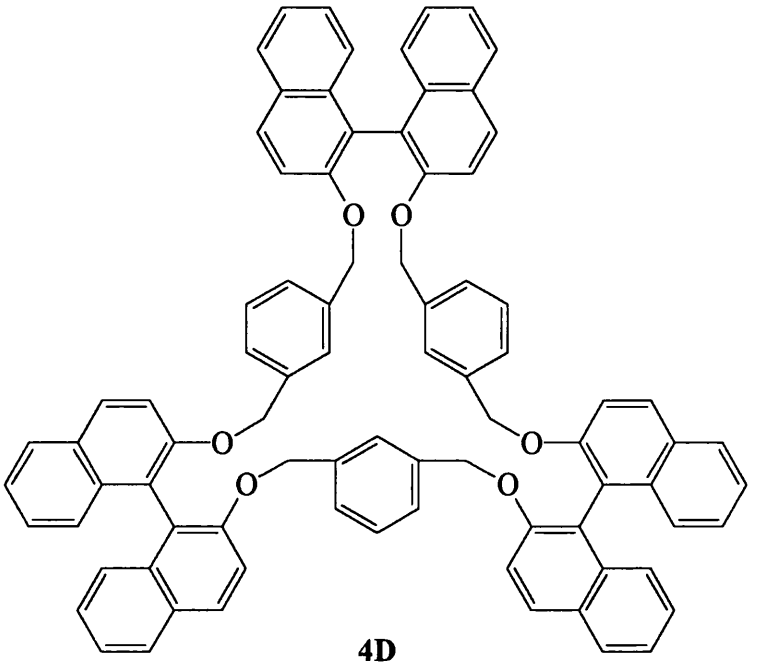
4B

2,3:4,5:14,15:16,17:26,27:28,29-Hexa-(1,2-naphtho)-
32,33,34,35-tri(1,4-phenyl)-1,6,13,18,25,30-hexaoxy-hexatriaconta-



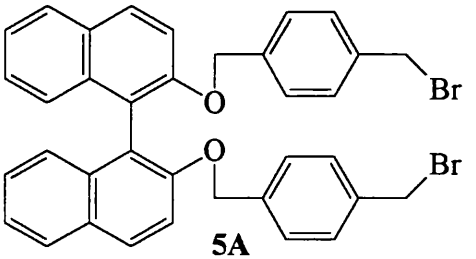
4C

2,3:4,5:13,14:15,16-Tetra-(1,2-naphtho)-8,9,10:19,20,21-
di(1,3-phenyl)-1,6,12,17-tetraoxy-docosa-heteraphane



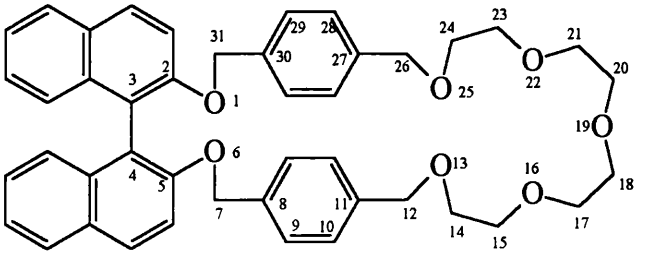
4D

2,3:4,5:13,14:15,16:24,25:26,27-Hexa-(1,2-naphtho)-8,9,10:19,20,21:
30,31,32-tri(1,3-phenyl)-1,6,12,17,23,28-hexaoxy-tristriaconta-heteraphane



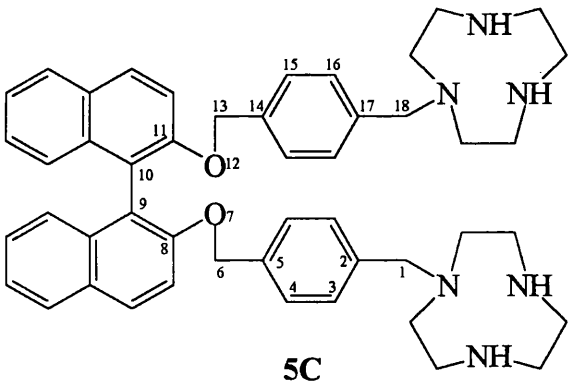
5A

2,2'-Bis(α'-bromo-α-oxy-para-xylyl)-1,1'-binaphthyl



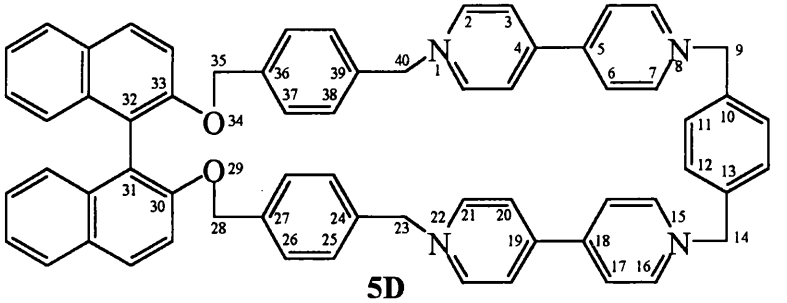
5B

1,6,13,16,19,22,25-Heptaoxa-2,3:4,5-di(1,2-naphtho)-
2,4-diene-8,11:27,30-di(1,4-benzyl)-hentriaconta-heteraphane



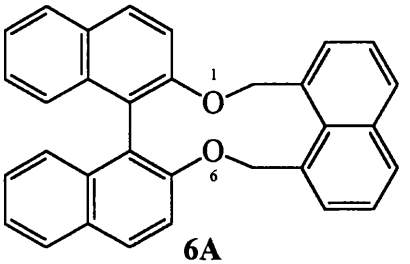
5C

2,2'-Bis(α-N-triazacyclononane-α'-oxy-p-xylyl)-1,1'-binaphthyl



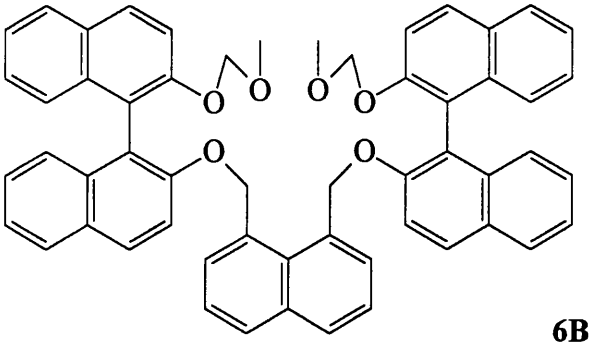
5D

1,8,15,22-Tetra-aza-29,34-dioxy-10,13:24,27:36,39-tri(1,4-phenyl)-1,8:15,22-N,N,N,N-di-(4,4'-bipyridinium)-30,31:32,33-di-(1,2-naphtho) tetraconta-heteraphane Tetrakis-hexafluorophosphate



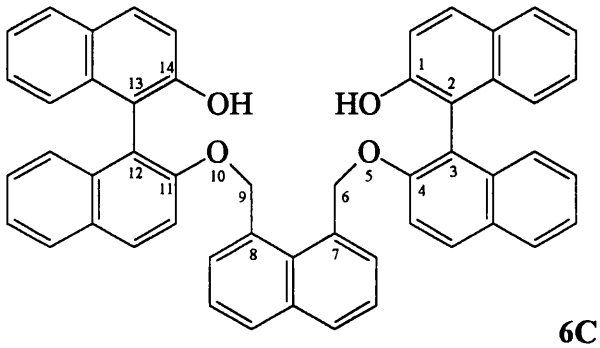
6A

2,3:4,5-di-(1,2-naptho)-8,9,10-(1,8-naphthyl)-1,6-dioxa-2,4,8-triene-undeca-heteraphane



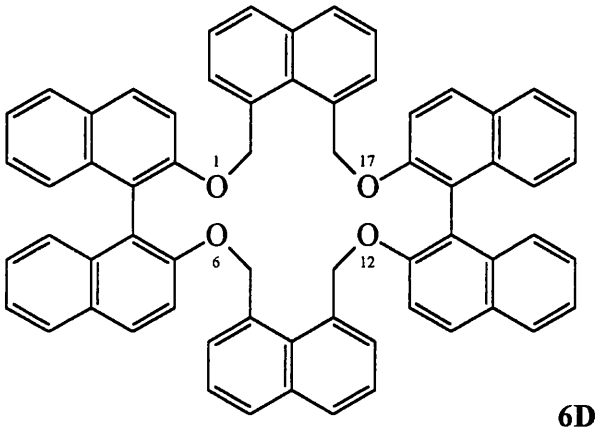
6B

1,17-Bis(methoxymethyl)-2,3:4,5:13,14:15,16-tetra(1,2-naphtho) -7,8,9-(1,8-naphthyl)-1,6,12,17-tetraoxa-heptadecane



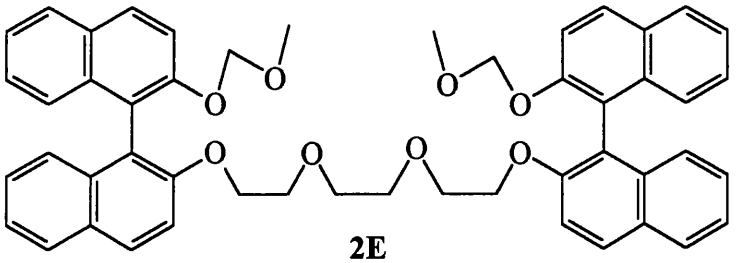
6C

1,15-Dihydroxy-5,10-dioxy-1,2:3,4:11,12:13,14-tetra-(1,2-naphtho)
-7,8,9-(1,8-naphthyl)-pentadeca-1,3,11,13-tetraene



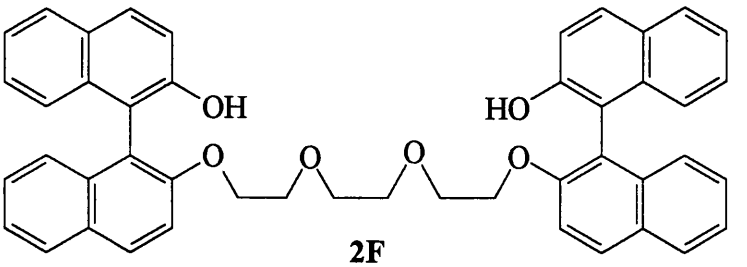
6D

2,3:4,5:13,14:15,16-Tetra(1,2-naphtho)-8,9,10:19,20,21-bis
-(1,8-naphthyl)-1,6,12,17-tetraoxy-docosa-heteraphane



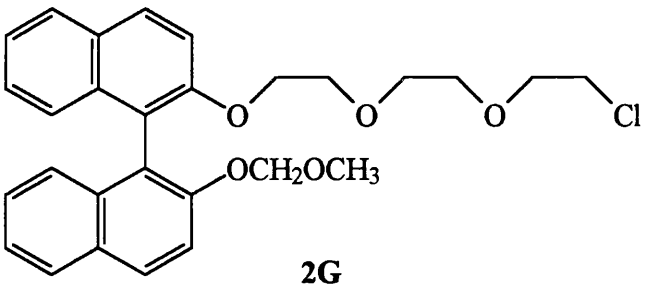
2E

1,20-Bis(methoxymethyl)-2,3:4,5:16,17:18,19-tetra-(1,2-naphtho)
-1,6,12,15,20-hexaoxa-eicosa-2,4,16,18-tetraene



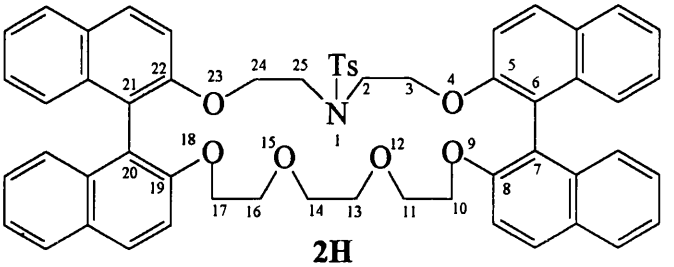
2F

1,18-Dihydroxy-1,2:3,4:15,16:17,18-tetra(1,2-naphtho)
5,8,11,14-tetraoxy-octadeca-1,3,15,17-tetraene



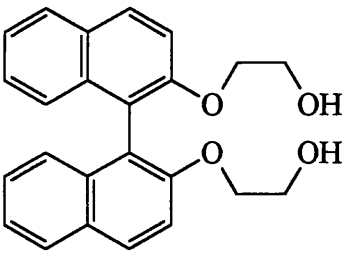
2G

2-(8-Chloro-7,4-dioxa-1-octyloxy)-2'-methoxymethyl-1,1'-binaphthyl



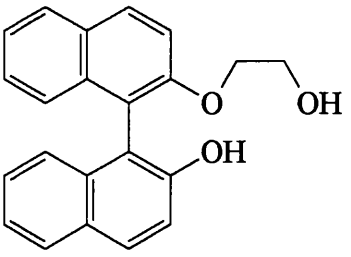
2H

1-Aza-4,9,12,15,18,23-hexaoxy-5,6:7,8:19,20:21,22-tetra(1,2-naphtho)-N-tosyl-pentaicosa-5,7,19,21-tetraene



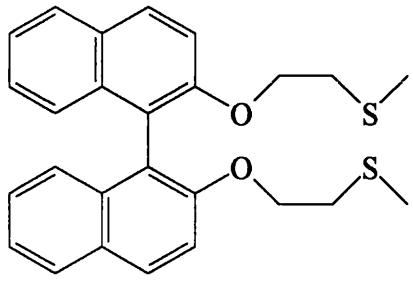
3G

2,2'-Bis-(2-hydroxy-1-oxy-ethyl)-1,1'binaphthyl



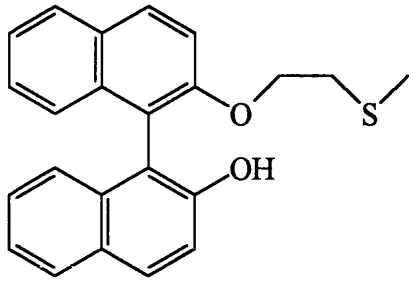
3H

1,7-Dihydroxy-4,5:6,7-di(1,2-naphtho)-3-oxahepta-4,6-diene / 2-(2-Hydroxy-oxyethyl)-2'-hydroxy-1,1'-binaphthyl



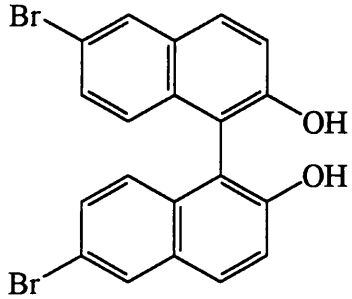
3I

2,2'-Bis(2-methylsulphide-1-oxy-ethyl)-1,1'-binaphthol



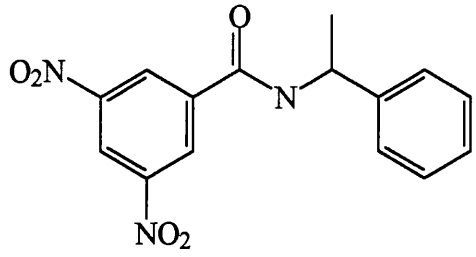
3J

2-Hydroxy-2'-(2-methylsulphide-1-oxy-ethyl)-1,1'binaphthol



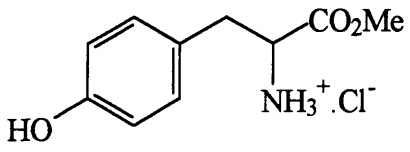
7A

6,6'-Dibromo-2,2'-dihydroxy-1,1'binaphthol



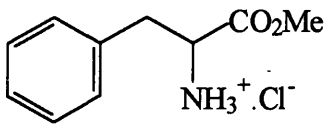
7B

(S)/(R)-N-(3,5-Dinitrobenzoyl)-α–methyl-benzylamine



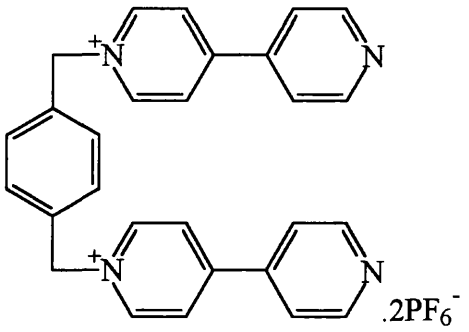
7C

Methyl Tyrosinate Hydrochloride



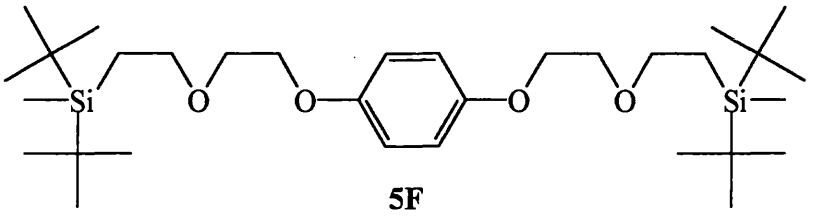
7D

Methyl Phenylalanate Hydrochloride



5E

1,1'-[1,4-Phenylenebis(methylene)]-bis-4,4'bipyridinium
-Bis hexaflurophosphate



5F

1,4-Bis[8-(ditert-butyl)methyl-silyl-3,6-dioxy-1-oxa]-benzene

CHAPTER THREE

PROJECT AIM AND SCOPE

The aim of this project was to build a molecule that was capable of 'sensing' the chirality of other analyte molecules. To achieve this, the project would have to combine the technology of molecular recognition with that of signal transduction. It became the specific aim of this work to design and prepare chiral fluorescent molecules (chemosensors), that could form reversible complexes with suitable chiral molecules to give characteristic optical changes. The long term aims being the evaluation of prototype sensors using various chiral 'guest' molecules to enable an optimisation of design and development of new technology.

As has already been outlined in the introduction the chirality of a molecule is known to play as important a role in its interaction with other chiral molecules as its structure or charge. This interaction, most notable in biological systems, can have very different consequences. There are many examples of the differing effects of the interactions of individual enantiomers with biological systems, one of the most notorious being the enantiomeric forms of Thalidomide (which is perhaps a dubious example as there is some evidence to show that it racemises with a half life of ~10 minutes in the blood[93]). There are other important molecules that can and do undergo *in vivo* racemisations with pharmacological advantages and disadvantages; this gives rise to a requirement to know the ratio of enantiomers present at any one time and that are giving rise to the biological effects seen. "The means of distinguishing between enantiomers of a chiral molecule are of critical importance in many areas of analytical chemistry and biotechnology, particularly in drug design and synthesis."[25]. Present methods of enantiomer identification can be tedious and indirect. A molecular chemosensor would offer real-time and real-space monitoring of chiral molecules.

Although one of the long term aims was for a molecule that could act as a chiral sensor of chiral molecules in general (or what is probably more realistic, a family of molecules that could act as sensors for particular families of chiral molecules) a target analyte or analyte family had to be chosen in the first instance in order that the necessary background knowledge of design and shape interactions could be achieved. Aromatic chiral primary amines were chosen as the initial target analyte with particular attention to their protonated salts. It was a longer term aim that from the initial analyte targets of primary amine salts, the research would expand to developing a more general sensor - towards non specific molecules or analytes within a specified group/family and then to non-specific molecules in non-specific families. This expansion would be achieved via

the use of multiple methods of binding, for example electron Acceptor-Donor complexes, hydrophobic/polarity interactions, acid base / ionic interactions etc.

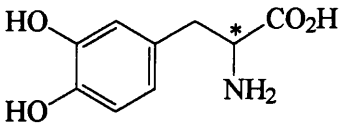
The design of sensors requires thought about more than just the analyte of concern and how to make a more general sensor. A major factor that must also be considered is the environment in which the sensor must operate - as it will be the change in the sensor's environment or micro-environment that will be the basis of any signal transduction and differentiation.

Why target chiral amines?

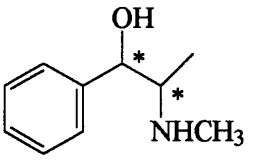
Molecules with amine functionality and in particular primary amine functionality are of great biological importance, for example amino acids (some of the building blocks of life) also many chemo-transmitters found in the synapses between nerve cells and psycho-active drugs/chemicals.

Examples include D-(-)-p-hydroxy-phenyl-glycine which is an intermediate in the production of semi-synthetic antibiotics, MDMA, amphetamine, phenyl alanine (used in a variety of foodstuffs) and noradrenaline (see figure 3.1).

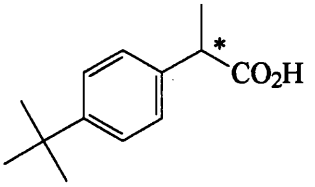
It is important to note that any substance that is to be used as drug intermediate or bulk drug substance is continuously being put under more up to date and very often more stringent rules, regulations and guidelines by the (governing body of the) Food and Drug Administration (FDA). These guidelines are pushing towards a much greater understanding of the different effects (if any) of all of the enantiomers of any proposed new food or drug. It is very likely that these guidelines will also push for greater understanding of the enantiomers of existing chiral drugs. All of which means a need for better methods of distinguishing enantiomers and a push for methods that would allow the measurement of chirality in a variety of different environments with perhaps the most obvious being for sensors that can operate within living systems and tissues.



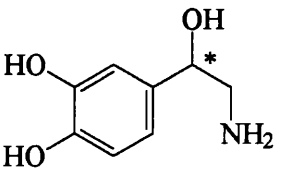
L-DOPA
[L-3-(3,4-Dihydroxyphenyl)alanine]



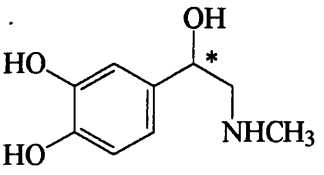
Ephidrine
[α (1–Methylaminoethyl) benzylalchohol]



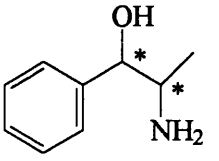
Ibuprofen
[(s)-(+)-4-Isobutyl-α-methylphenylaceticacid]



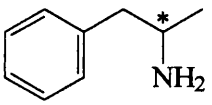
(L)-Noradrenaline



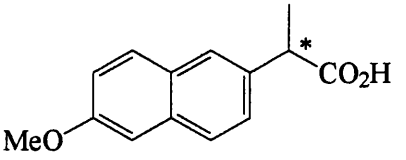
L-Adrenaline
[L-Epinephrine]



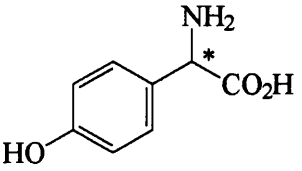
Norephidrine



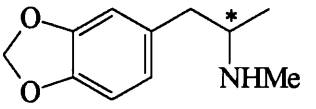
1-Phenyl-2-propylamine



Naproxen



p-Hydroxy-phenyl-glycine



MDMA

Figure 3.1; Some Potential Analyte Molecules

Thus there appear to be many applications, commercial and academic, for the use of primary amines as target analytes. Amines are a major class of biologically active compounds, there are many to choose from, many can be obtained inexpensively and in both enantiomeric forms. Also there is a lot of information already known about the chiral recognition and transportation of chiral amines by chiral host molecules which would form an invaluable library of background knowledge.

Chiral primary amines - design and binding principles

Chiral primary amines and their salts have been the attention of much recognition and transportation studies in which the chiral recognition has been achieved by utilising the binding power of chiral crown ether compounds towards primary amine salts (see introduction chapter). The design and binding principles for amines and their salts differ and require different strategies. Amine salt binding relies upon hydrogen bonding interactions with the amine cation, which has been achieved and exploited via the use of crown ether compounds; free amine binding often relies on an initial acid base interaction to give a virtual amine salt that is stabilised by ether interactions.

Sensor operation

The design requirements for sensor operation are at various levels - the broad requirements for a chiral sensor being chiral recognition with signal transduction. For this the sensor must be chiral, rigid enough to effect discrimination, yet flexible enough to allow strong complexation and spectral changes. The finer details of the sensor design should encompass all parameters that could affect the operation of the sensor in the designated environment.

The nature of the fluorescent probe for signal transduction is obviously a fundamental choice. Organic fluorophores have broad fluorescence spectra. However it may be possible to predict, obtain and observe interactions with organic fluorophores that give wavelength or intensity changes. The shape of the sensor molecule and whether this can be predicted and synthesised is another major choice. The sensor does not require to be macrocyclic e.g. the molecular tweezers shape of Shinkai's fluorescent chiral sensor[54].

Strategies behind the sensor design

The overall long term strategy behind the design of such sensors holds three important component parts:

a- will it work - is the design capable of chiral recognition with signal transduction of an analyte in the environment chosen?

b- is it practical - will the design be easy enough to synthesise and from simple, cheap materials?

c- will it be stable and continue to operate after one use - is the binding reversible?

Initial Thoughts on Sensor Design

One of the original ideas of this project was to utilise the fluorescence characteristics of compounds derived from anthracene as the probe into chiral-chiral molecular interactions. Anthracenes generally have very good quantum yields, their maximum absorptions and emissions are relatively long wavelength (so they are less likely to overlap other components in the system), they have low ionisation potentials (and so are good electron donors and could be incorporated into binding of electron deficient guests).

Another of the first ideas was to use an intrinsically chiral fluorophore and build a receptor around this. It seemed an ideal situation, that the signalling probe and the chirality of the chemosensor be incorporated into each other as the same unit - this would have the effect of keeping things simple and hopefully increase the transduced effects of any chiral-chiral interaction. From this background the idea to use substituted 1,1'-bianthryls as the chiral, fluorescent transducer was developed.

Shortly after the synthesis of functionally substituted 1,1'-bianthryls had begun, it became clear that such syntheses would be long, difficult and low yielding. Also the products would be racemates and as such would require to be resolved before they could be used in the synthesis of any prototype sensors. The 1,1'-bianthryls also suffer from the usual stability problems associated with anthracenes; they are easily oxidised across the 9,10 positions to the corresponding anthraquinone. These positions are also reactive toward dienophiles and at suitable concentration or intramolecular pre-positioning, anthracenes can also react with other anthracenes in reversible (photochemical) reactions across the 9,10 positions. With all this to contend with and more it was concluded that substituted 1,1'-bianthryls were not the most suitable building blocks. In keeping with the use of fluorescent aromatics with chiral axis, substituted 9,9'-bianthryls were investigated. It appeared that these systems were very suitable for use as building blocks in intrinsic, chiral, chemosensors in all but the length of synthetic route (and subsequent yield) before resolution and sensor synthesis. As the two anthracene subunits are bound at the 9 positions in these compounds, oxidation across the 9, 10 positions of each subunit becomes more difficult. The stability of such systems has previously been studied[94] in regard to their reactions with dienophiles. They found that whereas anthracene reacts readily with p-benzoquinone, 9,9'-bianthryl failed

to give the corresponding adduct. They also found that 9,9'-bianthryls react sluggishly and in poor yield with benzyne, while the corresponding anthracenes react readily and in good yields. Bianthrone formation is still possible but should be much more difficult.
Another very useful difference that would arise from the use of substituted 9,9'-bianthryls into a sensor is the natural formation of chiral cavity in the cleft of the bianthryl. The advantages of the incorporation of such large clefts are highlighted and discussed by Diederich[95] in his work on molecular recognition by cyclophanes. The length of the synthesis and the need for resolution was the reason for this work to be more of a sideline and to become a more long term goal.

Binaphthyls

While still keeping the advantages of the chiral bianthryls, the relative cheapness and ease of synthesis and resolution made the use of 1,1'-binaphthyls very appealing. This appeal may be borne out by the prevalence of papers that incorporate binaphthyl subunits in molecules that are used as chiral auxiliaries, chiral modifiers, chiral catalysts, chiral discrimination and resolving agents. Also with the number of procedures for the resolution of binaphthol it could be said that binaphthol itself has become a standard for resolving agents [see bibliography].
The minor groove of binaphthyl confers a degree of shape and rigidity to any macrocyclic molecule which incorporates it. As such its axial chiral constraints are also transferred into any cavity that may be formed. The degree of transference is also affected by the rigidity of the other cavity spacers, their pre-organisation and functional involvement in the binding of guests. The chiral influence originating from the minor groove of binaphthol has been fully exploited by Cram. The major groove should provide a larger cavity as the connections that form the cycle are further apart.
The binaphthol unit offers a great deal of flexibility in that after it has been incorporated into the basic structure it provides a site of derivatisation for fine tuning and radical change. For example the fluorescence of the binaphthyl unit may complicate the signal that is being studied and this can be altered by the hydrogenation of the outer half of the naphthyl unit (making it a di-phenyl - thus radically changing its spectra and solubility) or by derivatising the 6 or 7 positions with an amine on a carbon spacer to act as quencher of the naphthyl's fluorescence using PET.

To summarise: the binaphthol unit is an extremely versatile chiral building block of great potential - which has perhaps been enhanced by the many methods of resolution and the ease with which bulk quantities may be obtained. Most importantly there is an extremely fast and efficient enzymatic resolution available (Figure 3.2). The subsequent chapters in this thesis describe a variety of sensor molecules based on resolved binaphthol.

The initial use of the resolved binaphthol was in attempts to prepare mono-aza analogues of Cram's successful bis-binaphthyl crown compounds. This homo-chiral spacer was then used to synthesise a number of simple heteraphanes. From these heteraphanes the binaphthyl spacer was used in the synthesis of a number of intermediates for use in more complex prototype sensors.

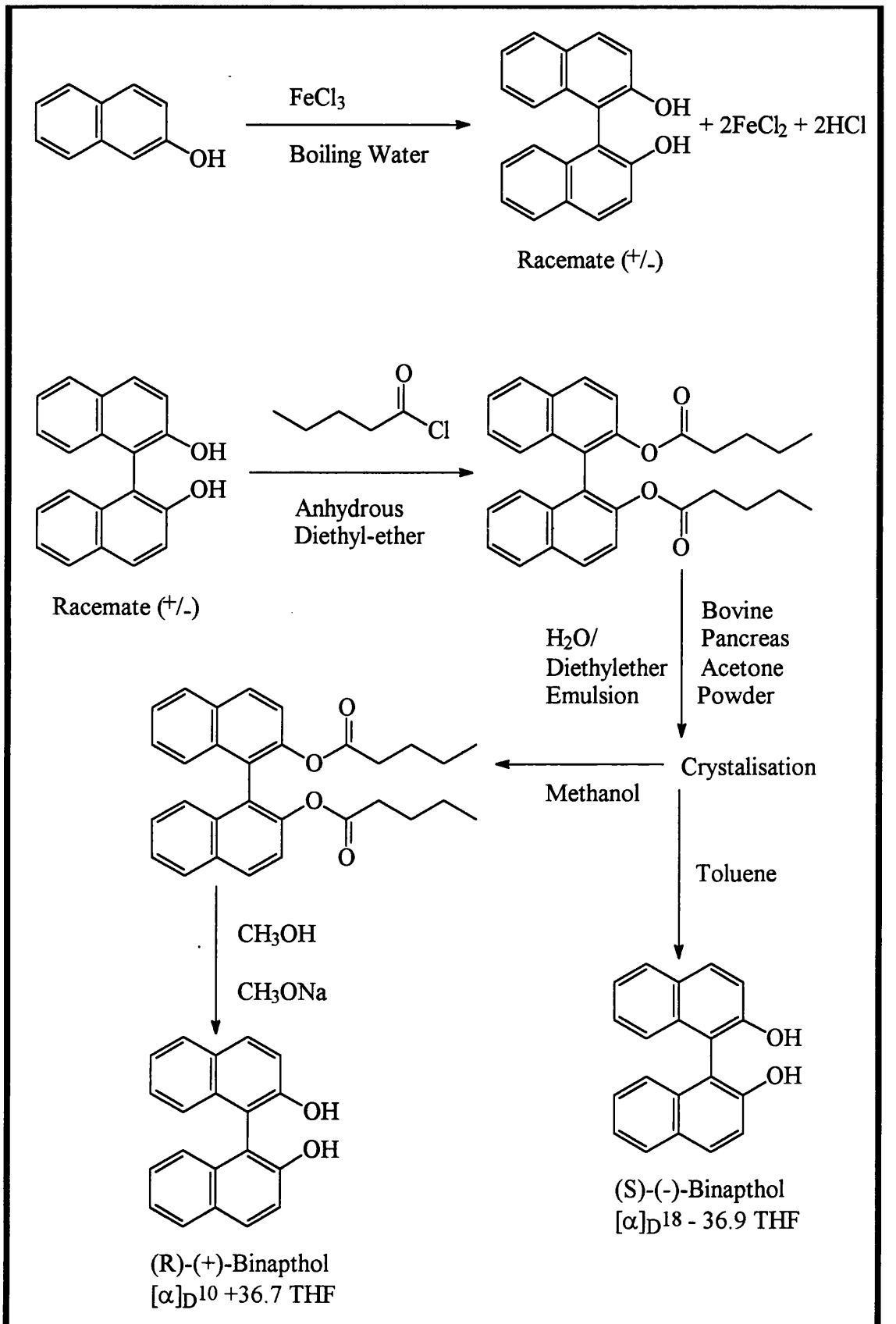


Figure 3.2; Synthesis and Resolution of Binaphthol

CHAPTER FOUR

SYNTHESIS, UTILITY AND SHORTFALLS OF HOMO-CHIRAL BINAPHTHYL MONO-AZA CROWN COMPOUNDS

4.1 - Preamble

The successful synthesis and resolution of 1,1'-binaphthol drove forward the work towards the design of a sensor that would incorporate and utilise this chiral unit with as simple a synthesis and operational mode as possible.

As an entry point into this field, a novel mono-aza analogue of bis-(dinaphtho)-22-crown-6 (fig.4.1), one of the most successful chiral crown compounds[86,92] synthesised by Cram, was chosen. It was hoped that the substitution of an oxygen with a nitrogen would not greatly affect the molecule's binding and chiral discrimination abilities. As an expansion, an alternative mono-aza crown (fig. 4.2) was also designed, which was expected to have improved complexation abilities over the first compound.

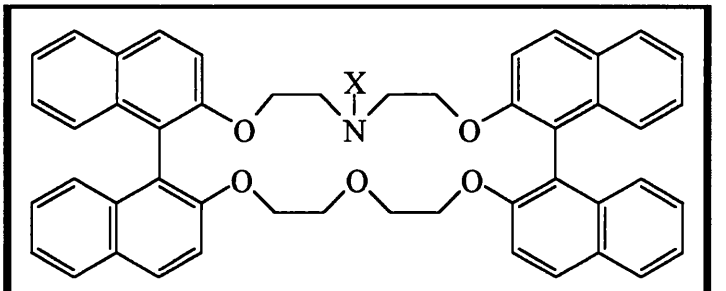


Fig. 4.1; X = H or Fluorophore

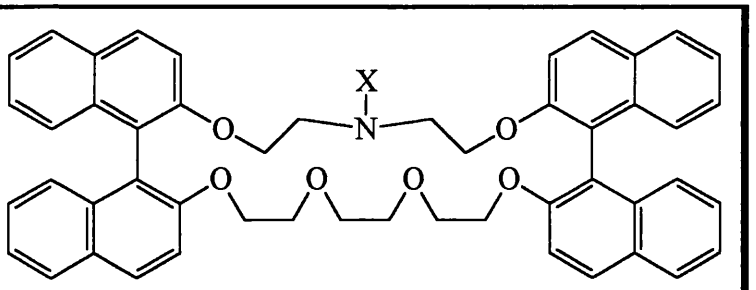


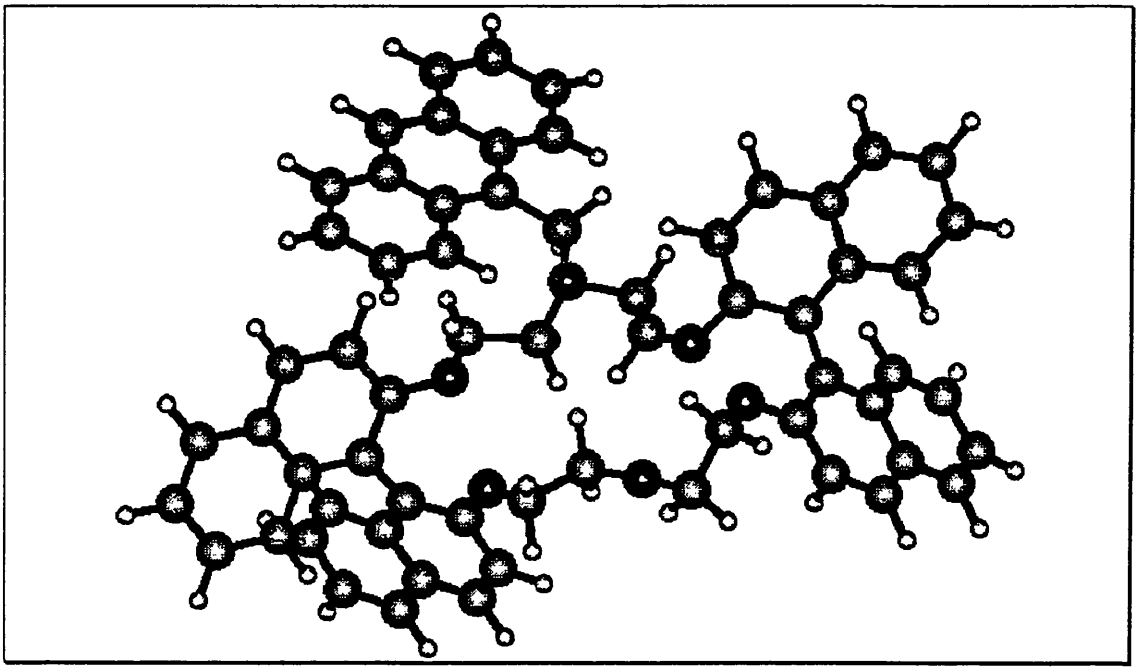
Fig. 4.1; X = H or Flurophore

The method of primary amine salt complexation of the proposed sensors would still follow Cram's three point binding principle, in which the three oxygens are hydrogen bonded to the protons of the amine salt (in bis-(dinaphtho)-22-crown-6 every second oxygen is hydrogen bonded). A question that arises from this is whether or not the binding mechanism is fluxional or rigid. The suggestion that it is rigid is far more likely when considering the re-organisation required in conjunction with the movement constraints that the binaphthyl units confer. However if the binding is fluxional, and this fluxionality contributes to the stability of the host-guest complex, then the replacement of an oxygen with a nitrogen would have a large effect (assuming the nitrogen has different binding abilities compared to those of the oxygen it replaces).

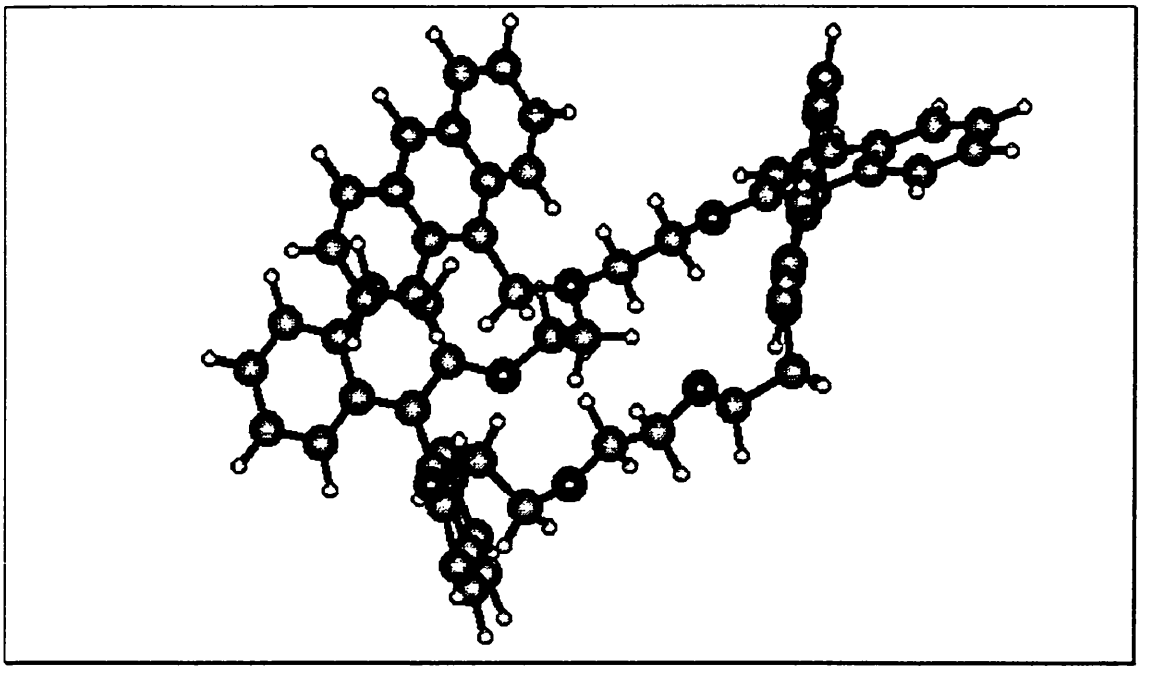
The second design should allow more conformations giving more stability. This design would also allow more freedom for movement in binding, which would allow a better fit for a guest but could lower selectivity. As this molecule would have more freedom to

move it would have more possible conformations and as such may require more re-organisation to wrap itself around a guest molecule. Hence the energy gained by complexation would be reduced by this re-organisation making complexation less attractive, according to Cram's energy rules of pre-organisation.

Model 4.1; Hyperchem Molecular Model of the Mono-aza 22-Crown Compound with 9-Methyl Anthracene as Fluorophore



Model 4.2; Hyperchem Molecular Model of the Mono-aza 25-Crown Compound with 9-Methyl Anthracene as Fluorophore



4.2 - Attempted Synthesis of 4,9,12,15,20-Pentaoxy-1-aza-5,6:7,8:16,17:18,19-tetra-(1,2-naphtho)-cyclodocosa-5,7,16,18-tetraene

The routes chosen for the synthesis of the desired parent compounds (see Figs. 4.3 & 4.4) were based on the initial synthesis of a mono-protected binaphthyl species. Papers[86,87] by Cram et al. had suggested that the synthesis of such species was quite simple with relatively high yields and easy isolation. However this proved to be the first in a line of difficulties experienced with this route, as yields were not as high as those obtained by Cram for his intermediates. This synthesis gave many problems, particularly when attempting to purify the products from each step, especially during the start whilst occupying the very lowly parts of a very large learning curve. As a consequence very few clean spectra were obtained for these intermediates, which made it difficult to appreciate if the reaction had gone to completion. The difficulties were compounded by the use of impure materials being taken through many synthetic steps. Impure mixtures of starting materials were used in the hope that they would not interfere, and that purification could be achieved more easily in later stages.

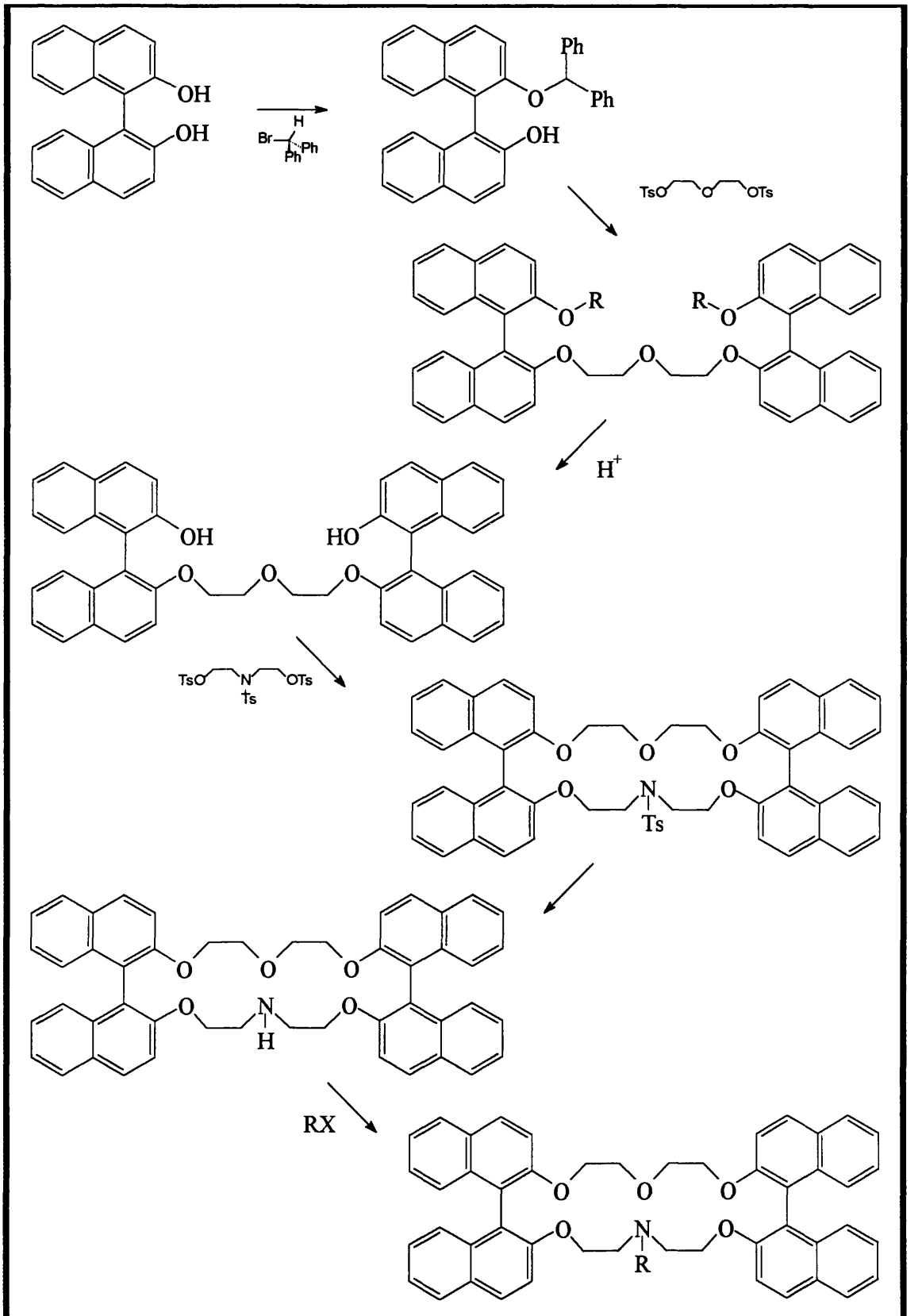


Figure 4.3; Synthetic Scheme for the Synthesis of First Mono-aza Crown Target

Although impure reactants were often used it was felt that this was not the only cause of the difficulties that were being experienced. This was reinforced later on in this work since there appeared to be many indications of inherent problems with the cyclisation reaction. The initial choice of the diphenyl methane protecting group is thought to have contributed much to the difficulties in purification. However from some of the spectral evidence it would appear that the initial tosyl protected crown compound was made, albeit in unknown quantity and purity. Attempts at the deprotection of these mixtures also failed to produce any of the desired compound in a pure or semi-pure state. The use of a tosylate as a protecting group perhaps shows poor synthetic strategy due to the harsh nature of the amine deprotection methods. It would probably have been better to have used alternative amine protecting groups, such as triflates, or to attach a stable fluorophore from the beginning. The use of a fluorophore would have its own difficulties associated with it and could only be accomplished with a few specific, unreactive, fluorophores.

4.2.2 - Attempted Synthesis of 1-Aza-4,9,12,15,18,23-hexaoxy-5,6:7,8:19,20:21,22-tetra(1,2-naphtho)-pentaicosa-5,7,19,21-tetraene

A clearer picture was obtained in the attempted synthesis of the larger mono-aza target compound (figure 4.2), the synthesis of which was undertaken some time after the initial investigations. In the synthesis starting from purified methoxymethyl ether mono-protected binaphthol, purification at each step resulted in the diol precursor to the parent crown compound being isolated. However it was found that all attempts at cyclising this intermediate failed and the target crown compound remained elusive.

The ^{1}H NMR spectrum for 1,20-Bis(methoxymethyl)-2,3:4,5:16,17:18,19-tetra-(1,2-naphtho)-1,6,12,1,20-hexaoxa-icosa-2,4,16,18-tetraene [2E] confirmed the synthesis of this molecule.

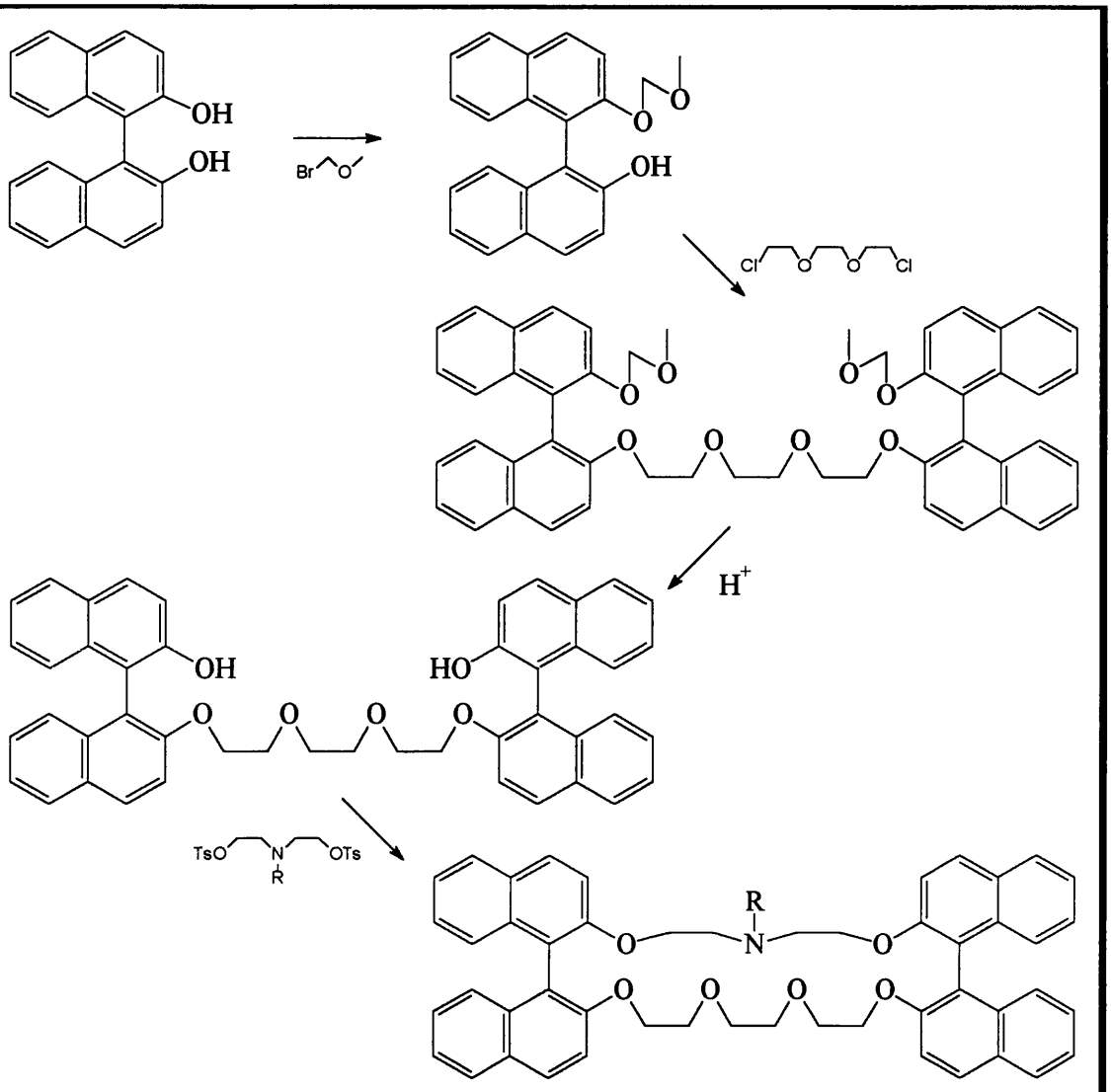
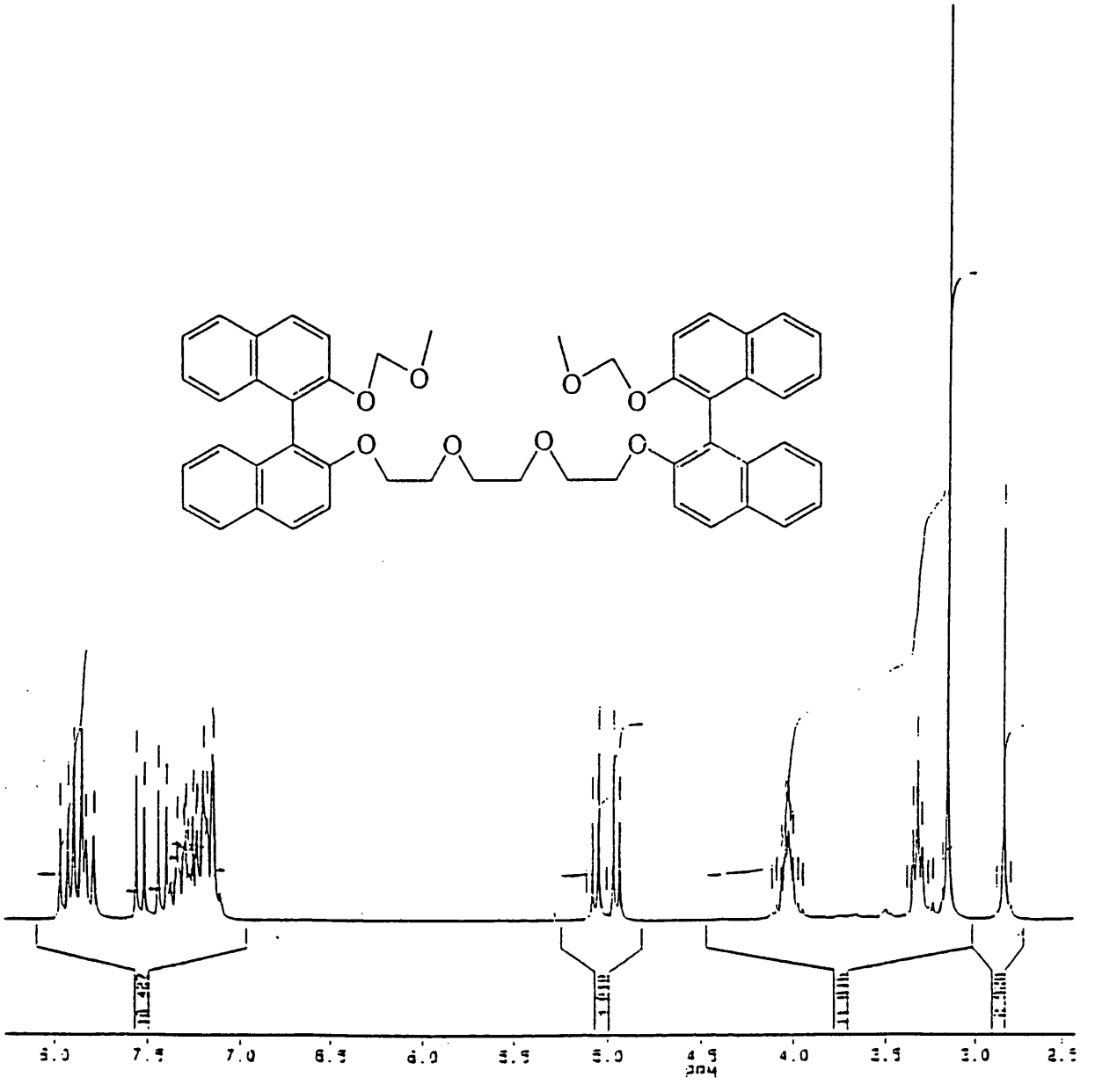


Figure 4.4; Synthetic Scheme for Synthesis of Second Mono-aza Crown Target Compound

The C_2 symmetry of the molecule simplified the spectrum to a certain extent, however the aromatic signals appear more complicated than they would normally as the binaphthyl unit has lost its C_2 symmetry axis. A number of doublets can be distinguished in the aromatic region with the rest appearing much more complicated. One of the most notable signals is that of the acetal methylene protons at ~5ppm which shows strong geminal coupling to giving the accustomed AA' splitting pattern. The acetal methyl group does not show any splitting and appears as a singlet at ~3.15ppm. The ether linkage between the two binaphthyl units appears as three signals at ~4ppm, ~3.3ppm and ~2.9ppm due to $ArOC\underline{H}_2$, $ArOCH_2C\underline{H}_2$ and $ArOCH_2CH_2OC\underline{H}_2$ methylene protons respectively. The signals at ~4 and 3.3ppm both show splitting patterns complicated by

geminal coupling arising from their proximity to the chiral axis, whilst the signal at ~2.9ppm appears as a singlet.

^{1}H NMR Spectrum of Protected Intermediate Diol [2E]

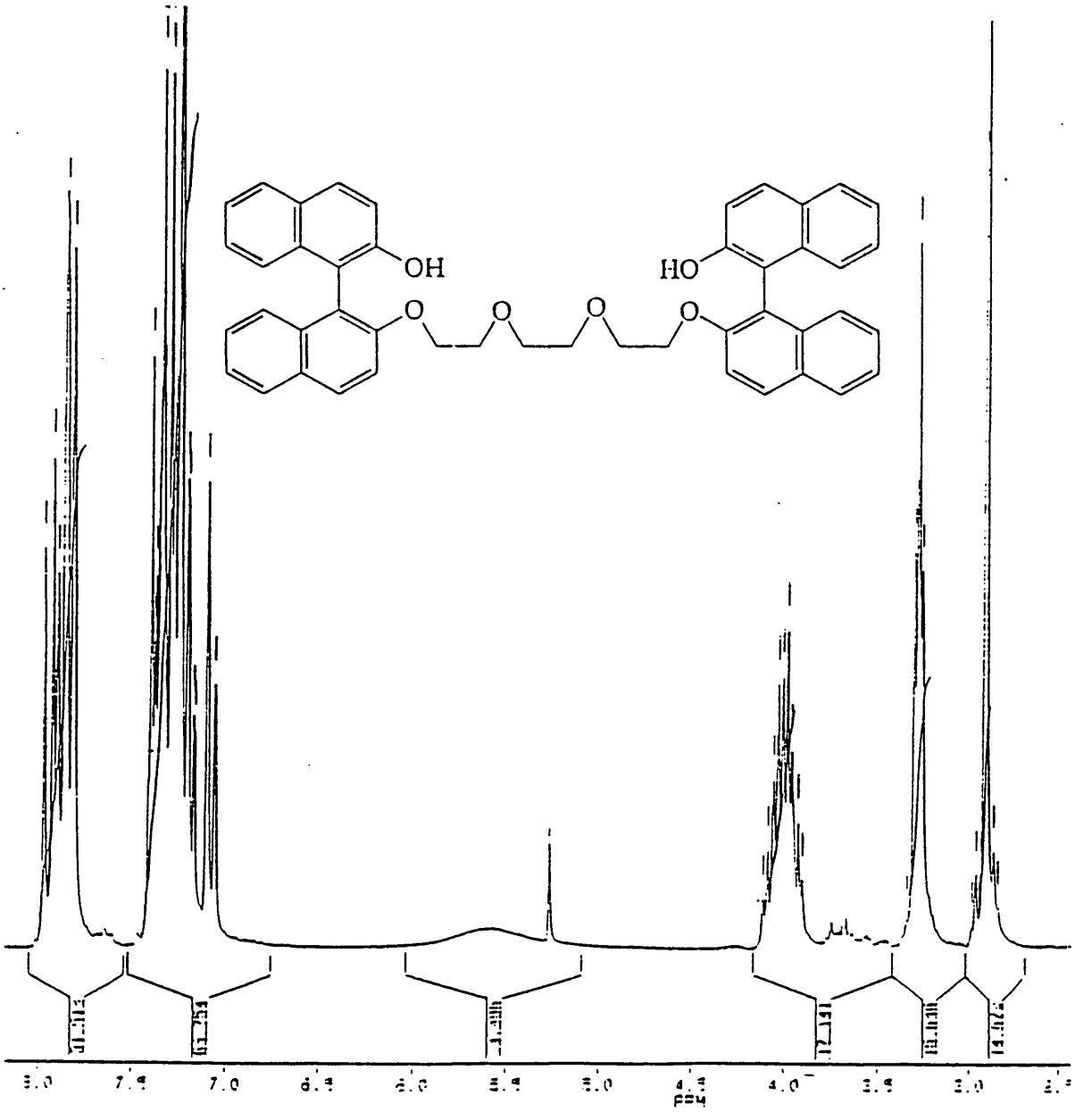


Deprotection of 1,20-Bis(methoxymethyl)-2,3:4,5:16,17:18,19-tetra-(1,2-naphtho)-1,6,12,1,20-hexaoxa-icosa-2,4,16,18-tetraene [2E] gives 1,18-Dihydroxy-1,2:3,4:15,16:17,18-tetra(1,2-naphtho)-5,8,11,14-tetraoxy-octadeca-1,3,15,17-tetraene [2F], the loss of the protecting methoxymethyl (MOM) group can easily be seen by NMR. In the ^{1}H NMR spectrum of 2F the aromatic region is seen to have changed slightly with all the signals now being difficult to distinguish. The acetal signals at ~5ppm and ~3.15 have both been lost giving rise to a very broad singlet at ~5.6ppm corresponding to the hydroxy proton of the naphthol groups. A sharp singlet can also be

seen in this region due to slight contamination with dichloromethane. The methylene protons of the ether linkage appear similar with three signals at ~4ppm, 3.3ppm and ~2.8ppm, again corresponding to the $ArOC\underline{H_2}$, $ArOCH_2C\underline{H_2}$ and $ArOCH_2CH_2OC\underline{H_2}$ methylene protons respectively. The signal at 4ppm shows a broad splitting pattern complicated by geminal coupling arising from its proximity to a chiral axis. The signal at 3.3ppm is not as complex, as it 'feels' the effects of the chiral axis less strongly as the protons are in more flexible sites. Again the signal at ~2.8ppm is much simpler as it is more flexible and further from the chiral axis and it can rotate into its nearest neighbour by a C_2 rotation.

Again this spectrum is as expected for this molecule with the integration fitting well even with a small amount of impurity present. Its ^{13}C NMR spectrum is also as expected.

^{1}H NMR Spectrum of Intermediate Diol [2F]



The diol compound [2F] appeared even less reactive than its smaller analogue in the reaction with diethanolamine-tritosylate. This may have been due to better co-ordination of alkali metals, with the larger diol being able to wrap itself around more efficiently. However there is no conclusive proof of this theory, only evidence loosely based on experiments that were not designed to prove or negate this.

It is not known whether the lack of reactivity shown by these intermediates arises mainly from steric hindrance or from any electronic effect of the bound oxygens which would make them far less nucleophilic. It was also noted that the synthesis of symmetrical compounds such as those of Cram are made preferentially via a route that goes through a di-armed binaphthol which reduces the possibility of alkali metal co-ordination and any subsequent loss in reactivity of the nucleophilic phenoxide oxygens. However Cram also used stepwise synthetic schemes where both di-armed binaphthyl and two binaphthyls are joined via a single arm are isolated which gave similar yields of macrocycle.

To overcome the proposed lack of reactivity of these compounds an alternative synthetic scheme was devised which would use intermediates which were less able to bind alkali metals (see figure 4.5).

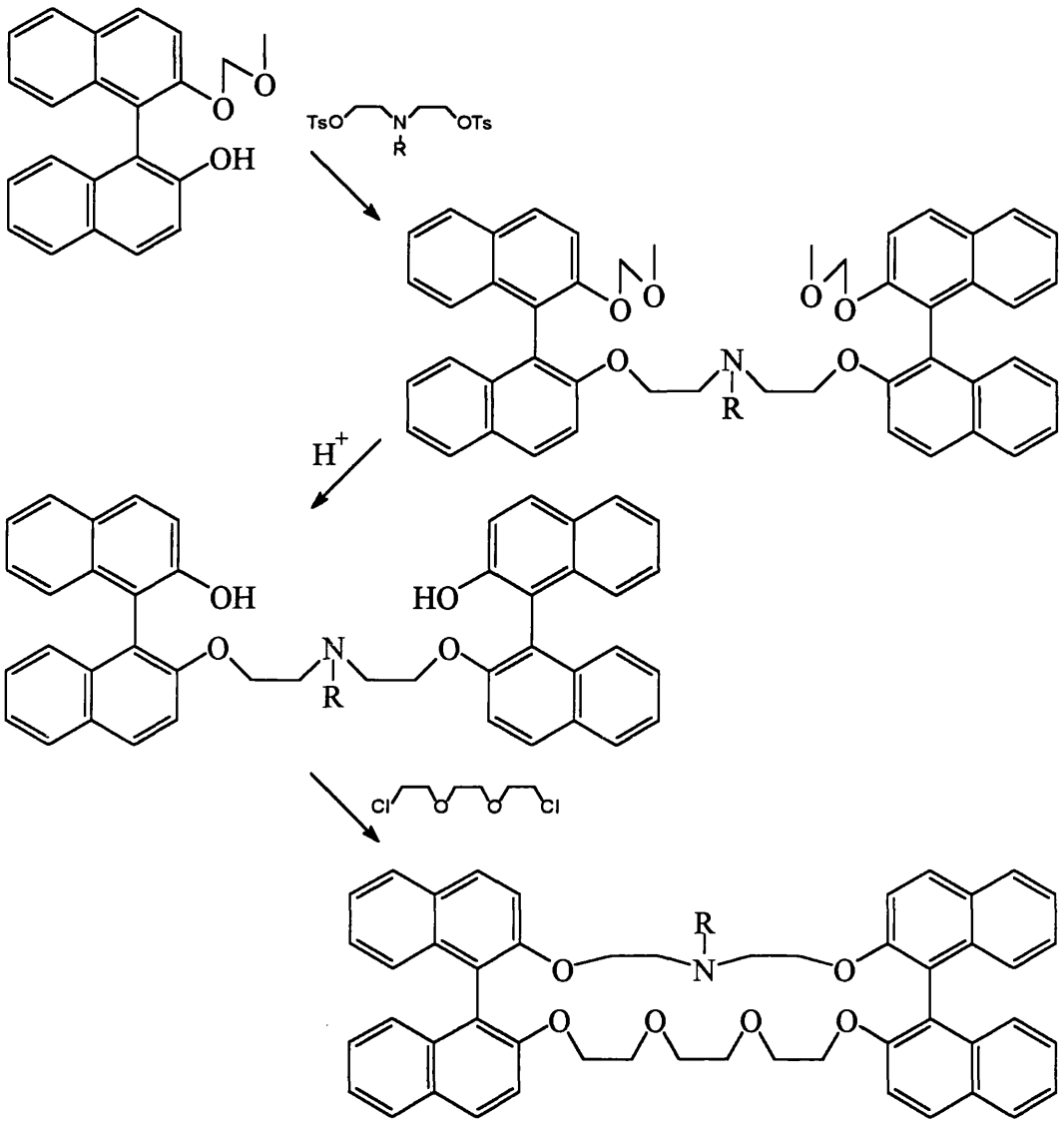


Figure 4.5; Alternative Synthetic Scheme for Target Compound 2

From the initial work design development progressed. In later strategies we became interested in π-π interactions and their potential for being incorporated into the binding mechanism for a larger variety of guests, where more functionality was required i.e. more than one type of binding site.

Would the sensors have worked?

The question of whether Bis-(dinaphtho)-22-crown-6 and related compounds would show any change in fluorescence when binding chiral primary amine salts must be addressed as there does not appear to have been any previous study. Spectral change

may be brought about by any spatial conformation change; however as the free host is flexible, which allows many spatial conformers, there is unlikely to be any great spectral change with respect to binding and any restraint this brings. Spectral change may also be brought about by electronic changes such as π-π overlap. If an aromatic primary amine guest was used there is the possibility that there would be overlap of host and guest aromatics resulting in π-π electronic interactions and with this spectral change. In his first full paper on host-guest chemistry, Cram noted with interest[87] that the complexes that formed between binaphthyl-20-crown-6 with arenediazonium ions exhibit yellow to red colours suggesting π-π interactions, whereas no such colours were observed for complexes between 18-crown-6 and arenediazonium ions. The proposed π-acid π-base interactions would also apply equally as well, if not more so, to the other compounds, of similar structure, shown in chapter one.

Why incorporate a Nitrogen?

The mono-aza compounds were chosen as any work involving them would be novel and the free amine or protected amine should offer some answers to the above questions. Also, more importantly, the mono-aza compounds offer far more possibilities for structural design flexibility and transduction methodology. The replacement of an oxygen with a nitrogen in the manner proposed allows the retention of a C_2 axis and all the implications that this entails.

If the nitrogen is able to play a role in the complexation of primary amine salts, which seems quite possible based on the pK_a values of amine salts and free bases, then this opens up the following arguments.

The use of a nitrogen may be an unfortunate or a very serendipitous arrangement (or have absolutely no effect what so ever). When acting as a sensor for amine salts, interactions between the sensor nitrogen (basic) and the amine salt (weakly acidic) should occur. Whether or not the base strength of the sensor nitrogen is stronger or weaker than the free amine of the guest salt is perhaps not very relevant as long as there is some interaction between the two. It is suspected that there would be some interaction between the sensor nitrogen and the amine salt, with the worst case scenario being complete proton exchange from analyte guest to host sensor which may cause loss of

complexation. This is unlikely as the pK_a difference between the two should not be conducive toward this.

Some pK_a values of protonated amines

Amine	pK_a
Methyl amine	10.65
Dimethyl amine	10.73
Trimethyl amine	9.81
Ethyl amine	10.80
Diethyl amine	10.49
Triethyl amine	11.01
Aniline	4.63
N-Methyl aniline	4.84
N,N-Dimethyl aniline	5.15
Glycine	9.78
N-Methyl glycine	10.12
N,N-Dimethyl glycine	10.34

An advantage gained by the molecule incorporating a nitrogen is that many derivatives could be relatively easily obtained from one parent compound. Substitution should be easily achieved from the basic aza macrocycle parent. This means that the need to incorporate the chosen arm from the very start of the synthesis, which would present its own difficulties, is not necessary. The derivatives made can then be adjusted to increase the molecule's binding and signalling ability.

Without further design strategy there are several groups that could be attached to the nitrogen that would change its binding capability its signalling capability or both. If a fluorophore was attached then this could be used to directly act as the integral component of signal transduction or as a concentration standard for intensity ratio methods.

With a well thought through design and a bit of good fortune the nitrogen may be integrally utilised as part of a PET (Photo-Electron Transfer) transduction system with the use of a chromophore such as 9-methyl-anthracene. This would require the nitrogen to perform two tasks; 1- it must have a low enough ionisation energy to quench the fluorophore's excited state and 2- it must play some part in the binding of the guest or at

least feel the effect of such binding, in order that its ionisation energy increases beyond that allowing the quenching of the fluorophore. With previous thoughts on the use of the nitrogen in the binding of amine salts and of other sensors which operate using PET strategies the requirements placed upon the nitrogen are not unlikely.

Photo-Electron Transfer systems are said to generally work best when the electron donor and the electron acceptor (the nitrogen and the fluorophore respectively) are separated by a single (aliphatic) carbon spacer. It is unlikely that the nitrogen, in its designated situation, could quench the fluorescence of any of the naphthyl units (of the binaphthyls) let alone all of them. Thus when unbound, a suitable fluorophore connected to the nitrogen via a single carbon spacer could have its fluorescence quenched and when bound, the oxidation potential of the nitrogen should be sufficiently increased such that it becomes energetically unfavourable for PET and thus quenching to take place. A PET system could allow the use of a fluorophore arm, as the chiral discrimination would originate with which guest bound more strongly and with how each guest actually bound to the macrocycle such that one isomer may be more inclined to interact with the nitrogen more strongly and as such give a greater PET diminished fluorescent signal.

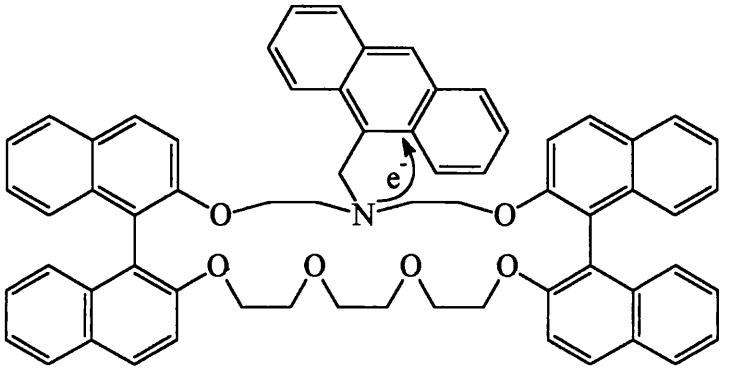


Fig. 4.6; Proposed Sensor Showing Photo-Electron Transfer Quenching Mechanism

A simple system that could act as a PET system could be synthetically achieved using 9-bromo-methyl-anthracene, which is relatively cheap and could be incorporated from the start.

In these investigations it is presumed that the fluorescence signal being looked at will be that coming from the fluorophore that has been attached to the nitrogen of the macrocycle and that the fluorescence spectra of this, and that of the binaphthyl units making up the molecule do not overlap with each other. To overcome fluorescence overlap it would be possible to partially hydrogenate the binaphthyl units.

Another strategy that could be employed would be for a suitable arm, containing a naphthol unit, being attached to the nitrogen, such that upon complex formation with a

free amine the naphthol could lose its proton, causing a very large electronic effect with consequent fluorescence changes. This methodology of spectral change through 'saltex' formation would be the fluorescent equivalent to the phenolic azo-acerands of Kaneda[33,35] (see chapter 1).

Another very basic idea would be to attach a thiol to the nitrogen such that the molecule could be bound to a gold electrode.

CHAPTER FIVE

SYNTHESIS, UTILITY AND SHORTFALLS OF SIMPLE XYLYL-BINAPHTHYL HETERAPHANES

5.1.1 - Preamble

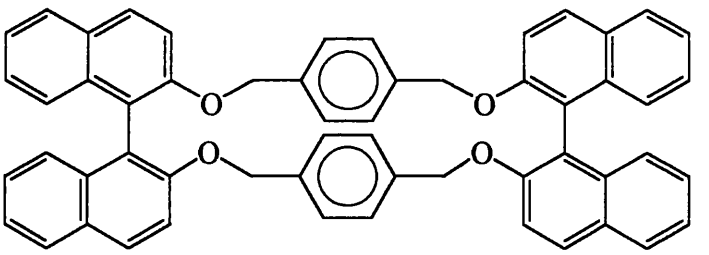


Figure 5.1 para-Xylyl-Binaphthyl

With the lack of success in the synthesis of the mono-aza crown compounds, other designs were sought after in the area of chiral sensors. It was felt that the designs chosen should be kept as simple as possible in order that they could be easily made, which should also serve the purpose of increasing synthetic confidence. Also the designs should be kept as symmetrical as possible so that their structures belong to as high a point group as possible which would minimise the number of host-guest complexes formed by the sensor (a C_2 axis is all that is required in a macrocycle to make the approach of an analyte the same from both directions). The first designs were of heteraphanes that could be easily derived from homo-chiral binaphthol in one pot reactions with α,α'-dibromo-para-xylene and meta-xylene precursors (see figures 5.1 and 5.2). Heteraphanes are members of the cyclophane family with the further stipulation that they contain hetero-atoms within the links between the aromatic units.

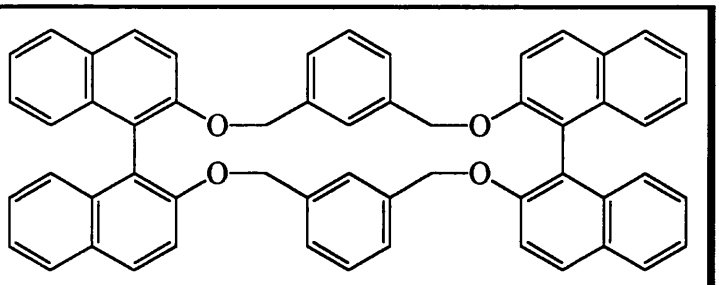
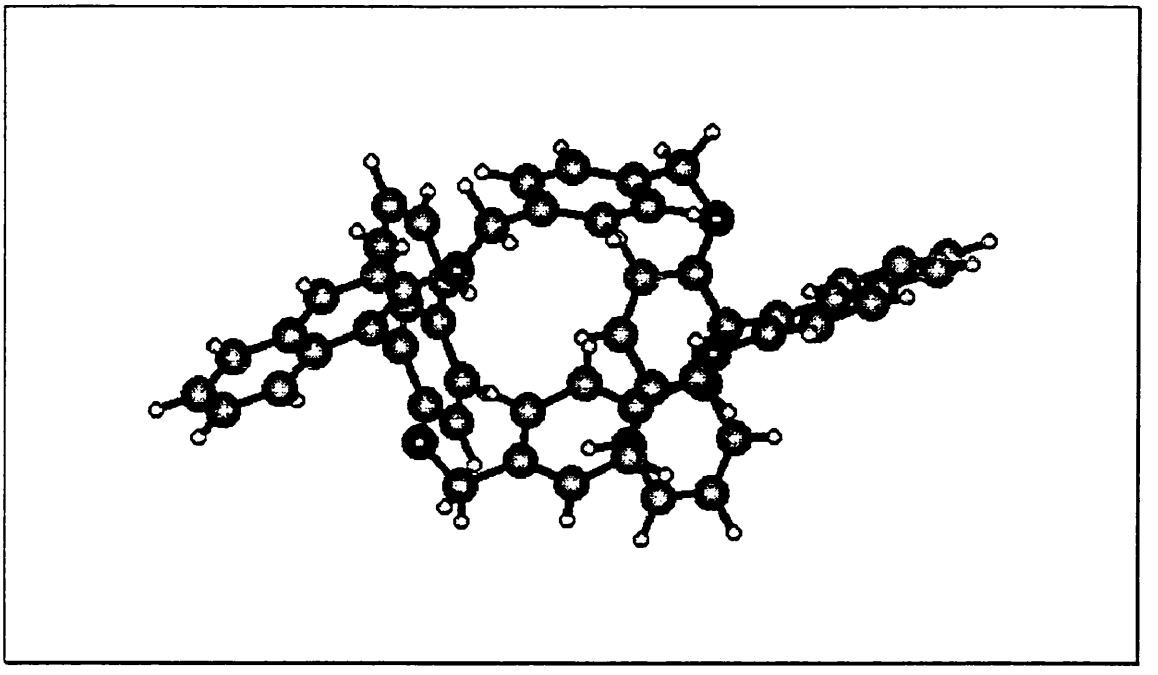


Figure 5.2 meta-Xylyl-Binaphthyl Dimer

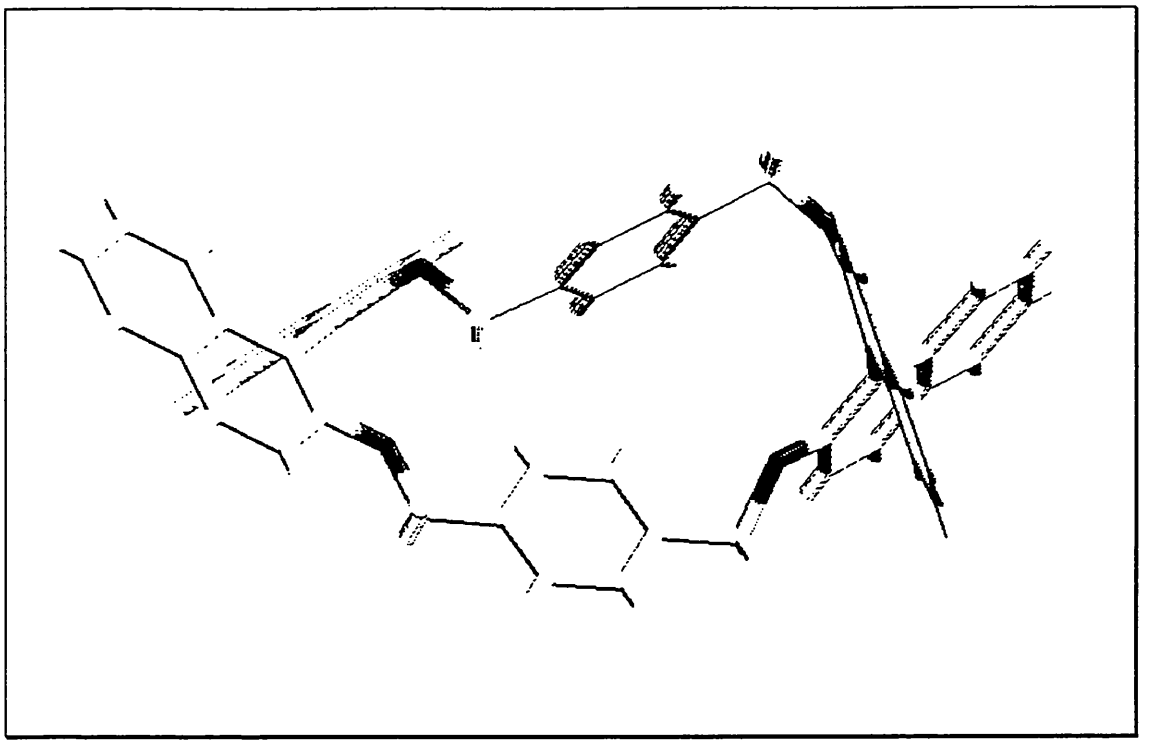
Molecular models of these compounds showed that the cavities formed could be capable of including suitable guest species. These cavities would have a high degree of chirality conferred upon them due to the molecule's rigidity, which arises from the limited number of points of rotation and bending. These compounds belong to the D_2 point group. However it was thought that depending on their rigidity they may show some loss of this symmetry. Molecular models showed two basic structural forms, in which the xylyl groups are situated face to face and in which they are face to edge. Where they are situated face to face excimer formation is possible, which if observed could act as an indicator of intramolecular distance and strain and of guest inclusion.

The target compounds were synthesised using similar methods. The conditions used were chosen such that they would hopefully promote the formation of a bis(α'bromo-xylyl)-binaphthyl intermediate compound which would in turn promote the formation of the preferred di-oligomeric product. However all of the reactions gave mixtures of products (see spectra 5.1 - ^{1}H NMR).

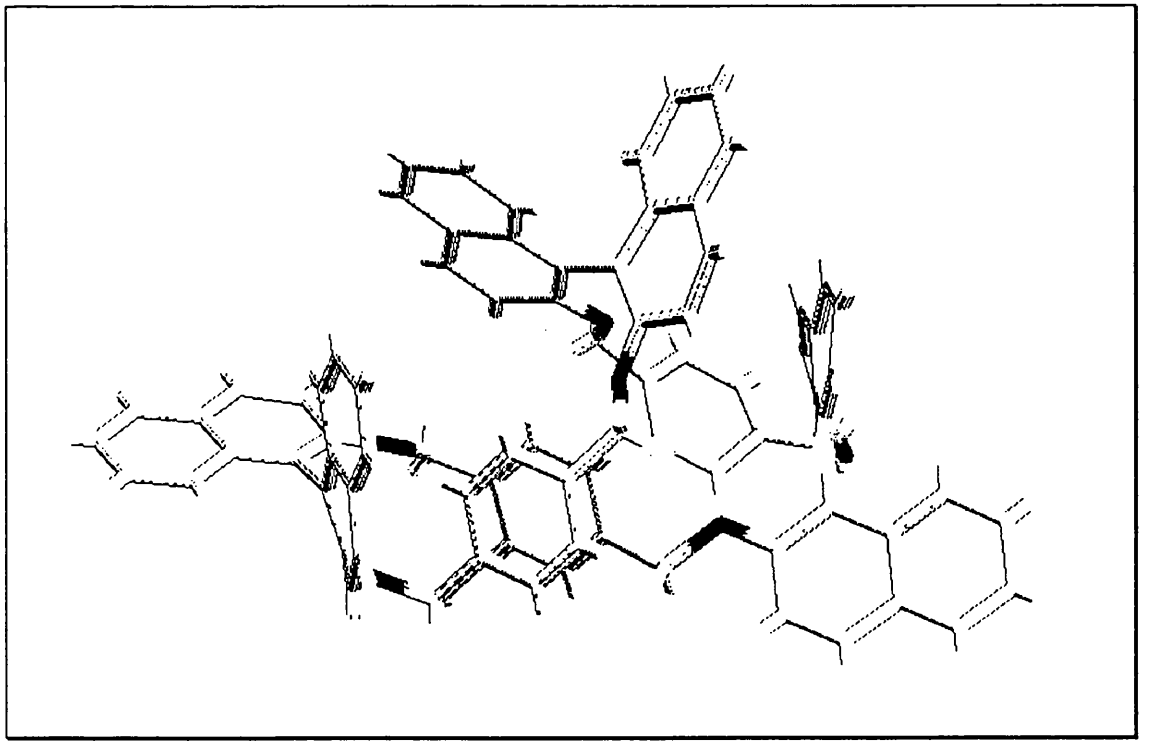
Model 5.1; Hyperchem Molecular Model of para-Dimer Heteraphane



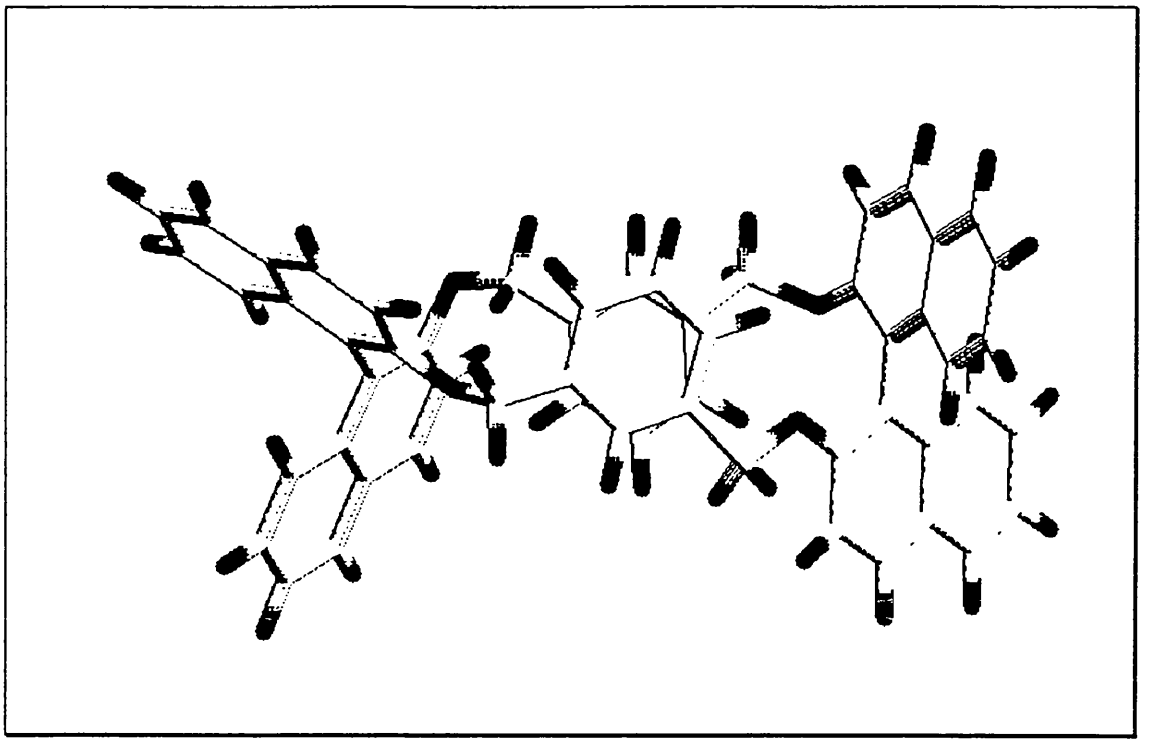
Model 5.2; Alchemy Molecular Model of para-Dimer Heteraphane



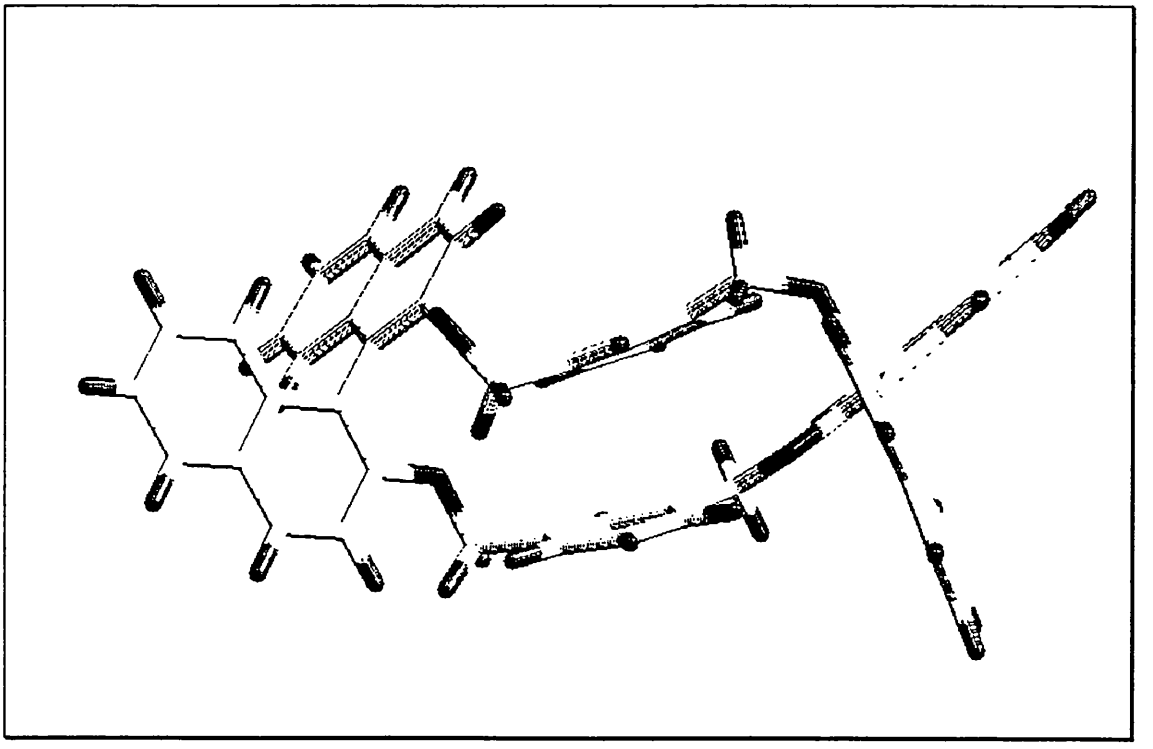
Model 5.3; Alchemy Molecular Model of para-Trimer Heteraphane



Model 5.4; Alchemy Molecular Model of meta-Dimer Heteraphane



Model 5.5; Alchemy Molecular Model of meta-Dimer Heteraphane



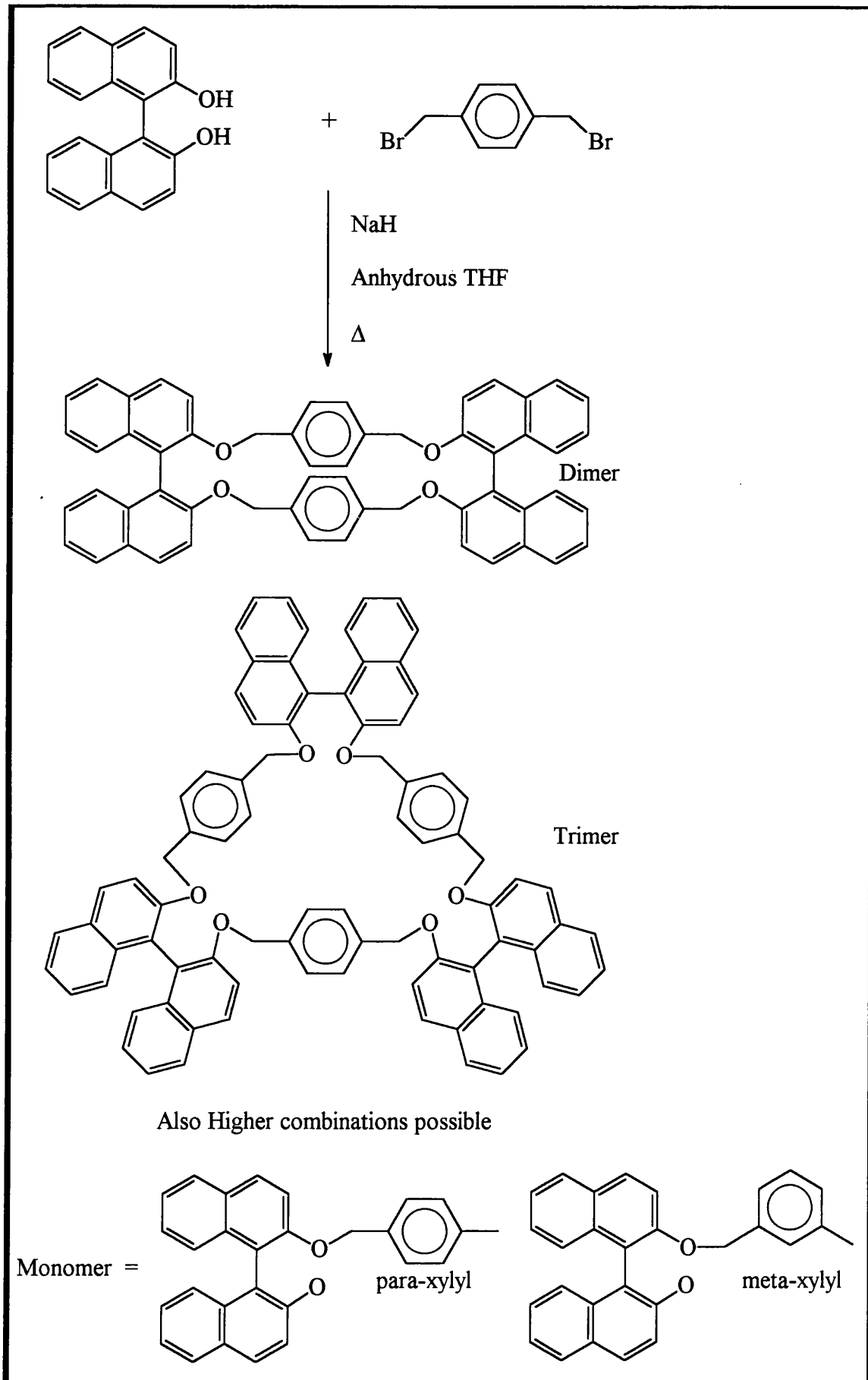
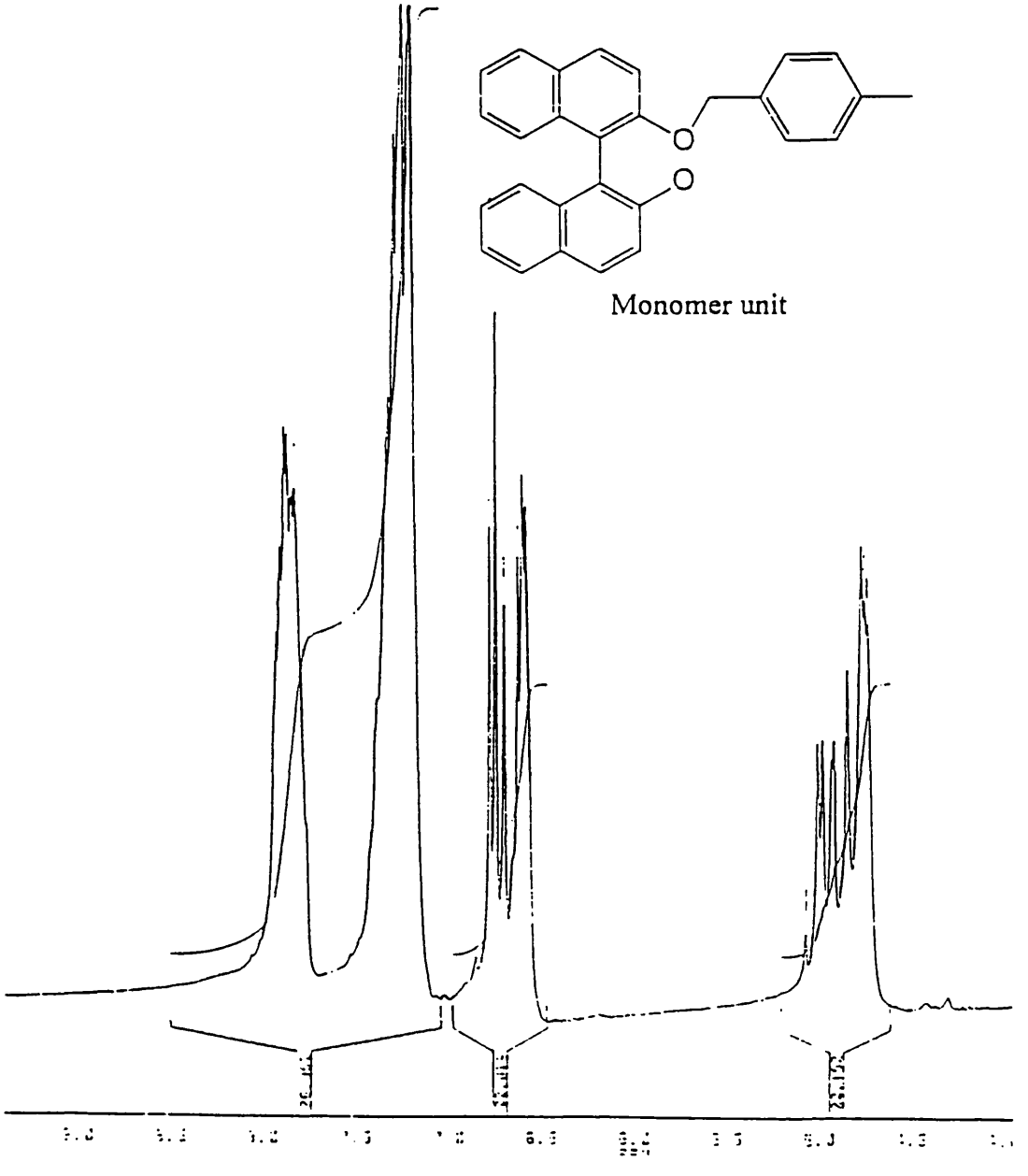


Figure 5.3 - General Synthetic Scheme for Synthesis of Xylyl-Binaphthyl Heteraphanes

Base catalysed racemisation was not considered to be a problem in these reactions as the bromo-xylyl unit is very reactive towards nucleophilic attack and as such the reaction should take place rapidly. The mixtures of oligomers obtained were difficult to purify, most likely due to their similar solvation properties and the relatively low concentration of each. The mixtures were purified by column chromatography after fractional crystallisation was unsuccessful.

5.2.1 - Heteraphane Spectral Interpretation

^{1}H NMR Spectrum of para-Heteraphane Mixture



Monomer unit

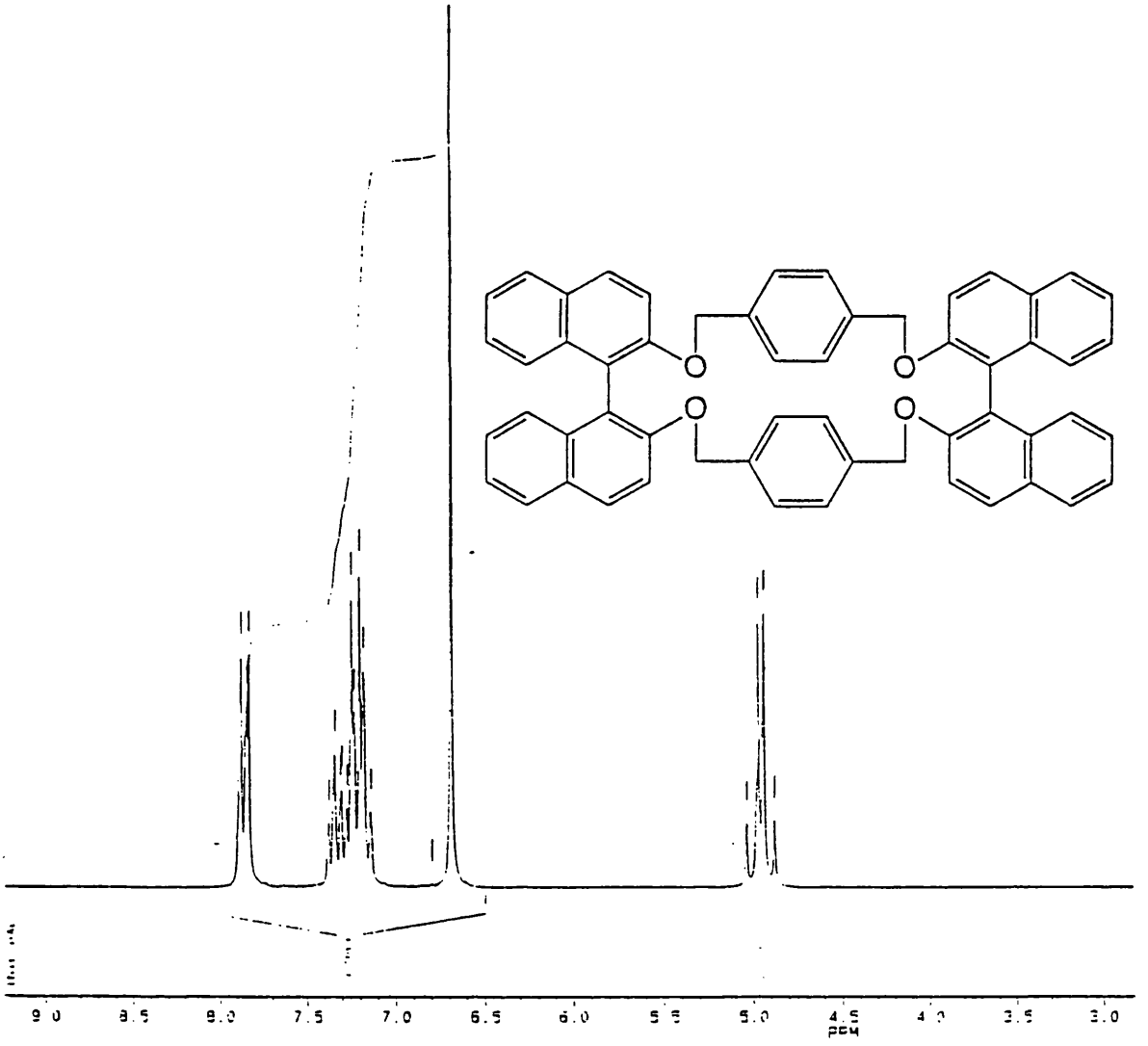
The ^{1}H NMR spectrum of the crude product from the reaction for the para-xylyl heteraphanes shows four distinct groups of protons. The two groups of signals at ~8ppm and ~7.5ppm correspond to the naphthyl protons and appear broad and indistinguishable. The signals at ~6.8ppm correspond to the xylyl protons where ~5 different signals can be made out. The signals at ~5ppm correspond to the xylyl methylene protons, where at least four different signals can be distinguished. Thus there are at least three discrete oligomers in this mixture, a dimer, trimer and tetramer or higher, with polymer and the possibility of catenanes also being present.

The NMR data shows no CH_3 groups, no CH_2Br groups and no hydroxyl groups. The splitting of CH_2 groups seen in the ^{13}C NMR spectrum of the crude products is due to the presence of similar quantities of very similar products.

For all of the heteraphanes discussed their IR spectra show CH_2 and CH stretching peaks and there no -OH peaks. The FAB Mass Spectral data, although not accurate MS, do show molecular ions in the correct positions. They also show ions at $(M+Na)^+$ and $(M+K)^+$, which in these cases is more likely to have arisen from the leaching from glassware into solvents, than any great metal ion complexation ability of the phanes themselves. It is clear however that there must be some association however weak, at least in the mass spectrometer itself.

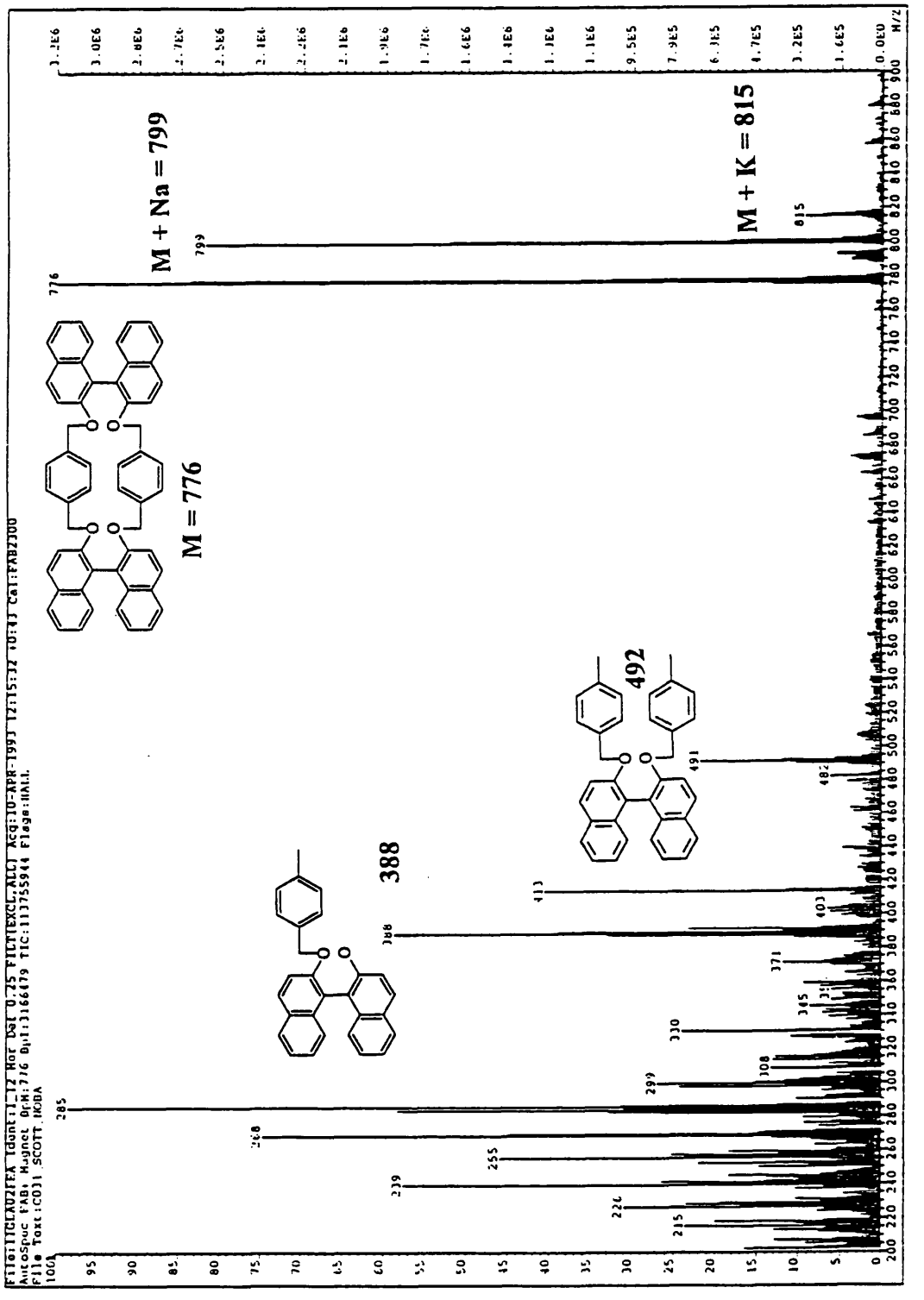
The ^{1}H NMR spectrum of the purified para-dimer 2,3:4,5:14,15:16,17-tetra-(1,2-naphtho)-8,9,10,11:20,21,22,2-di(1,4-phenyl)-1,6,13,18-tetraoxa-tetraicosa-heteraphane appears as we expected and gave good correlation with the integration. There are four groups of signals, two at ~8 and 7.4ppm which correspond to the naphthyl protons, a singlet at 6.7ppm which corresponds to the xylyl protons and a signal at ~5ppm which corresponds to the xylyl methylene protons. The xylyl protons give rise to a singlet which shows that the xylyl must be symmetrically substituted. The xylyl methylene protons show a splitting pattern of two doublets [AB' type splitting] with a coupling constant of ~12Hz which is consistent with geminal coupling. The splitting between these two doublets (12-13 Hz) indicates that each proton occupies a distinct environment which is attributed to the conformational rigidity of the molecule. The ^{13}C NMR spectrum also appeared as expected.

^{1}H NMR Spectrum of para-Heteraphane Dimer [4A]

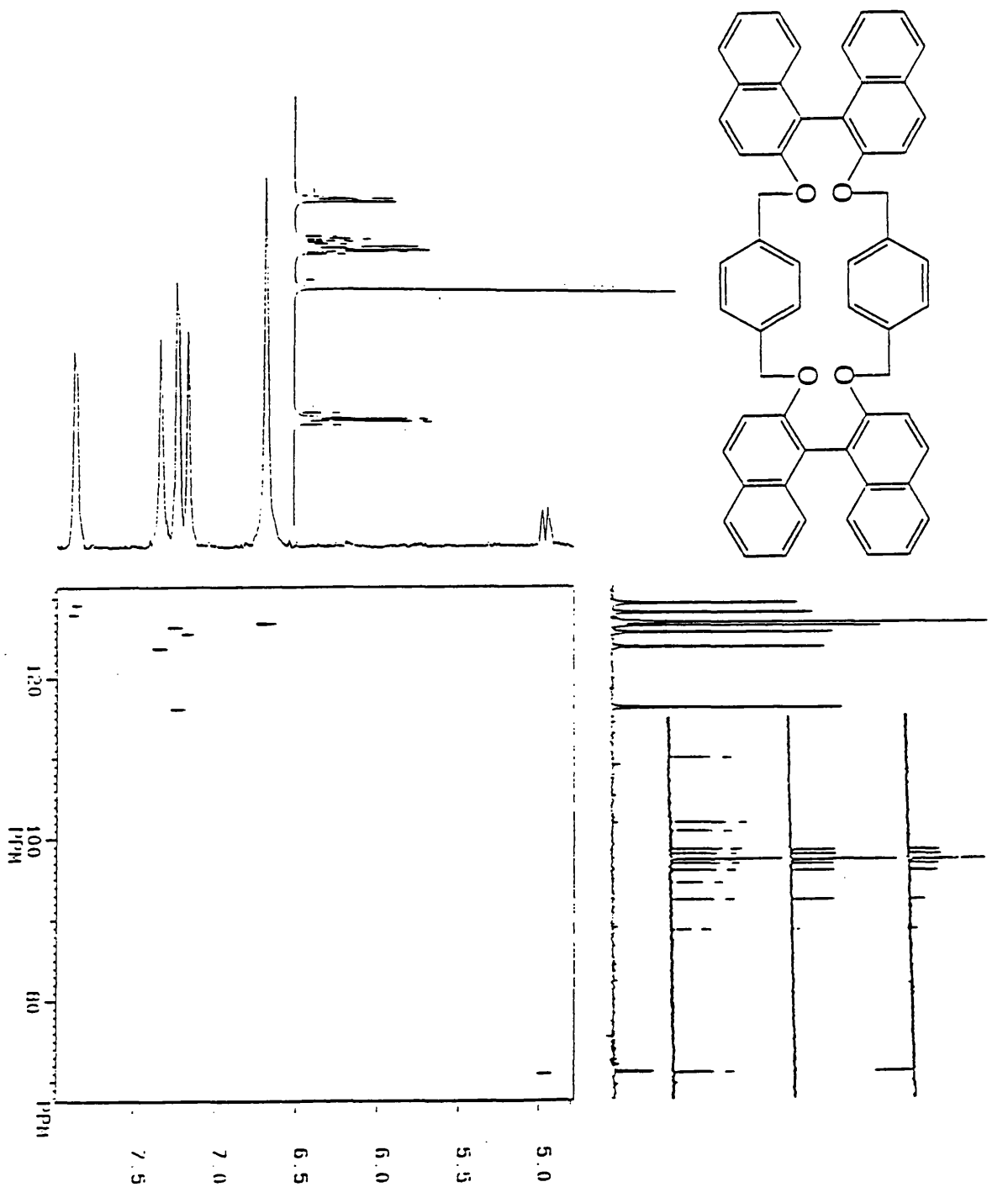


The FAB mass spectrum of the dimer clearly shows the expected parent ion at M = 776 with $(M+Na)^+$ = 799 and $(M+K)^+$ = 815 also observed. No ions of heavier mass were observed, confirming that it was the dimer species. The fragment ions correlate well with the expected fragmentation of a molecule with the proposed structure. It should be noted that the areas between the molecular ion and the fragment ions, which contain little but noise, are a good sign that this is a discrete molecule.

para-Heteraphane Dimer FAB Mass Spectrum



4.7 Tesla Proton-Carbon 2-Dimensional COSY Spectrum of para-Heteraphane with ^{1}H and ^{13}C NMR inserts



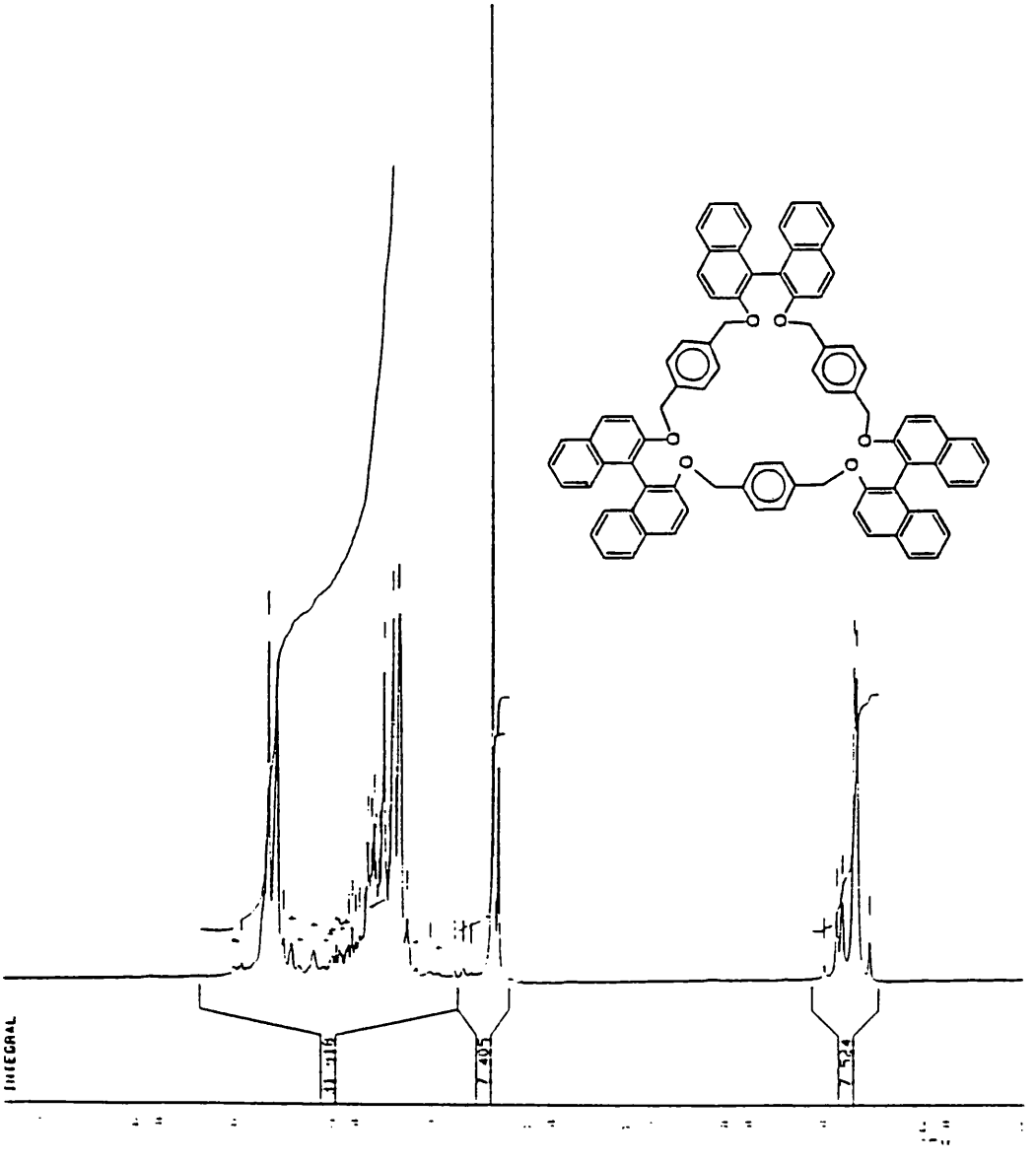
A ^{13}C versus ^{1}H 2 dimensional NMR spectrum was also obtained for the dimer p-heteraphane. This clearly shows that the doublets at 5ppm are due to geminal coupling of the xylyl methylene protons. This also shows that the naphthyl aromatic signal at

8ppm arises from two proton environments and the naphthyl signal at ~7.5ppm arises from four proton environments. Also the xylyl signal at ~6.7ppm does indeed arise from a single proton environment which confirms the suspected symmetry of a fully cyclised species.

As there is only one xylyl aromatic and methylene signal the D_2 symmetry of the dimer appears to be real, at least in the NMR time-scale. The difference in environment that each proton shows is a direct result of the chirality imposed by the binaphthyl units.

If the sample was not enantiomerically pure (if a mixture of R,R, S,S and R,S was present) then more than one xylyl signal would be expected. If enantiomerically pure R,R or S,S compound was present then we would only expect a single signal. Thus racemisation does not appear to have been a problem at least to the extent of the purity levels observable by NMR.

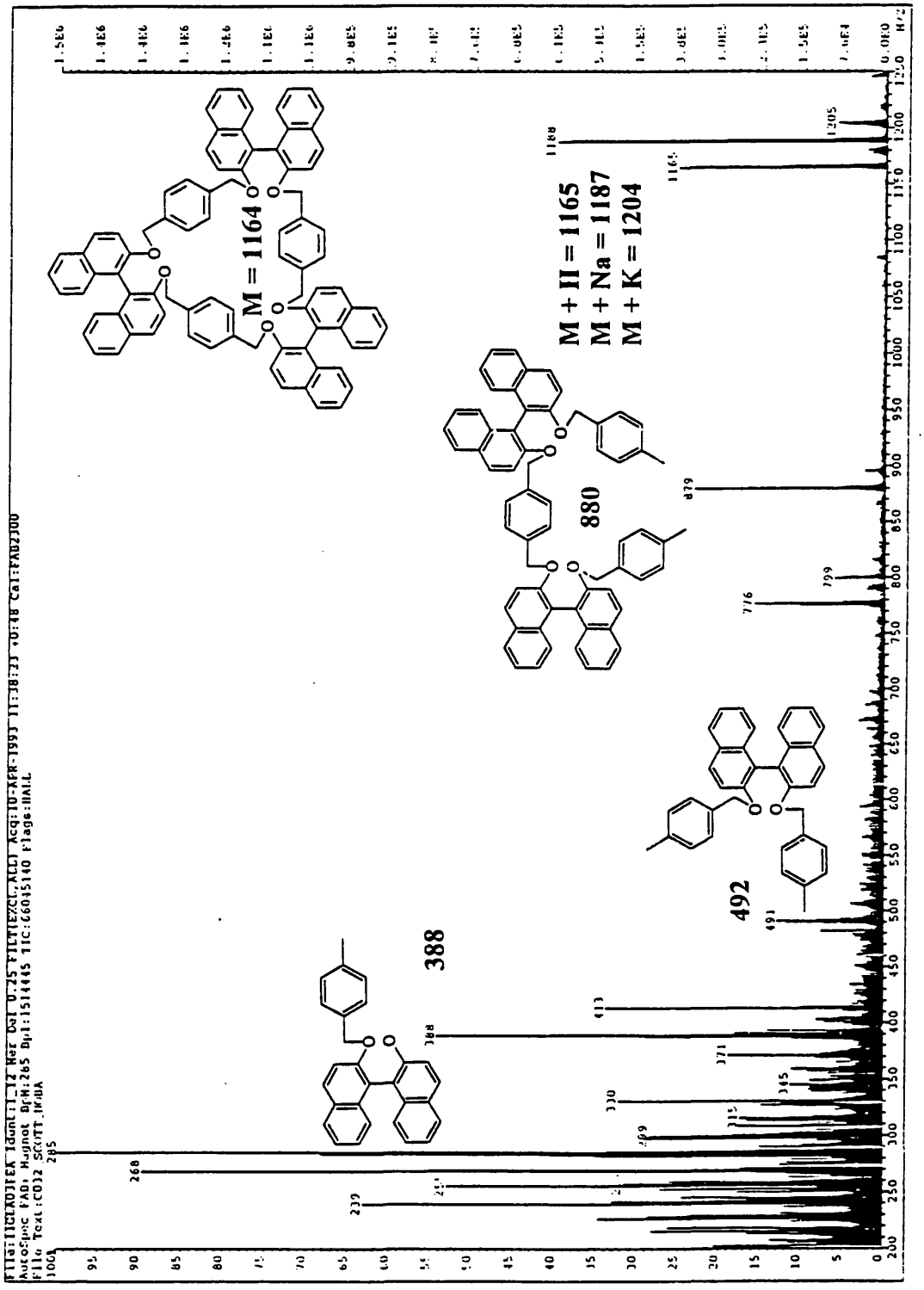
^{1}H NMR Spectrum of para-Heteraphane Trimer [4B]



The trimer essentially shows the same coupling pattern as the dimer with differences arising around a slight shift downfield for the xylyl aromatic protons and a slight upfield shift for the xylyl methylene protons. From the NMR of the crude mixture it is clear that the methylene protons of the different oligomers do have slightly different shifts. The trimer methylene signals are however almost coalescent appearing at first glance to be a non-stoichiometric triplet. Again this is an AB system arising from the chirality imposed by the binaphthyl units with the signal peaks closer together signifying that the protons have a greater similarity in their environment than those seen in the dimer. The coupling constant is ~13Hz which is as expected for such enantiotopic coupling.
The para-trimer NMR sample is clearly slightly impure containing an amount of the dimer species. It is also of note that the trimer xylyl protons are found at higher ppm - shifted downfield - and the xylyl methylene protons are at lower ppm - shifted upfield - in comparison with the corresponding dimer.

The FAB Mass Spectrum (SIMS) of the para-trimer clearly shows the expected parent ion $(M+H)^+$ = 1165 (alternatively M^+ = 1165, if contains one ^{13}C) with $(M+Na)^+$ = 1187 and $(M+K)^+$ = 1204 also observed. No ions of higher mass were observed, confirming that this was indeed the tri-oligomer. The expected fragmentation pattern is observed with the corresponding regions with no detectable fragments.

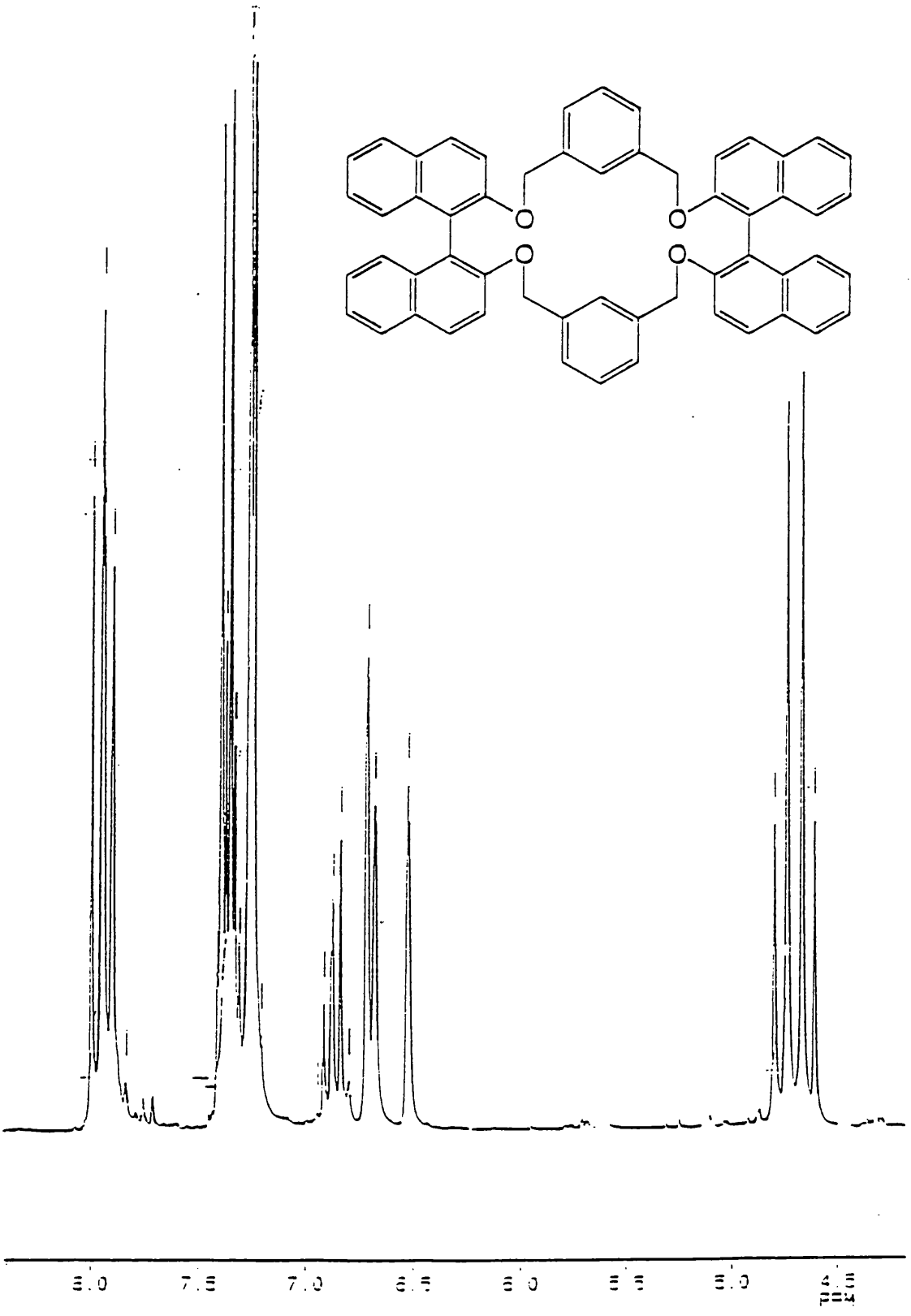
para-Heteraphane Trimer FAB Mass Spectrum



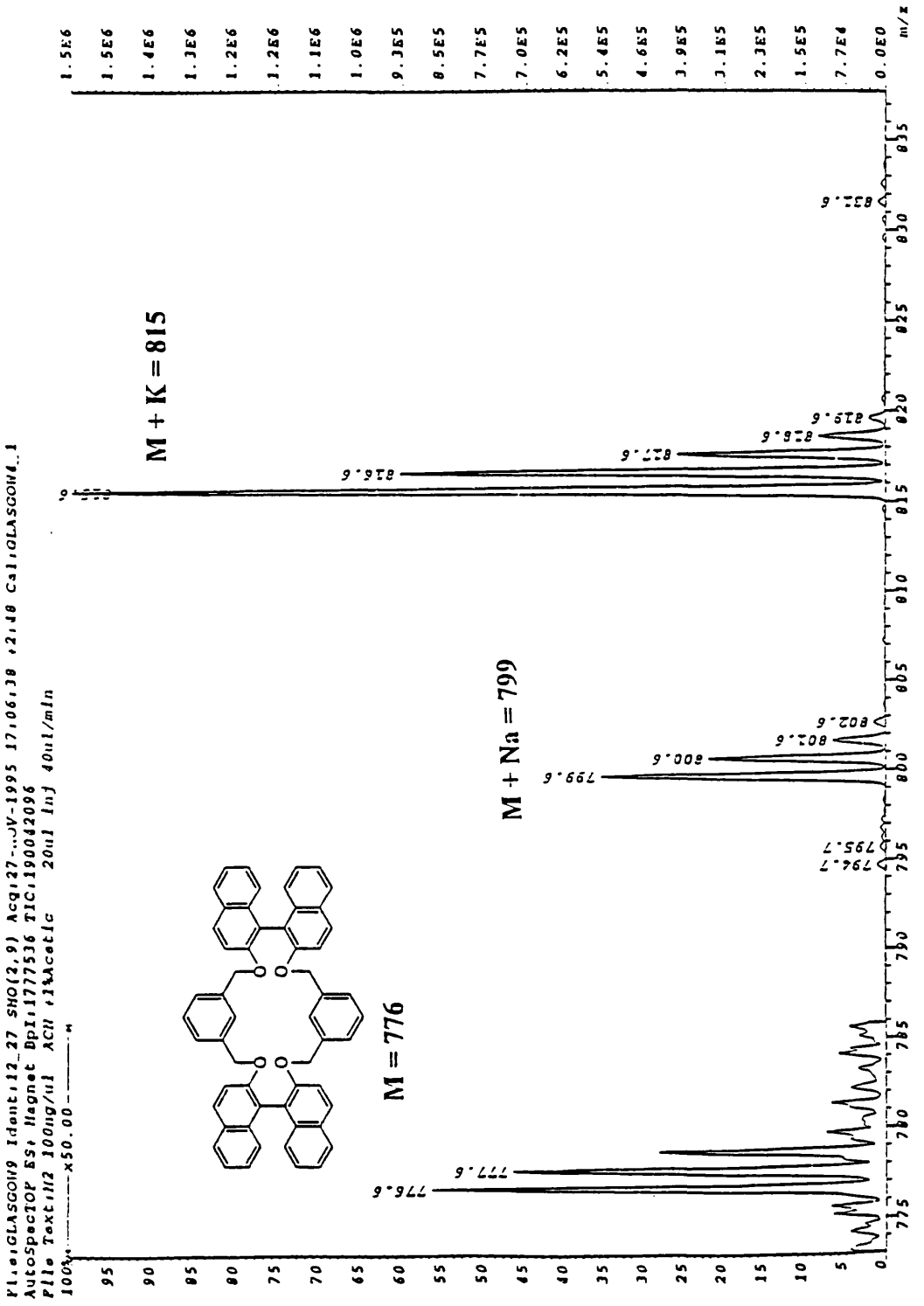
The ^{1}H NMR spectrum of the crude product from the reaction for the meta-xylyl heteraphanes again shows four distinct groups of protons. These correspond to the same groups as in the para heteraphanes. The signal for the xylyl protons is more complicated, as expected, due to the different positioning of its methylene substituents. The crude ^{13}C NMR spectrum for the meta-phanes showed at least three CH_2 peaks, two of which were very similar and the third was at higher ppm (downfield). The downfield peak was very sharp and was possibly due to a small amount of monomer, a small quantity of which was later obtained in a semi pure form.

The ^{1}H NMR spectrum of the purified meta-dimer 2,3:4,5:13,14:15,16-tetra-(1,2-naphtho)-8,9,10:19,20,21-di(1,3-phenyl)-1,6,12,17-tetraoxy-docosa-heteraphane is as expected. The xylyl signal can be broken down into the expected triplet (integrating for 1) at ~6.9ppm, doublet (integrating for two) at ~6.7ppm and singlet (integrating for one) at ~6.55ppm. The signal for the xylyl methylene protons at ~4.75ppm, is found at lower shift (upfield) compared with the equivalent para-heteraphane. There is very distinct geminal coupling (~12Hz) with each proton in a well defined environment again corresponding to the molecules size and rigidity.

^{1}H NMR Spectrum of meta-Heteraphane Dimer [4C]

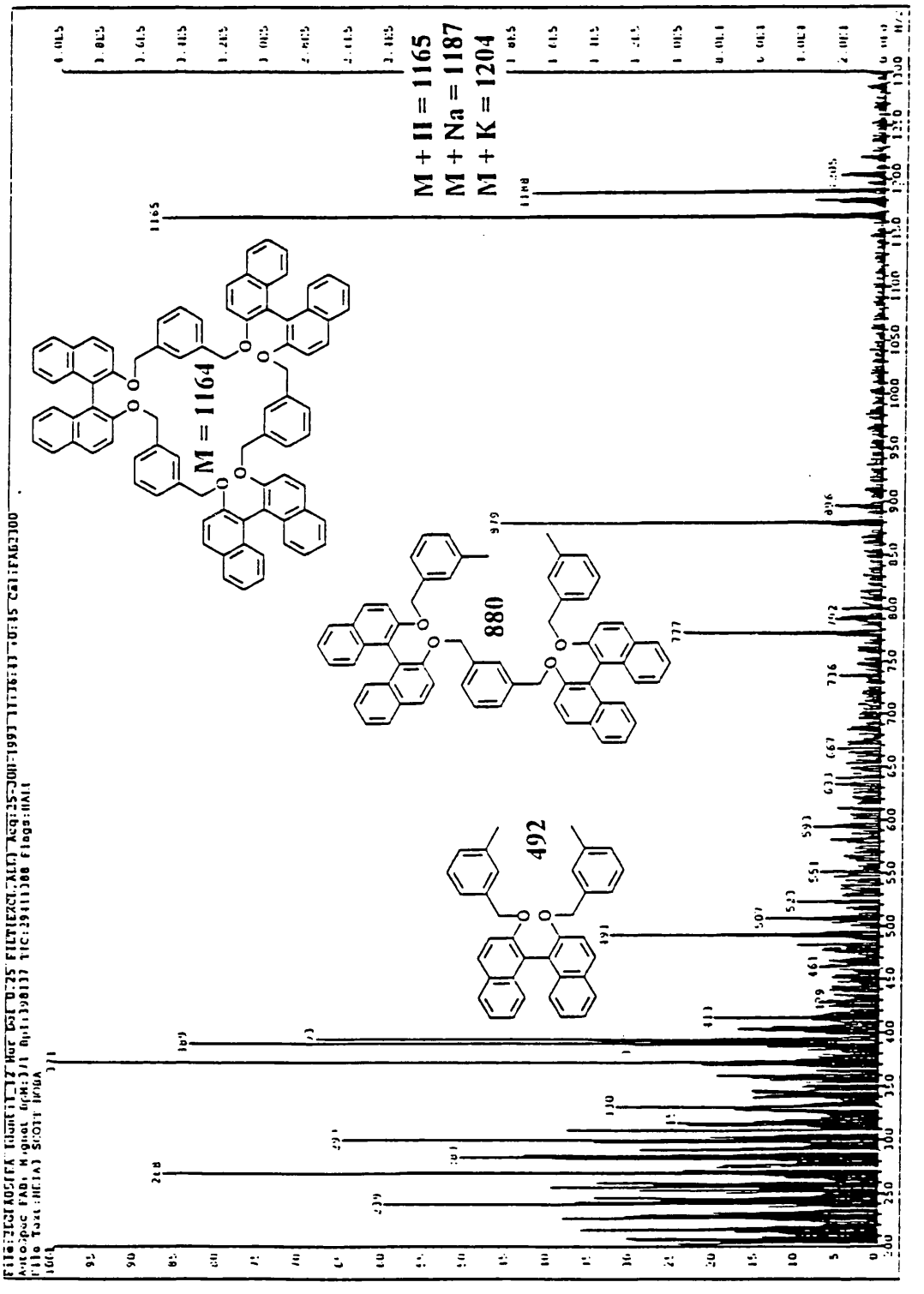


meta-Heteraphane Dimer Electrospray Mass Spectrum



The FAB mass spectrum clearly shows the expected parent ion at M^{+} = 776 with $(M+Na)^{+}$ = 799 and $(M+K)^{+}$ = 815 also observed. No ions of heavier mass were observed, confirming that it was the dimer species.

meta-Heteraphane Trimer FAB Mass Spectrum [4D]



The FAB mass spectrum of the meta-trimer clearly shows the expected parent ion $(M+H)^+ = 1165$ (alternatively $M^+ = 1165$, if contains one ^{13}C) with $(M+Na)^+ = 1187$ and $(M+K)^+ = 1204$ also observed. No ions of higher mass were observed, confirming that this was indeed the tri-oligomer. The expected fragmentation pattern is observed with

the corresponding regions with no detectable fragments. The NMR spectrum of this oligomer was also consistent with what is expected.

In the para-xylyl synthesis there was, as molecular models predicted, no monomer formation observed. However in the meta-xylyl reactions a small amount of what was believed to be the monomer was unexpectedly obtained. The NMR spectrum of this sample, which was not purified further, revealed that it was impure with eluent residue. The THF used in the column eluent gave very good separation however it tended to give residues which were not very volatile, no matter how rigorously purified beforehand.

5.2.2 - General NMR

The purified samples show single methylene carbon signals, which were confirmed to correspond to the peaks at around 5ppm in the proton spectra from the para-xylyl dimer 2-D NMR spectrum. The proton NMR spectra, especially those of the lower oligomers show definite splitting patterns that correspond to geminal protons in a chiral environment. The splitting appears as an AB type pattern, with the doublets being more distinct the smaller the oligomer which also relates to an increased rigidity. This is to be expected as the smaller the oligomer, the more rigid with less (degrees of) freedom the molecule would have. This expectation is reinforced when these spectra are compared with the spectra of much more conformationally free molecules. In the spectra of the higher oligomers the splitting of the geminal protons is much less distinct, more coalescent, however the coupling constants are still in the expected range of 12-13Hz. The spectra of related non-cyclic compounds show much simpler signals arising from their respective methylene protons. In compound 5A the OCH_2 protons appear as a triplet with splitting ~13Hz and the CH_2Br protons as a singlet; in the failed first synthesis the major binaphthyl-bis(xylyl-butyl ether) shows both sets of CH_2 protons as singlets.

5.2.3 - General Mass Spectrometry

Fast Atom Bombardment Mass Spectrometry was performed using a NOBA matrix (Nitro-ortho-benzyl alcohol), which is a relatively π-electron deficient aromatic and therefore could interact with these type of heteraphane hosts although no interaction was

observed. The observation of $(M+Na)^+$ and $(M+K)^+$ is common for samples that have been standing in glass vessels in solution where metals are liable to leach out. In FAB MS sodium salts such as NaCl are sometimes added to the matrix mixture to promote cationisation, thus increasing the intensity of any $(M+Na)^+$ peaks seen.

Other common factors in the interpretation of mass spectra, include the elements present and their isotopic masses and abundance. Elements present in these compounds are C H O Br Cl and N, the important isotopes with their masses and relative abundance are as follows;

Isotope	Mass	Abundance
^{1}H	1.0078	99.98
^{12}C	12.000	98.90
^{13}C	13.003	1.10
^{14}N	14.003	99.64
^{16}O	15.995	99.80
^{35}Cl	34.969	75.80
^{37}Cl	36.965	24.20
^{79}Br	78.918	50.50
^{81}Br	80.916	49.50

Hence for a molecule with 50 carbons, the abundance of the peak containing one ^{13}C isotope would equal $50 \times 1.1\% = 55\%$ of the peak containing only ^{12}C isotopes. For a 1:1 ratio of parent molecular ions with the expected mass and with the expected mass plus one, the molecule would have to contain 91 carbon atoms.

5.3.1 - Evaluation

Although it was recognised early on that it would be unlikely that these compounds could act as chiral sensors, it was hoped that they would show some useful discrimination.

It was an aim of the synthesis of these compounds to investigate the actual cavity shape with the specific aim of determining if the cavity could and would include a guest and if so if there was any observable chiral discrimination.

5.3.2 - NMR Experiment

To determine if the dimers 4A and 4C could form complexes an NMR experiment was carried out. A series of ^1H NMR spectra were taken of the dimer heteraphane over which the concentration of a homo-chiral electron accepting organic shift reagent [N-(3,5-dinitrobenzoyl)-α-methyl benzyl amine] was increased (from 0.25:1 to 1:1). The spectra were taken with the concentration of the host remaining constant. No changes in the shift, splitting pattern or intensity of the xylyl protons were observed over the course of this experiment. There were also no obvious changes in the appearance of the binaphthyl protons throughout this experiment. However these signals were much more difficult to follow as they are subject to more complex coupling and some of the guest proton signals also appear in this area.

A change in the shift of some of the guest protons was thought to have been observed between the original NMR spectrum of the chiral guest on its own and in the presence of the host. There were no changes in shift of any of the host proton signals throughout the experiment. The experiment was not reversed to investigate the possibility of a shift in the guest proton signals.

From this experimentation it was concluded that there were no obvious signs that the guest was included into the host's cavity. However the possibility that the guest was interacting with the naphthyl units is not excluded.

Thus we are looking at a molecule whose cavity does not have very good complexation capabilities and any it does have are likely to be in competition externally with the naphthyl units.

4B and 4C have four oxygens which may be used to bind amine salts. However if a 3-point binding principle operates, any host guest complex formed would be strained at the very least. With the para-xylyl spacer the dimer heteraphane oxygens could not interact with a primary amine salt within reason, due to the length and rigidity of the para-xylyl spacer so could not form complexes this way. The meta-xylyl spaced heteraphane is more flexible than the equivalent para-xylyl and as such has more conformational freedom, however it is again unlikely that a primary amine salt could be bound (via the ether oxygens in a three point binding arrangement) without a large amount of strain or at the very least binding would be high energy and as such would be unlikely except in very unusual circumstances.

In these xylyl heteraphanes we were assuming that charge transfer interactions would be the driving force behind guest inclusion. However as xylyl groups are not donating enough in character to allow strong interaction (have high ionisation energy) it was not unexpected that no interaction was seen. The NMR experiments were performed in $CDCl_3$, which is not very polar and as such there is not likely to be much difference in the micro-environments inside and out of the cavity, thus little or no energy would be gained from inclusion. The use of other solvents that may have been more conducive towards guest inclusion was not looked at as in the end it would still be a poor sensor.

As there was still a strong interest in the actual shape of all of the molecules cavities it was hoped that crystals of suitable quality, of the free host or with included guest, could be grown in order that a structure could be determined. Many solvents and conditions were tried without success, including solvents that would themselves perhaps be included in the cavity, for example nitro-benzene and benzene.

5.3.3 -Attempted synthesis of para-dimer molybdenum tri-carbonyl complex

With the crystallisation attempts of these compounds being unsuccessful for both the free host and inclusion compounds other possible methods for obtaining a crystal structure were sought after. It was noted that the ionisation potential of the xylenes is very similar to that of mesitylene and as such it may offer a small chance for the formation of a π-bonded organo-metallic complex which, if lucky enough to form, could be highly crystalline (form crystals of crystallographic quality). A small amount of the purified para-dimer was heated with molybdenum hexacarbonyl in an attempt at forming a heteraphane-molybdenum-tricarbonyl complex. The product hoped for would most likely be bound to one of the xylyl units in the dimer, as such it would lose its symmetry, making it sided. Thus the CH_2 groups and the xylyl units would be in very different environments which would give rise to different splitting pattern which is not seen. It was not expected that the molybdenum would lose all its co-ordinated carbonyls, especially under such mild conditions. Even if the molybdenum co-ordinated to one of the binaphthyl units, which it was probably more likely to do on energy grounds, a shift

in the aromatic and methylene protons would still be expected. These attempts at the formation of organometallic complexes were unsurprisingly unsuccessful.

One of the more convincing reasons for the lack of binding of these compounds was that the ionisation potential of the xylyl groups is very high and as such it is not a good donor thus it is unlikely to provide any driving force for binding. We were looking for a minimum of a hydrophobic driving force and with luck EDA (electron donor acceptor) complexation, however this was very naive as the xylyl group is a poor electron donor and is a poor acceptor. If this is considered in conjunction with the ionisation potential of naphthalene (and binaphthyls) it becomes clear that any binding that may have taken place with the xylyl groups is very likely to be in direct competition with the naphthalene groups. This is in keeping with an observation that was made by Cram et.al., which concludes that for some mixtures they were not seeing inclusion but rather complexation to the outside of the cavity and in particular binding to the naphthalenes of the binaphthyl.

With many more advanced design thoughts arising from and during the initial work on these compounds experimental initiative moved on from these compounds, having served a useful purpose.

5.4.1 - Progression

There are several possibilities for developing and improving this design which include :

1- Changing the central spacer/fluorophore unit from the current xylyl. However any changes to the spacer used would also dramatically change the overall shape and flexibility of the molecule. From molecular models, those spacer units that did not appear to change the cavity shape and apparent flexibility, tended to have precursors that would be difficult to synthesise. For example an attempted synthesis of 9,10-bis(bromomethyl)-anthracene gave low yields of poor quality product.. Some alternative designs also had long reaction schemes and the end products appeared to be too flexible. Other spacer units that were commercially available threw up their own synthetic difficulties - see later. If you increase flexibility then you increase conformational freedom which was felt to allow a decrease in chiral discrimination.

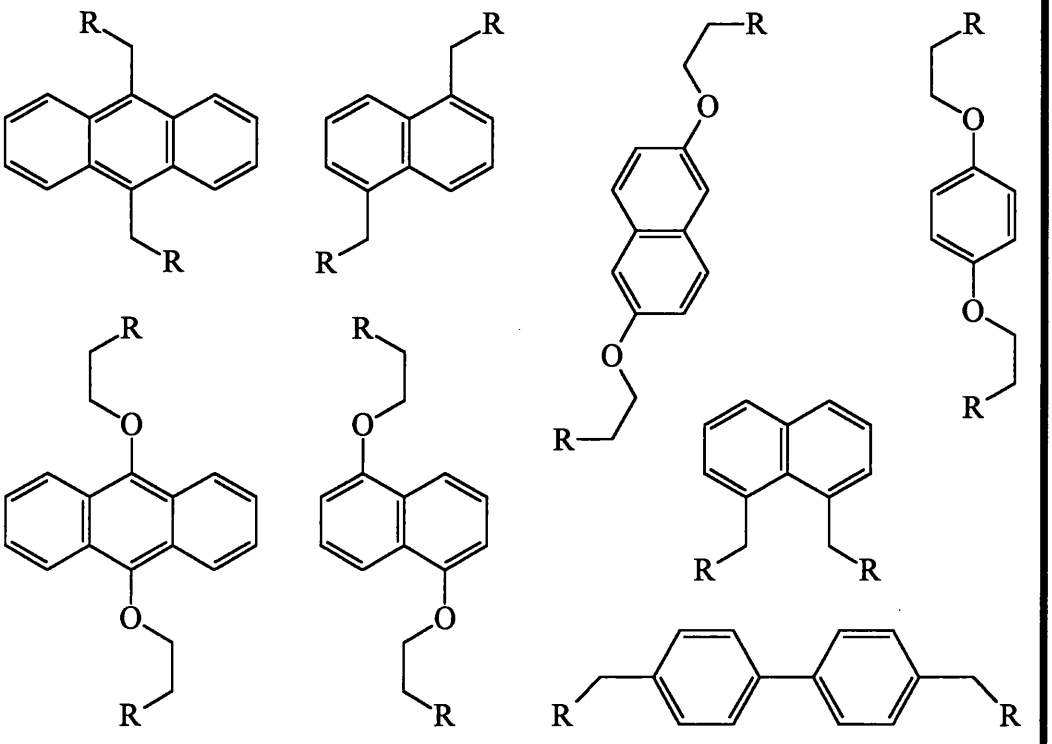


Figure 5.4 - Alternative Binaphthyl Spacer Units

2- The possibility of modifying the xylyl groups via functionalisation could also be explored. This could be undertaken before or after the heteraphane synthesis (both of which would present problems). Any functionalisation of the xylyl group would have to be symmetrical in order that the molecule's overall symmetry was not affected detrimentally. Functionalised, let alone symmetrically functionalised α,α'dibromo-xylyl precursors could easily be described as exotic synthons for what in essence could be little or no gain. Also we would have to investigate and determine whether the functionality should be used for further synthetic manipulations to change the molecule's shape, binding capacity or signalling ability. The latter can be changed by substituting with a species that donates into the aromatic unit thus decreasing the ionisation potential - however we would still have to move out of the range of overlap from the naphthalene groups. Alternatively there is a slim chance that if the xylyl rings were brominated then this may change the time-scale of photo-emission, if not the wavelength, pushing a fluorescent mechanism into a phosphorescent mechanism, which could certainly improve the signalling capability, however we would still be suffering from a lack of binding ability.

3- If the binaphthyl unit was partially hydrogenated to form a fused benzene cyclohexane system this would reduce the overlap and drowning out of xylyl fluorescence (discrete or excimer) by the naphthyl fluorescence. However this would not help increase the cavity's binding capability. It may, if anything, only increase cavity inclusion by reducing any competitive binding by naphthalene groups.

4- We could also substitute functionality into the naphthalene units and derivatise before or after making the heteraphane dimers. Derivatising could then be used in order to change the molecule's solubility in various solvents i.e. we could attempt to make them water-soluble thus increasing the binding ability of the cavity. We could also derivatise with the view to attaching the molecule to a solid support to be used as a column packing or as a chiral modifier.

Throughout this search it would appear that there was a push towards the requirement for more complex molecules - complex in that they contain more than one binding mechanism possibility.

CHAPTER SIX

SYNTHESIS AND UTILITY OF A HOMO-CHIRAL PARA-XYLYL HETERAPHANE INTERMEDIATE

6.1 - Synthesis of 2,2'-Bis(α'-bromo-α-oxy-para-xylyl)-1,1'-binaphthyl

After recognising the need for more advanced binding systems, and while the investigation into the properties of the para- and meta-xylyl heteraphanes was still ongoing, it was decided that the synthesis of an intermediate for these heteraphanes would prove to be useful. It was also recognised that these intermediates would be very versatile in their own rights as they could act as rigid chiral spacer units which could be combined with ligating groups to form simple prototype sensors.

An aspect of the intermediate's structure that could give concern was that the bromo-methyl groups may point in opposite directions and thus would be pre-positioned for the formation of polymers. However it is also possible that the bromo-methyl groups may also be pre-positioned for the formation of monomeric adducts as there could be some interaction between the xylyl groups.

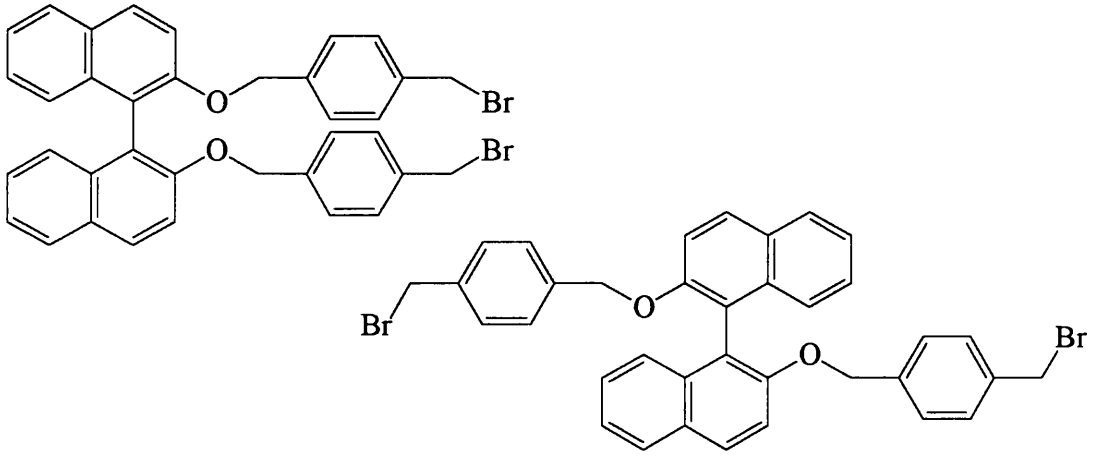
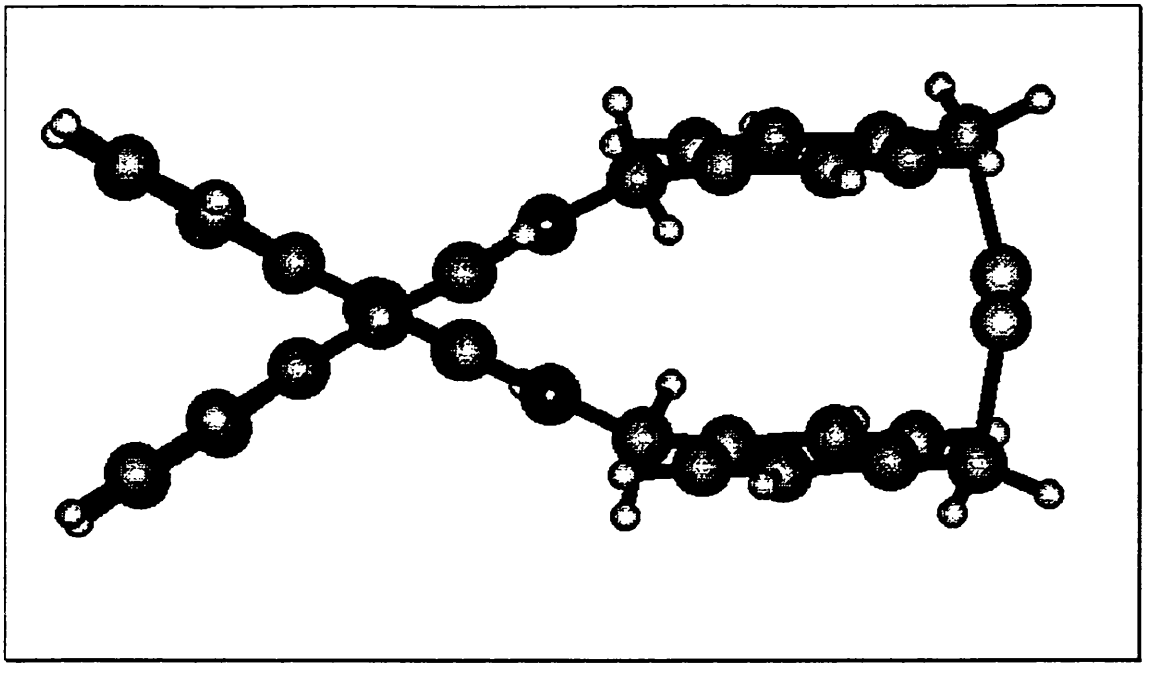
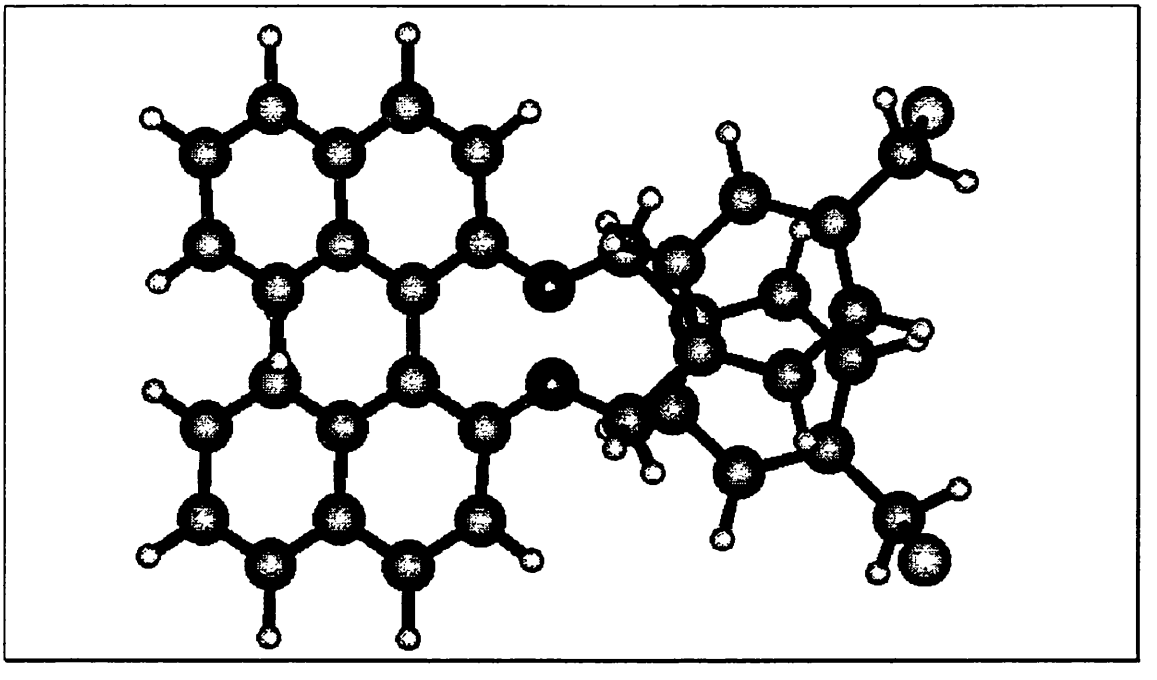


Figure 6.1; Two extremes of configuration of intermediate

Model 6.1; Hyperchem Molecular Model of Bis-Bromo Intermediate [5A], View 1



Model 6.1; Hyperchem Molecular Model of Bis-Bromo Intermediate [5A], View 2



The p-xylyl intermediate was synthesised via a slow addition of a solution of homo-chiral binaphthol into a solution of a large excess of α,α'-dibromo-p-xylene. The use of such large quantities of dibromo-p-xylene was feasible as it was relatively cheap and could not form a cyclic monomer as the dibromo-o- or -m-xylenes could. Purification was relatively simple, much more so than for the xylyl macrocycles, as much of the

excess dibromo-p-xylene could be crystallised out easily, after which the compound in the largest abundance was the desired dibromomethyl product. Also, as the physical properties of each component of the mixture were very different, it was relatively simple to purify by column chromatography (with the non-polar dibromo-p-xylene starting material coming off first).

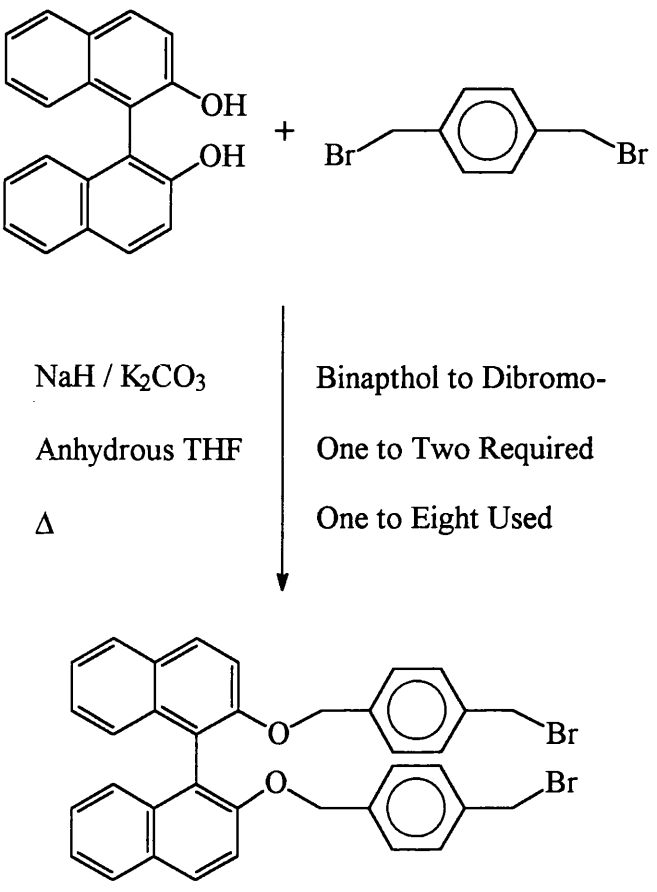
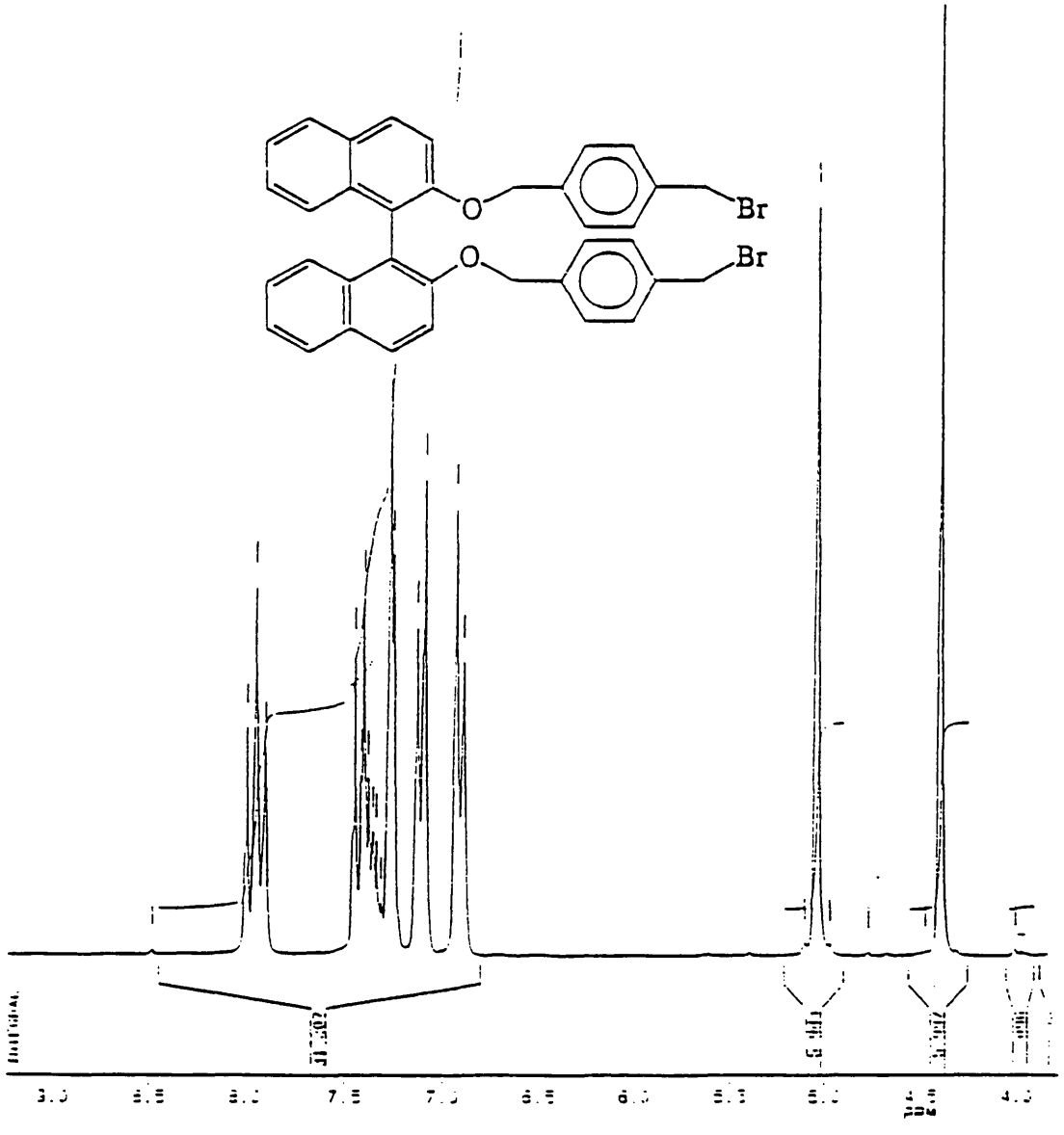


Figure 6.2; Synthetic Scheme for Synthesis of Bis(bromoxylyl)-binapthyl Intermediate

Good spectroscopic evidence was obtained for the existence of the product. The ^1H NMR integration ratio of xylyl : naphthyl : methylene protons is consistent with the proposed structure. The xylyl protons show an AA'BB' splitting pattern with doublets at ~7.15 and ~6.9ppm, which is as expected for the asymmetry of the xylyl group. There are now two discrete methylene signals, one at ~5ppm ($ArOC\underline{H}_2Xy$) showing slightly greater chiral induced geminal coupling than the other at ~4.4ppm ($XyC\underline{H}_2Br$). The ^{13}C NMR spectrum was also as it should be, with the correct number of quaternary, methyne and methylene carbons present. The mass spectral data, although not of high accuracy,

also agreed with the proposed structure, in that it contained the expected parent ion and the expected fragmentation pattern (parent minus bromo and bromo-xylyl units).

^{1}H NMR Spectrum of Bis-Bromo Xylyl intermediate [5A]



Enantiotopic coupling can be seen in both of the methylene signals with the ether linked methylene group having a significantly stronger coupling compared with the bromo-methylene group. The oxy-methylene geminal proton signals show the expected coupling constant of ~13Hz and appear almost coalescent (even more than the para-xylyl heteraphane trimer).

As a control system, ^{1}H NMR experiments were also tried for this compound, with the same homo-chiral organic shift reagent as the xylyl heteraphane dimer, which

unsurprisingly gave the same result of no apparent interaction. These ^1H NMR experiments were not tried with any of the compounds made using the above intermediate.

The versatility of this type of intermediate arises from several factors much of which arises from the reactivity of the benzyl bromide groups (Ar-CH_2Br) and the rigidity of the molecule's sub-units (the xylyl and binaphthyl groups), which have few points about which the molecule can pivot. Hence it should give good induction / transmitance of chirality to any macrocyclic cavity produced in reactions carried out with this intermediate. It should also be noted that this intermediate possesses C_2 symmetry.

Synthetic Utility of Bis-bromoxylyl Intermediate

The reactions that this xylyl intermediate were used in are as follows;-

6.2 - Synthesis of 1,6,13,16,19,22,25-Heptaoxy-2,3:4,5-di(1,2-naphtho)-8,11,27,30-di-(1,4-benzyl)-hentriaconta-heteraphane [5B] (Fig 6.3)

This was carried out at higher dilution in an attempt to maximise the desired monomer. It was hoped that the cavity of this crown heteraphane would be a step towards a better shape for the complexation of aromatic primary amine salts. Orbit molecular models certainly reinforced this suggestion as they showed that aromatic primary amine salts could be bound using a three point hydrogen binding system via the amine protons interacting with the oxygens of the ether linkage. It was also hoped for, and indeed appeared feasible that, the aromatic unit of such amine salts could fit into the cavity formed by the binaphthyl and xylyl spacer units.

The experiment used to synthesise the target compound gave a mixture of products by TLC. This mixture was purified by flash chromatography to give the desired monomer species and a small amount of what is believed to be the di-oligomer species.

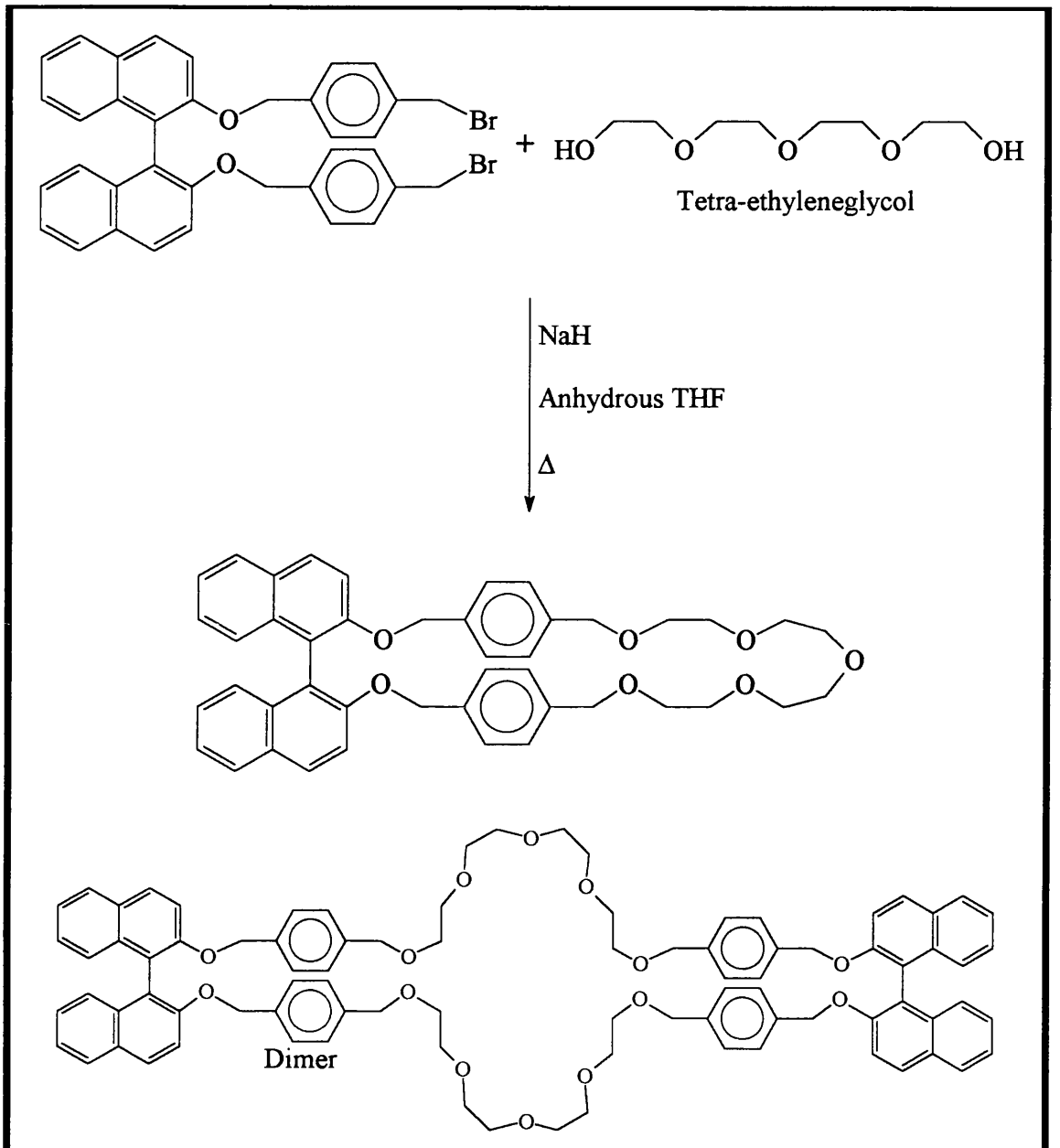


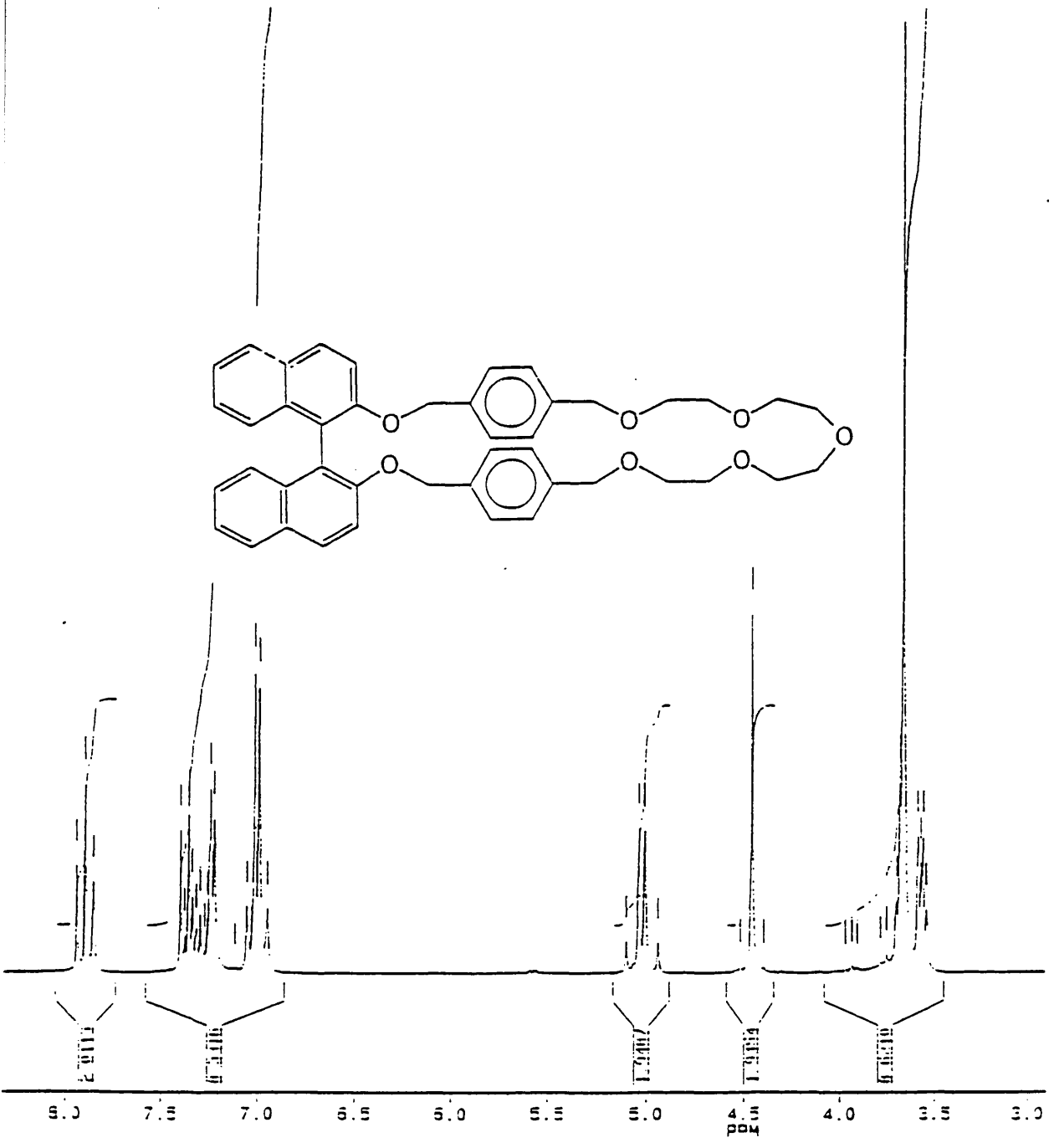
Figure 6.3; Synthesis of Heteraphane Crown Compound

Monomer

The ^{1}H NMR spectrum of this compound is as expected with good integration. It shows a relatively simple splitting pattern, which indicates symmetry between each naphthyl unit, similar to that which was seen in the spectra of its precursor. The xylyl aromatic protons again show an AA'BB' type splitting pattern however; the doublets are in a more similar environment as can be seen by their near coalescence. This is expected as both ends of the xylyl unit now have ether linkages. Again both of the xylyl methylene groups have different shifts and "feel" the chirality of the binaphthyl unit to different

extents. The coupling constant observed, is around the 13Hz expected for geminal enantiotopic protons.

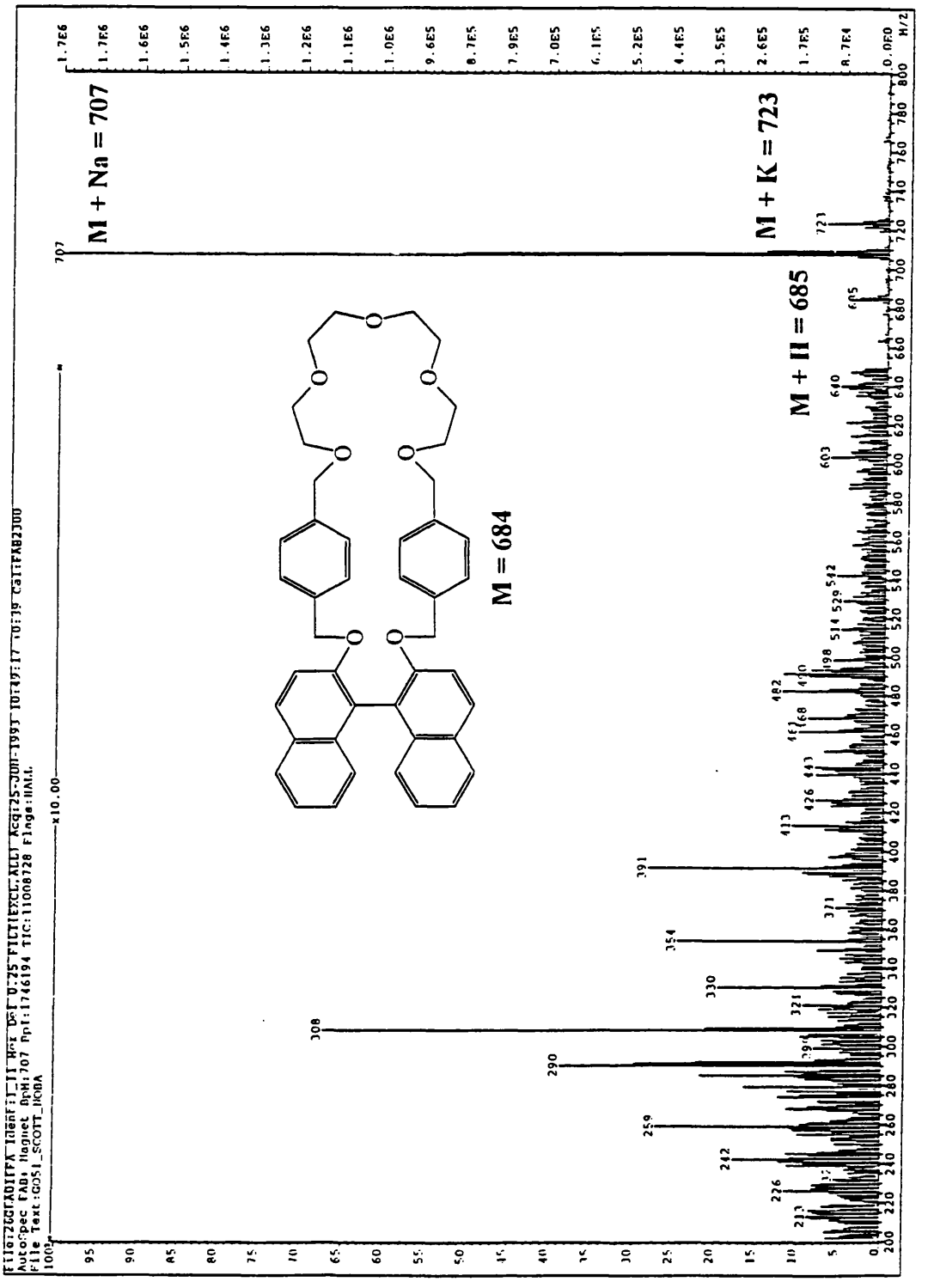
^{1}H NMR Spectrum of the Monomer Crown Heteraphane [5B]



The methylene group attached to the ether link has a similar shift to that of the precursor and again there is only a suggestion of enantiotopic geminal coupling. The signal at ~5ppm ($ArOCH_2Xy$) now shows a very distinct AB' splitting pattern which arises from the greater rigidity of this molecule compared with its precursor. The xylyl methylene

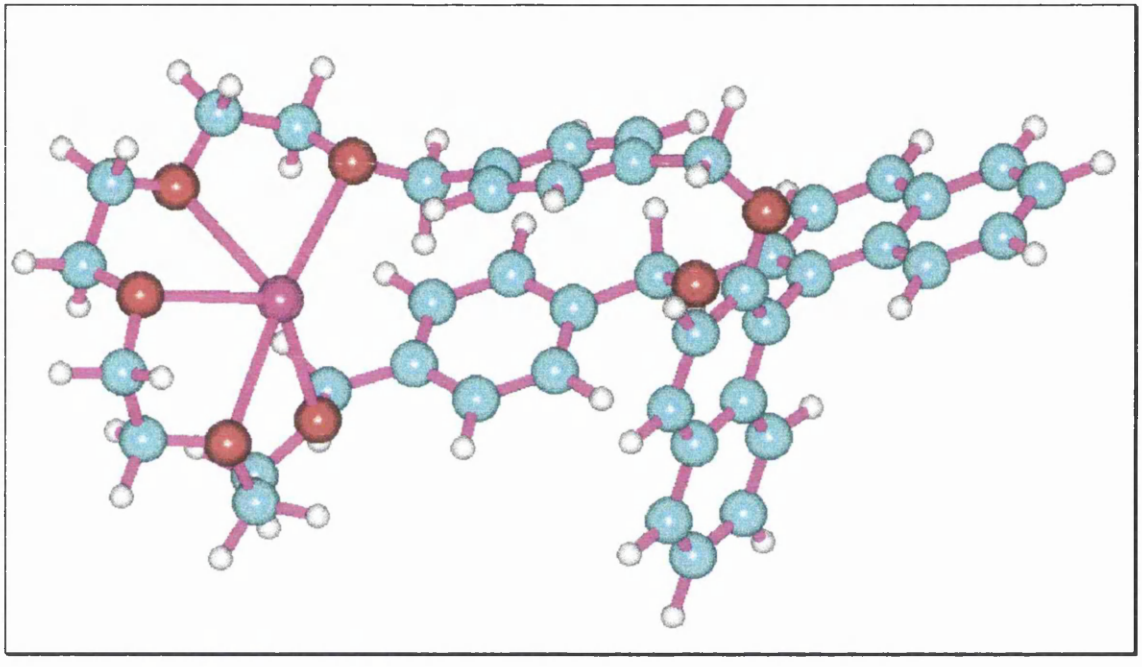
signal at ~4.45 (XyC$\underline{H_2}$OR) now shows a small degree of geminal coupling implying that the methylene group retains a large amount of flexibility. The other methylene protons appear to be in similar environments as the positioning of their signals at ~3.6 and 3.7ppm suggests.

FAB Mass Spectrum of the Monomer Crown Heteraphane [5B]



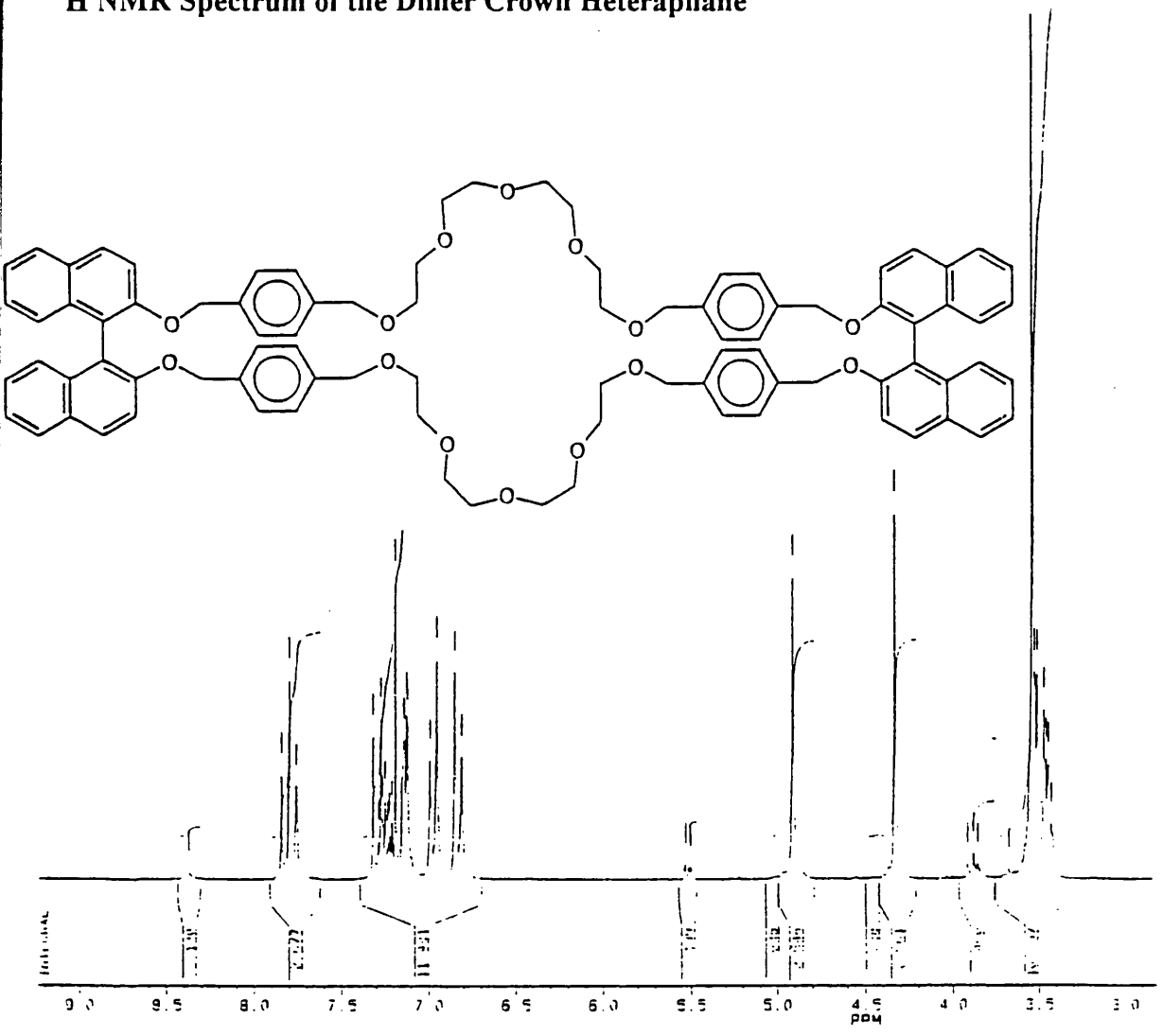
The FAB mass spectrum of this molecule shows a good parent ion $(M+H)^+$ at 685, a very strong peak at 707 arising from $(M+Na)^+$ and a peak at 723 from $(M+K)^+$. The rest of the spectrum below the parent ion is weak and shown here at ten times its original strength. There were also some weak peaks seen due to ions with larger mass than that seen for $(M+K)^+$, the strongest of which were at 860 and 883. It is possible that these are due to combinations of the parent ion with sodium and a molecule of the matrix used (ortho-Nitro-benzyl alcohol, NOBA) as $(\text{parent ion} + \text{NOBA} + Na)^+ = 860$.

Model 6.3; Hyperchem Molecular Model of the Crown Heteraphane [5B] Complexed with an Alkali Metal



Dimer

^{1}H NMR Spectrum of the Dimer Crown Heteraphane



The ^{1}H NMR spectrum for the dimer shows a similar splitting pattern to that of the monomer, with two distinct differences. The xylyl aromatic protons again show a distinct AA'BB' splitting pattern which appears to have greater similarity to the very flexible dibromo-precursor than to the monomer. The protons giving rise to the two doublets appear to occupy quite different environments which appears to arise from the flexibility of the molecule [the splitting between the AA' and BB' proton signals is large, ~20-30Hz in each however the coupling constants are different]. The molecule's greater flexibility can also be assumed to be responsible for the xylyl methylene protons showing little to no geminal coupling arising from their proximity to the chiral axis. The other methylene protons appear quite similar to the monomer however the two signals do appear to be more coalescent.

The dimer would be expected to have a greater flexibility, even with the consideration that macrocycles tend to try and fill their own cavities. The dimer molecule does not appear to be a catenane from the NMR spectrum, as we would expect to see two types of xylyl units both with AA'BB' splitting pattern. This expectation is not absolute, as it may be possible for two of the mono units to be linked with the closest points being the ether threads, however we would then expect the xylyl aromatic and methylene signals to be very similar to the monomer's (also the ether linkage splitting pattern would be more complex).

Evaluation

Initial evaluation experiments were carried out to investigate the complexation capabilities of the host, with the view to seeing how well it might be expected to interact and complex with other guests (primary amine salts). These experiments, which were carried out in DCM, investigated the ability of the host to solubilise sodium and potassium salts of picric acid. The attempted dissolution of the alkali metal salts was followed by UV spectroscopy for the first few hours, however the spectra taken over this period were not very convincing as no definitive absorption had become prominent. A shoulder could be seen to form and the solution took up a very pale yellow colour, indicative of picrate absorption. Solutions of the host over the picrate salts that were left overnight became very visibly yellow indicating that the host had solubilised the picric acid salt by complexation (slow dissolution of picrate by host). It should also be noted that solutions only containing the picrate salt and solutions only containing the host compound did not appear to change colour (turn yellow). Thus it would appear that the host does form complexes with alkali metals however its own absorption may complicate the spectra.

As has been seen previously the molecule's cavity will only accomplish inclusion of the guest molecule if there is an energy gain driving the complexation. Again as EDA complexation involving the xylyl groups is not very likely (as they have too high an ionisation energy) the only driving force will be the hydrophobicity of the cavity, which is redundant in most organic solvents.

The xylyl and binaphthyl units give the molecule good shape, but more of a driving force for complexation is required, either from arms or substituents on the xylyl units or on the 3 position of the naphthyl units. Due to the rigidity of the spacers any guest interaction

with the xylyl groups (EDA or otherwise) should be felt by the binaphthyl unit, even if only in the torsion angle of its axis, but would this give a recognisable difference? Also as before, any EDA complexation would be caught up in competition between the xylyl groups and the naphthyl groups, of which the naphthyls are far more likely to win due to their lower ionisation energy making them better donors.

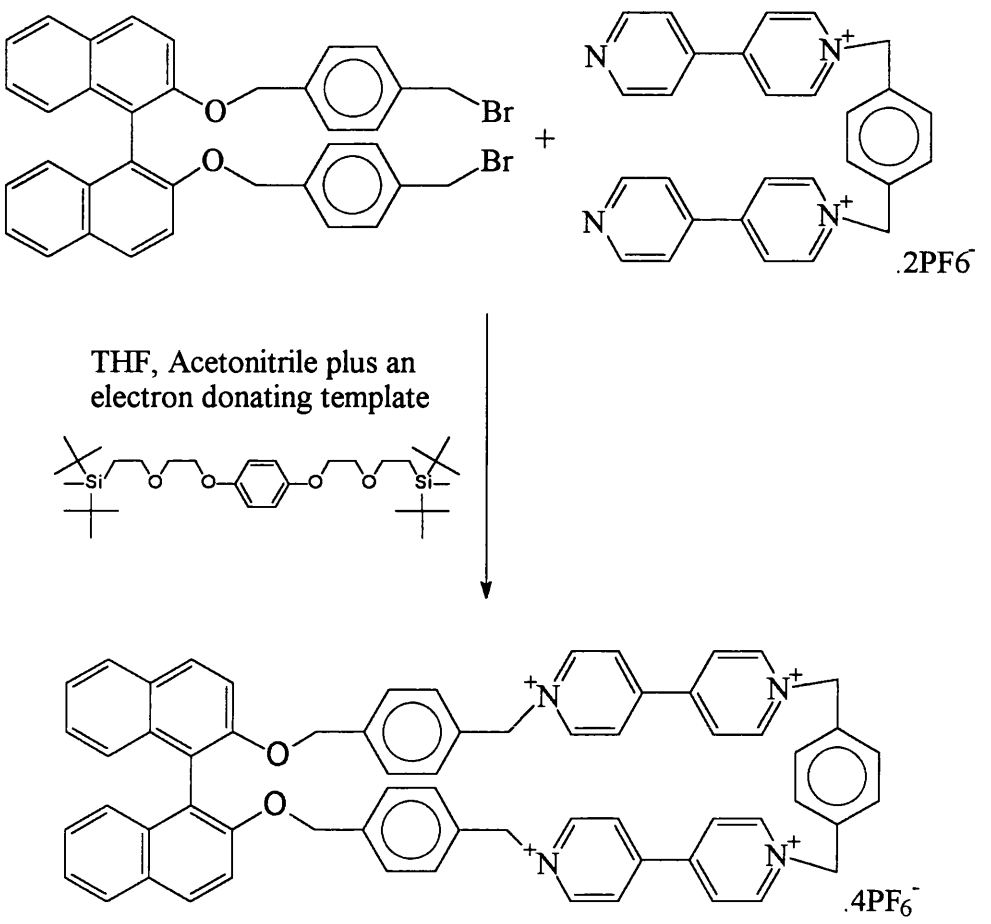
If we could solubilise this molecule, by modification, into aqueous solution then hydrophobic type cavity (non-polar) would/should be attractive towards non-polar aromatic units.

6.3 - Synthesis of 1,8,15,22-Tetra-aza-29,34-dioxy-10,13:24,27:36,39-tri(1,4-phenyl)-1,8:15,22-NNNN-di(4,4'-bipyridinium)-30,31:32,33-di(1,2-naphtho)-tetraconta-heteraphane Tetrakis-hexafluorophosphate - A Chiral Box [5D]

The synthesis of this 'chiral box' was performed both with and without a template (the template was used to help promote the monomer). There was little apparent difference in outcome between the two experiments, however it was thought that the reaction using the template was cleaner (more monomer formed).

The ^{1}H NMR spectrum of the purified 5D shows broadened signals and splitting patterns that are poorly defined. It also shows a slight impurity, most noticeable in the pyridinium region. Proton groupings can be identified with their respective integrations generally supporting the assigned structure.

The signal at ~9.5ppm arises from the protons α to the pyridinium nitrogen and the signal at ~8.7ppm, with similar splitting pattern, arises from the protons β to the nitrogen. The splitting pattern seen for the pyridinium protons originates from an AA'BB' type pattern which is complicated by the slightly different environments of the α / β protons on each pyridinium ring.

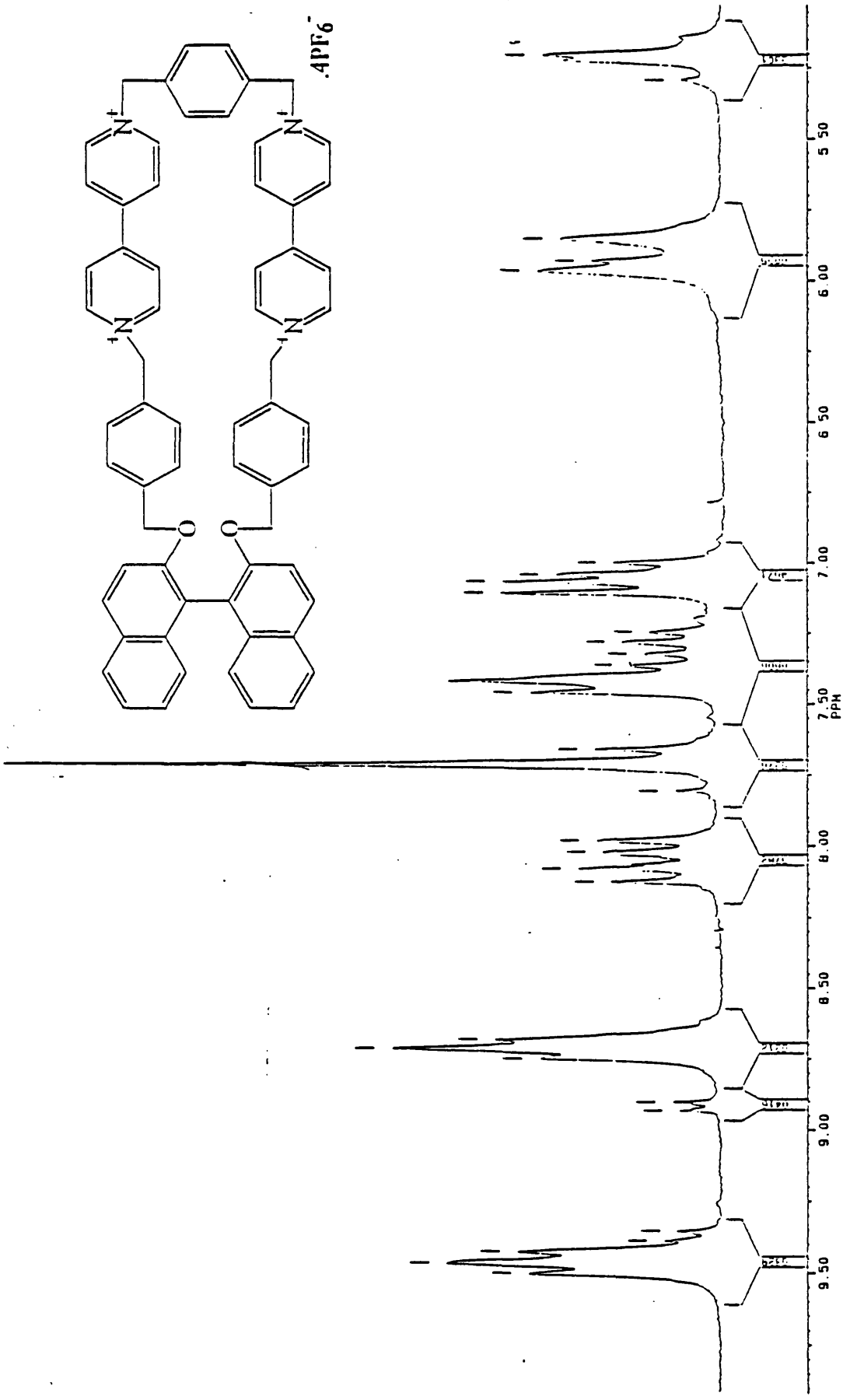


Plus small ammount of higher oligomer

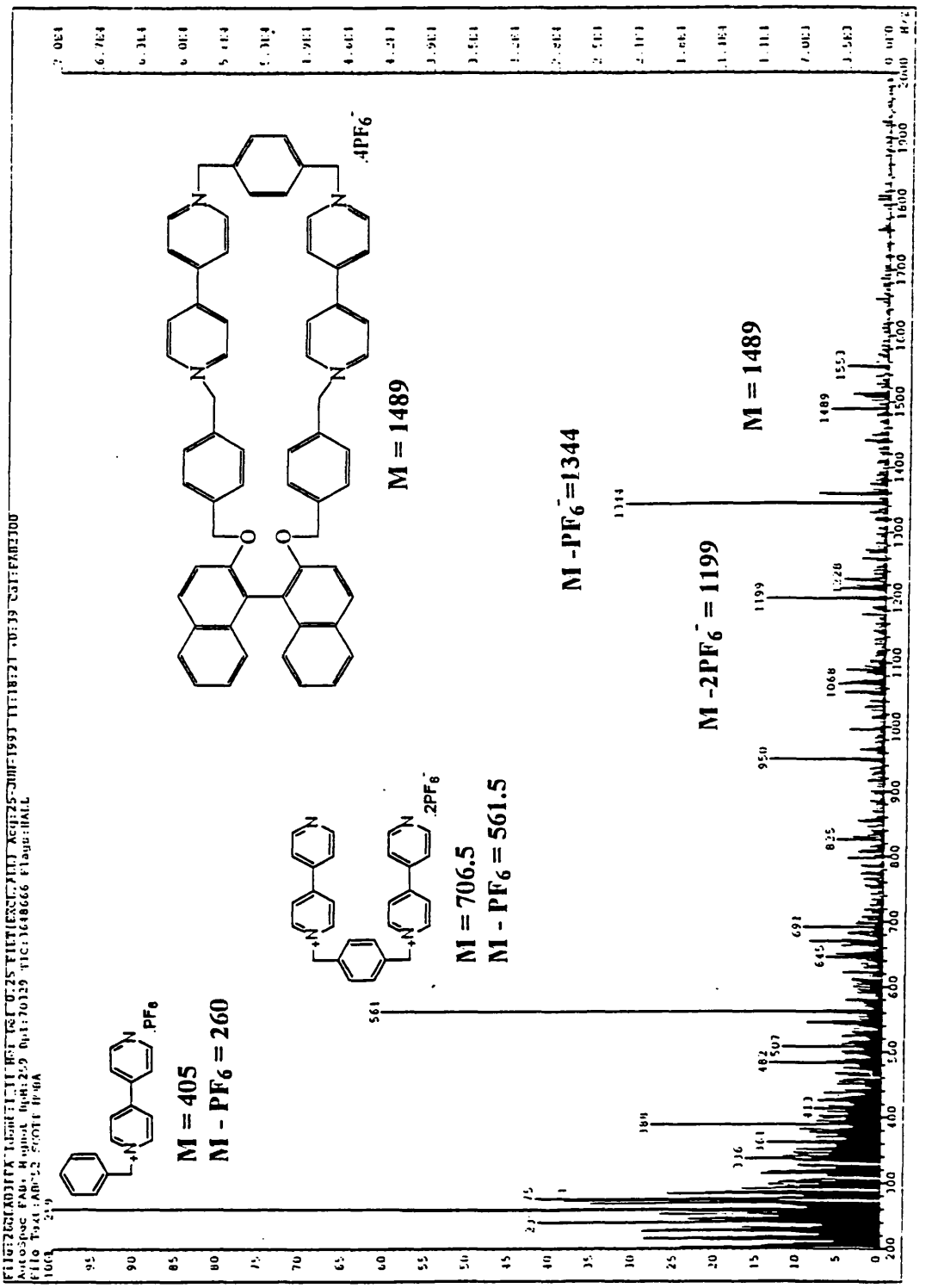
Figure 6.4; Synthesis of Tetra-cationic Heteraphane (Chiral Box)

The signal at ~8.1ppm, which appears to be two doublets, arises from two (four as C_2 symmetry axis) of the binaphthyl protons. The rest of the aromatic protons are more difficult to assign with great confidence however the signal at ~7.6ppm may be due to xylyl protons, with the signals at ~7.4 and ~7.3ppm due to the other binaphthyl protons and the signal at ~7.1ppm is due to other xylyl protons (which potentially shows an AA'BB' type splitting pattern). The signals at ~5.85 and ~5,95 ppm arise from the xylyl methylene protons at positions α to the pyridinium nitrogen ($XyC\underline{H_2}N^+Py$). The signal at ~5.2ppm, which shows a potential AB' splitting pattern, arises from the xylyl methylene protons α to the binaphthyl oxygen's ($XyC\underline{H_2}OAr$).

^{1}H NMR Spectrum of the Chiral Box [5D]

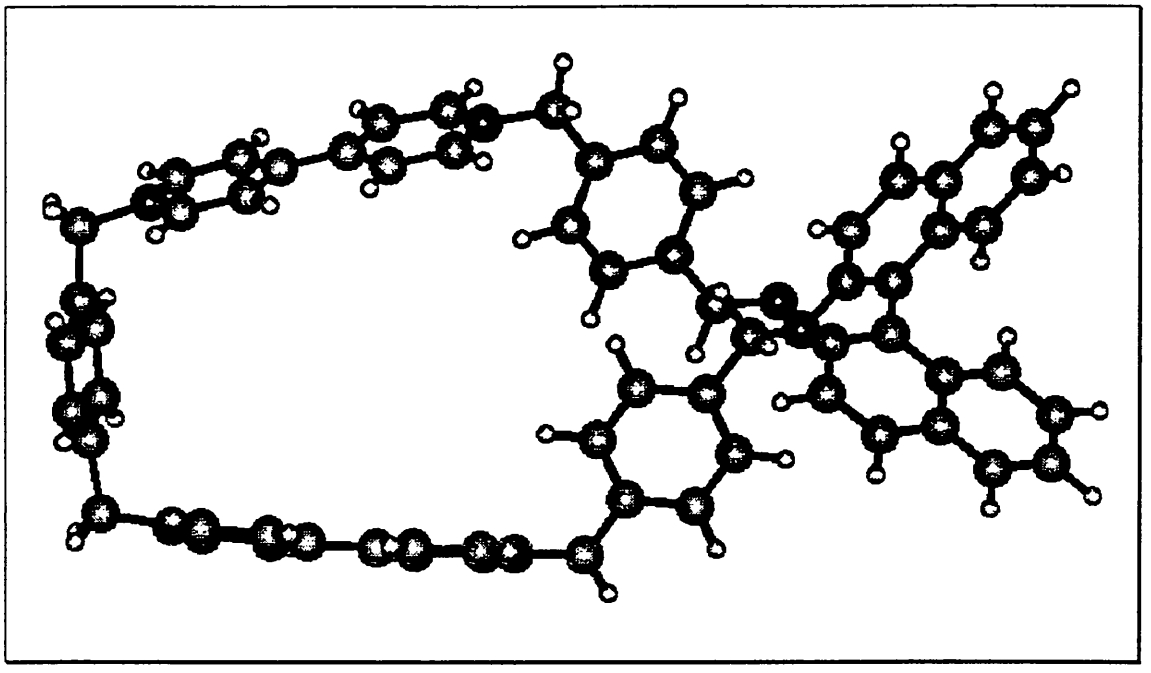


FAB Mass Spectrum of the Chiral Box [5D]

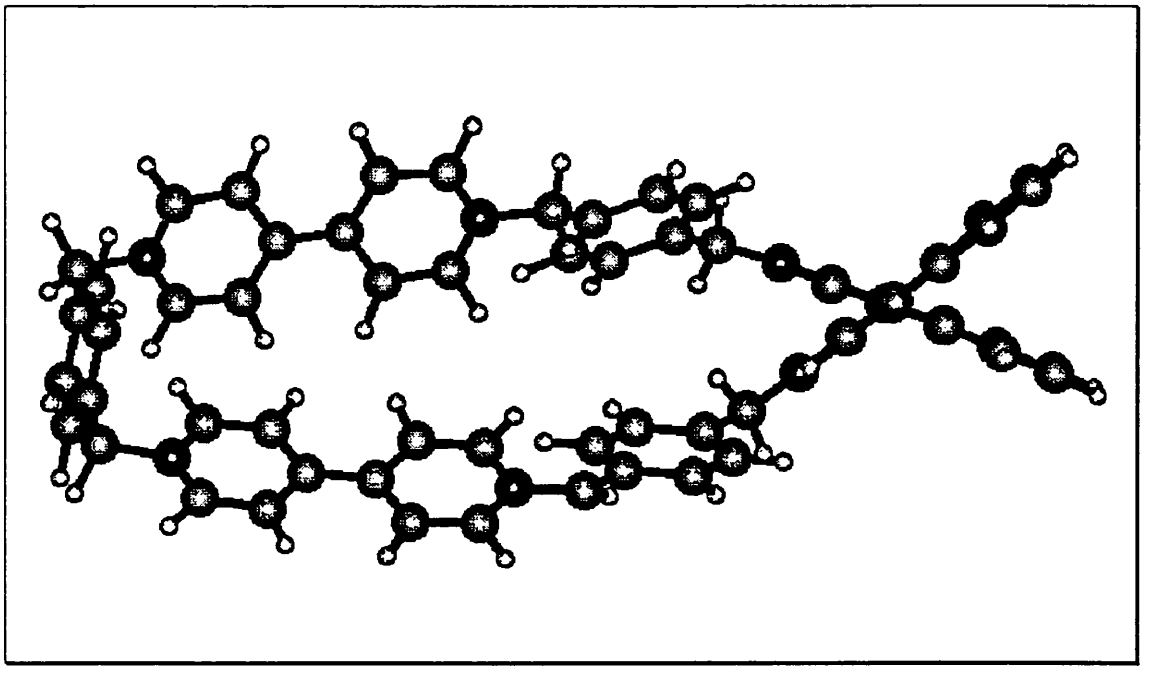


The FAB mass spectrum of this chiral box clearly shows the parent ion with all four $[PF_6]^-$ counterions and ions of the parent that have lost one and two $[PF_6]^-$ counterions. The spectrum also shows other fragment ions that would be expected.

Model 6.4; Hyperchem Molecular Model of the Chiral Box [5D], Conformation1, View 1



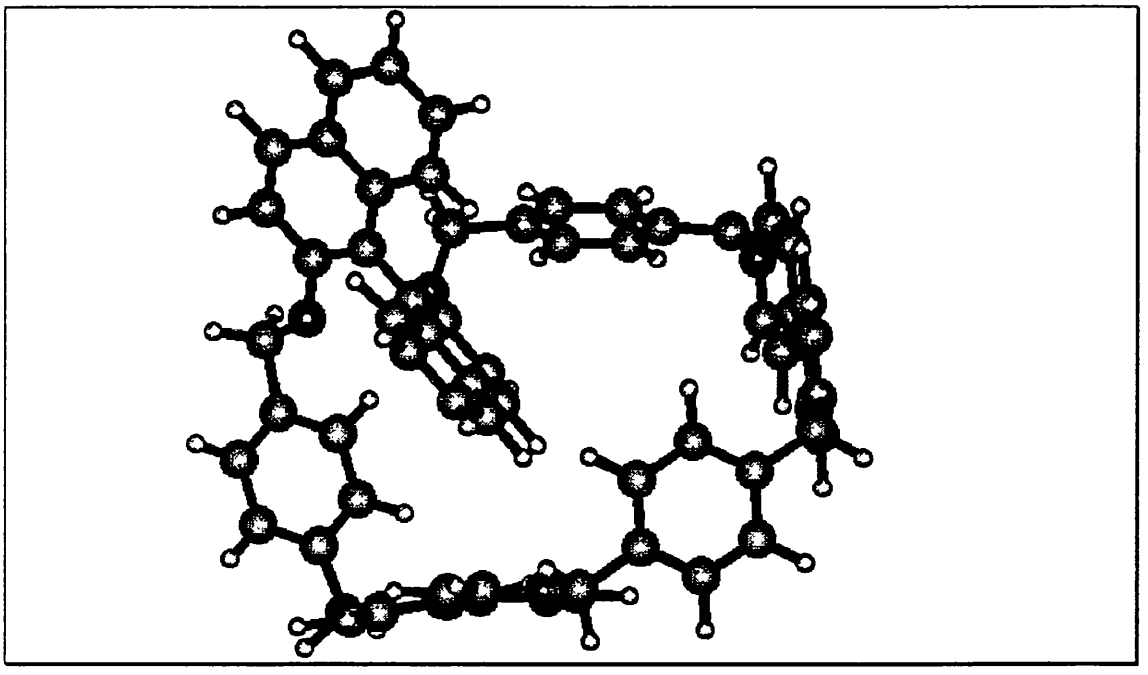
Model 6.5; Hyperchem Molecular Model Of the Chiral Box [5D], Conformation 1, View 2



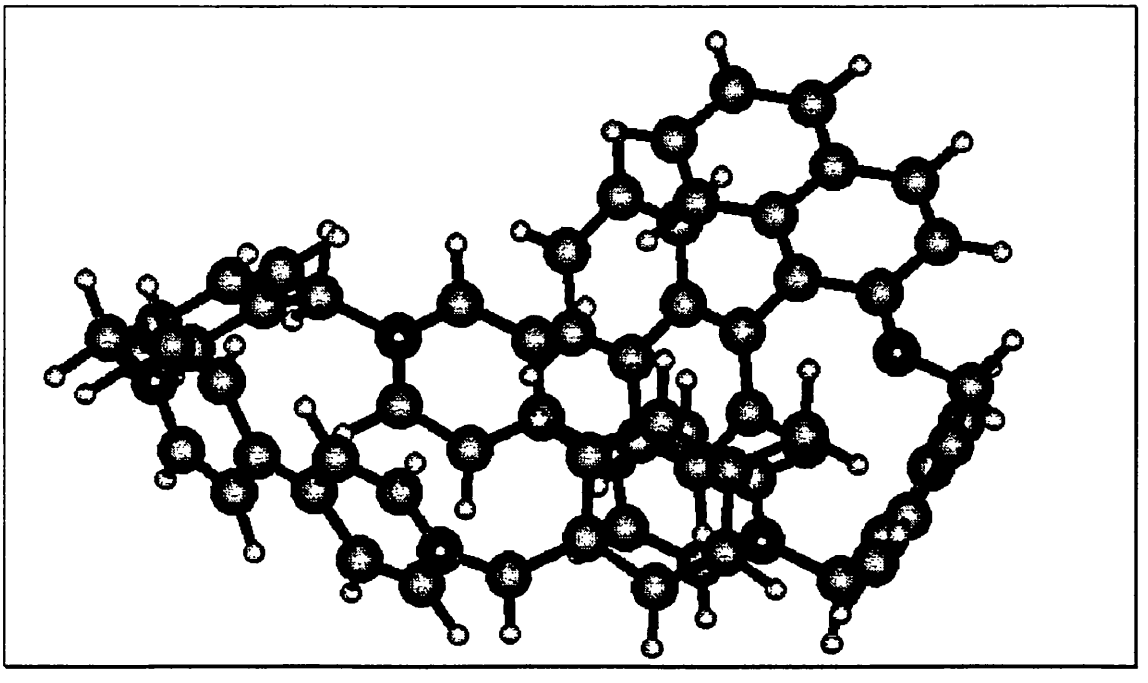
Note: The chiral box appeared to be very unstable especially in the presence of solvent (acetone). Attempts at recrystallisation were unsuccessful and resulted in tar formation which fumed when the closed container was opened to surrounding atmosphere. Solid

samples left in the light and exposed to the atmosphere did not appear to decompose. Reasons for the instability in solution are unclear. The possibility of a EDA (Electron Donor Acceptor) complex with the acetone followed by decomposition is a possibility.

Model 6.6; Hyperchem Molecular Model of the Chiral Box [5D], Conformation 2, View 1



Model 6.7; Hyperchem Molecular Model of the Chiral Box [5D], Conformation 2, View 2



The second conformation of the chiral box, from the molecular modelling package, models 6.6 & 6.7, shows signs of the molecule filling its own cavity. The filling of a hosts cavity by the host itself has been noted by Cram to be a powerful trend.

6.4 - Synthesis of 2,2'-Bis(α-N-triazacyclononane-α'-oxy-para-xylyl)-1,1'-binaphthyl

The synthesis of this molecule may perhaps appear side-tracked from the main goal of chiral sensors. However it is in keeping with the overall direction of an investigation into relationships of shape between chiral molecules and macrocycles.

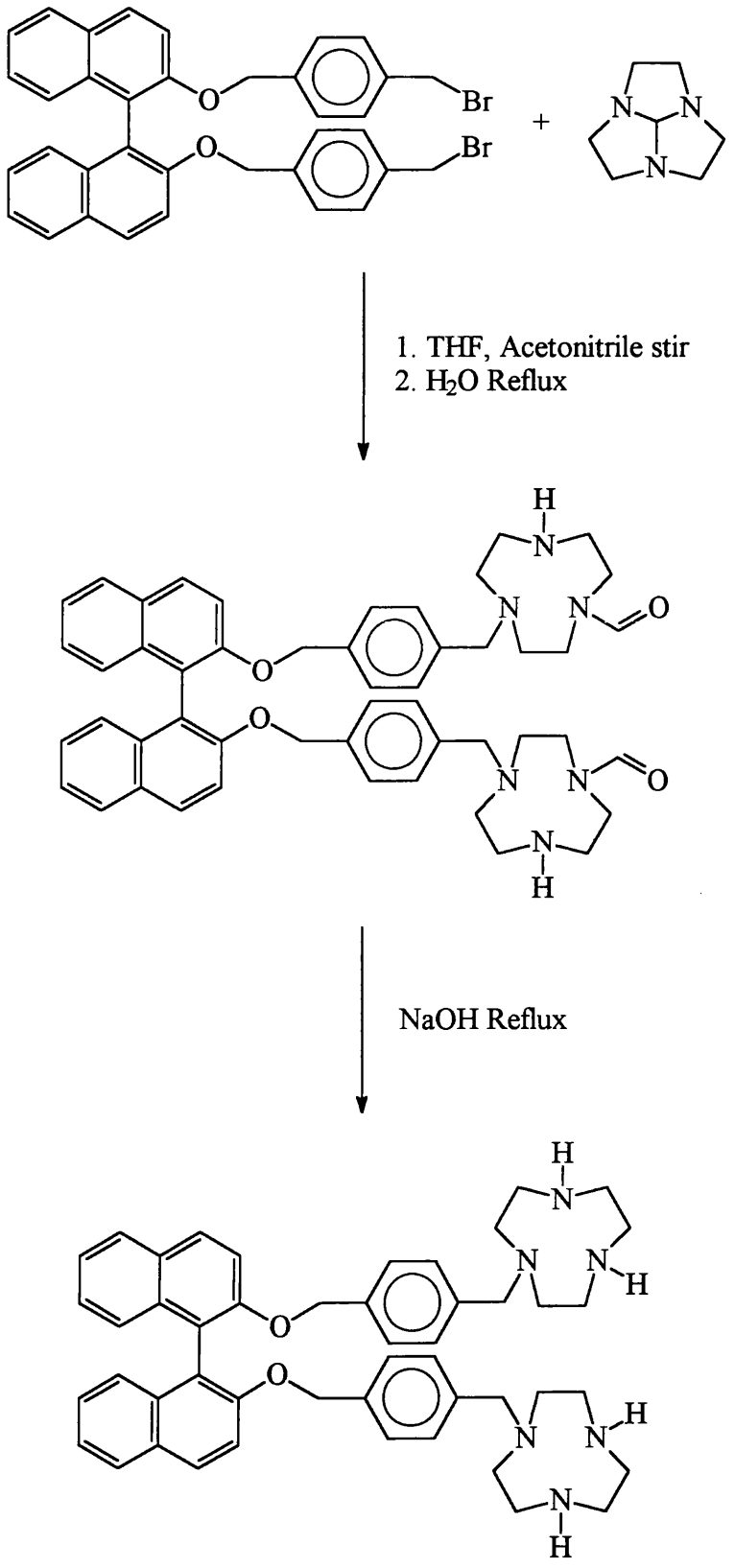
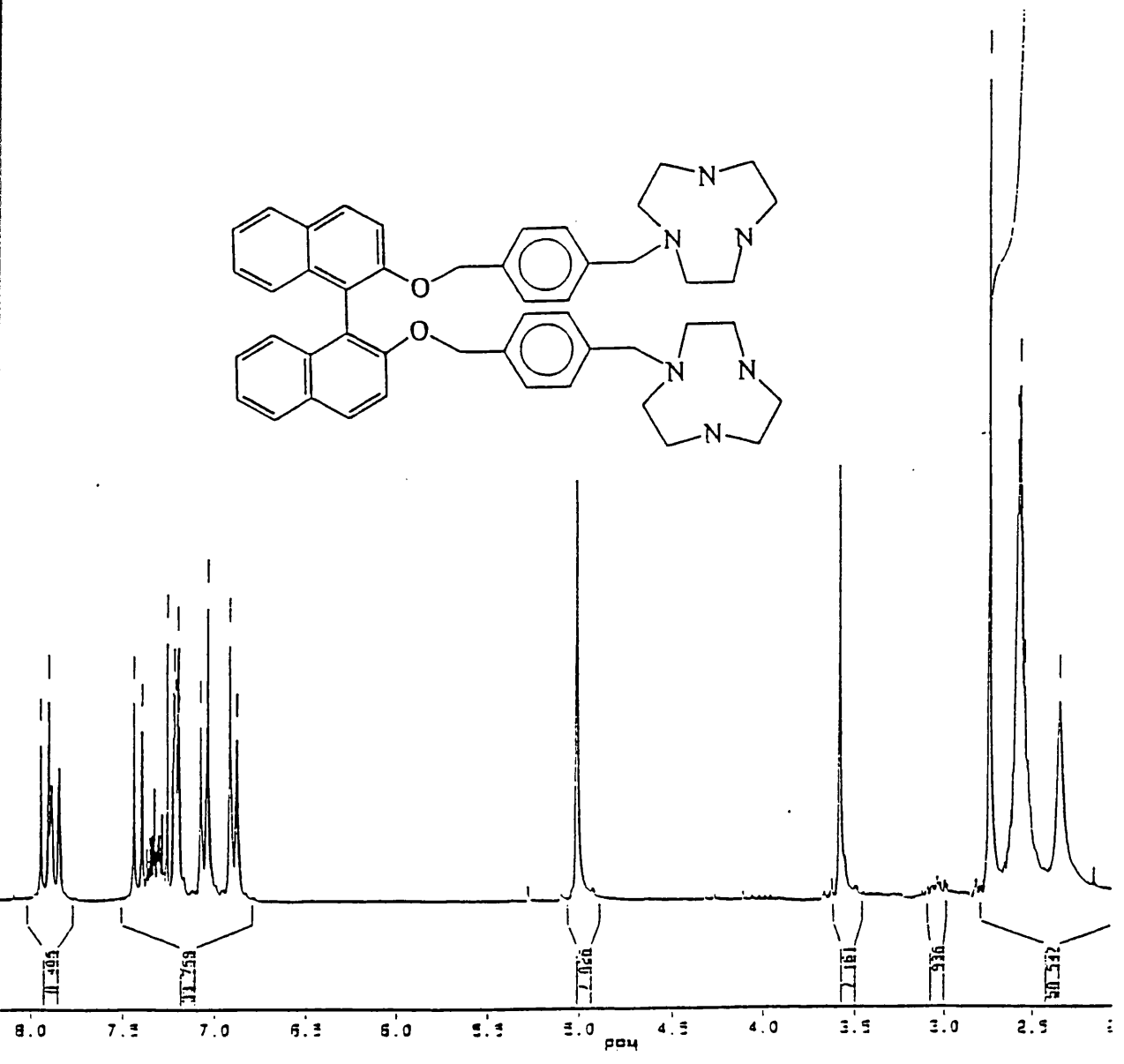


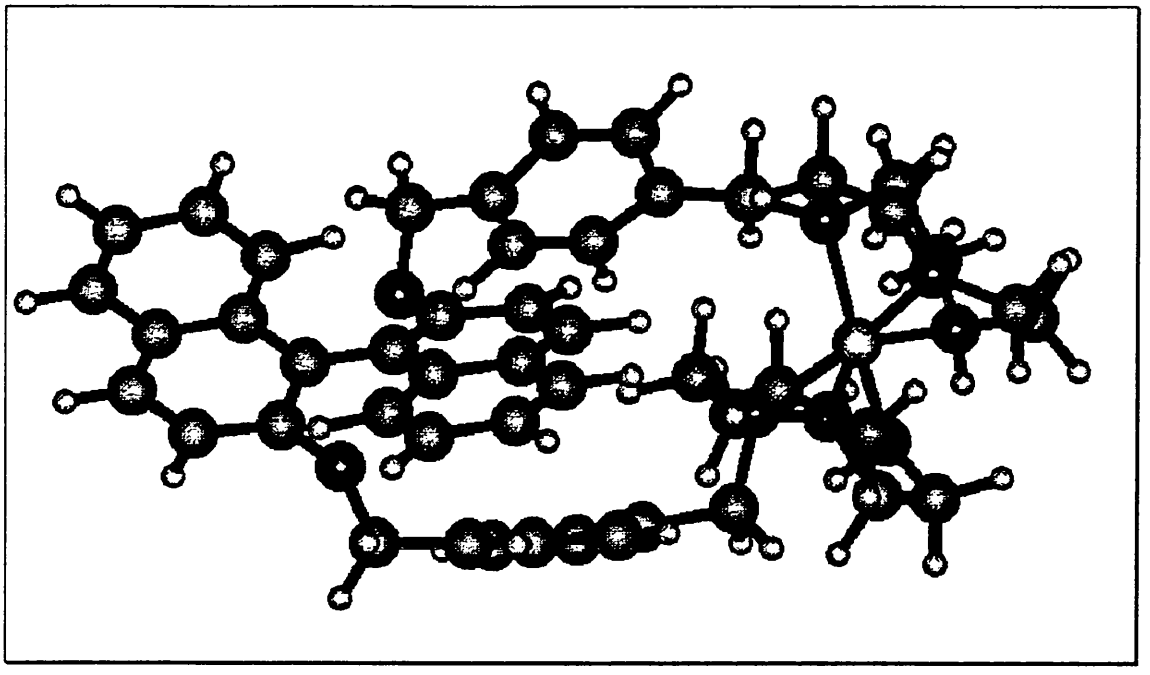
Figure 6.5; Synthetic Scheme for Synthesis of Bis-Xylyl-TACN Binaphthyl Compound

^{1}H NMR Spectrum of the Bis-TACN Binaphthyl Compound [5C]

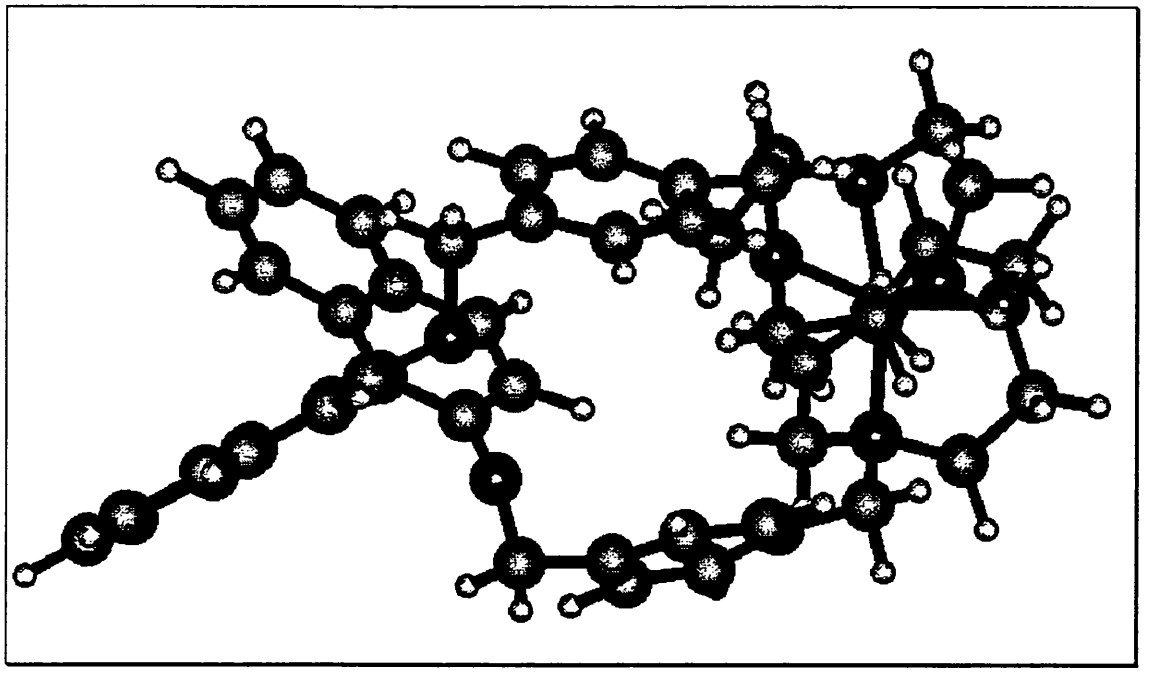


The ^{1}H NMR spectrum of the purified compound shows many of the typical attributes associated with the other molecules of similar structure (from the parent precursor). The binaphthyl protons occupy the expected positions with typical splitting patterns (two doublets at ~7.9ppm, a doublet at ~7.4ppm and the rest being more difficult to assign). The xylyl protons again show a distinct AA'BB' type splitting pattern similar to those molecules with much flexibility. The xylyl methylene protons, at ~5 ($ArOC\underline{H}_2Xy$) and ~3.6ppm ($XyC\underline{H}_2N$) also show flexibility in that there is only a hint of geminal coupling present in one of the signals. The other proton signals arising from the TACN unit appear as would be expected.

Model 6.8; Hyperchem Molecular Model of the Bis-TACN Binaphthyl Compound [5C], As a Discrete Complex with a Transition Metal, View 1



Model 6.9; Hyperchem Molecular Model of the Bis-TACN Binaphthyl Compound [5C], As a Discrete Complex with a Transition Metal, View 2



CHAPTER SEVEN

SYNTHESIS, UTILITY AND EVALUATION OF HOMOCHIRAL BINAPHTHYL HETERAPHANES INCORPORATING 1,8-DIMETHYL-NAPHTHALENE SPACERS

The synthesis and corresponding investigations of the xylyl spaced heteraphanes brought about an active interest in binaphthyl spacer design improvements. With these thoughts the investigation into the next design looked into changing the spacer such that it would provide better binding possibilities with increased EDA complexation abilities and greater flexibility.

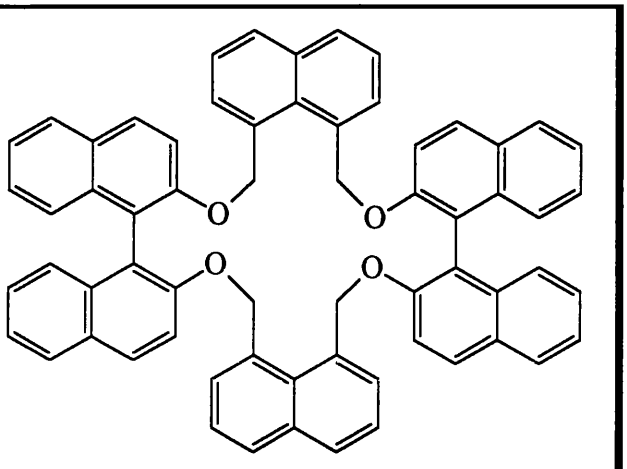


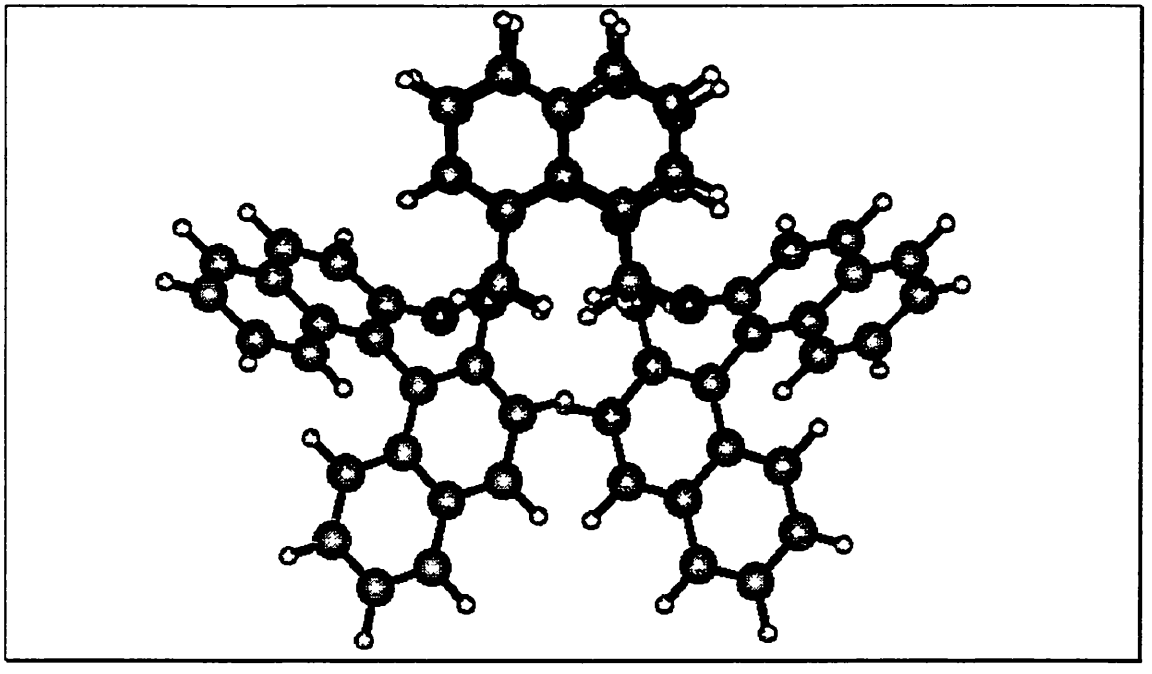
Figure 7.1; Target 1,8-naphthalene Heteraphane

The spacer chosen was 1,8-dimethyl-naphthalene as it provided a simple solution to some of the poorer aspects encountered with the xylyl spacers. More attention was paid to the physical properties of the spacer and the likely shape of the completed molecule with respect to both overall and intra molecular interactions.

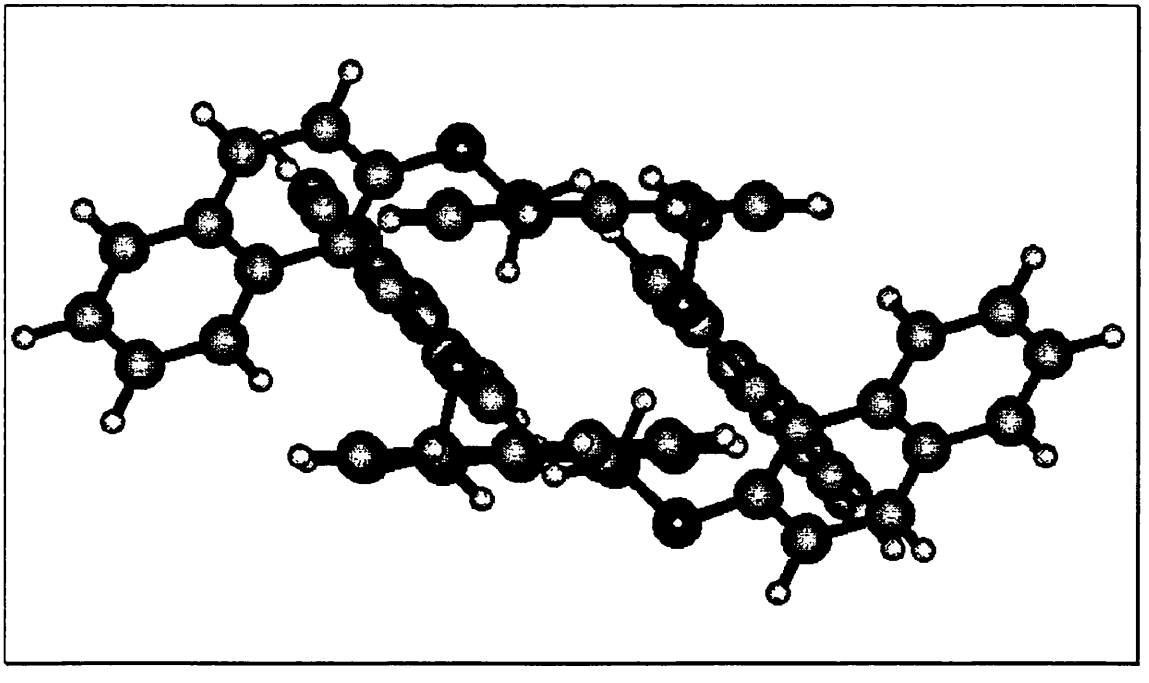
The 1,8-naphthyl unit has far better donating properties compared with the xylyl unit. This should be good enough to provide useful donor properties, however there is still the possibility of overlap of fluorescence spectra with the binaphthyl unit. Again the partial hydrogenation of the binaphthol unit could be attempted as a possible cure for this problem, however this would have drastic effects to the overall shape of the molecule.

The probable formation of an intramolecular exciplex between the naphthyl and binaphthyl units changes any possible problem that may have been encountered along the lines of spectral overlap giving rise to too much interference or blotting out sought after information.

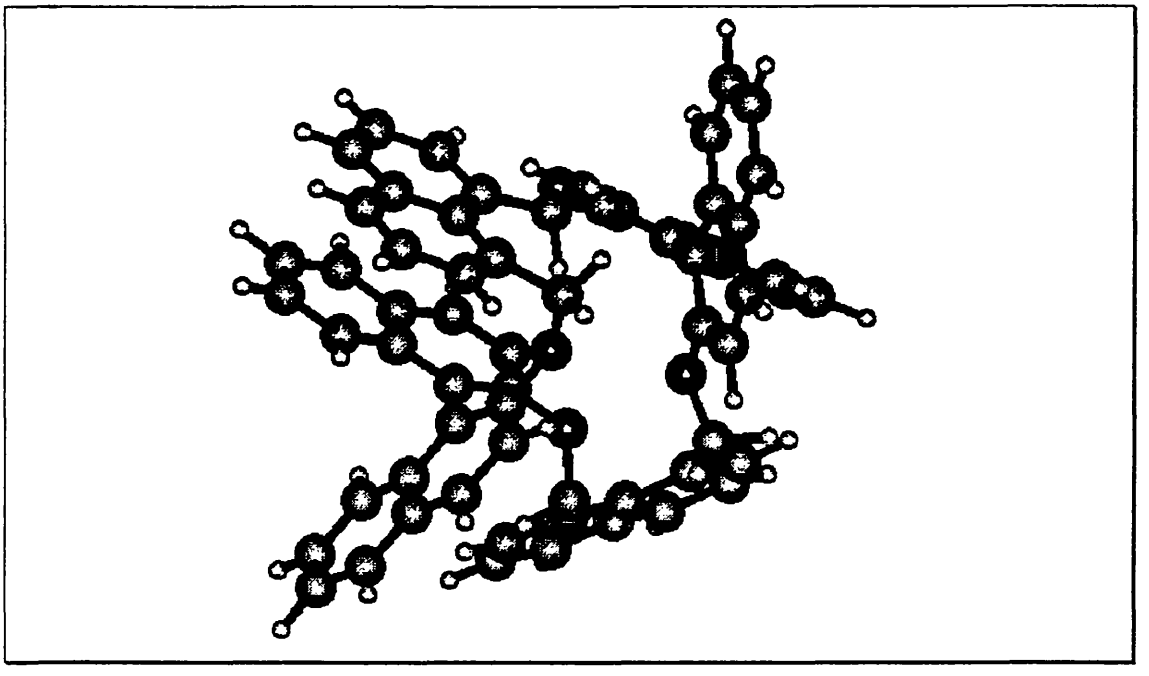
Model 7.1; Hyperchem Molecular Model of Target 1,8-Naphthalene Heteraphane [6D] - Conformation 1 View 1



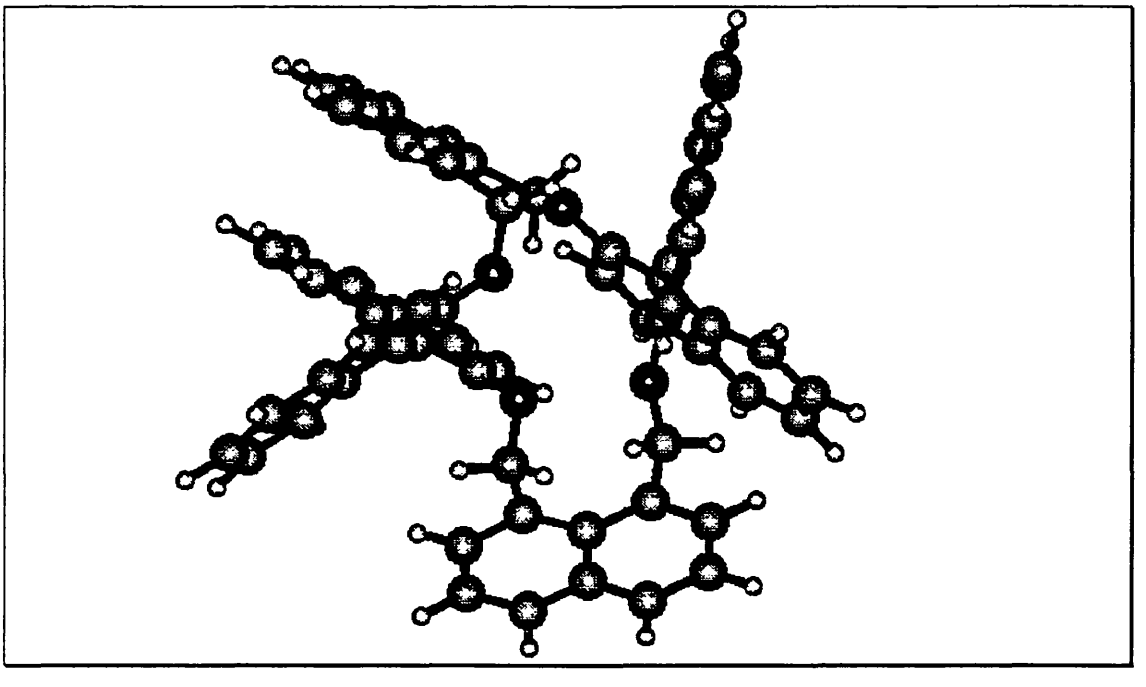
Model 7.2; Hyperchem Molecular Model of Target 1,8-Naphthalene Heteraphane [6D] - Conformation 1 View 2



Model 7.3; Hyperchem Molecular Model of Target 1,8-Naphthalene Heteraphane [6D] - Conformation 2 View 1



Model 7.4; Hyperchem Molecular Model of Target 1,8-Naphthalene Heteraphane [6D] - Conformation 2 View 2



Compared with the xylyl heteraphane inspiration, the cavity size of this dimer species would be increased (the molecular model being completely different and showing the possibility of two extremes of conformation). The molecule would still have similar pivoting points and thus rigidity. However due to its size it could allow more overlap of the spacer and binaphthyl units, their size giving greater flexibility. The two extremes of conformation are seen in their models (see above).

The 1,8-bis(bromomethyl)-naphthalene precursor was readily available and although not the cheapest of compounds it was still very affordable on a small scale (only a small amount would be required for initial studies). Several synthetic strategies were looked at including a route similar to the dibromo p-xylyl intermediate and a two step synthesis starting from a mono-protected binaphthol species. The dibromo- intermediate technique may have worked, but was not attempted as the 1,8-di-bromomethyl-naphthyl was always very likely to form mono-oligomer (as the first experiment with this combination found out). The 1,8-di-bromomethyl naphthalene was considered to be too expensive for use in the quantities required in such a test experiment even although the sought after molecule had good potential.

Synthesis

The actual synthesis of this target heteraphane was attempted using two methods. The first was a one pot attempt at going through a binaphthol - dimethylnaphthalene (1:2 ratio) adduct similar to those tried in the xylyl synthesis (without great success). In this a concentrated solution of the di(bromomethyl)naphthalene was slowly added into a 0.5 molar ratio solution of (what should have been) the di (sodium/potassium) naphthoxide [which was left at reflux for~45 minutes before the rest of the binaphthol was added]. It was thought that although the monomer was shown to be feasible by molecular models it would be too high energy to form in any great quantities. Thus it was hoped that the concentration of the di-(bromomethyl)naphthalene and its (presumed) high reactivity would promote the formation of the desired intermediate adduct and thus the desired oligomer and higher. However from all the data obtained from this reaction it would appear that (with the conditions used) the monomer was the dominant if not the only product with no evidence of any higher oligomers being present.

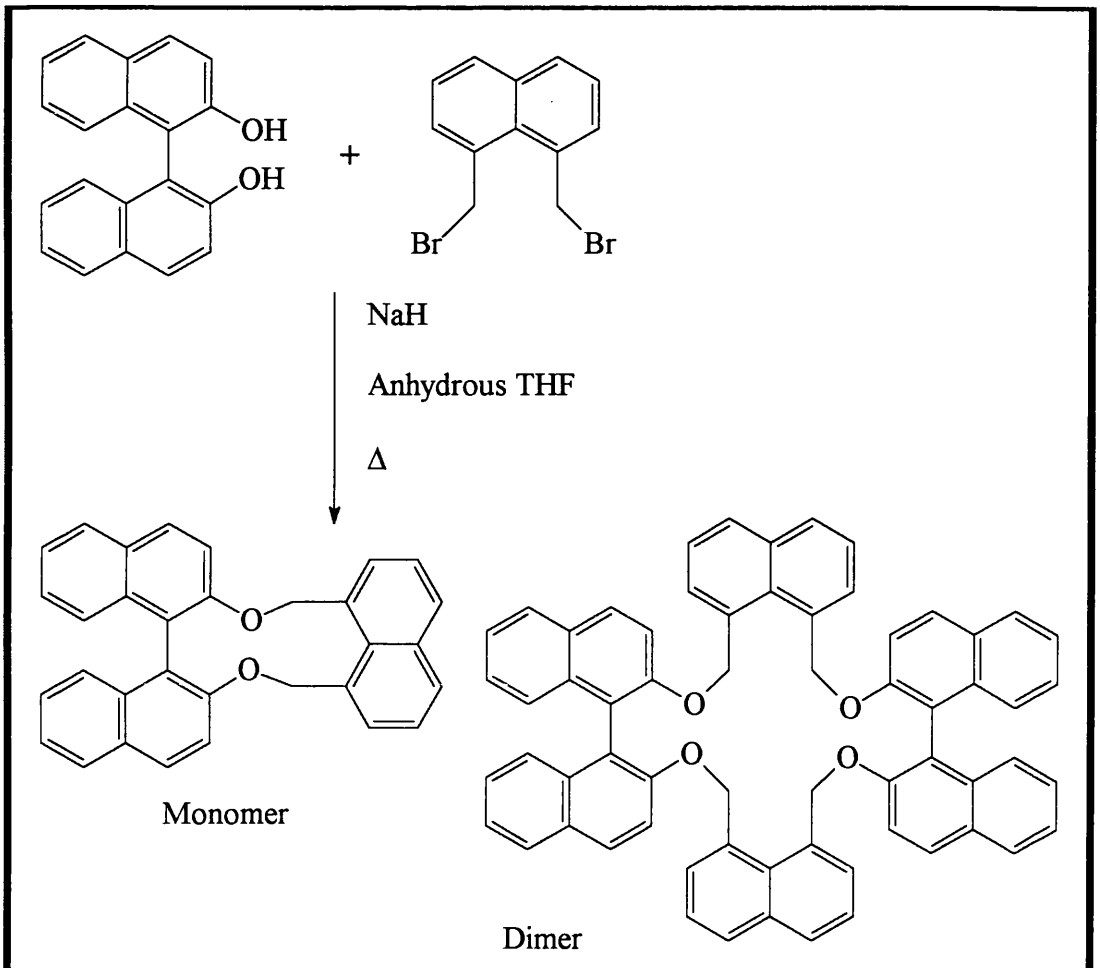
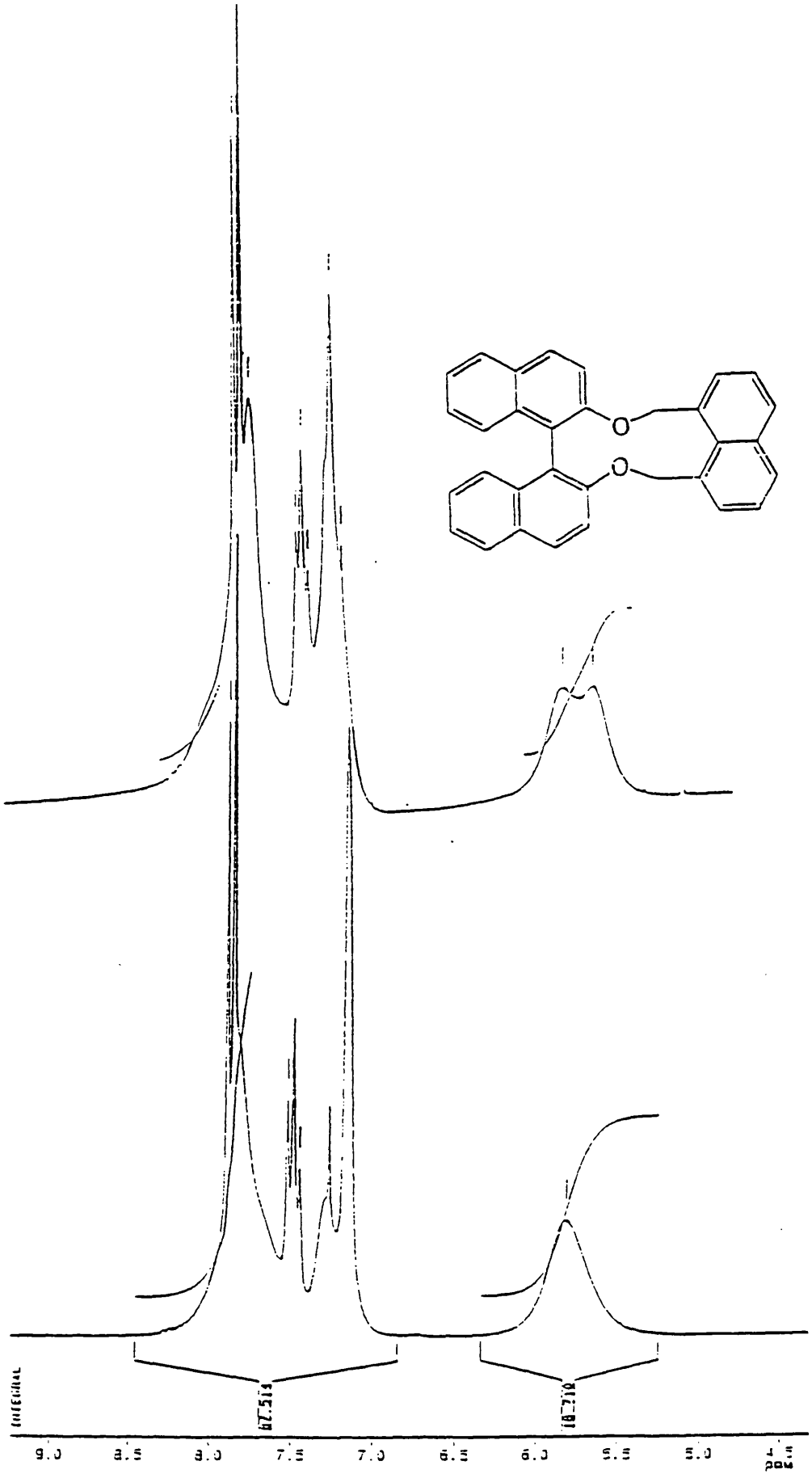


Figure 7.2; Synthesis of 1,8-Dimethyl-naphthalene Heteraphanes

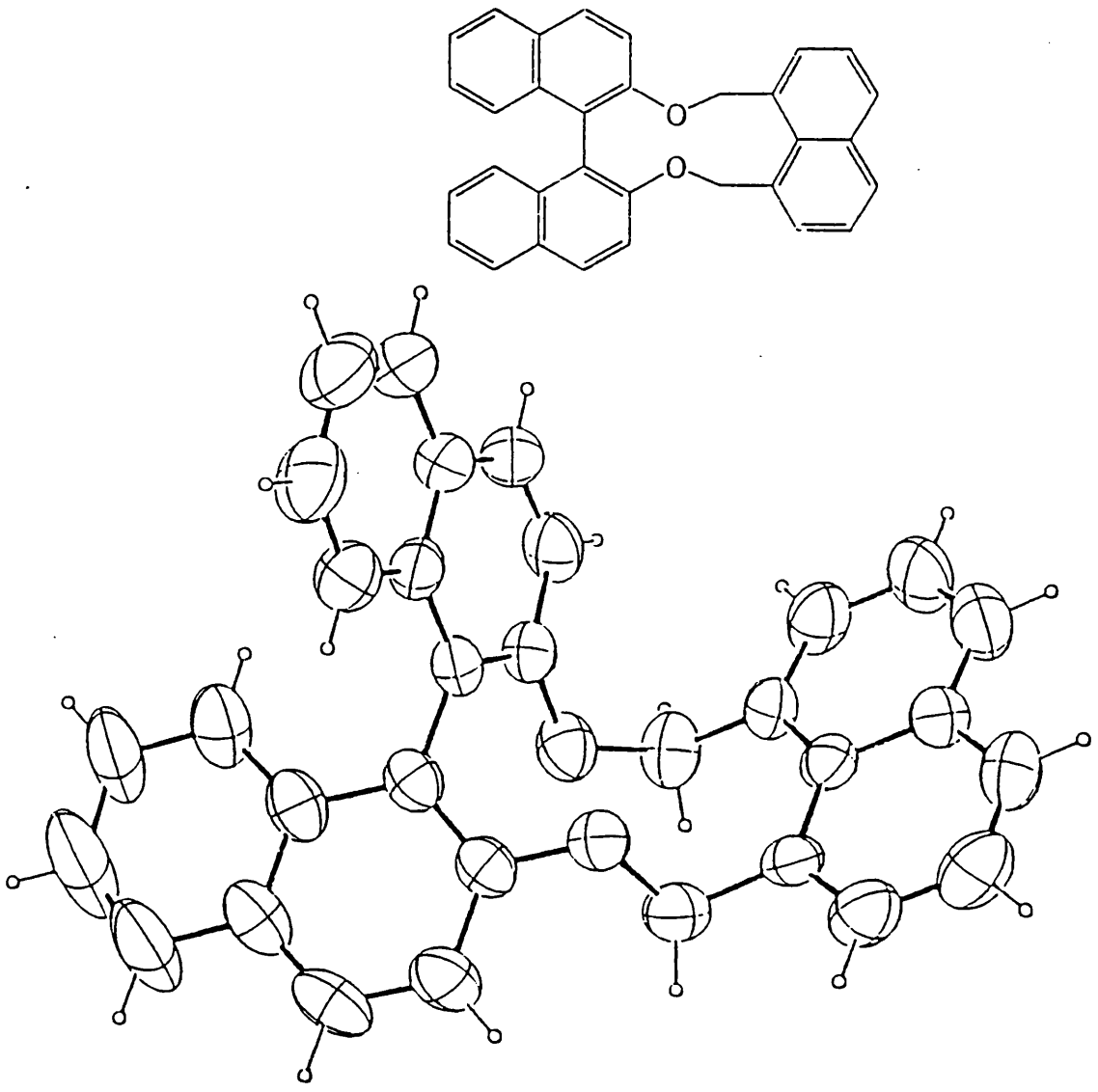
The ^{1}H NMR spectra, at different dilutions, of the purified 1,8-naphthalene monomer [6A] appear quite different from each other with both being very broad for such a relatively simple molecule. The lower spectrum was obtained from a more concentrated solution than the upper (which was diluted by a factor of ~2). The binaphthyl and naphthyl protons in both spectra can not be distinguished, as may be expected, and although both are similar there is a definite shift in some of the signals observed. The naphthyl methylene proton signal shows the most distinct differences between the two spectra, at higher dilution the very broad methylene signal splits into two which may be due to less π-π intermolecular associations, similar to those observed in the molecule's crystal structure.

^{1}H NMR Spectrum of 1,8-Naphthalene Monomer Heteraphane [6A]



The mass spectrum of this molecule shows the parent ion and no other peaks of higher mass. Also a slightly impure sample from the purification attempt which later shown to be the monomer, when mixed with NOBA formed a solid thus we could not obtain FAB MS. The ^{13}C NMR spectrum also appears broad.

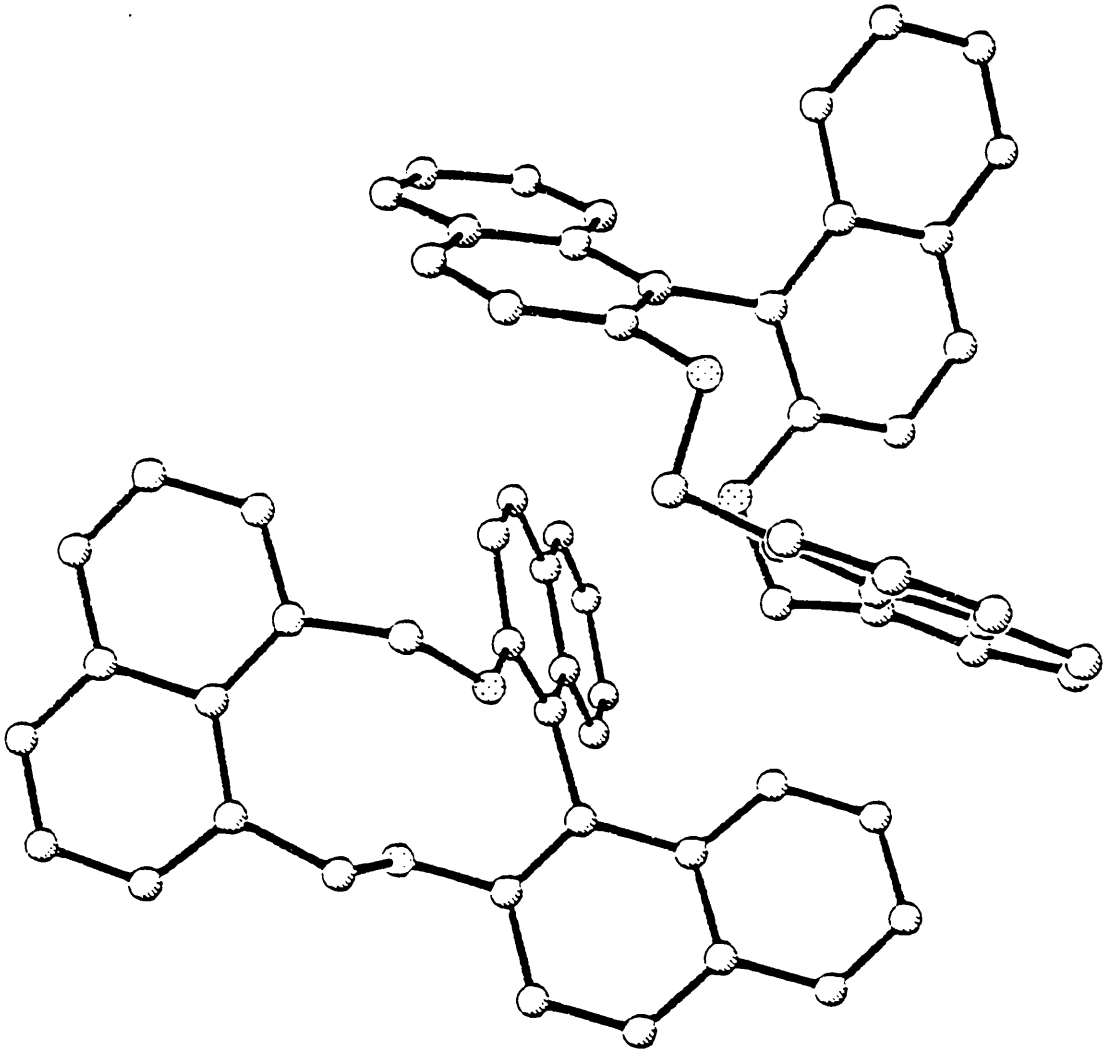
Crystal Structure of 2,3:4,5-Di(1,2-naphtho)-8,9,10-(1,8-naphthyl)-1,6-dioxa-2,4,8-triene-undeca-heteraphane [6A]



The assigned monomer structure was confirmed with the isolation of high quality crystals and their subsequent structural determination by x-ray diffraction. The unit cell was found to contain two molecules of the monomer with slightly different

conformations due to π-bonding interactions between a 1,8-dimethyl-naphthalene unit and one of the naphthol units of the binaphthyl of the other molecule.

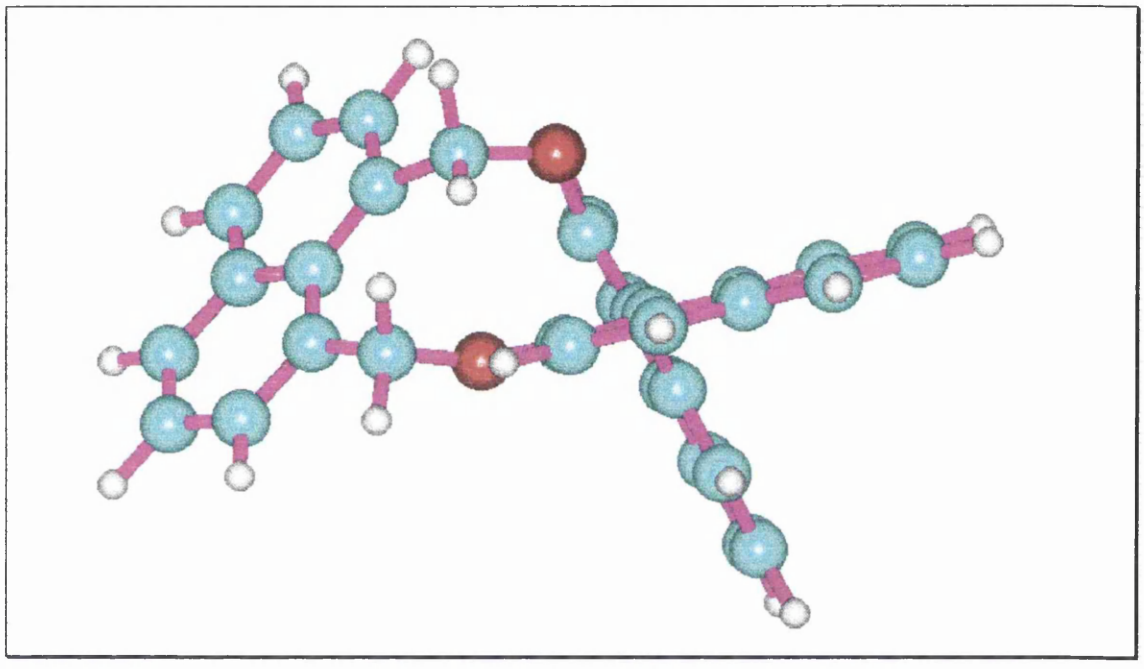
Ortep Displayed Plot of the Two Distinct Packing Forms of the Monomer Crystal



Monomer

The monomer crystal structure shows two distinct molecular geometries, arising from π interactions between the 1,8-naphthyl unit of one molecule and one of the 2-naphthol units of the other. The geometry of the monomer molecular model correlates well with the actual geometries seen in the crystal structure.

Model 7.5; Hyperchem Molecular Model of the Monomer Heteraphane [6A]



Attempted Synthesis of Target Dimer Via Isolated Intermediate [6C]

With the failure of the first attempt at synthesising the desired heteraphane, a second, more structured synthesis was undertaken. In this the starting binaphthol was mono-protected, to the methoxy methyl acetal which was then used to form an intermediate adduct with the bis(bromomethyl)-naphthalene (2:1 ratio binaphthol : bis(bromomethyl)-naphthalene). This adduct was then de-protected, purified and used in efforts at forming the full heteraphane under various conditions. There was good evidence obtained for the formation of the desired intermediate (see NMR and MS data). However from the experiments carried out it would appear that this intermediate was remarkably unreactive towards the bromo-naphthyl.

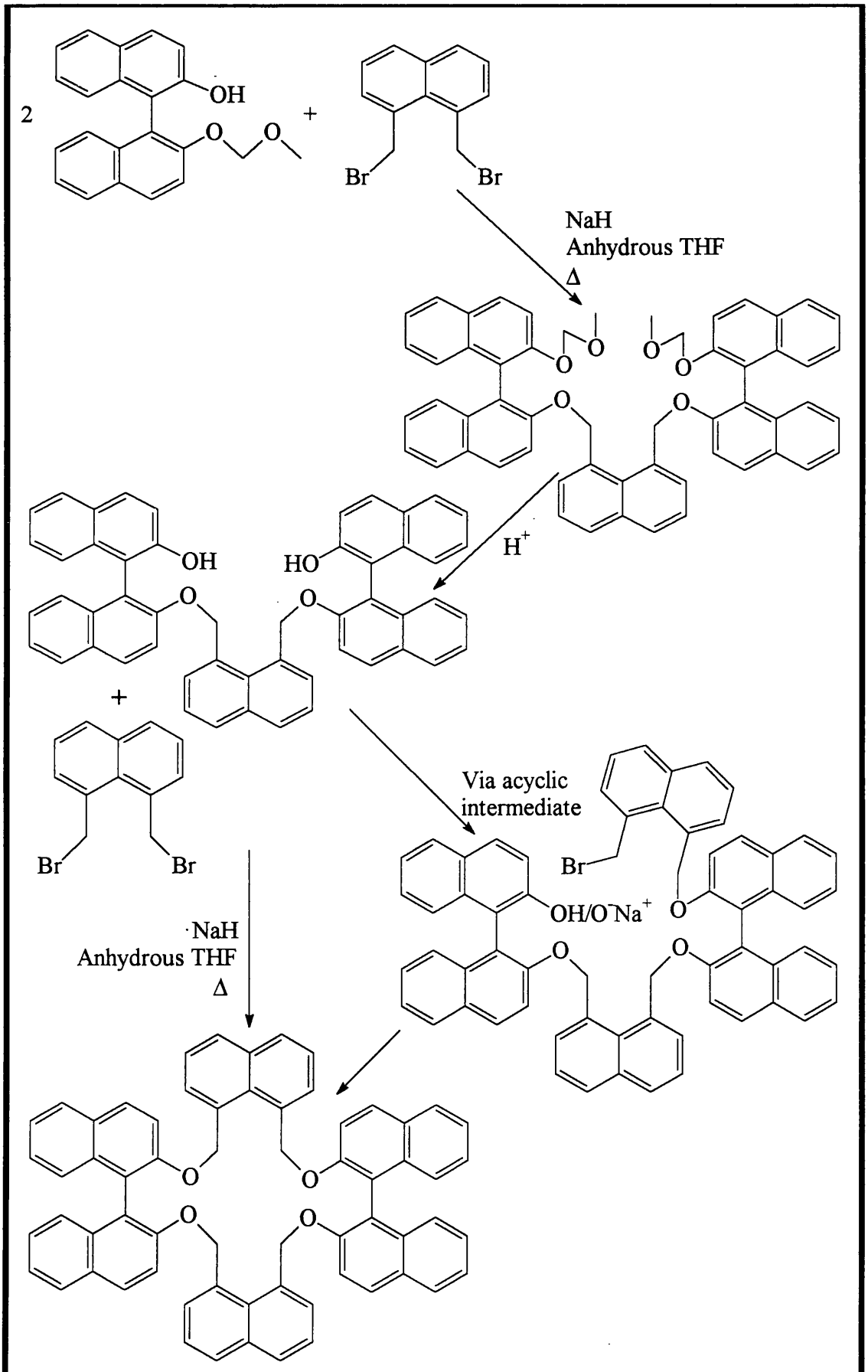
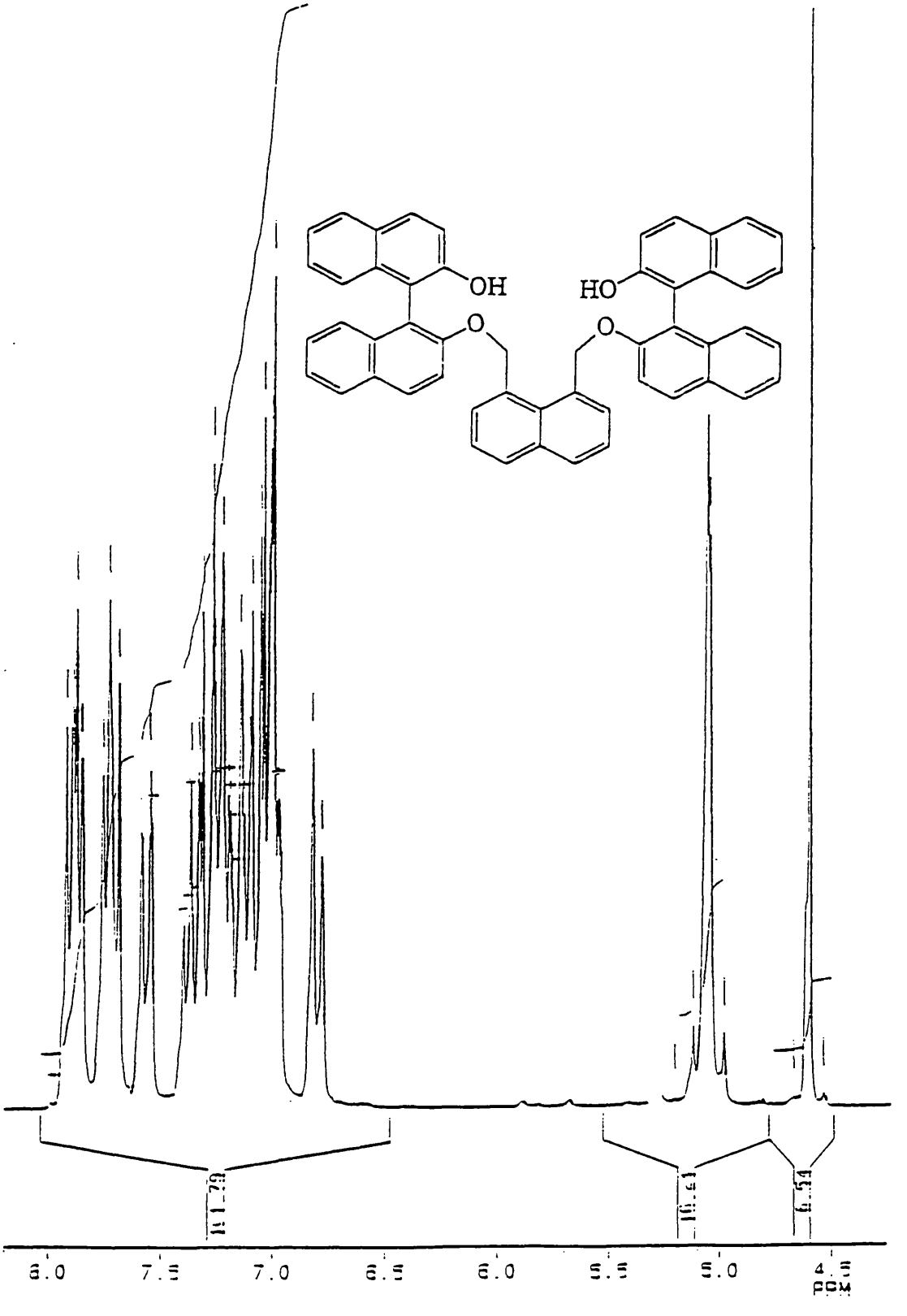


Figure 7.3; Alternative Synthesis for Target Heteraphane

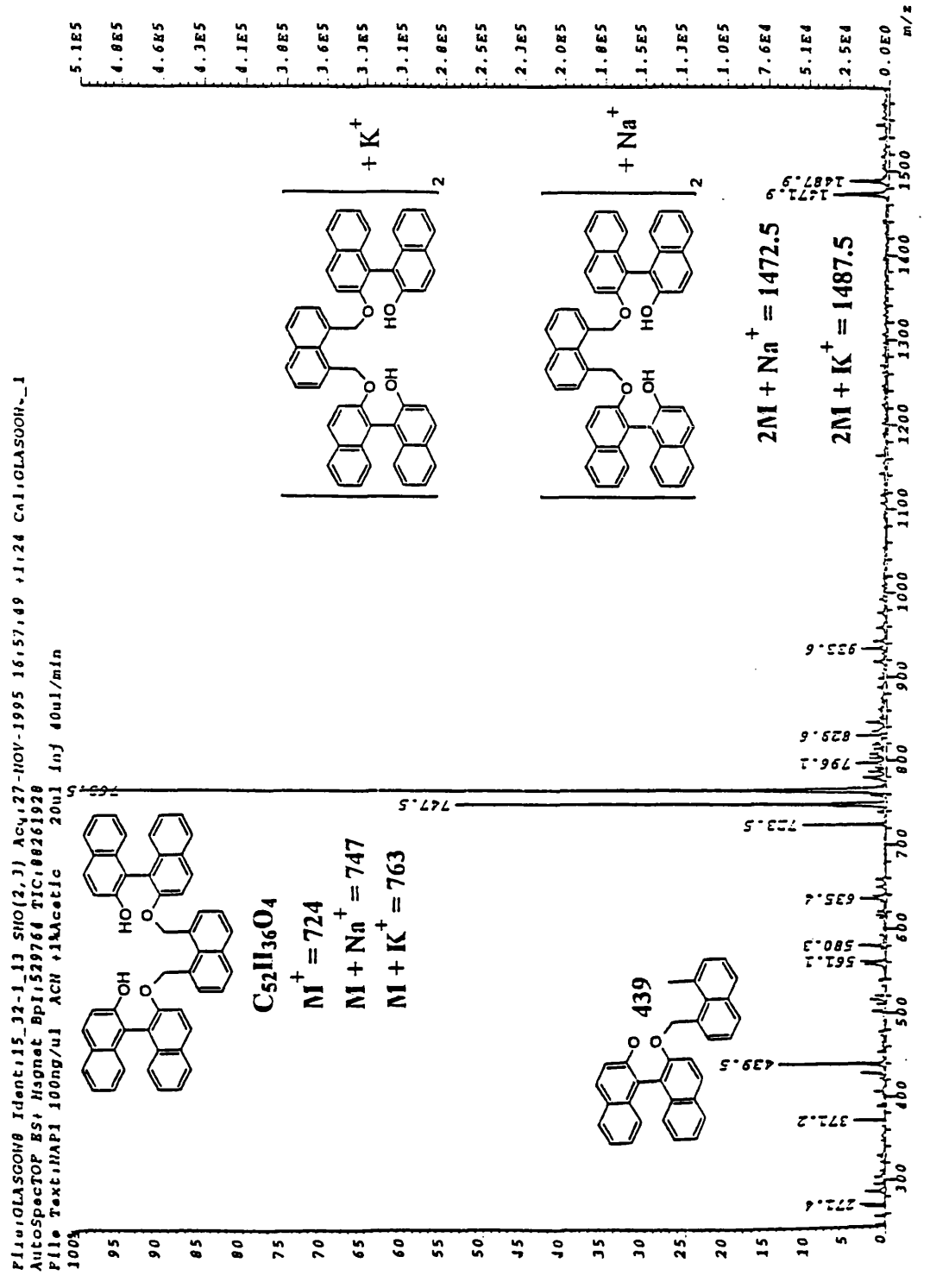
^{1}H NMR Spectrum of 1,8-Naphthalene Intermediate Heteraphane [6C]



The ^1H NMR spectrum of the purified bis(binaphthyl)-1,8(dimethylene)naphthalene compound [6C] shows a complex aromatic region in which the binaphthyl and naphthyl protons can not be distinguished. In comparison with the binaphthyl-1,8-naphthyl monomer compound [6A] the spectrum is relatively sharp and some splitting patterns can be assigned. the naphthalene methylene proton signal at ~5.1ppm shows a weak but distinct geminal coupled AB splitting pattern. The binaphthyl hydroxyl protons are seen as a sharp signal at ~4.6ppm which disappears on mixing with D_2O. This is suggestive of a well, narrowly-defined proton environment with little/no hydrogen bonding, which could be explained by an isolated environment due to steric hindrance. The far less stericaly hindered di-naphthol [2F] shows a very broad hydroxyl proton signal in its ^1H NMR spectrum.

The mass spectrum of this compound was taken using several different methods (CI, FAB and Electrospray), with all of the spectra obtained clearly showing the parent ion. The spectrum obtained using the electrospray method proved to be the most interesting in that as well as the parent ion the parent ion with sodium and with potassium (M^+ = 724, $(M+Na)^+$ = 747 and $(M+K)^+$ = 763 respectively), two relatively strong signals were seen with masses of 1472 and 1488. These signals could correspond to molecular complexes formed between two parent molecules and one alkali metal. It should also be noted that no peaks were seen that would correspond to a simple doubling of the parent ion or the parent ion plus sodium or potassium. This reinforces the idea that these are real complexes and not just an artefact of the method of detection/analysis. It should be noted that these peaks were only seen using the electrospray spectra which is probably due to it being the most sensitive (least destructive/harsh) of the methods used, however the peaks were not being specifically searched for in any of the spectra.

Electrospray Mass Spectrum of the Bis-binaphthyl 1,8-Naphthalene Intermediate [6C]



Conjecture

There are perhaps two main possible reasons for why the bis-binaphthyl intermediate compound does not react with the di-(bromomethyl)naphthalene. These are electronic and steric in nature and do not exclude contributions from both.

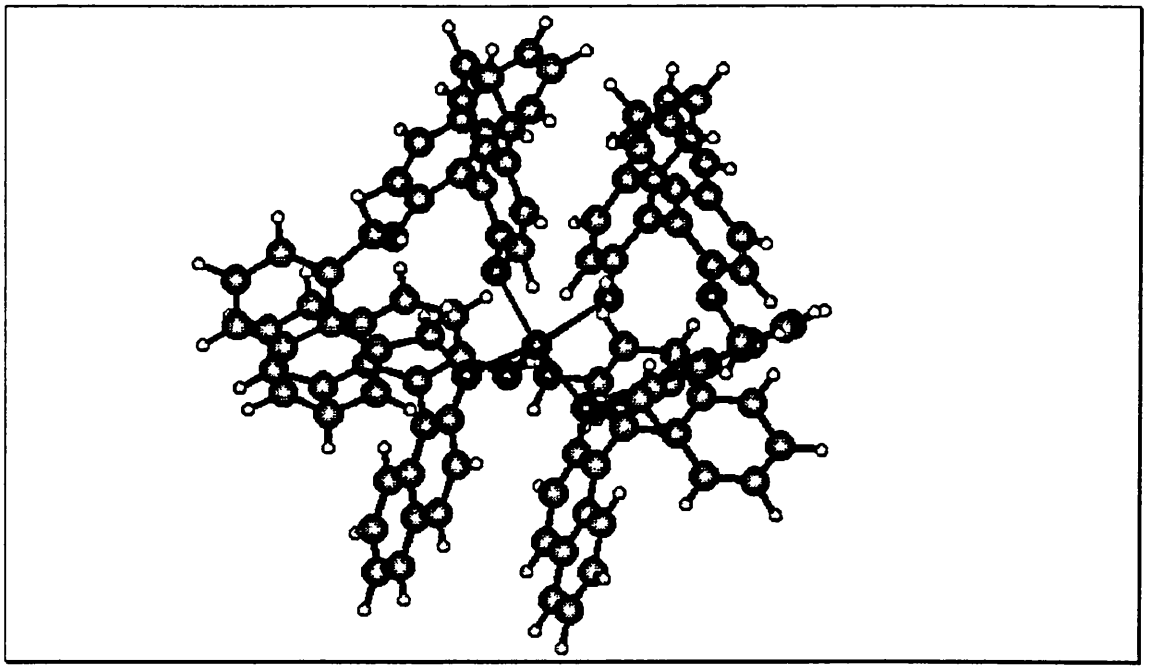
It is of note that the bis(bromomethyl)naphthalene does not even appear to react with one of the naphthyl hydroxyls to form a non-cyclic adduct.

It is also of note that the apparent low reactivity of this intermediate was reminiscent of the reactions involving the ether linked and single alcohol/ether armed bis-binaphthyl compounds in their respective cyclisation attempts. It is very possible, if not likely, that these ether linked intermediates would suffer from the same problems with proposed reasoning.

From the spectral data obtained, with particular reference to the electrospray mass spectrum and the peaks found at $(2M+Na)^+$ and $(2M+K)^+$ (and molecular models based on this theory), it is thought that alkali metal co-ordination is the reason for this intermediate's unreactive nature. The co-ordination of an alkali metal by two of the intermediate molecules would give both steric and electronic reasoning towards the lack of reactivity. Molecular models of this theoretical complex lends credence to the possibility of it being able to form. The model also shows that there would be a great deal of steric hindrance for the nucleophilic attack of the phenyl bromide by the naphthoxide ion. Also if the naphthol/naphthoxide oxygen was co-ordinated to the alkali metal, no matter how weakly, then it would lose its corresponding nucleophilicity. For this alone to be the reason for the low reactivity, there would have to be very strong co-ordination to the metal cation.

It was also noted that the bis-binaphthyl intermediate compound went off in solution (it turned yellow and gave several spots by TLC analysis), which is possibly due to some oxidation of the naphthol to a naphthaquinone (only small amount of degradation as NMR appears as pure compound).

Model 7.6; Hyperchem Molecular model of the Proposed Bis Intermediate - Alkali Metal Complex



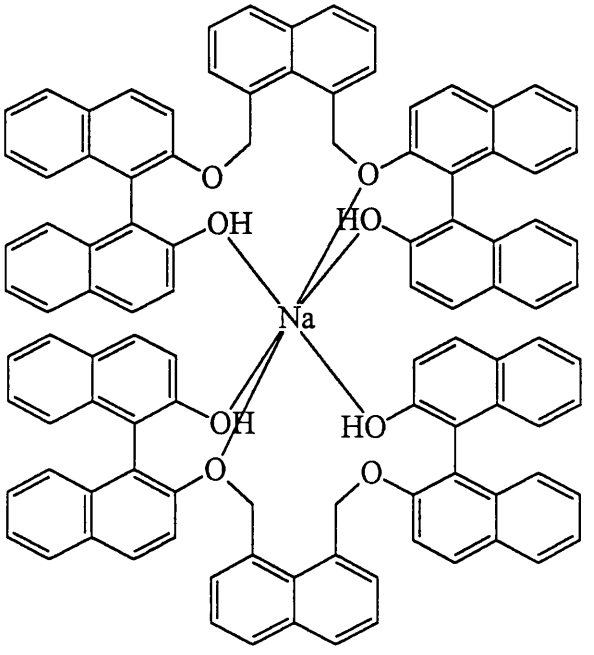


Figure 7.4; Proposed Intermediate - Alkali Metal Co-ordination Complex

The molecular model, shown above, was based on the idea that if it was possible to arrange two 1,8-naphthyl intermediates around an alkali metal centre it may go part of the way to explaining the intermediate's low/non reactivity. The model does give some

credence to this idea such that it is still a reasonable possibility for the cyclisation reactions not working even to the extent of forming the first step intermediate. There are at least two possible reasons for this lack of reactivity, those being a very greatly reduced nucleophilicity of the naphthoxides due to template type complexation and the steric hindrance that would be created with any complexation, especially if two molecules were situated around one metal centre - or what is more likely is a mixture of the two reasons or more. There are perhaps other possible metal complexation structures that would give rise to these reasons, including small alkali metal complexes and two metals to two intermediates - however the only evidence, a faint but definite mass seen in the electrospray spectra would point to the proposed model. Time certainly was not available to push this idea forward nor for other experiments with other metal bases to attempt to synthesise the sought after heteraphane.

Appeal of Target Dimer Heteraphane

The dimer would have 3 C_2 symmetry axes, perpendicular to each other and would probably show D_2 symmetry on the NMR timescale. How large would any energetic barrier be between any individual shapes and would both exist discretely or would they be in different states of fluxionality?

There are two views, from molecular modelling, on the shape that the dimer would take on. There could be overlap of a 1,8-naphthyl unit with a binaphthyl naphthyl unit, with exciplex formation likely to arise from close proximity interactions. There could be 1,8-naphthyls overlapping with each other, giving rise to excimer formation. If these are the only two shapes, then there is a possibility of two different cavity shapes being formed.

The possibility of the host molecule showing intramolecular exciplex fluorescence is seen in one of these models, where the dimethyl-naphthyl spacer overlaps well with one of the naphthol units of a binaphthyl chiral spacer. This conformation is perhaps strengthened by the crystal structure obtained for the monomer species. In this the unit cell contains two different monomer packing forms arising from the π bonding of the dimethyl-naphthalene spacer with one of the naphthol units of the binaphthol spacer.

With increased flexibility this molecule may also have been able to bind primary amine salts, using a three point binding system, whilst retaining a π-EDA binding capability.

Another possible use for this dimer heteraphane would be as an electron donating chiral box for use with electron accepting chains such as bipyridyls. The use of this or any similar molecule as a chiral box would come under the same reasoning and uses as for the previous electron deficient chiral box. The use of this heteraphane, or other similar development encompassing the larger major cleft bi-aryls, would depend on the actual configuration that the molecule took up and the energy required to change between the conformers.

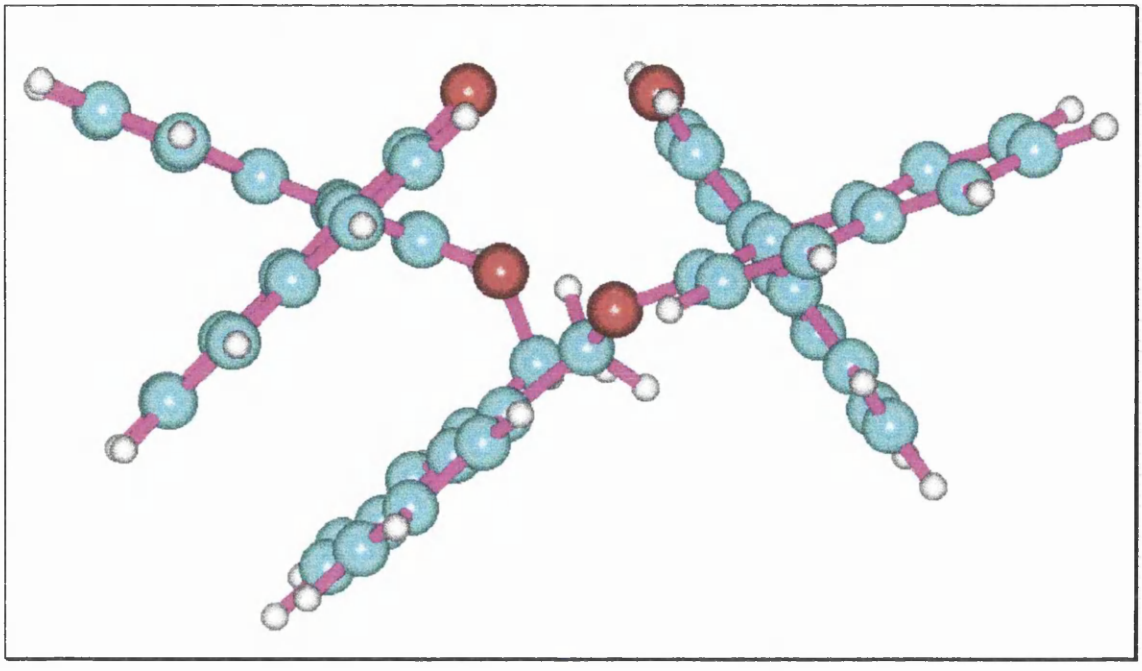
The cavity would certainly have the capability of being larger than any of the xylyl heteraphanes, it would also have more freedom for internal overlap of aromatic sub-units hence excimer or exciplex formation is possible and even very likely. With greater flexibility the actual position of the oxygen atoms may not be too opposed for binding to cations like primary amine salts (this requires more investigation and model building). The models of both the dimer intermediate and the dimer suggests that there would be an interaction between the 1,8-naphthyl (one of) and one of the naphthyl units of the binaphthyls and as such exciplex formation is possible. However this is just a model and no solvent parameters were incorporated in its calculation, although the monomer crystal structure reinforces this thought.

These models show very interesting shapes which may even allow analyte binding to the ether/hydroxyl oxygens which should be investigated further. 'Orbit' molecular modelling kit models also show that good overlap between the two 1,8-naphthyl units is possible/likely. This overlap can also be seen with the modelling packages, however they tend to require to be fixed with bridging units between the 1,8-naphthyl units.

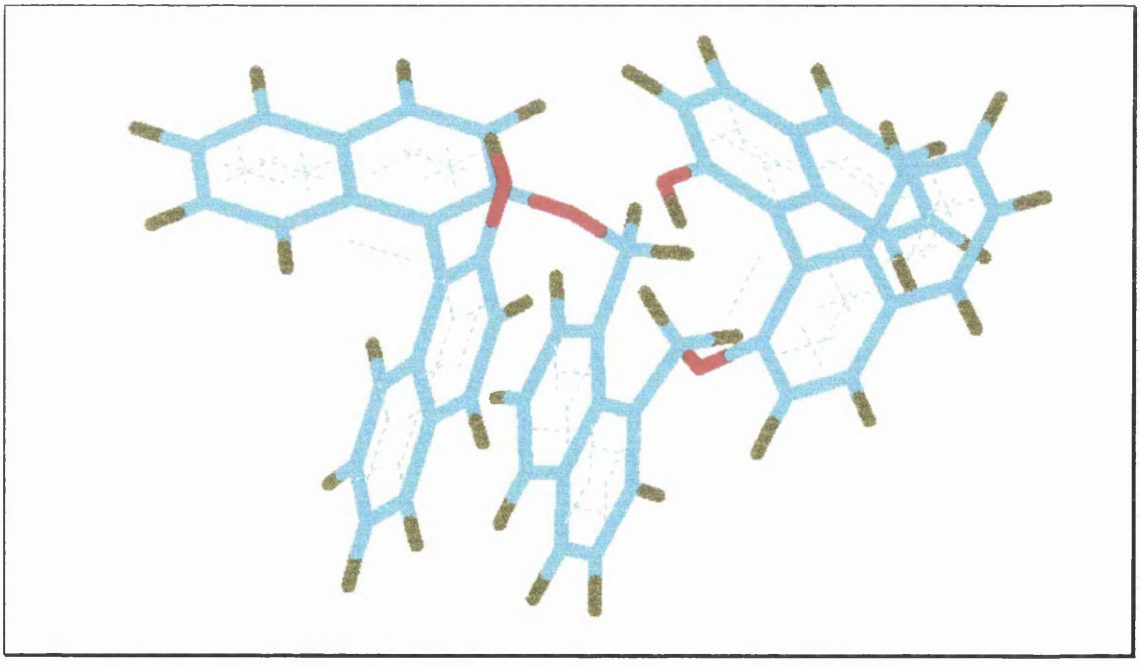
Intermediate

The intermediate appears to be very unreactive towards cyclisation. Its model suggests that exciplex formation is possible and as such its interaction with amine salts and more pertinently any interaction with primary amines should be investigated with the view to saltex formation possibilities. Any saltex formation involving naphthol, if the mono-arm scenario is correct, could show very large differences in fluorescence spectra, between bound and unbound naphthols.

Model 7.7; Hyperchem molecular Model of Dimer Intermediate [6C] - View 1



Model 7.8; Hyperchem molecular Model of Dimer Intermediate [6C] - View 2



CHAPTER EIGHT

SYNTHESIS OF LONG AND SHORT ETHER ARMED BINAPHTHYLS, THEIR INTENDED UTILITY AND SHORTFALLS

The interest in these compounds arose predominantly for their proposed use as intermediates for the synthesis of more involved, better binding, better signalling prototype sensors. The initial target compounds (figure 6.1) had previously been synthesised by Cram et.al.[18,92]. Attempts were made at following some of these synthetic routes and other more direct methods were also used.

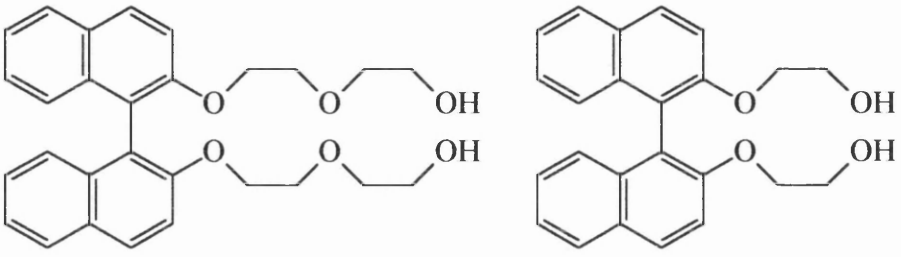
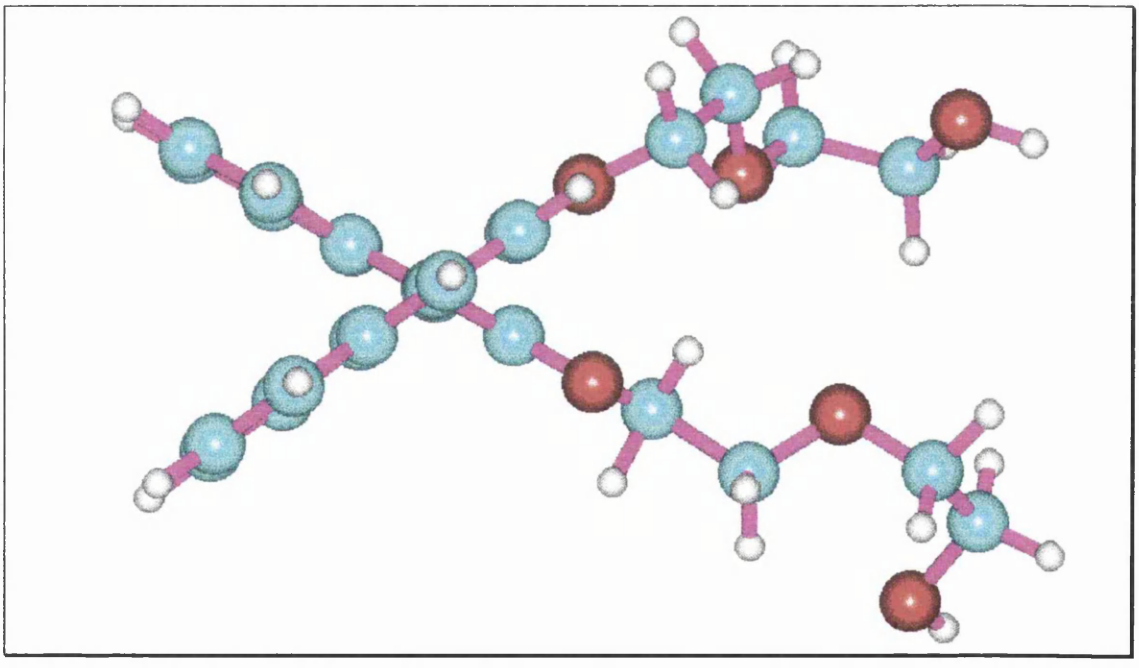
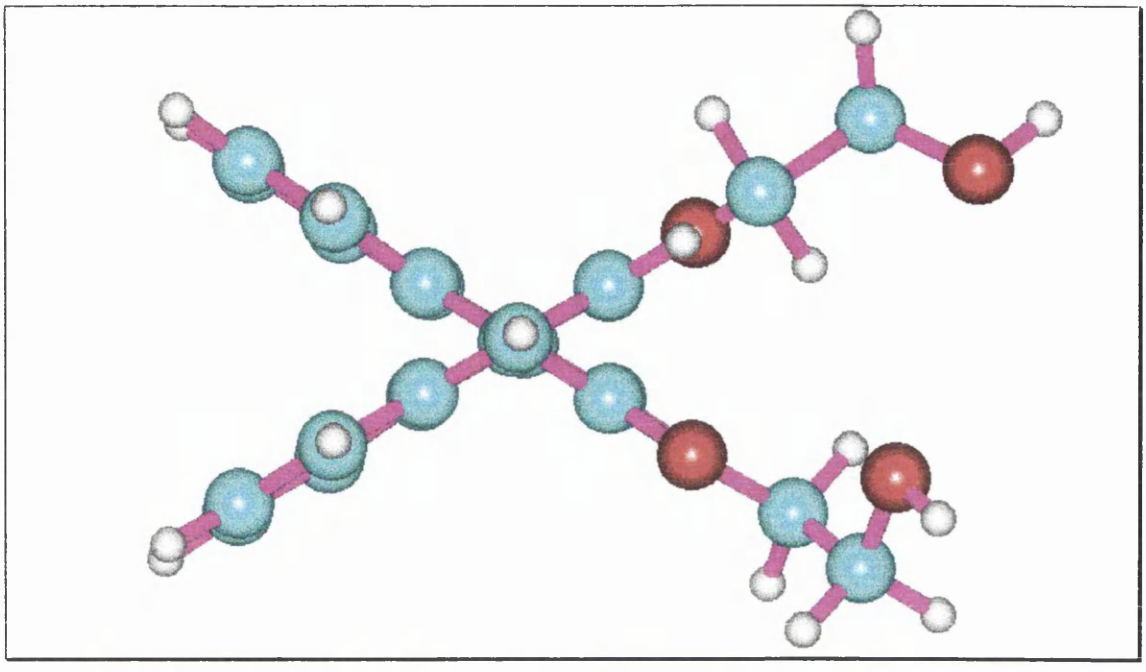


Figure 6.1; Target Synthetic Intermediates

Model 8.1; Hyperchem Molecular Model of the Di-ethyl ethanol armed intermediate



Model 8.2; Hyperchem Molecular Model of the Di-ethanol armed intermediate



Intermediate Synthesis

The actual synthesis of these intermediates were difficult. However they were possible with low yields and difficult purification.

Synthesis of 2,2'-Bis-(5-hydroxy-3-oxa-1-pentyloxy)-1,1'-binaphthyl [3C]

The synthesis of the ether alcohol armed intermediate was attempted using several methods, using both the protected and the free chloro-ether alcohol. The direct attempts were performed using a mixture of homochiral binaphthol and the chloro-alcohol precursor in refluxing THF over potassium carbonate. These were left for several days over which time an amount of the desired di-armed binaphthyl and its mono-armed precursor would form. The method of Cram, which goes through the pyranyl ether protected alcohol was also attempted

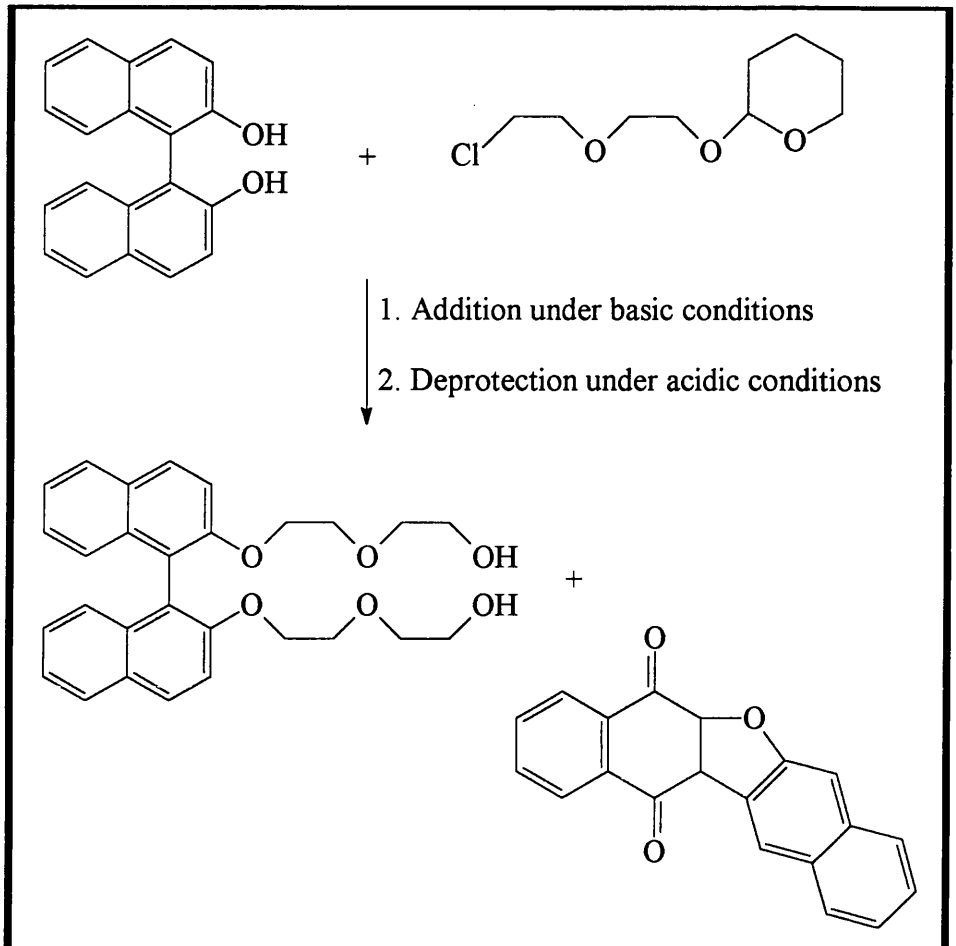
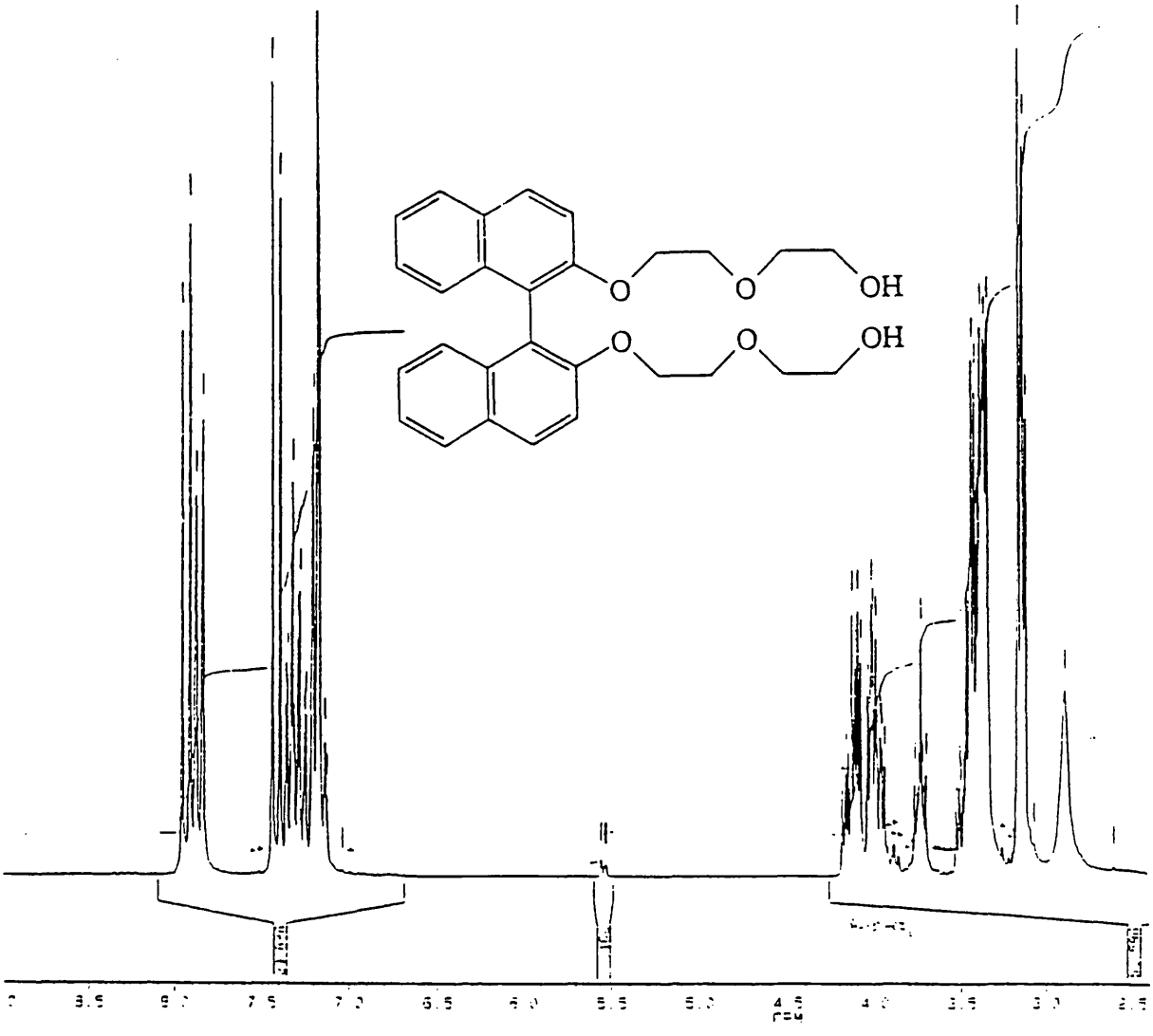


Figure 6.2; Synthesis of Bis(ethoxy-ethanol) Armed Binaphthyl

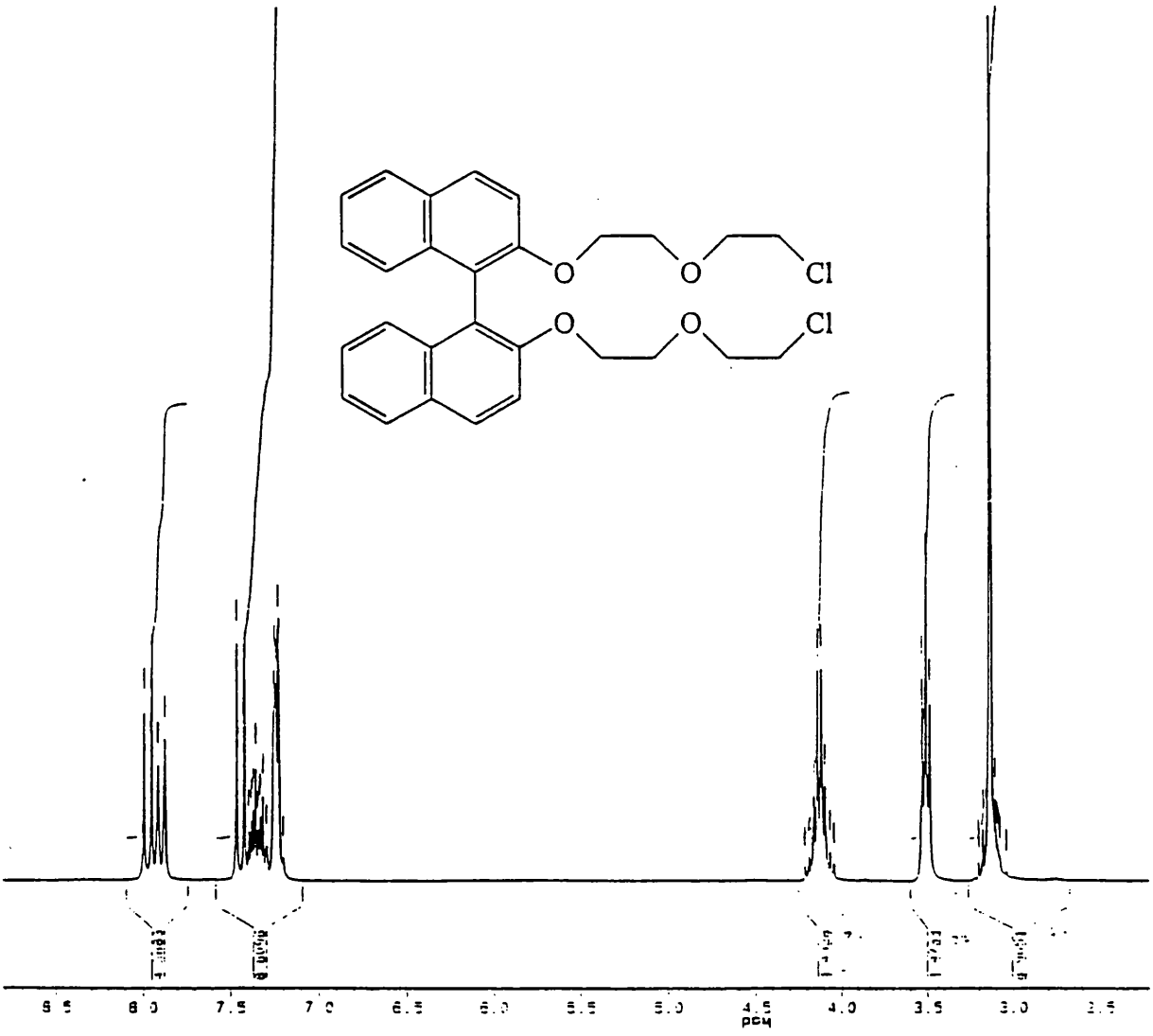
The ^{1}H NMR spectrum of the purified bis(ethyl-ethanol) armed compound again shows characteristics of its symmetry. The naphthyl protons splitting patterns are well defined (perhaps not as much as with the bis-ethanol armed compound). The methylene protons appear in sequence, with the protons closest to the naphthyl oxygens appearing downfield (higher shift) of the others. The methylene protons α to the aromatic oxygens again show a complex splitting pattern with the dominant coupling arising from the geminal protons looking down onto the chiral axis. The hydroxy protons are seen as a broad singlet at ~2.85. Again an amount of the column eluent residue can be seen in this spectrum.

^{1}H NMR Spectrum of the Di-ethyl ethanol armed intermediate [3C]



This diol was converted to a useful dichloro compound, 2,2'-Bis(5-chloro-3oxa-1-pentyloxy)-1,1'-binaphthyl [3F], using thionyl chloride. The purification of this compound, by column chromatography, was far easier than the diol due to it having more favourable elution characteristics.

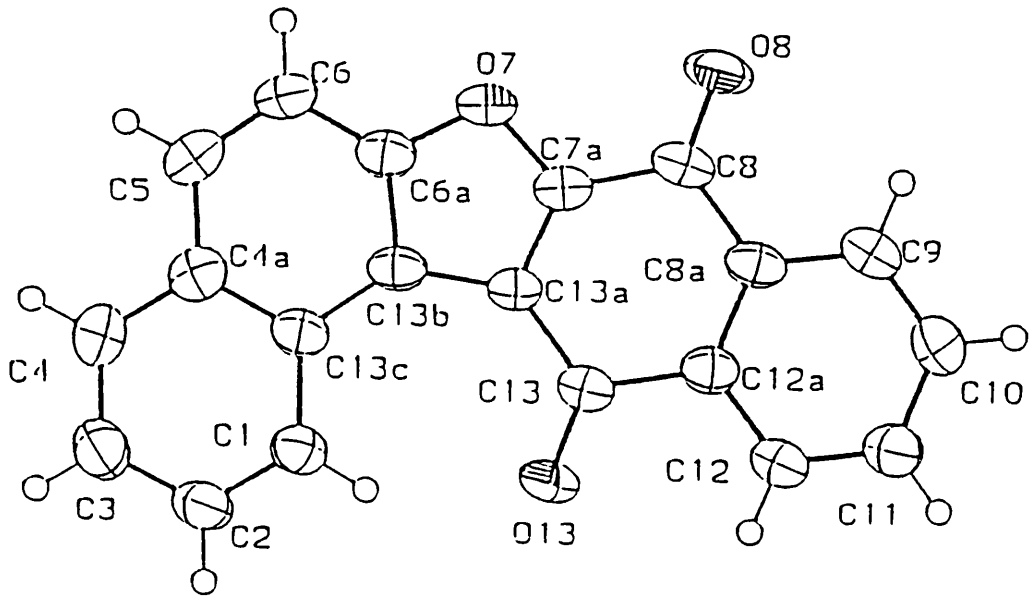
^{1}H NMR Spectrum of the Di-ethyl -dichloroethyl armed intermediate [3F]

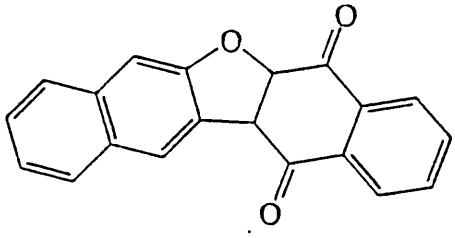


The ^{1}H NMR spectrum of the di-chloro-ether armed compound shows a cleaner, simpler spectrum compared with its hydroxy precursor. There is a slight change in the aromatic region, with it appearing clearer, and the geminal coupling of the methylene protons α to the naphthyl oxygens is far less well defined.

The harshness of some of these reactions were perhaps cause for concern, for effects of racemisation and degradation. This concern was reinforced by the crystallisation and subsequent identification of a naphthofuran oxidation product from the low yielding synthesis of the ether alcohol using (R)-binaphthyl by Cram's method.

Crystal Structure of Dinaphtho[2,1-b:2',3'-d]furan-8,13-(8H,13H)-dione





This compound has previously been synthesised by Ishikawa etal.[89] (1988) in order to help in the characterisation of organic pollutants released from coal and to assess their health effects. It was synthesised by the condensation of phenols with 2,3-dichloro-1,4-naphthoquinone in pyridine. It would appear to have formed here via an oxidative rearrangement in which the C-C bond in the 1,1' position is broken, to allow quinone formation and two new bonds are formed, creating the furan structure. This rearrangement may have gone through complete cleavage of the 1,1'-binaphthyl or through an intermediate such as that shown in figure 6.4.

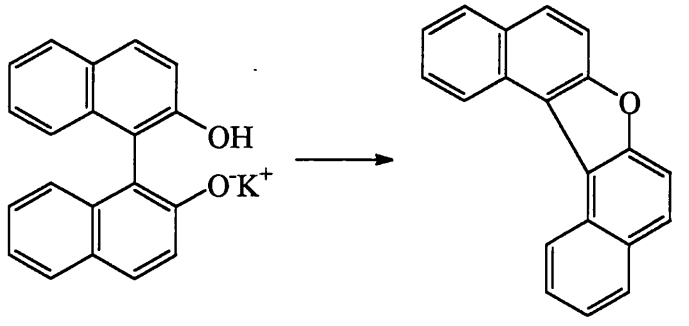


Figure 6.3; Possible Naphtho-Furan Intermediate

This naphtho-furan had the R-configuration, however the twist was within the limits of thermal variance so it is of little meaning. No optical rotation could be seen. There was also no circular dichroism change observed.

The synthesis of the longer armed intermediates were not working as quickly or easily as desired thus we moved onto smaller ethanol arms as we thought that the synthesis might be simpler. However again low yielding mixtures were obtained.

Synthesis of 2,2'-Bis(2-hydroxy-1-oxy-ethyl)-1,1'-binaphthyl

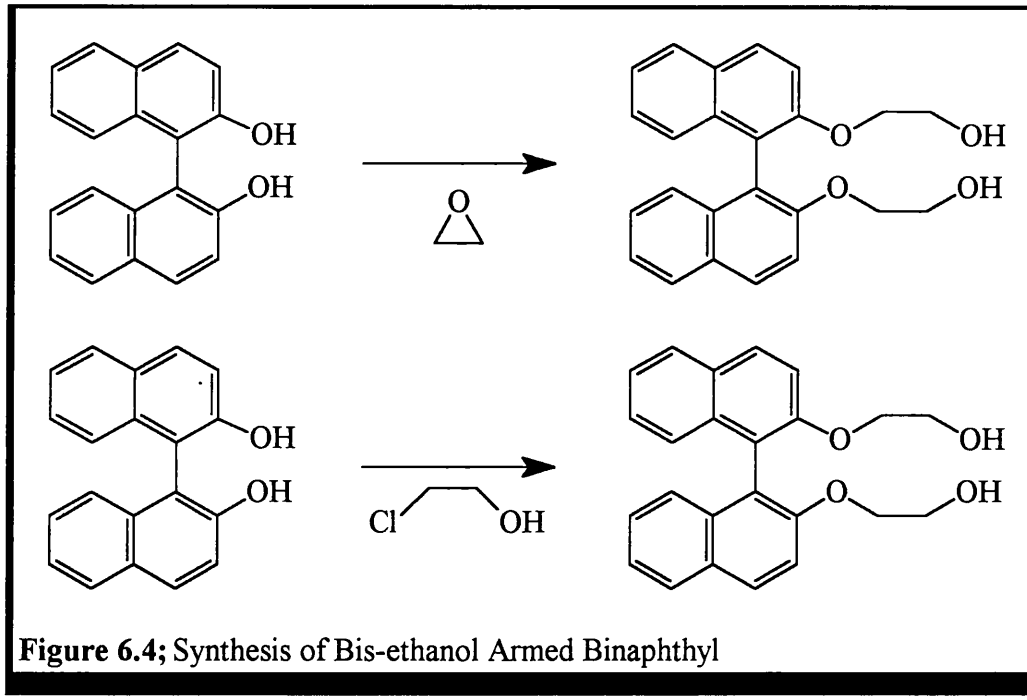


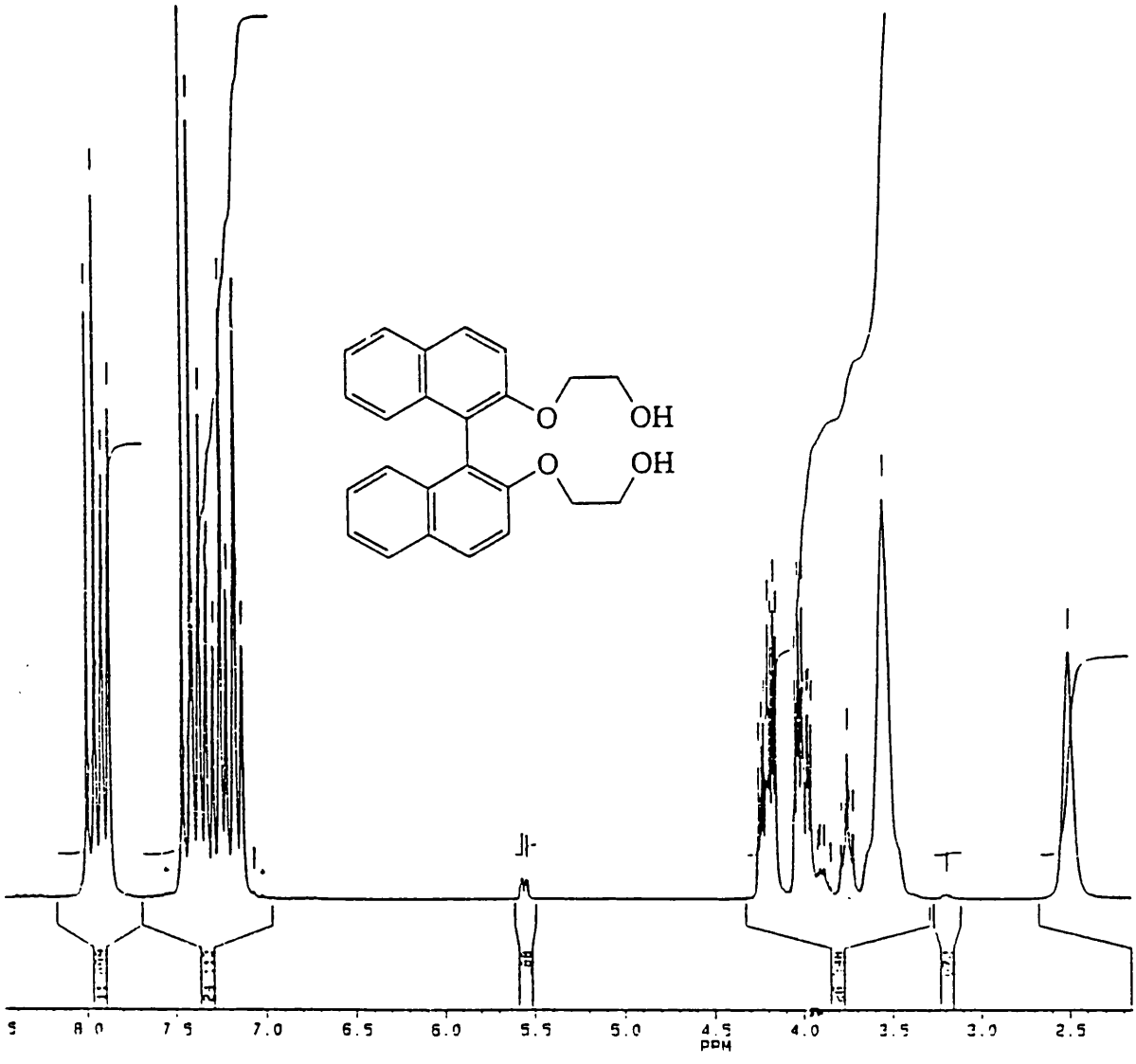
Figure 6.4; Synthesis of Bis-ethanol Armed Binaphthyl

The methods used for the synthesis of the bis-ethanol armed binaphthyl incorporated the use of 2-chloroethanol and ethylene oxide. It is perhaps worthy of note that Cram also went through a bis-ethyl-ester armed binaphthyl (using the acetate of 2-chloro-acetic acid). This perhaps highlights the difficulties that were encountered in the synthesis of these ether armed compounds, with respect to the assumption that the mono-armed

intermediate of this ester would be far less likely/able to co-ordinate to an alkali metal and thus deactivating itself. The yields obtained in the synthesis of these compounds were very often below those quoted by Cram.

Spectral Interpretation

^{1}H NMR Spectrum of the Di-ethanol armed intermediate [3G]



The ^{1}H NMR spectrum of the purified ethanol armed binaphthyl [3G] shows all the distinctive characteristics that would be expected for a molecule with this structure. The symmetry is seen in the relative simplicity of the spectrum. The binaphthyl protons are very distinctive in that the expected splitting pattern can be made out in full without much difficulty - there are two doublets at ~7.9ppm, then moving upfield there is a doublet at ~7.45, a triplet at ~7.3ppm and a doublet and triplet both centred on the same shift at ~7.2ppm. The methylene protons α to the naphthyl oxygen show complex splitting pattern at ~4.1ppm (doublet of multiplets), with the major splitting arising from geminal coupling due to the effect of the chiral axis. The methylene protons α to the hydroxyls are seen as what appears to be a broad, very poorly defined triplet at ~3.55ppm. The hydroxyl protons are seen as a broad singlet at ~2.5ppm. A small amount of impurity is also seen in this spectrum, at 5.55 and at ~3.8ppm, which is felt to be an artefact of the eluent used in the purification process (very similar peaks were often seen in samples from columns that had been run using THF : petroleum spirit as eluent).

The mass spectrum of this compound, with parent ions with mass M^+ = 374 (CI MS) reinforced its assigned structure.

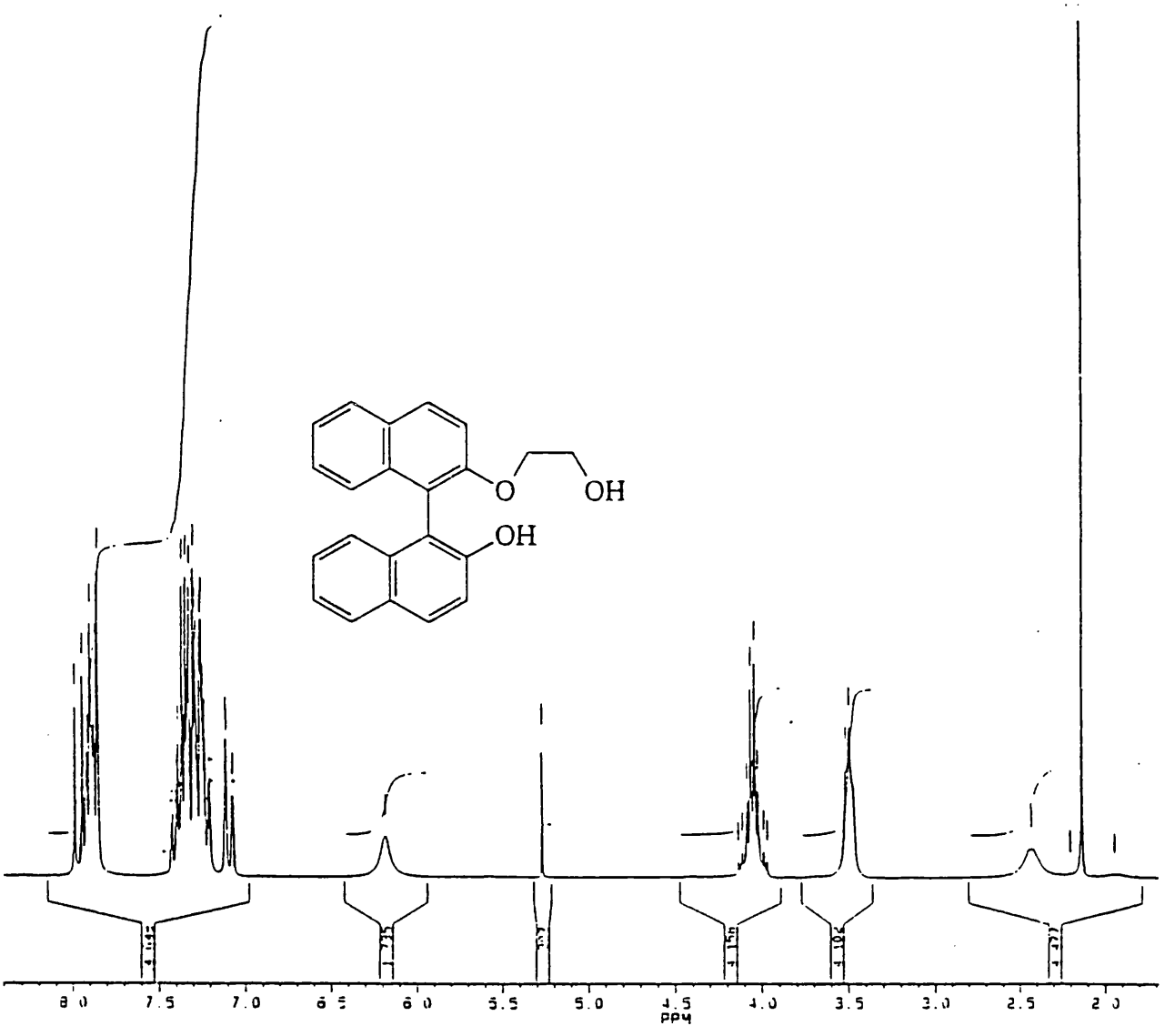
Mono-ethanol Armed Binaphthyl

The ^{1}H NMR spectrum of the purified mono-ethanol armed binaphthyl was, as expected more complicated as there was no C_2 symmetry axis. The two groups of aromatic protons are much more complicated, with little being easily identified. The methylene protons α to the naphthyl oxygen are seen as a multiplet at ~4.1ppm, with some appearance of geminal coupling, and the methylene protons α to the hydroxyl group are seen at ~3.5ppm as a broad undefined singlet. The naphthyl hydroxy proton is seen as a broad singlet at ~6.2ppm and the ethyl hydroxy proton is seen at ~2.45ppm. The spectrum also shows some dichloromethane impurity at ~5.25ppm and some acetone impurity at ~2.1ppm. This was purified by precipitation and/or column chromatography using DCM as base solvent.

The mass spectrum of this compound gave a parent ion with mass of 330. The FAB mass spectrum of this compound was not obtained as its mass did not require it, however it was thought that if it had been it would show a very large peak for M + Na,

as it appeared to have a great affinity for alkali metals which is one possibility for its lack of reactivity.

^{1}H NMR Spectrum of the mono-ethanol armed intermediate [3H]



One of the major concerns with the above syntheses was about the length of reaction allowing substantial racemisation to take place, which would be accelerated by the basic conditions used. As with the synthesis of many of these prototype sensors difficulties were also encountered with the production of these intermediates. It was from the difficulties encountered here, in particular the synthesis of the bis-ethanol armed binaphthyl, that explanations for these unexpectedly problematic syntheses were proposed. It is thought that steric and/or electronic effects caused the lack of reactivity

which arose from the complexation of the mono armed intermediates with the alkali metal base during the synthesis. For the longer ether-hydroxy arms the same reasoning holds perhaps with slightly greater co-ordination effects being expected.

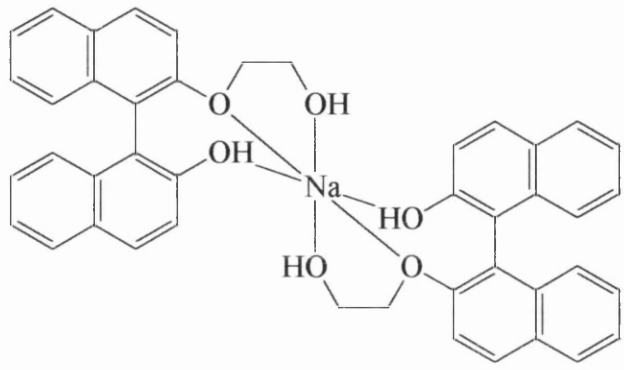
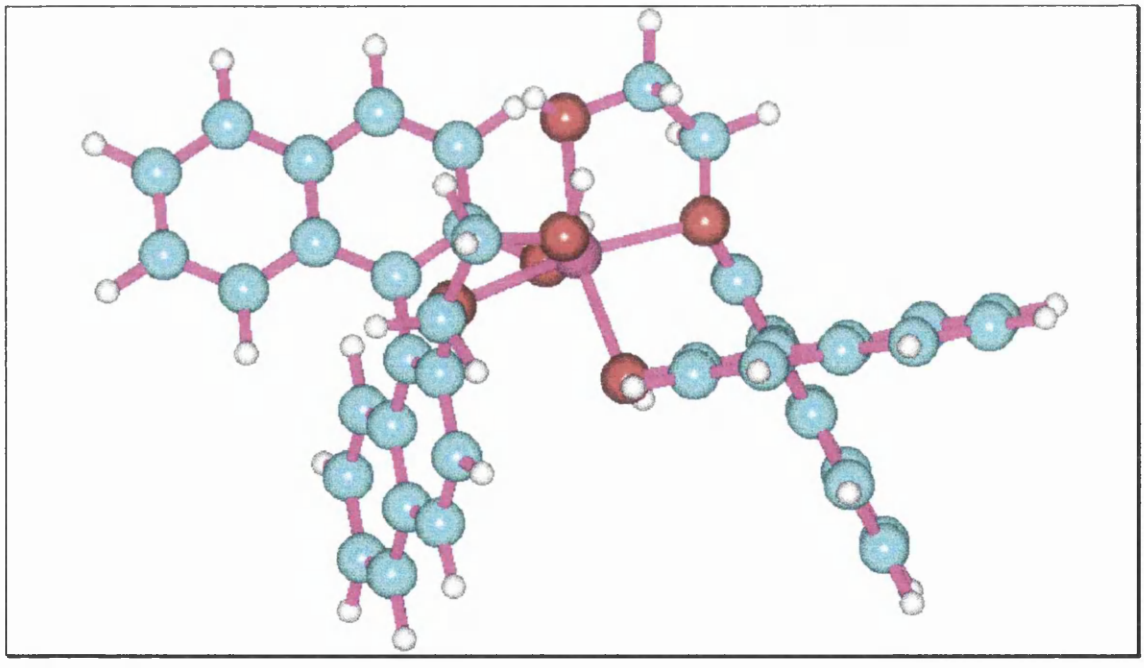


Figure 6.5; Possible Sterically and Electronically Hindered Intermediate complex

Model 8.3; Hyperchem Molecular Model of Possible Mono-ethanol Armed Intermediate Alkali Metal Complex



One of the reasons that we became interested in these intermediates is that it was thought that if the hydroxy groups were replaced with thiol or thio-ether ends then they would be good prototype models for binding to gold surfaces thus making a chiral gold electrode for use as a prototype sensor.

A major difficulty that would have to be overcome for this idea to have any chance of working was how this flexible, acyclic molecule's conformation could be kept coherent/discrete and with a high level of uniformity when it is absorbed onto the gold surface.

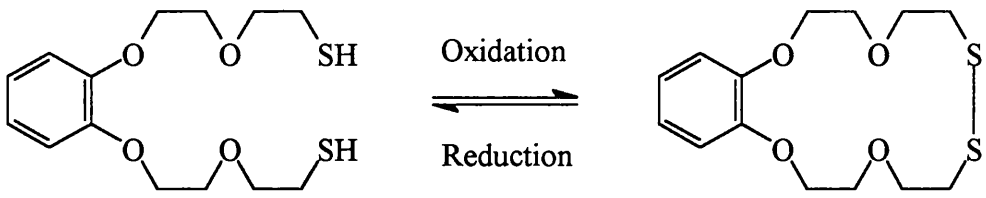


Figure 6.6; Shinkai's reversible crown ether

An answer to this problem came from a paper by Shinkai[96], where he had synthesised an analogous compound (figure 6.6). If the thiol was made then this could be chemically oxidised to the disulphide which could then be absorbed onto a gold surface under reducing conditions (figure 6.2b). Thus the two sulphur-gold bonds should be relatively close together and there should also be high conformational uniformity across the surface.

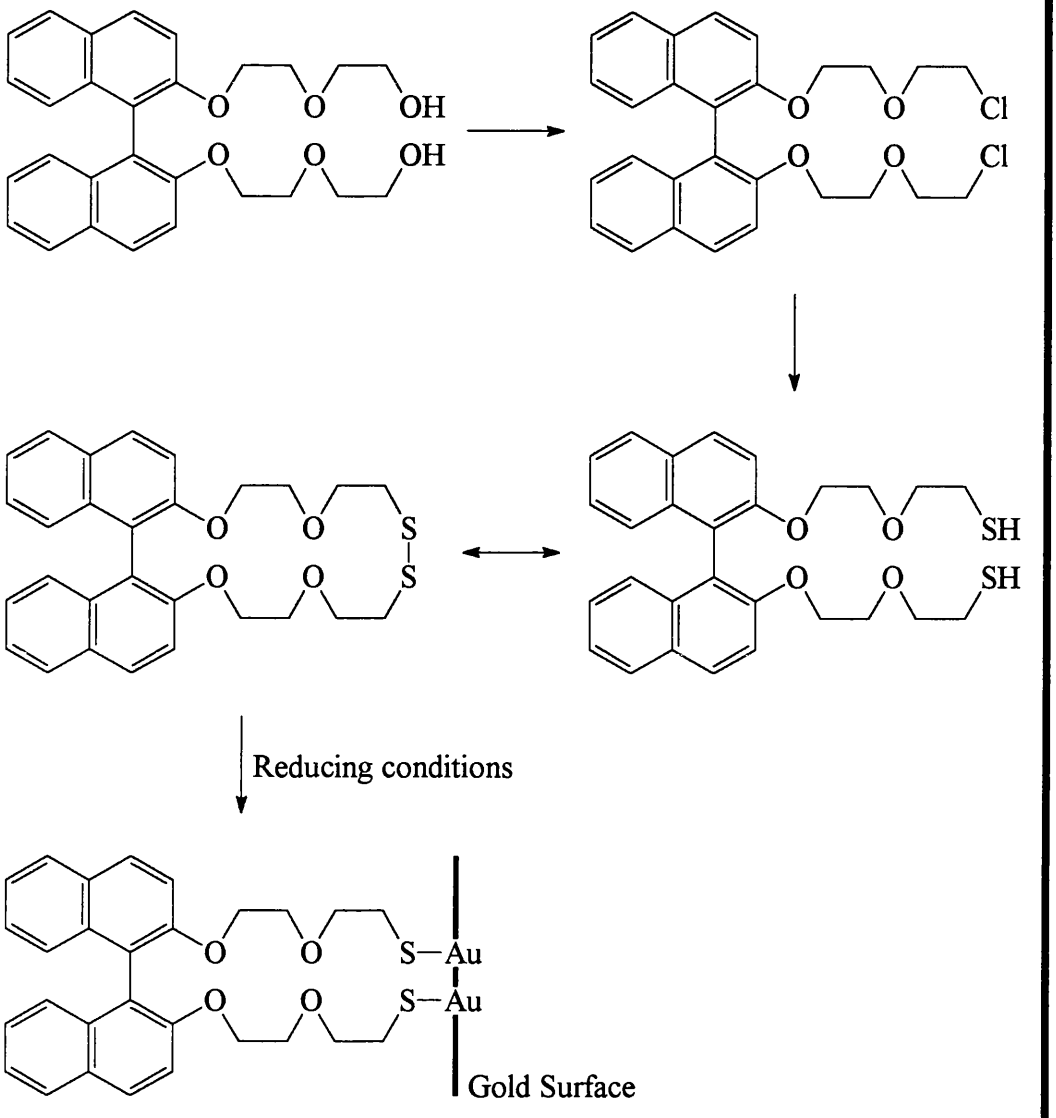


Figure 6.7; Discrete Molecular Chiral Modification of a Gold Surface

Synthesis of small thiol armed binaphthyls

With the difficulties encountered in the synthesis of these intermediates the direct synthesis of thiol armed binaphthyls (2,2'-oxy-ethanthiol-1,1'-binaphthyl in particular), for the absorption onto gold surfaces, was attempted. The efforts involving the use of ethylene sulphide, with and without the use of base(phenoxide/naphthoxide formation) all resulted in the mixture becoming cloudy and a polyethylene sulphide compound precipitating out. Clearly there was polymerisation of the ethylene sulphide, which could take place via a number of mechanisms 1-autopolymerisation 2-base catalysed via either initial base used or through the basic phenoxide ion formed with other base. The polymerisation may have been accelerated by the presence of the binaphthol and base.

The same reaction was also attempted using a variety of temperature regimes with different bases (including no base), all with the same result.

The synthesis of the analogous thio-ether armed binaphthyl, 2,2'-bis(2-methylsulphide-1-oxyethyl)-1,1'-binaphthyl, was successfully attempted. This was synthesised from 2-chloroethane methyl sulphide and was purified from the mono-armed analogue by column chromatography. Although this could not undergo the same oxidation reaction to form a disulphide, with its conformational consequences [and thus be able to adsorb onto a gold surface with some degree of retention of conformation], it should still be able to adsorb onto a gold surface to give some indication of coverage, modification potential and stability. This compound was found to be able to adsorb onto a gold surface from a simple test involving a quartz microbalance.

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