THE DESIGN AND SYNTHESIS
OF CHIRAL AND ACHIRAL
INCLUSION COMPOUNDS

BY

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CONTENTS

SUMMARY

An overview of inclusion phenomena, both in the solid state and in solution, is given. Following this orientating survey, a study of the systematic modification of some selected hexahosts is described. The versatile hexahost hexakis(benzylthiomethyl)benzene was chosen for detailed study. Substitution of each of the six outer aromatic rings was found to give a series of hosts with wide-ranging inclusion behaviour and differing guest selectivities. General inclusion properties have also been established for hexakis(2-phenylethylthiomethyl)benzene, the first hexahost possessing a four atom inter-ring chain. An X-ray analysis of the 1,4-dioxan adduct of hexakis(benzylthiomethyl)benzene has revealed a true clathrate structure for this material.

Employing trigonal symmetry as a key design feature, new hosts have been synthesised which do not possess any structural relationship to previously known systems. 1,5,9-Tris(4-methylphenylthio)-cis,cis,cis-cyclododeca-1,5,9-triene, for example, is a new general host discovered by this trigonal-symmetry approach. This versatile host forms stable adducts with a wide range of guests. The structures of two hexabromocyclododecanes, intermediates isolated in the synthesis in the above, and a related, trigonal host, have been reassigned on the basis of ^{13}C n.m.r. and X-ray analysis. One of the hexabromides, the less symmetrical 1,2,5,6,9,10-hexabromocyclododecane, also possesses the ability to form inclusion compounds.

The first chiral hexahost has also been synthesised, this being hexakis(<u>R</u>-1-phenylethylsulphonylmethyl)benzene. The acetic acid adduct has been the subject of a detailed X-ray study. As in other hexahost inclusion compounds, the 'legs' point alternately above and below the plane of the central benzene ring, though in this case the host molecule occupies a general position in the unit cell. This analysis is also noteworthy in that it allows the first direct observation of dimeric acetic acid.

INTRODUCTION

Chapter 1. General introduction

The trapping of a molecule within a restricted space, defined by another molecule or group of molecules, without the use of formal bonds between the two species is a phenomenon of great interest. This formation of a "molecular complex" may take place in solution or in the solid state. In both cases, however, a fundamental requirement is that the trapped species, termed the guest, be of an appropriate size and shape to fit into the cavity produced by the complexing agent, called the host.

Crystalline complexes, or adducts, are referred to, in a general sense, as inclusion compounds. Cram[1] refers to the association between macrocyclic polyethers and their bound species in solution as "host-guest complexation", while Lehn[2] calls his cryptates, macrocyclic inclusion complexes. The term "clathrate" was introduced by Powell[3] to describe a particular type of crystalline multimolecular inclusion compound where the guest is situated in a three-dimensional cage; completely enclosed within a cavity in the crystal lattice of the host. It is therefore inappropriate to refer to the channel-type adducts of urea and thiourea, for example, as clathrates, yet this practice is frequently encountered.

Some hosts are capable of unimolecular guest binding in solution and also of forming crystalline inclusion compounds. For example, crystalline adducts of the macrocyclic polyethers, and of the cyclodextrins, are well-known, and X-ray structure analyses confirm the host-guest nature of the complexes.

The first documented inclusion compound was the chlorine hydrate, prepared by Davy in 1811.[4] The nature of the complex was not understood despite the formation of a number of similar examples.

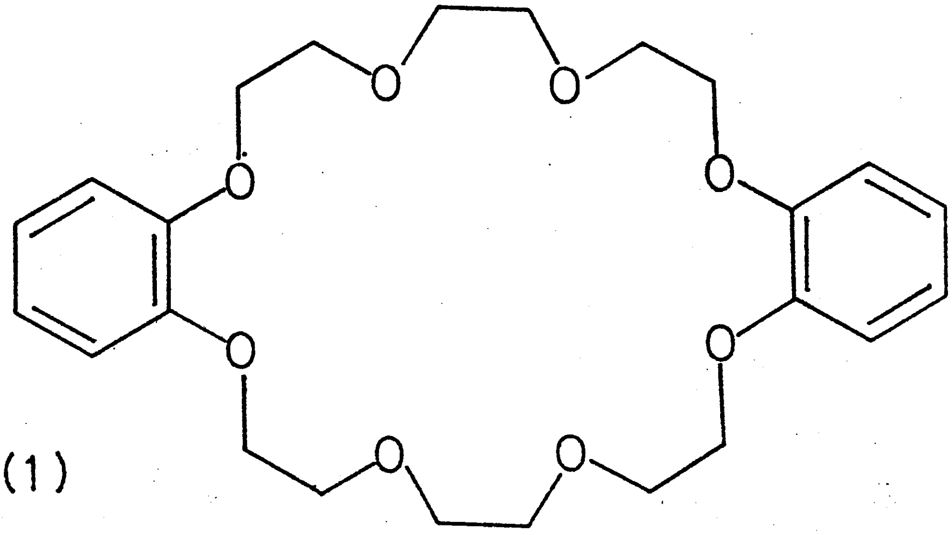
The sulphur dioxide clathrate of hydroquinone was discovered in 1859,[5] when it was reported that the smell of sulphur dioxide could be detected on grinding the crystals in a mortar. Mylius, one hundred years ago, suggested that in the hydroquinone - formic acid complex, one molecule was enclosing the other.[6] However, it was only when the X-ray structural analysis of the hydroquinone clathrates was carried out by Powell[7] in the 1940's that the true nature of the adducts could be understood.

It is generally only by determination of the crystal structure that the form of the inclusion compound may be accurately defined. Information may be gained from the size and shape of the guests, and the rate of guest loss.

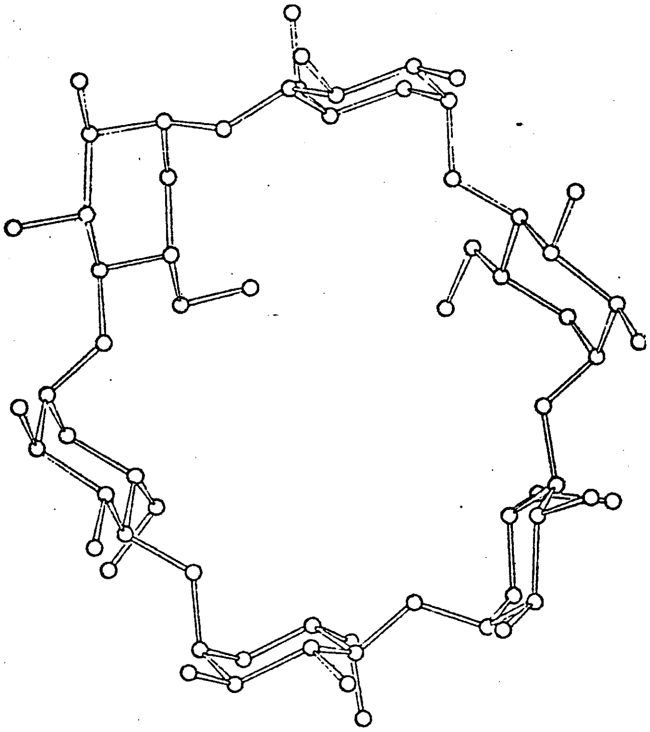
The solution complexes are detected by indirect means, as the properties of the individual components are altered in a predictable and quantifiable manner.

A very important aspect of inclusion chemistry is the design of new hosts to carry out specific tasks. Modification of known host structures is the most common way of obtaining changes in the inclusion properties. This is an easier and more predictable method for the unimolecular host species as changes in the molecular structure of the host may have a direct effect on the shape of the cavity without disturbing its ability to form complexes. Small changes in the structure of a host, which forms multimolecular inclusion compounds, may completely alter the packing arrangement of the molecules leading to the complete loss of its ability to form adducts.

For example, crown ethers and cyclodextrins are related in that both are large ring structures possessing a central void in which guests may be bound (figure 1). Unless drastic changes are carried out to alter the central cavity, the complexing power will be retained. In some crown ether compounds the host will fold to provide a more stable complex.


(1)

dibenzo-24-crown-8


(2)

α-cyclodextrin

Figure 1 Unimolecular hosts possessing a central cavity.

The shape of the cavity in multimolecular crystalline inclusion compounds is generally not predictable from the molecular structure of the host. The cavities are a result of the packing of the host molecules in an open structure. Three types of inclusion compound may be identified and classified according to the cavity shape found.

1. Layer

   typified by the graphite intercalation compounds.

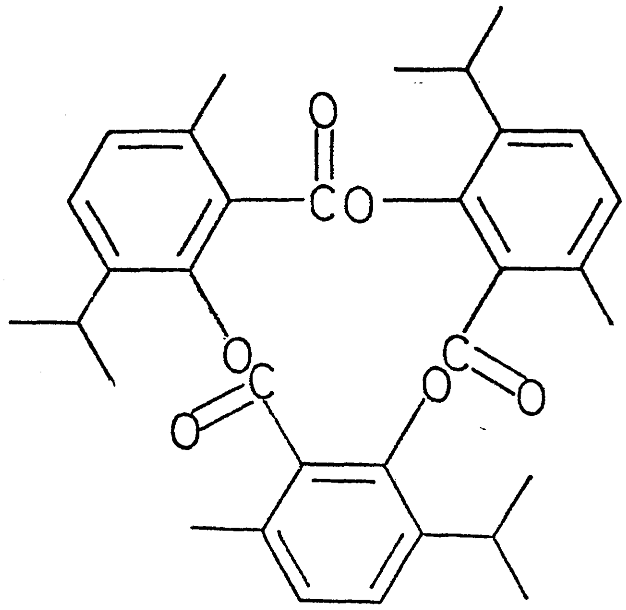
2. Channel

   a group often referred to simply as inclusion compounds, of which urea and thiourea are members.

3. Cage

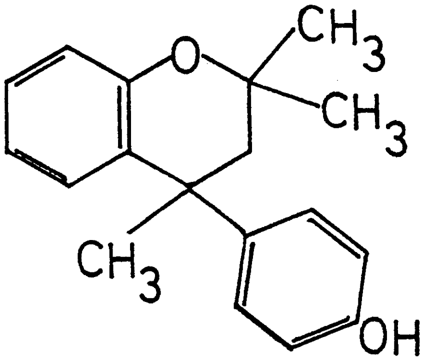
   the true clathrates, a widely studied class being the hydroquinone clathrates.

Two hosts are particularly interesting in that the void geometry may vary dramatically depending on the guest included. Tri-o-thymotide (3), forms a channel-type inclusion compound with cetyl alcohol as guest, but traps ethanol in a cage-type system.[8] α-Cyclodextrin (2) displays similar behaviour with iodine in polymeric form,[9] as a channel complex, and krypton in a cage-type.[10]



(3)

There has been only limited work on the systematic modification of multimolecular hosts, an important exception being the investigation of Dianin's Compound (4) and its synthetic analogues by MacNicol,[11] which will be discussed later.

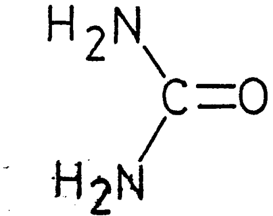
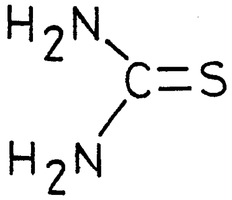
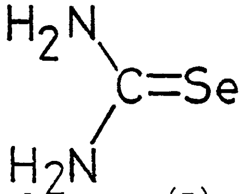


(4)

The channel inclusion compounds of urea (5), thiourea (6) and selenourea (7) form a series within which variable behaviour is observed.

Urea and thiourea have been particularly well-studied, the difference in the diameter of the channel having a considerable effect on the type of guest which may be included (table 1).

Table 1

Host	Guest	Channel Diameter (A)
 urea (5)	n-octane[12, 13]	5•2
 thiourea (6)	cyclohexane[13]	6•1
 selenourea (7)	camphor[14]	6

A more regular trend is observed in the channel adducts of the cyclodextrins,[15–17] where channel diameter increases with the number of glucopyranose units in the ring (Figure 2).

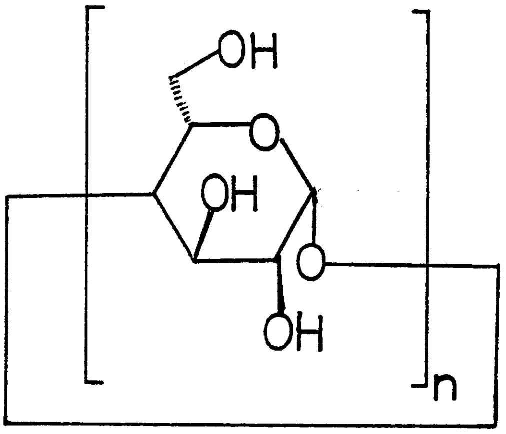
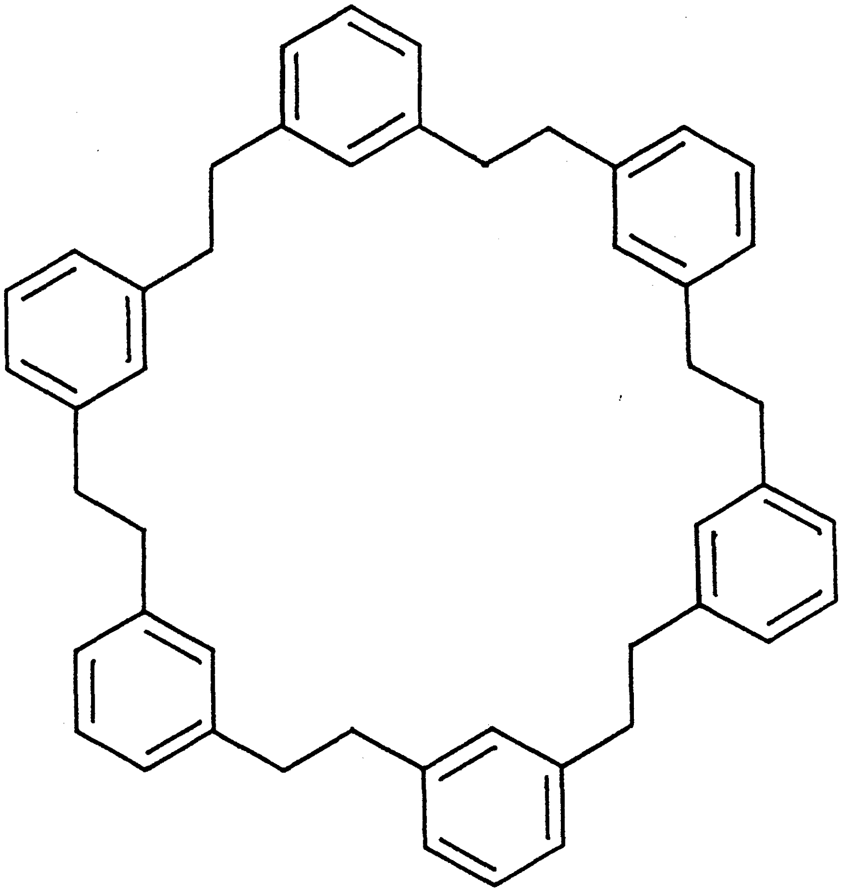


Figure 2 The Schardinger dextrins, cyclodextrins or cyclo-amyloses.

	Host	Guest	Channel Diameter (A)
n=6	, α -cyclodextrin (2) ,	$(I_2)_n$	6
n=7	, β -cyclodextrin (8) ,	naphthalene	8
n=8	, γ -cyclodextrin (9) ,	anthracene	10

Much interest has been centred upon the properties of trapped species. However, study of a particular guest is often precluded by its failure to form an inclusion compound with the range of hosts available. Ultimately, however, it should be possible to design a host with cavity dimensions suited to the desired guest. A part of the introduction will be directed, therefore, to efforts in this direction, namely, the designed modification of inclusion behaviour.

Inclusion compounds are known to exhibit high structural recognition between guest molecules and this ability has received wide application. A well-known example is the separation of linear and branched hydrocarbons by selective inclusion in the channels of urea, which has received industrial application.[18] A wide range of procedures have been patented, one of the most recent being the use of a metacyclophane host (10).



(10)

Recrystallisation of (10) from a 20:15:15:15:100 mixture of para-xylene, ortho-xylene, meta-xylene, ethyl benzene and methanol gave an inclusion compound containing 94% para-xylene in the guest composition.[19] Similar selectivities were observed for other 1,4-disubstituted aromatics. A preference for trans-substituted terpenoids has also been established:[20] from a sample of geranyl-acetone of which 65% was in the trans-configuration, an inclusion compound of 99% trans-isomer was obtained.

Ion selectivities are exhibited by crown ethers in solution. The extraction of barium ions from a large excess of calcium ions has been achieved by 18-crown-6, which is of appropriate size to complex the larger barium ion while leaving the smaller calcium ions relatively untouched.[21]

This type of selectivity is found in nature in ion-transport and associated processes. An important phenomenon, also found in biological systems is the property of chiral recognition. The bulk of naturally occurring compounds, which are asymmetric, are found in one enantiomeric or diastereomeric form; enzymes will bind and catalyse one enantiomer while rejecting its mirror image.

The complexity of these molecules is many factors higher than most synthetic organic compounds, but it is possible to imitate nature by constructing model systems capable of discriminating between enantiomers by means of favourable and unfavourable diasteromeric interactions. Normally the interactions are produced by specific bond formation as in resolutions by diastereomer formation. Chiral shift reagents do allow observation of different enantiomers but without physical separation. Inclusion compounds provide a good model for enzyme-substrate complexes, as in both cases size and shape are critical factors. Hosts which also show chiral recognition would produce superior models, while a method for the physical separation of enantiomers without chemical modification would be of tremendous value. Progress to date in this area will also be discussed in a later chapter.

A large number of host systems are available for discussion, so representatives of the various classes have been chosen. For the multimolecular host systems particular reference will be made to attempts to alter inclusion properties by modification of host structure.

(i) Crown ethers and related systems
(ii) Channel-type inclusion compounds
(iii) Clathrates.

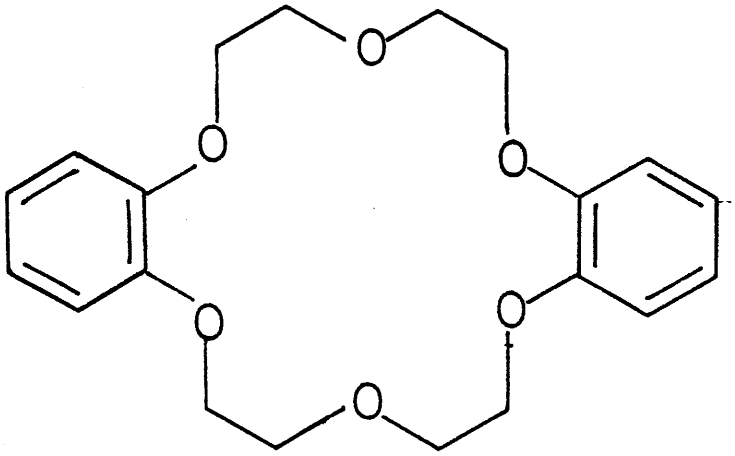
A number of hosts are related in that their molecular structures possess trigonal symmetry. Other hosts form inclusion compounds which show trigonal or hexagonal symmetry in the crystal structure. This feature will be discussed in chapter three.

The very important aspect of chirality in inclusion will be examined in chapter four of the introduction.

Chapter 2. Host Systems

(i) Crown ethers and related systems

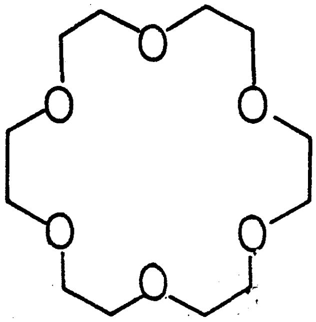
Up until 1967, molecular complexation in solution was, for research purposes, restricted mainly to the cyclodextrins. Particularly, there had been little work done on the synthesis of molecules capable of forming such complexes. Compounds related to the crown polyethers were known but no complexing properties had been reported.[22, 23, 24, 25] At this time, however, the first crown compound, dibenzo-18-crown-6 (11), was synthesised, curiously by chance, being an unexpected side-product in the preparation of bis 2-(o-hydroxyphenoxy) ethyl ether from bis(2-chloroethyl) ether and the sodium salt of 2-(o-hydroxyphenoxy)-tetrahydropyran, containing catechol, as a small impurity.[26, 27] Pederson recovered this material and noted that it was solubilised in methanol by the addition of sodium salts.



(11)

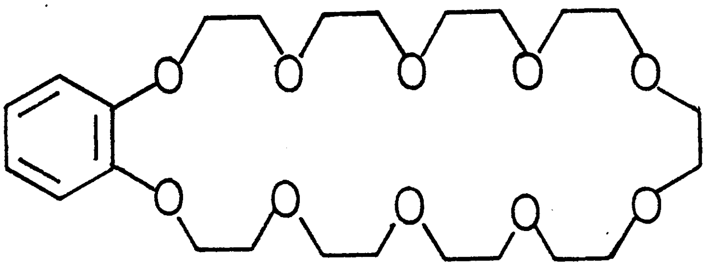
Hundreds of papers have since been published on the properties of the crown ethers, and their utility in organic synthesis is well-established.[28]

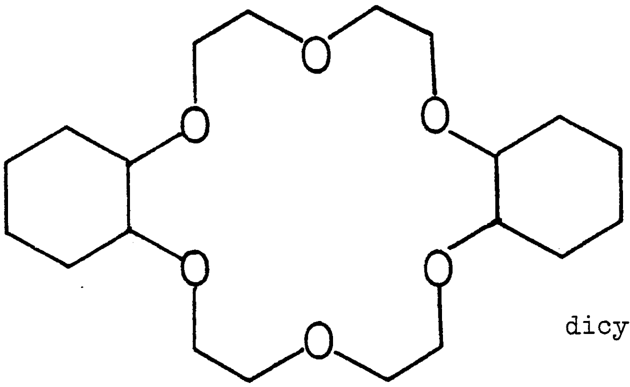
To name the macrocyclic polyethers a new system of nomenclature was devised.[26] The original classification of Pedersen has been retained to describe the crown ethers which are formally addition polymers of ethylene oxide, or copolymers of ethylene oxide and benzene oxides. The naming of "18-crown-6" (12) illustrates the system; the two numbers representing the total number of ring atoms, and the number of heteroatoms respectively. The names, however, are not unambiguous and are usually accompanied by the formula (Figure 3).



18-crown-6 (12)

benzo-30-crown-10 (13)

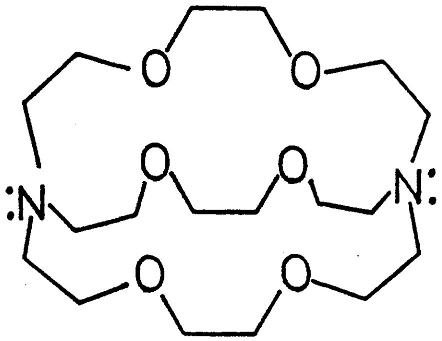




dicyclohexyl-18-crown-6 (14)

Figure 3 Nomenclature for macrocyclic polyethers.

In comparison to the crowns, first studied by Pederson, and more recently by Cram and Stoddart, among others, the "cryptates",[29] devised by Lehn, are multidentate macroheterocycles of a topologically more complex nature. The term cryptate refers to the complexes, the ligands themselves being called cryptands or crypts. For example, the simple case (15) is known as [2.2.2] crypt, or even [2.2.2].



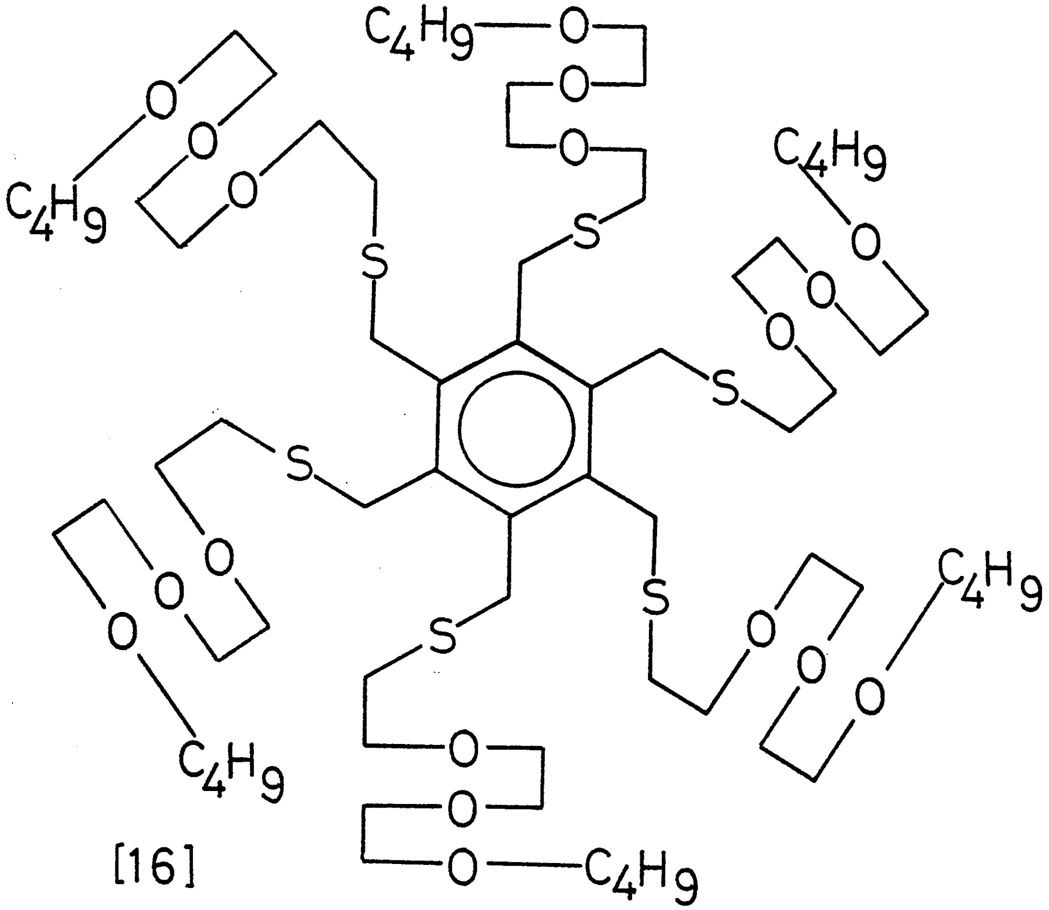
[2.2.2] crypt (15)

A new type of isomerism, not present in the crowns, is available to this series; the bridgehead nitrogens having the option of facing outwards or inwards with respect to the central cavity. Hence, three forms of [2.2.2] crypt are possible, the "in-in", "out-out" and "in-out".[30] All three isomer have been observed in various complexes. The "in-in" isomer is found in the free ligand and in the hydrate rubidium isothiocyanate complex RbNCS.[2.2.2]H_2O; the "out-out" is present in the bis-(borane-amine) derivative H_3B[2.2.2]BH_3, while the monoborane derivative of a simpler crypt is of the "in-out" type, H_3B[1.1.1].

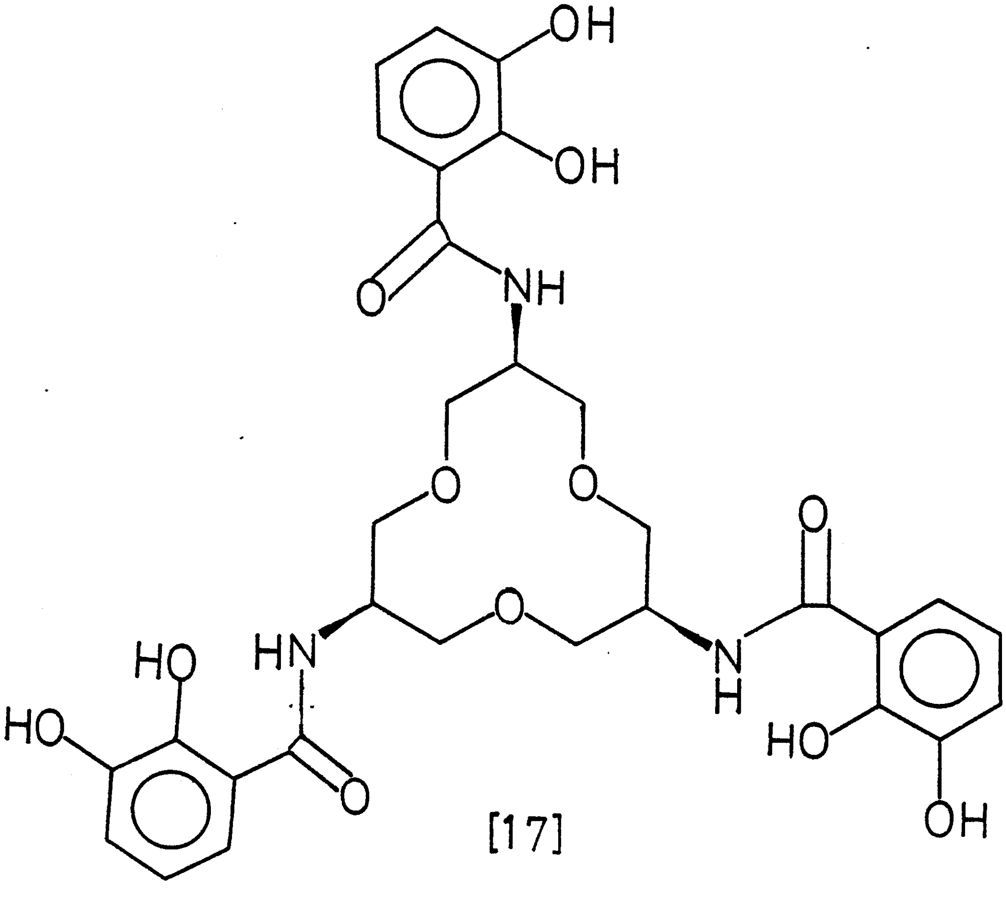
Lehn has developed an extensive range of compounds with very interesting complexing properties, however, it is the simpler "two-dimensional" crowns which have received the bulk of attention and which will be discussed in greater detail. Most of the principles and applications discovered for the crown ethers have analogies in the three-dimensional cryptates.

Various studies have demonstrated that the binding of species by the cyclic polyethers is several factors of ten better than that achieved by linear examples.[31] However, cation carriers developed by Simon,[32] resemble the crowns in a number of aspects. Both cyclic and acyclic cases have their precedents in nature, where both large ring macrolides, for example nonactin, and linear antibiotics, for example monensin, have important biological activity.

Of great interest to future discussion are the curiously named "octopus" molecules[33] (16) which possess the ability to complex metal cations, and enterochelin[34] (17), whose action is concerned with ion-transport. In both, high levels of symmetry are present in the molecular structure



[16]



[17]

The synthesis of crown ethers would, at first sight, appear to be a frustrating task, given the difficulty encountered in the formation of other large rings. The very binding, however, which the completed complex exhibits, greatly assists the ring closing step by means of a template effect [35] (Figure 4).

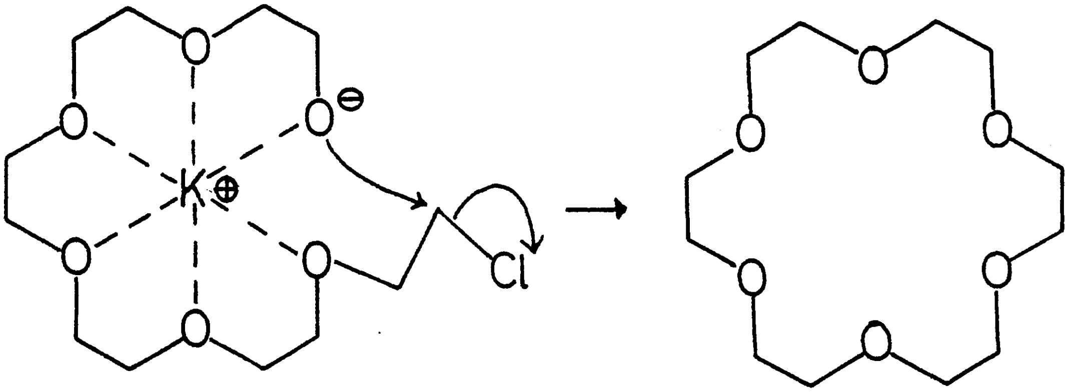
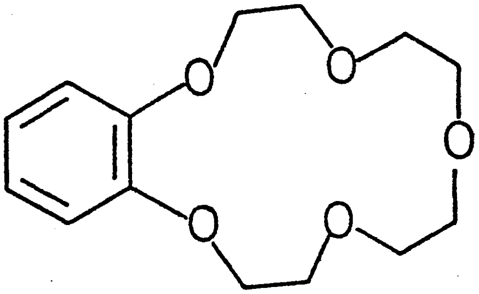


Figure 4 Template effect in the synthesis of crown ethers.

If *tert*-butyl ammonium hydroxide is used as the base, the template effect is reduced and the yield falls. The preferential complexation of sodium ion by 15-crown-5, and of lithium by 12-crown-4 has been utilised in their preparation. [36] Different methods of synthesis have been employed in the preparation of more complex systems.

Many structures of crown complexes and cryptates have been determined and a greater number have been deduced from physical and spectroscopic data. The crystal structure analysis of the uncomplexed 18-crown-6 shows that the methylene groups are directed towards the centre of the "hole". [37] This is in contrast to that found in the complexes in which the oxygen atoms point inwards and a gauche conformation about the carbon - carbon bonds is found. [37, 38] The C–O bond lengths are normal but the aliphatic C-C bonds appear shorter than 1.54 Å, though this has been assigned to an artifact of vibration.[39] The structures are generally guest dependent, a simple example, being the benzo-15-crown-5 (18) complexes of sodium iodide, which is a 1:1 monohydrated system, and potassium iodide which has a host to guest ratio of 2:1 and is anhydrous.


benzo-15-crown-5 (18)

The former complex crystallises with the sodium ion at the apex of a pentagonal pyramid of oxygen atoms,[40] the water molecule being further away from the crown, co-ordinated to the ion. The iodide counter-ion is bound to the complex cation via the water molecule by hydrogen bonding.

The potassium iodide complex[41] is as shown, (Figure 5), with the ion at a centre of symmetry with the ten oxygen atoms forming a pentagonal antiprism. A change in the crown conformation enables all the methylene carbons to be on the opposite face of the plane of oxygen from the potassium ion.

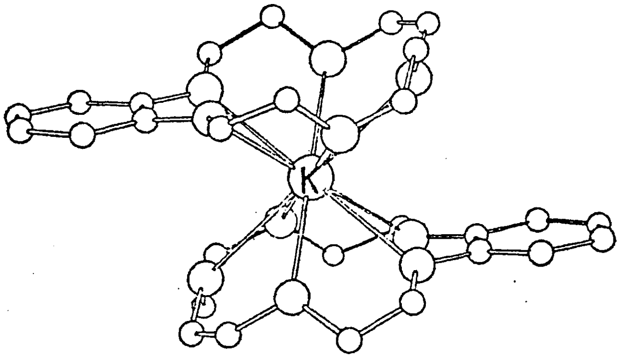
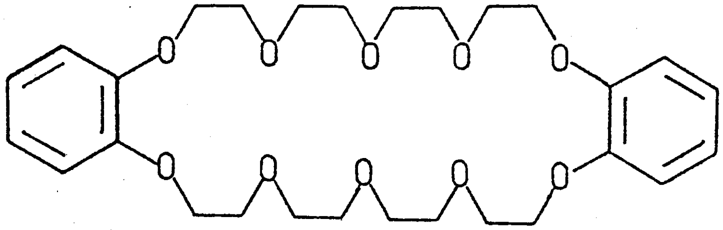


Figure 5 The potassium (benzo-15-crown-5)$_2$ complex in KI.

The relationship between the synthetic macrocyclic polyether complexes and the naturally occurring systems is strikingly illustrated by the structures of the potassium complexes of dibenzo-30-crown-10 (19), 42 and nonactin (20), 43 both possessing a two fold axis of symmetry between the two halves of the respective molecules (Figure-6).



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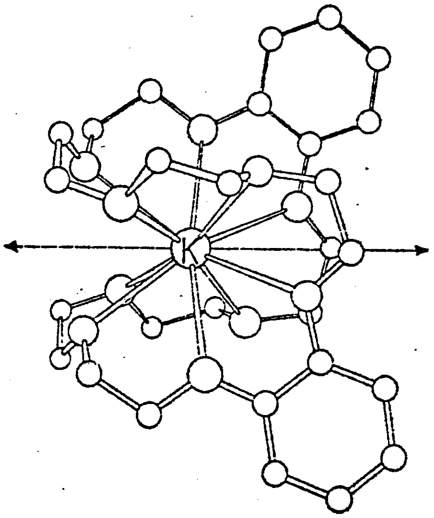

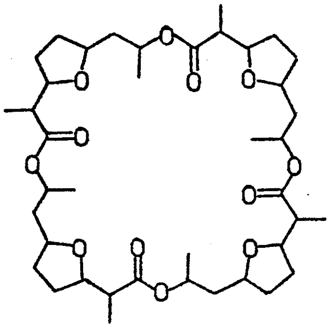

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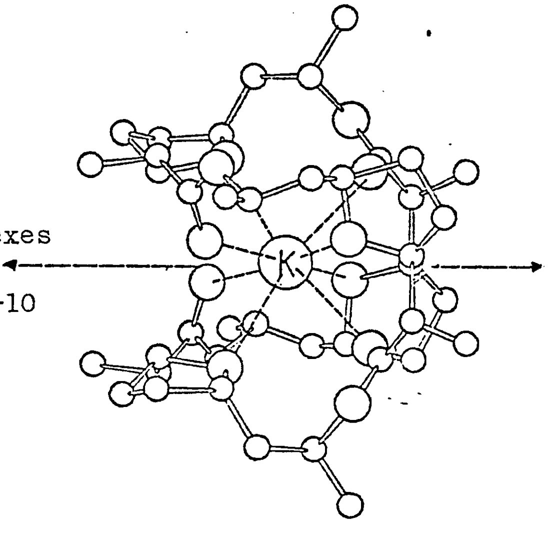
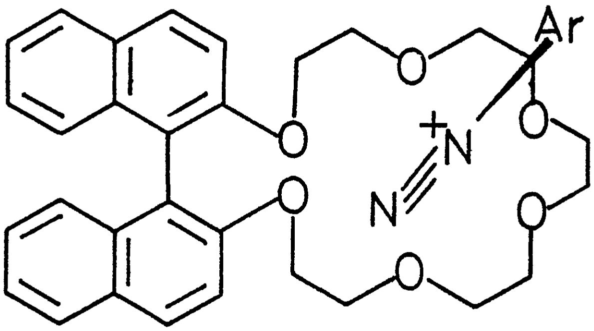


Figure 6 The potassium complexes of dibenzo-30-crown-10 (above) and nonactin (below).

Guests are not restricted to alkali metal ions; organic molecules, from alkyl ammonium salts to amino acid ester salts have also been found. Further molecules of solvation are sometimes present, usually to complete the co-ordination sphere of the complex ion.

In Cram's programme of host design, he makes extensive use (as do others) of space-filling models in predicting behaviour and rationalising observations. They assisted in explaining the results found for complexes of a binaphthyl crown with various aryl diazonium cations [2, 44] (Figure 7).



<u>Figure 7</u> Crown ether complex of aryl diazoniun salts.

Models (Corey-Pauling-Koltun, CPK) showed that the $^+N{\equiv}N$ group fitted tightly into the host cavity, with all oxygens turned inwards.

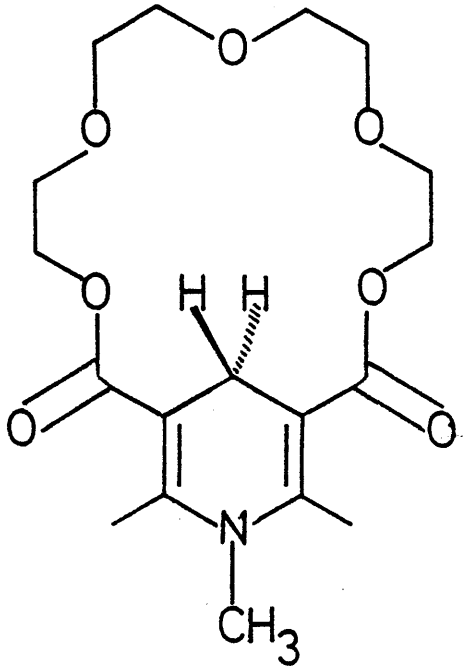
The host did indeed solubilise <u>para</u>-toluene diazonium tetra-fluoroborate into chloroform, with a guest to host ratio of 0.9, the chemical shift of the host protons changing. The tightness of the fit was confirmed by the failure of the penta-oxygen analogue to solubilise the salts, and the open chained version also failed, indicating the need for organisation within the host molecule. Substitution in the 3, 4 positions of the aryl cation did not prevent solubilisation, but 2,6-dimethyl benzene diazonium tetraphenyl-borate could not be solubilised, as indicated by the models which showed that the 2,6-dimethyl groups were hindering stable complex formation. Conformational information was obtained by the appearance of colour due to charge-transfer interactions between the host and guest. The complexation also stabilised the guest towards reagents with which they would ordinarily react.

Many types of structure have been found for even the most simple crowns. For metal cations, host to guest ratios of 1:1, 1:2, 2:1, 3:2 and 4:3 have all been examined. In the case of the Lanthanoid series $Ln(NO_3)_3$ with 15-crown-5 and 18-crown-6, 1:1 complexes were found to change to 4:3 complexes at temperatures greater than 170°C.[45] Evidence for its existence as a genuine complex include its stability to water, since the free nitrates are hygroscopic.

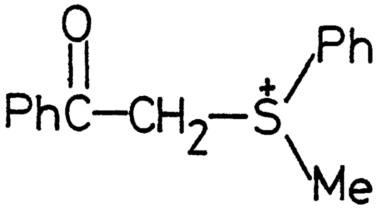
Most commonly, the solvents of crystallisation found in crown complexes are water and alcohols, as in the benzo-15-crown-5 adduct with calcium isothiocyanate, where the co-ordination sphere of the calcium ion is made up of the five ring oxygen atoms, two counter ions and a water or methanol solvate.[46] Magnesium does not require this level of co-ordination and as a result the crystal structure of the analogous complex is different with no solvated molecules.

In the interesting crown complex of the host (21) with sulphonium salts, a molecule of acetone is an integral part of the complex. 47

The host, incorporating a dihydropyridine unit acts as a reducing agent against the sulphonium salt (22) to give phenyl methyl sulphide and acetophenone. Simple dihydropyridines do not easily perform this reaction suggesting that complexation preceeds the reaction. The sodium perchlorate complex has been analysed by X-ray crystallography and shows that the solvated acetone molecule is not in a position where it can be reduced.



[21]

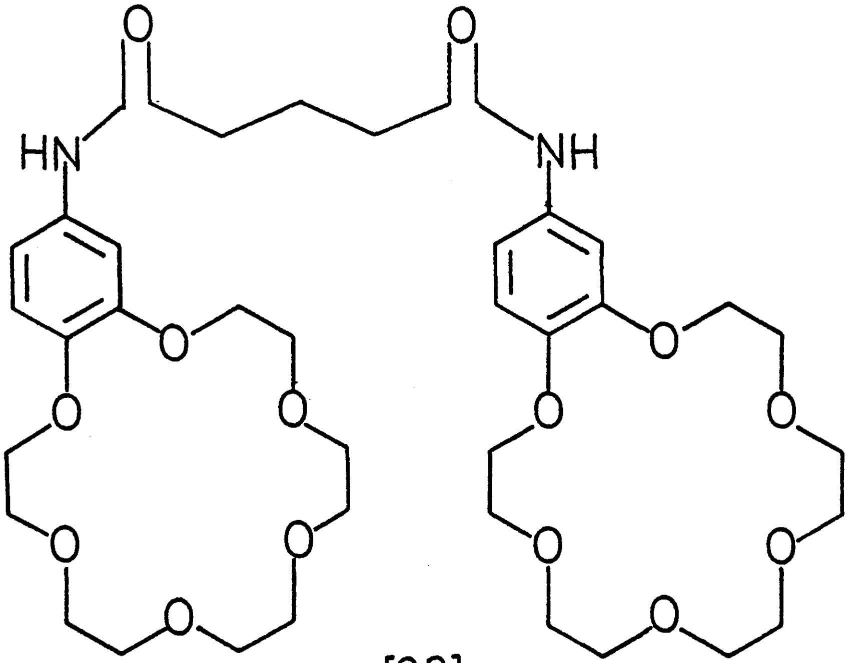


[22]

A number of unusual crown complexes have been identified. The bromine-crown system probably involves only oxygen-bromine interactions as changing the cavity size does not affect the binding of the bromine molecule. [48] It is related to the bromine-1,4-dioxan adduct, which although formally an ethylene oxide oligomer hardly merits the crown classification.

Recognised at an early stage was the relationship between the hole diameter of the simple crown ethers and the ions with which they form the strongest complexes. [49] For example, the stability constants for 18-crown-6 and the alkali metals reach a maximum at potassium whose cation diameter lies within the range of hole diameters found for its complexes.

Much work has been done on the design of host molecules which may selectively bind a particular metal cation. Much will be said later about the work of Cram and his studies on molecular recognition, but some striking examples and uses of ion selectivity have been published. The bis-crown ether (23) was found, not surprisingly to form stable sandwich-type complexes, for those ions which require the oxygens on both rings to complete their co-ordination spheres. A number of such compounds were prepared, (23) being found to be an efficient extraction agent for caesium ions. [50] This is not unexpected as caesium ions form 2:1 host-guest complexes with benzo-15-crown-5 or benzo-18-crown-6. [51]



[23]

A more spectacular example, briefly mentioned earlier, involves the determination of barium ions when present in small concentration within a large pool of calcium ions. [21] Environmental samples requiring an assay for barium, tend to contain large quantities of calcium ions which hinder the quantitative measurement of barium through interference in the emission and atomic absorption spectra. The ionic diameter of barium is 2.70Å which is comparable to the hole diameter of 18-crown-6 (2.6-3.2Å), being considerably larger than the calcium ionic diameter which is 1.98Å. The difference in stability constants is therefore considerable, reflected in the results of an extraction procedure. From a 100:1 mixture of calcium and barium ions, 18-crown-6 quantitatively extracted the barium, with an ion ratio of 1:4 in favour of the barium ions, allowing more accurate determination of the barium content by spectroscopic means.

Crown ethers have been attached to polymer supports (Figure 8) in order that they may be facily recycled after use. [52] This is done by preparing the crown ethers with additional functionality on the ring, which is not a difficult task. These solid phase catalysts were found to promote the halogen exchange reaction of n-octyl bromide with potassium iodide.

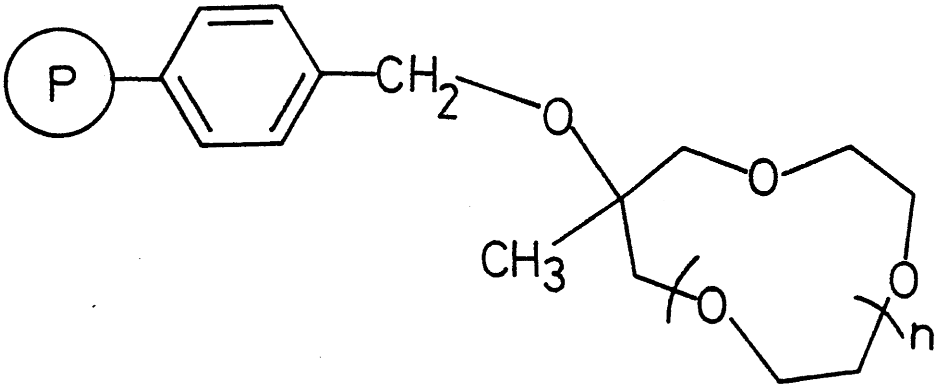
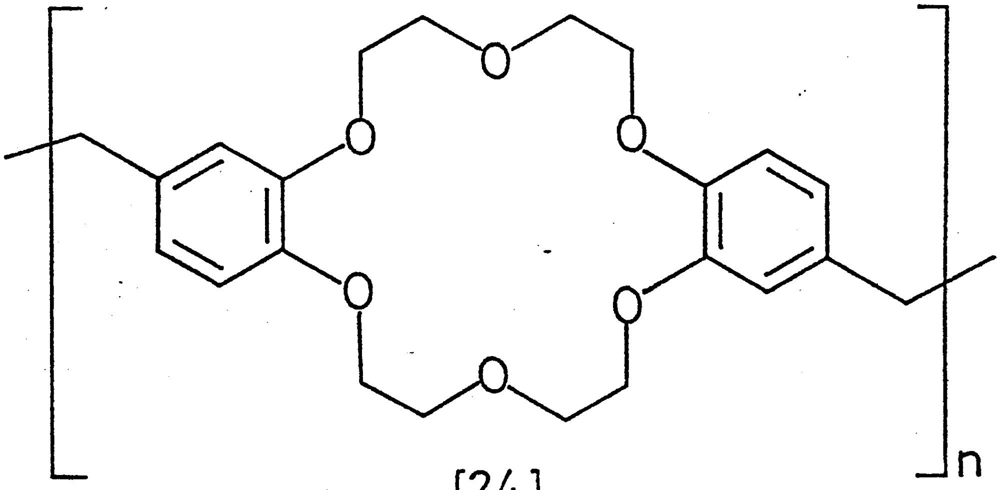


Figure 8 Crown ether attached to polymer support.

On a similar theme, exchangers, possessing a cyclic polyether repeat unit, have been prepared and have been applied to a variety of tasks [53] including:

(i) Separation of cations with common anions,
(ii) Separation of anions with common cations,
(iii) Separation of organic compounds,
(iv) Anion activation in organic synthesis.

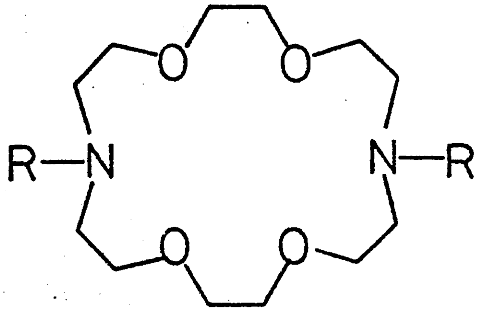


[24]

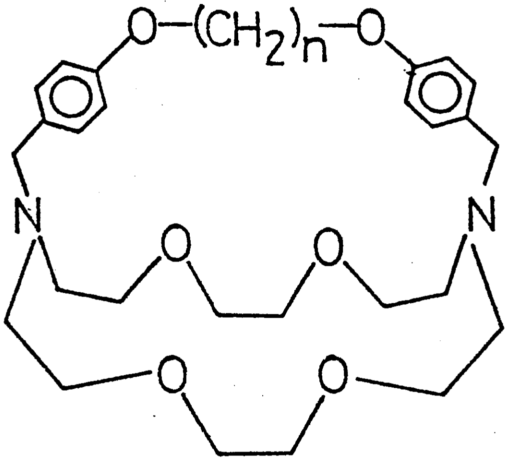
Stability sequences correspond, with few exceptions, to those found in the monomer, therefore, for the polymer with dibenzo-18-crown-6 as the repeat unit (24) $K^+ > Rb^+ > Na^+ > Cs^+ \gg Li^+$, in both water and methanol. The exchanger with a dibenzo-24-crown-8 repeat unit exhibits selectivity for caesium ions. Diphenyl disulphide and thianthracene have been separated chromatographically using the exchangers as the stationary phase. Some vitamins and antibiotics have been separated by the same systems. A very simple recycling procedure allows renewed application of the exchangers unlike their monomer counter-parts.

Vogtle has carried out a study on diaza-crowns and cryptates in order that the ion selectivity may be gradually altered by planned modification. [54]

By changing the nitrogen substituents in crowns (25) or extending the length of the nitrogen-nitrogen bridge in the cryptate (26) it was hoped that the stability constants for the various guests could be systematically altered. Little differences were observed however particularly in the cryptates.



[25]



[26]

It has been suggested that the increased catalytic potential of dibenzo- and dicyclohexyl crowns over the simpler 18-crown-6 is due to their greater solubility, or affinity for organic solvents. A series of substituted crowns has been prepared, whose solubility properties have been improved.[55]

Tada has looked at the photochemistry of the host-guest complexes as a means of functionalising the macrocyclic ring [56] (Figure 9), but standard techniques seem superior at the moment for synthetic purposes.

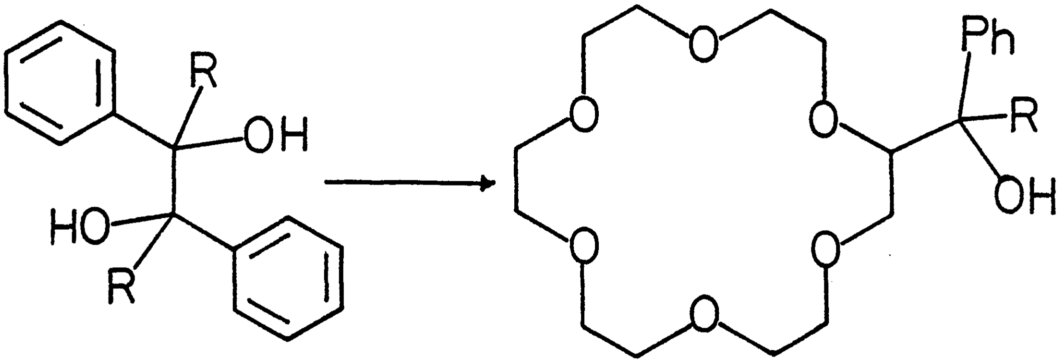
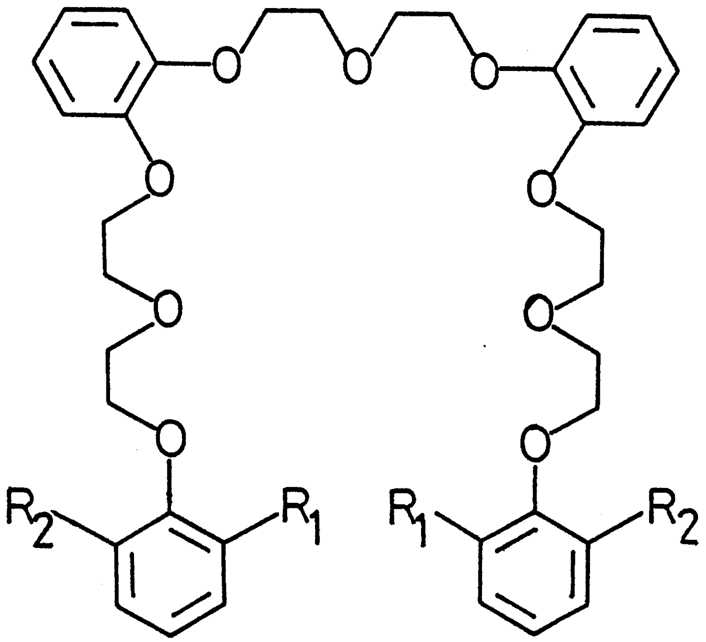


Figure 9 Photochemical functionalisation of crown ethers.

The superiority of cyclic polyethers over their linear counter-parts has been established, but work continues to be done in this area. Yanagida has studied some linear polyethylene glycols and has observed solution effects. [57] Solid complexes of calcium, barium and strontium have been isolated through their thiocyanates. Glyme complexes have also been prepared.

Vogtle has also synthesised some interesting linear ligands and crystalline adducts have been obtained. [58] In the 1:2 potassium thiocyanate complex of the polyether (27), the host is coiled around the two potassium ions in an S-shape.



[27]

The applications of crown ethers are numerous, particularly in synthetic organic chemistry where vast rate enhancements are possible and product distributions may be altered. The complex of 18-crown-6 with bromine has provided a highly stereoselective brominating agent. [48] The [2.2.1] cryptate of lithium aluminium hydride can alter the attack on cyclohex-2-enone to conjugate addition. [59]

A few papers have appeared recently on the enhanced basicity of cryptated species. Enolates of cyclohexanone when complexed with cryptands shows unexpected basicity. [60] Prepared by reaction with potassium <u>tert</u>-butoxide, the cryptated enolate will abstract a proton from ether and will undergo quantitative alkylation with methyl iodide.

Pedersen, in his early studies, noted that potassium hydroxide would hydrolyse esters of mesitoic acid, which are ordinarily difficult to saponify, in the presence of dicyclohexyl-18-crown-6. [26] A most important discovery was the solubilisation of potassium permanganate in benzene by the same crown ether to give "purple" benzene. [61] Permanganate oxidations in benzene are now routine, a recent example being the aromatisation of non-conjugated cyclohexadienes [62] (Figure 10).

Conjugated dienes are not affected by the same reagent providing a method of separating them from a mixture.

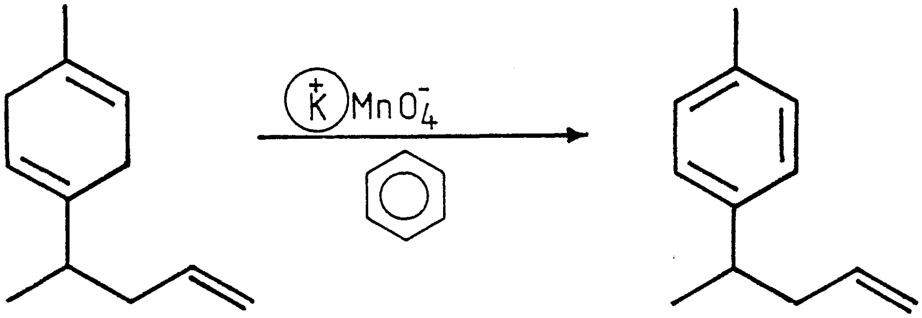


Figure 10 Selective oxidation of non-conjugated cyclohexadienes by "purple" benzene.

When the cations of inorganic salts are encapsulated by the crown the anion is often relatively free from the complex in solution. Of these "naked" anions, the best known is the fluoride anion, which becomes a very efficient nucleophile once the strong ion pair is broken. Interaction of this very reactive system with a number of substrates can often give quantitative yields even with aromatic halides. [63] (Figure 11)

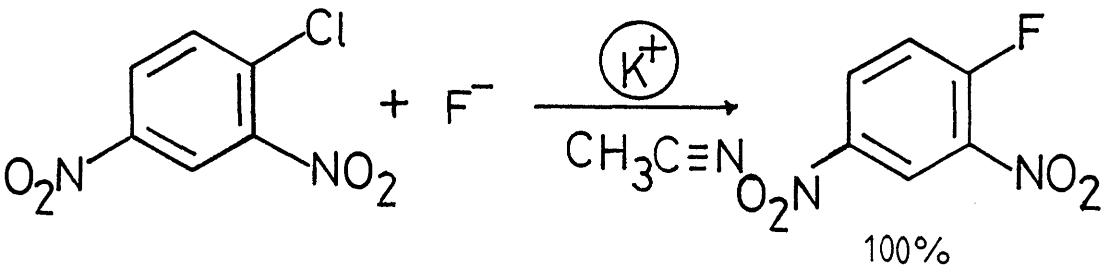


Figure 11 Quantitative substitution of aromatic halides using "naked" fluoride.

Among other naked anions which have been used are acetate and cyanide.

Cation-anion separation has found application in the "Gabriel-like" synthesis of secondary amines from primary amines.[64] The intermediate trifluoroacetamides are N-alkylated and then hydrolysed to the secondary amine. (Figure 12)

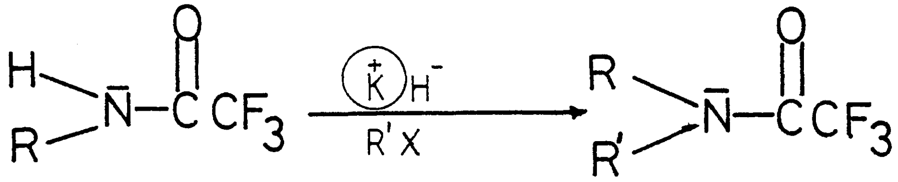


Figure 12 Application of ion separation by crown ethers in the Gabriel synthesis of secondary amines.

The trifluoroacetamides are deprotonated using potassium hydride. Addition of crown ethers gives a very reactive nucleophile for which only alkylation at nitrogen has been observed.

Another ambident nucleophile studied recently is the β-naphthoxide anion. [65] O-alkylation predominates in solvents of high dielectric constant, for example, dimethyl formamide and acetonitrile, crown ethers having little effect on the product distribution. In solvents of low dielectric constant, a high proportion of C-alkylation is found as ion pairs are present to a greater extent. Crown ethers separate the ion-pairs giving a higher proportion of O-alkylation.

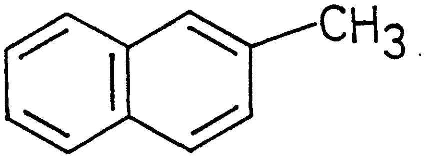
The normal activation of nucleophiles was reversed when the acylation of primary and secondary amine salts was studied by Barrett. [66] The normally more reactive primary amine salt was supressed by preferential complexation by 18-crown-6, thereby allowing the secondary salts to compete favourably. Yields of secondary amides from this procedure were up to 98%.

(ii) Channel Inclusion Compounds

This group of multimolecular inclusion compounds in which the guest is situated in a tunnel which runs through the crystal lattice of the host are widely referred to as channel complexes, canal complexes, or simply inclusion compounds. Although, in overall number, there are only several genuine examples, the diversity of host structure is remarkable with few relating features. The simple ureas have been mentioned as have the versatile tri-o-thymotide (3) and complex cyclodextrins. Other hosts are formulated below (Figure 13) and range from the simple hydrocarbons eg β-methyl naphthalene (28), to the highly functionalised amylose (29)

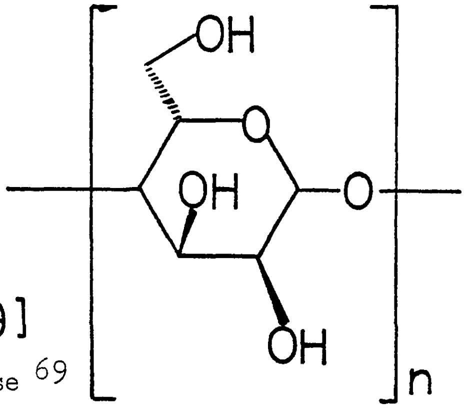
Historically the first example of these complexes were the "choleic acids". In the middle of the nineteenth century the bile acid, cholic acid, was isolated by Strecker. Later, two more acids were discovered and called choleic acid and desoxycholic acid (30). Attempted high vacuum distillation of choleic acid yielded desoxycholic acid and a significant amount of palmitic, stearic and oleic acids. [67] They were later recognised as having been inclusion compounds, but the term "choleic acid" was retained.

It is interesting to note that the discovery was made by chance. This is not surprising for the earlier examples, when theories of bonding were still fairly primitive, but, with very few exceptions, all inclusion compounds have been found through the chance formation of crystalline material or through "strange" physical properties being observed.



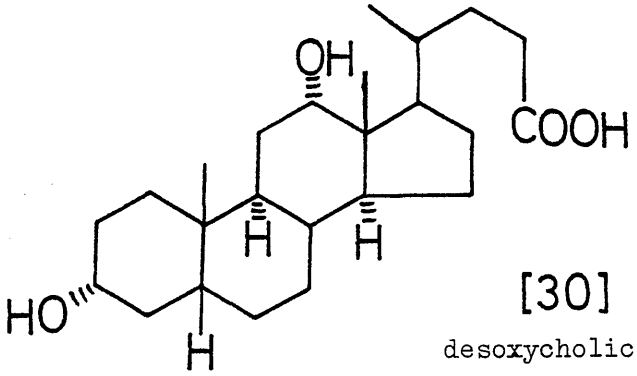
[28]

β -methylnaphthalene [68]



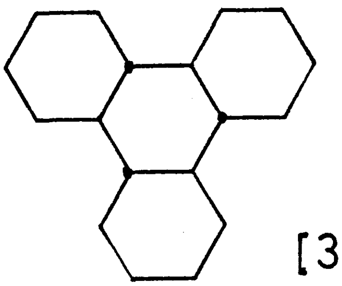
[29]

amylose [69]



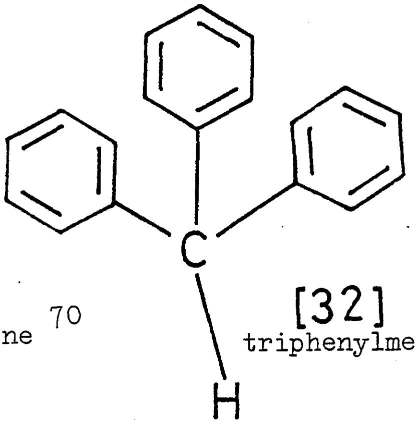
[30]

desoxycholic acid [67]



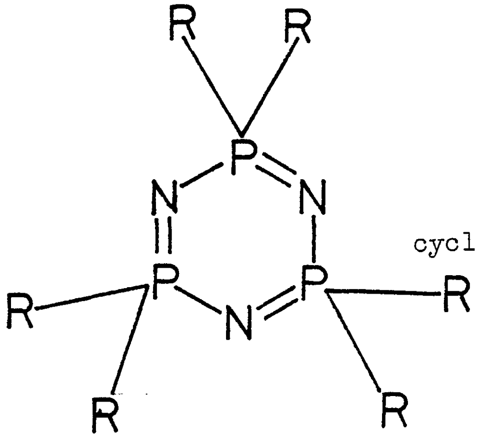
[31]

perhydrotriphenylene [70]



[32]

triphenylmethane [71]



[33]

cyclotriphosphazenes [72]

Figure 13 Some examples of inclusion hosts which form channel-type adducts.

Of all channel-type hosts, the ureas are by far the most studied particularly urea (5) and thiourea (6). The most important difference between their adducts lies in the channel diameter, which for those of urea is approximately 5Å, but which in thiourea can reach 7Å due to the larger sulphur atom.

This difference in size is reflected in the type of guests which may be accommodated in their respective channels. Urea, with its narrower tunnel will include linear hydrocarbons, alcohols, acids, etc, while prohibiting the inclusion of any branched species. Thiourea forms its most stable complexes with larger molecules, including cyclic hydrocarbons, and branched alkanes. It will form inclusion compounds with linear molecules but less easily, and on occasions the host structures will collapse under mild conditions.

Host to guest ratios have been studied for both systems and are found to be dependent upon the length of the guest molecule.

As the length of the guest, or endocytic component, is increased, the host guest ratio also increases.[73] For linear molecules, in urea, an estimation of 0.7 moles of host per carbon atom in the guest has been proposed, and this is confirmed by results obtained for a number of adducts.

In thiourea, the potential guest should have a uniform cross-section of between 5.9 and 7.6Å, otherwise stable adduct formation will not take place. Clearly straight-chained hydrocarbons do not fall into this category. The graph indicates the effect of increasing chain length on the host to guest ratio (Figure 14).

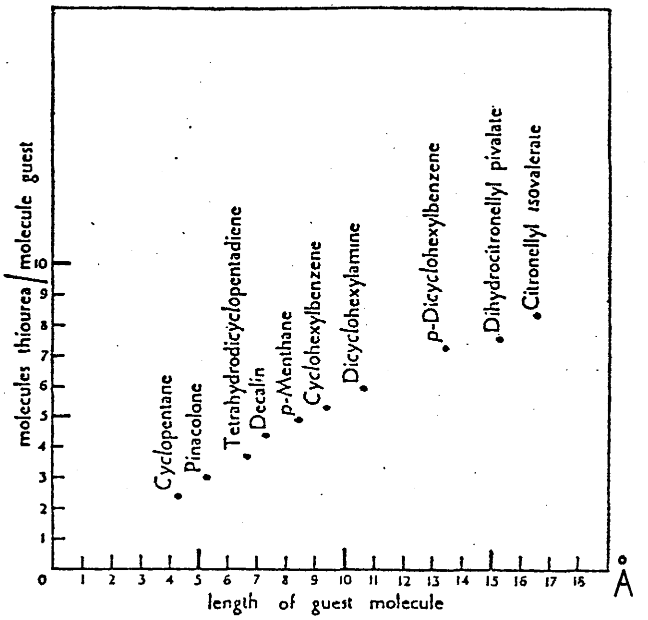


Figure 14 Lengths of the included guest molecules plotted against the molar ratio thiourea:guest.

There is almost no scope for modification of the basic skeleton, as the constituent parts of the molecule are all necessary for the construction of the crystal lattice which incorporates the open channels. The host structure is held together by a network of hydrogen-bonding between the amino-function and the other hetero atom, oxygen, sulphur or selenium. Any changes which would affect this interaction would be expected to destroy the adduct forming ability.

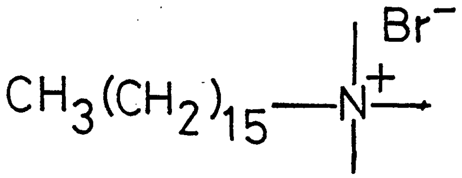
Most work has centred, therefore, on the type of guests which are included and the interesting properties they have as a result of being constrained within a restricted space. Various studies have been directed towards conformational changes which are found for guests in the channels. Monosubstituted cyclohexanes are known to exist preferentially as the equatorial conformer in the gas and liquid phases and in solution. They also crystallise in the equatorial conformation at low temperatures. In inclusion compounds of thiourea, most are found to preferentially adopt the axial conformation. A recent Raman and infra-red study [74] has confirmed this behaviour for a series of monosubstituted cyclohexanes, and some disubstituted examples as their adducts of thiourea. The limits of the cross-sectional diameter are *ca* 5.8-6.8Å, thereby prohibiting guests of greater size. Cyclohexane falls within these bonds and in the adduct the molecules may be stacked with the three-fold axis centred along the channel axis. Whereas an equatorial substituent will increase the cyclohexane diameter, an axial substituent, being parallel to the three-fold axis will not significantly increase the diameter of the molecule. Generally for mono- and 1,4-di-halogenated cyclohexanes the axial conformers have smaller volumes than the equatorial conformers. More efficient packing is possible with the axially substituted cyclohexanes which accounts for the situation which is observed.

The selectivity of urea towards linear species has been used for the isolation and purification of a reaction product. Nitric acid oxidation of cyclododecane and cyclododecanol gives decane - 1,10-dicarboxylic acid which is purified by formation of the urea adduct, any non-linear products being unable to do so. This procedure gave the linear di-acid in 99.5% purity. [75]

Other well-known uses of the urea and thiourea inclusion compounds include their stabilisation of easily oxidisable substances, for example, vitamin A, [76] unsaturated fatty acids [77] and decalin, [78] and their use as matrices for polymerisation processes. In the polymerisation of dienes, 1,4-trans addition is obtained as the channel holds the monomer guest in a straight conformation. [79]

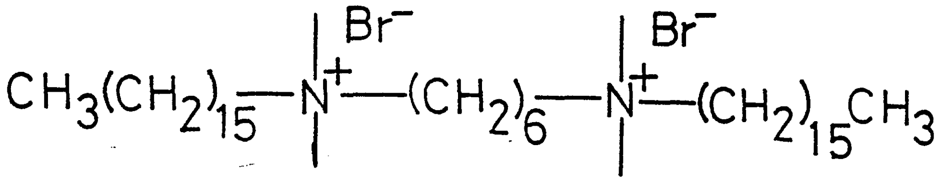
Not all complexes of polymers with urea and thiourea are of the same type. Polyethylenes and aliphatic polyesters do form adducts of an inclusion nature, [80] but poly-(ethylene oxide) forms complexes which are not regarded as being inclusion compounds. [81] Quaternary ammonium salts with long alkyl chains, such as cetyl trimethyl ammonium bromide (34) form inclusion compounds with thiourea. In contrast, the hexamethylene-bis (cetyl dimethyl ammonium) dibromide (35) complex is of an ionic-type.

Comparisons with these two cases have been used to determine the nature of the complexes of some ionene (36) polymers with thiourea. Infra-red and X-ray diffraction studies indicated that the complexes were ionic in nature, not of an inclusion type. [82]



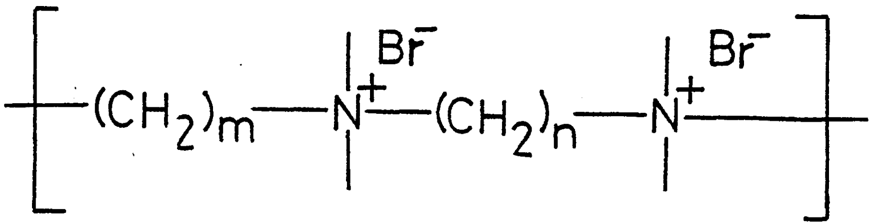
$CH_3(CH_2)_{15}-\overset{|}{\underset{|}{N}}{}^{+}\rightarrow \; Br^-$

cetyl trimethyl ammonium bromide (34)



$CH_3(CH_2)_{15}-\overset{|}{\underset{|}{N}}{}^{+}-(CH_2)_6-\overset{|}{\underset{|}{N}}{}^{+}-(CH_2)_{15}CH_3 \quad Br^- \quad Br^-$

hexamethylene-bis (cetyl dimethyl ammonium) dibromide (35)



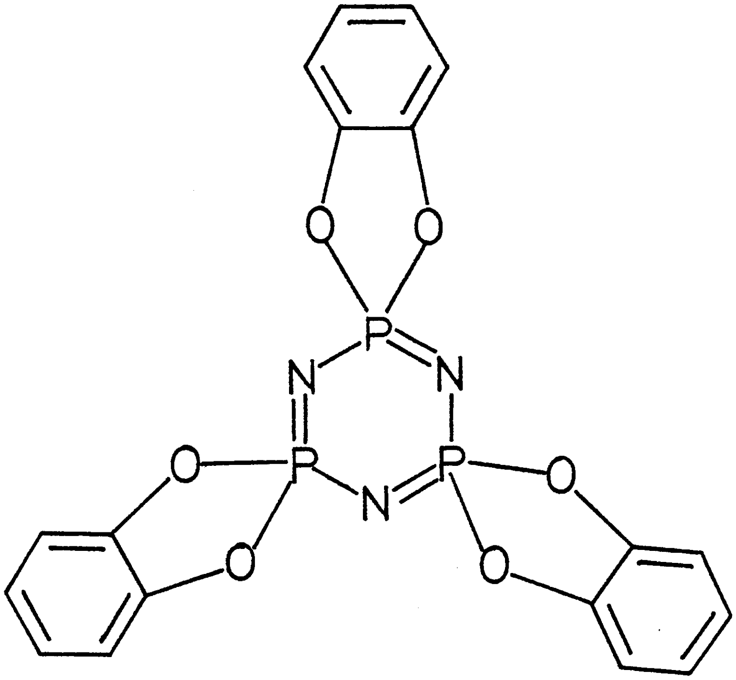
$\left[-(CH_2)_m-\overset{|}{\underset{|}{N}}{}^{+}-(CH_2)_n-\overset{|}{\underset{|}{N}}{}^{+}-\right] \quad Br^- \quad Br^-$

m,n-ionene (36)

The channels of urea have also been used as a matrix for the study of radical formation and decay. 83 This is normally done by irradiation of the pre-formed inclusion compound. Also reported has been the formation of trapped electrons in the n-octane urea adduct which has been studied by electron spin resonance. 84

Urea adducts have been suggested as a stationary phase in gas chromatography. Both the urea-n-hexadecane 85 and urea-cetyl alcohol 86 inclusion compounds have been tried. In the former case retention times of a variety of n-alkanes, branched alkanes, alkenes, aromatic compounds, n-alcohols and ketones have been determined. The cetyl alcohol adduct has been used as an analytical method, allowing rapid analyses, even at low experimental temperatures.

Just as it was the chance observation of crystals by Bengen which led to the inclusion properties of urea being discovered, so it was that the cyclophosphazene "clathrates" were discovered by accident.[72] The failure of Tris (o-phenylenedioxy)-cyclotriphosphazene (37), to give satisfactory microanatytical data, despite consistant infra-red, ultra-violet, nmr spectra and correct molecular weight by mass spectrometry, and its curiously broad melting range, were recognised as being artifacts of inclusion behaviour, only after X-ray analysis of the adducts had been carried out.



Tris (o-phenylenedioxy)-cyclotriphosphazene (37).

(37) not only includes guests on recrystallisation, but will also directly absorb molecules like n-heptane and chloroform from the liquid itself or from the vapour. A very wide range of guests is found with host to guest ratios ranging from 1:0.6 to 1:0.03, with a very high stability for most adducts being observed.

X-ray analysis of the benzene inclusion compound indicated layers at 5Å separation, but this is too narrow to accommodate the guest. Instead they are occupied in tunnels formed by the side-groups of (37) (Figure 15). The term clathrate [87] although now established for this series is again misused.

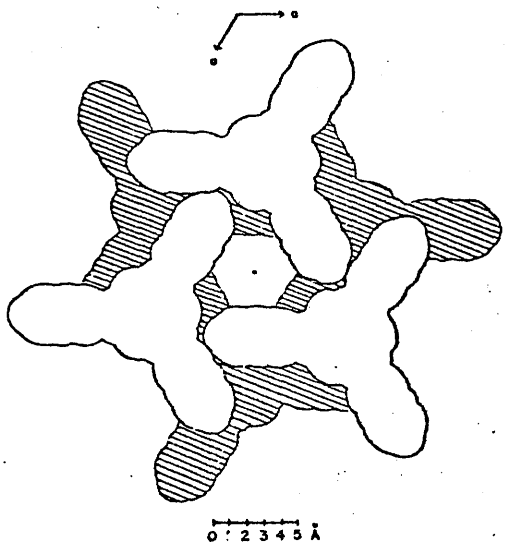
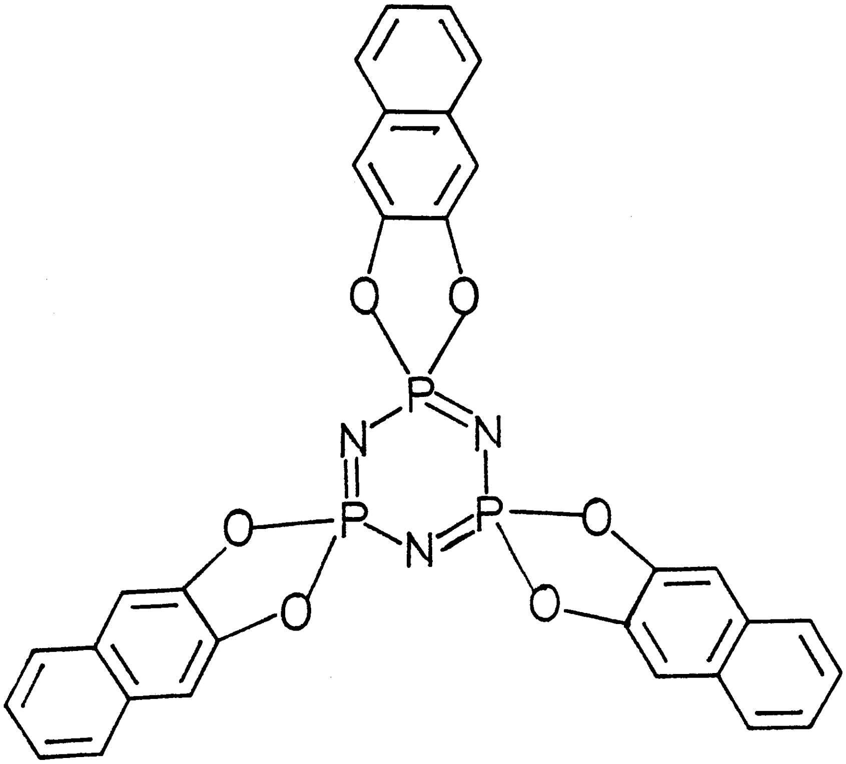


Figure 15 The 4.5-5Å diameter tunnel formed by the van der Waals boundaries of (37).

This system exhibits guest selectivity in absorption from a mixture of liquids. From n-heptane and cyclohexane, the linear molecule is included with 100% exclusion of the cyclic component. Various separation procedures have been patented [88, 89, 90] and the cyclophosphazene inclusion adducts have been suggested as the stationary phase in gas-solid and liquid-solid chromatography.

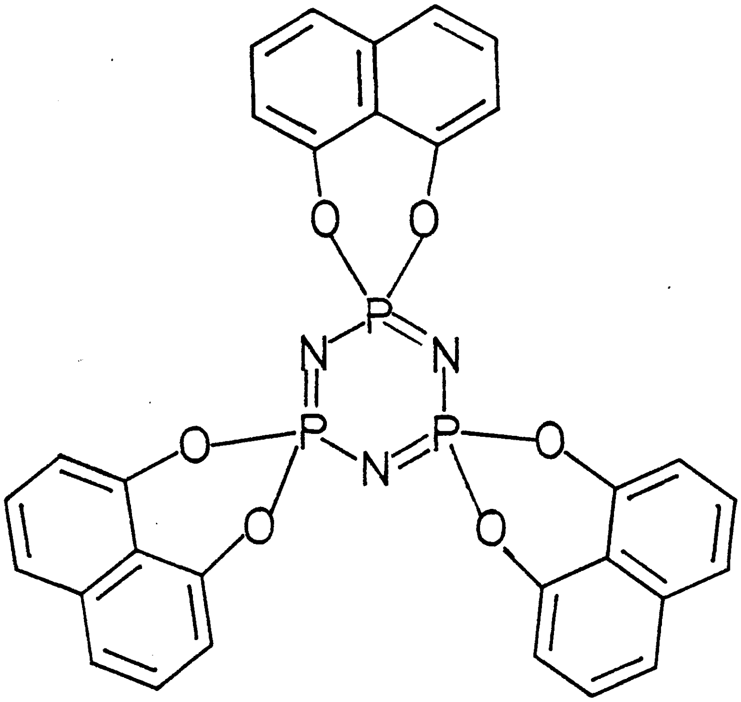
Attempts to alter inclusion behaviour by modification of the host structure has been carried out by Allcock. The method of preparation allows facile changes to be made and a number of analogues have been made.



Tris (2,3-naphthalenedioxy) cyclotriphosphazene (38).

Increase in the length of the side-group as in tris (2,3-naphthalene dioxy) cyclotriphosphazene (38) leads to retention of inclusion properties but with a higher ratio of guest molecules per host molecule. [91] Examination of the crystal structure [92] indicates the same "paddle-wheel" arrangement of side-groups, but the longer naphthalene ring causes greater separation of the molecules. This is reflected in the tunnel diameter which is 9-10Å at its narrowest point, compared to 4.5-5Å in the narrower tunnels of (37). This widening reduces the stability of the adducts since guest escape is now much easier.

The tris (1,8-naphthalene dioxy) derivative (39), also forms inclusion compounds when recrystallised from a wide range of solvents. [93]



Tris (1,8-naphthalenedioxy) cyclotriphosphazene (39).

The structure [94] of the adducts differs from those of (37) and (38), in that the side-groups are bent at the oxygen atoms, and that inclusion is observed as a consequence of one of the side-groups being bent in the opposite direction from the other two. A symmetrical relationship of the three groups would result in the third group filling the tunnel (Figure 16).

The adducts are stable possibly due to constrictions in the tunnel at various points. In the p-xylene case, the guest molecule is fixed and undergoes only minimal thermal motion at room temperature.

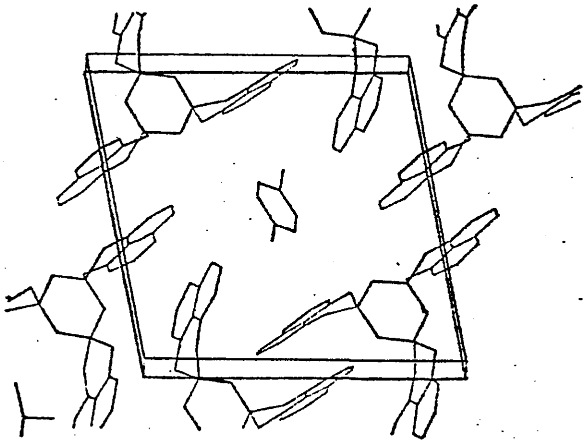
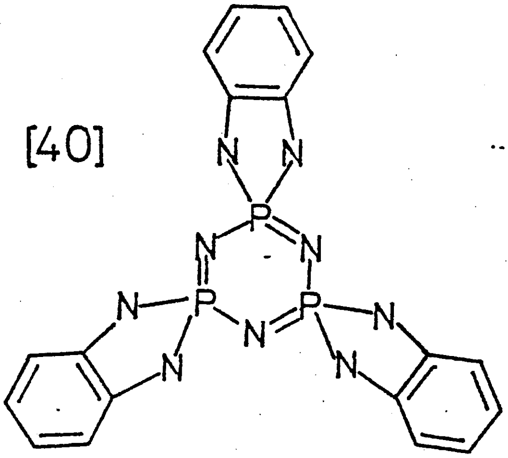
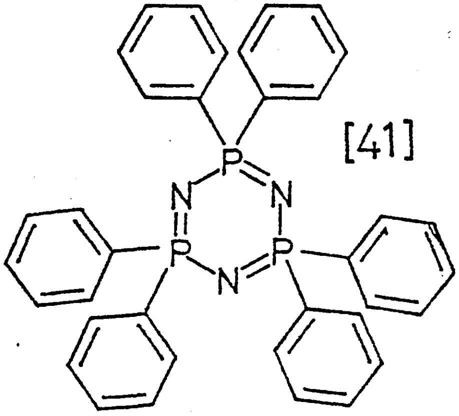


Figure 16 View of the unit cell contents of a xylene clathrate of (39).

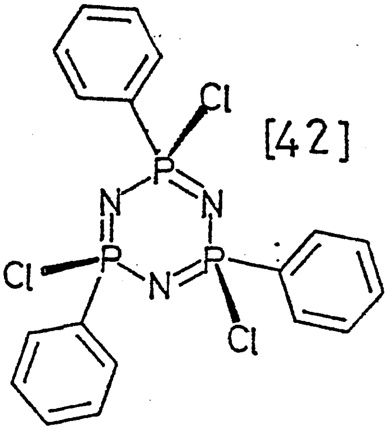
Other cyclotriphosphazines, for which inclusion behaviour has been observed are the nitrogen analogue (40), with methyl ethyl ketone, [91] cis-1,3,5-trichloro-1,3,5-triphenylcyclotriphosphazine (41) with benzene [95] and hexaphenylcyclotriphosphazine (42) with 1,1,2,2-tetrachloroethane. [96]

[40]





[41]



[42]

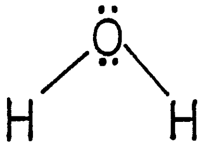
These studies have shown that changes in inclusion ability by modification can be rationalised, though the specific changes were not predicted. Though the changed behaviour of (38) with respect to (37) could well have been foreseen by examination of the crystal structure of (37) the completely different structure of (39) could not be predicted.

An interesting area for future study might be the attachment of an asymmetric side-group to produce a chiral tunnel, with possible application to enantiomer separation by selective inclusion.

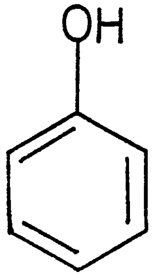
(iii) Clathrates

When a guest is completely trapped within a cavity which is closed on all sides by a wall made up of host molecules the inclusion compound is called a clathrate. Few genuine examples of this form of molecular complex have been established, yet, one of the most abundant compounds, water, possesses this amazing ability. The true clathrate nature of a complex may only be established by a crystal structure analysis which shows the cage-type cavity.

A group of clathrate hosts are related in that the individual molecules are held together in the lattice by hydrogen-bonds. Apart from water (43), other members of this class are phenol (44) and substituted phenols, hydroquinone (45) and Dianin's Compound (4).



[43]



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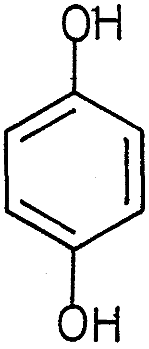


[45]

In the clathrates of hydroquinone, for example, six molecules are held together via hydrogen bonding to give an almost planar hexagon of oxygen atoms.[97] The rest of each molecule angles away from the plane to form the wall of the cage. The other hydroxyl group is similarly a part of another hexamer unit, leading to an infinite array of hexagons and cages (Figure 17).

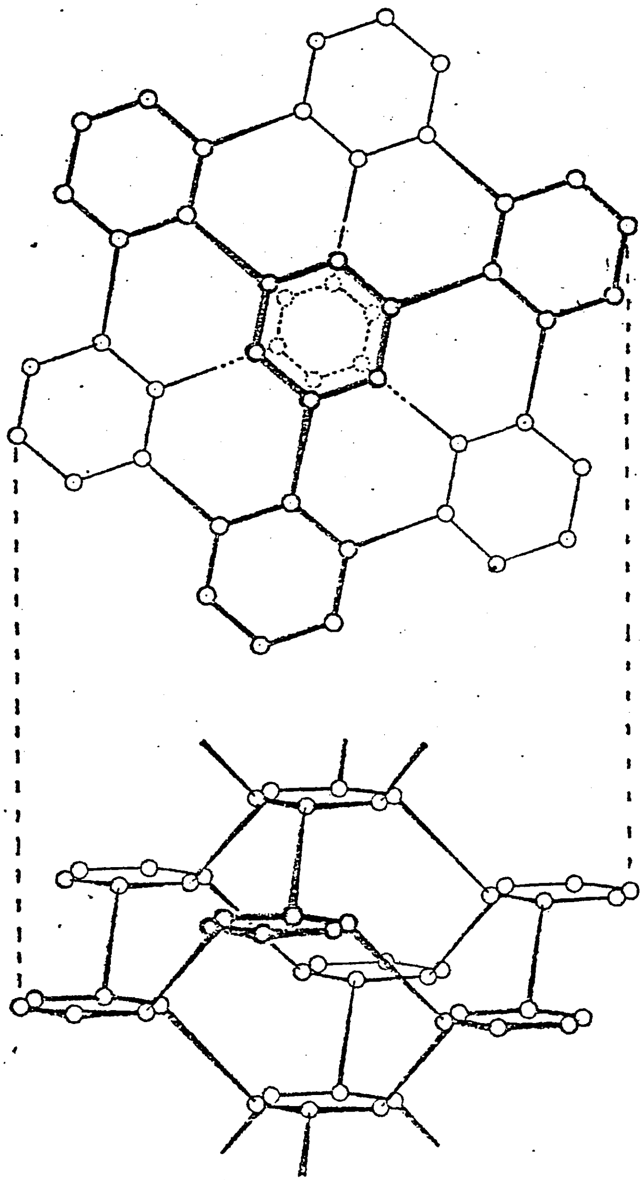
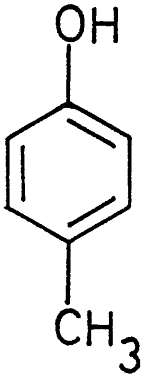


Figure 17 Manner of hydrogen bonding of hydroquinone molecules. Each regular hexagon denotes six hydrogen bonds between oxygen atoms.

Clathrates are usually formed by recrystallisation from the desired guest, however, water,[98] phenol[99] and hydroquinone[99] have been shown to be able to absorb gases and vapours when the host crystals are agitated in the presence of the gas. This simple method allowed the facile study of a series of para-substituted phenols and their clathrates in relation to the parent phenol.[100]

A number of phenols were found to form clathrates with noble gases and gaseous hydrocarbons.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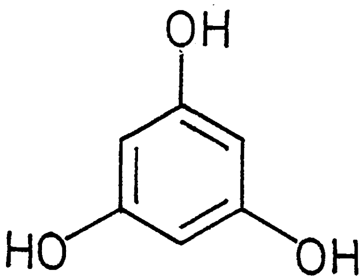
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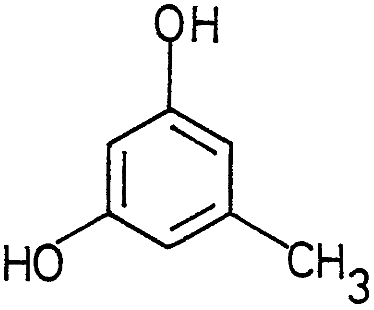

[48]

The ability of phenol to separate the noble gases has been established. From a xenon/krypton mixture phenol includes xenon to the almost complete exclusion of krypton, but when p-cresol (46) is used only a 4.8:1 Xe/Kr ratio is found.

In 1910 a study[101] of polyhydritic phenols and related ethers showed that phlorglucinol (47) and orcinol (48) formed adducts with hydrogen bromide but a clathrate nature has not been established. Similarly, a group of dimethyl and trimethyl phenols have been reported[102] to form adducts with simple alcohols for which a clathrate structure is claimed. Complexes of higher alcohols are of a different type.

The three monofluorophenols have all been found to include gases, the ortho and meta cases only under large guest pressures.

Hydrates and deuterates have been widely used for spectroscopic studies of guests at low temperatures. [103]

Recently the formation of hydrates of the noble gases has been proposed [104] as an explanation for their relative abundances in the atmosphere.

As in urea, there is little scope for modifying the inclusion properties of these simple molecules, and their low stability except at very low temperatures prevents their widespread application. The other member of the "hydrogen-bonding" series, Dianin's Compound has been the subject of detailed investigation into the effects of structural modification on inclusion behaviour.

Dianin's Compound (4), 4-p-hydroxyphenyl-2,2,4-trimethyl chroman was prepared in 1914, [105] by the condensation of mesityl oxide with two phenol molecules.

After Powell's work on the hydroquinone clathrates, these interesting hosts were examined by Baker and McOmie. [106–108] The range of guests included by this versatile compound is wide and varied from gases to moderately sized organic molecules. Table 2 lists some illustrative examples.

Table 2

Representative Inclusion behaviour displayed by Dianin's Compound

Guest	Mole Ratio of host:guest
methanol	3:1
ethanol	3:1
acetone	3:1
carbon tetrachloride	3:1
nitromethane	3:1
acetic acid	3:1
n-pentanol	6:1
diethyl ether	6:1
n-butyl bromide	6:1
hexanoic acid	6:1
benzene	6:1
p-xylene	6:1
Iodobenzene	6:1

The cage-type nature of the cavity was first suggested by Powell and Wetters; [109] the accuracy of their prediction being illustrated by comparison of their view of the hexameric unit of Dianin's Compound with the structure found in the clathrate and unsolvated form [110] (Figure 18).

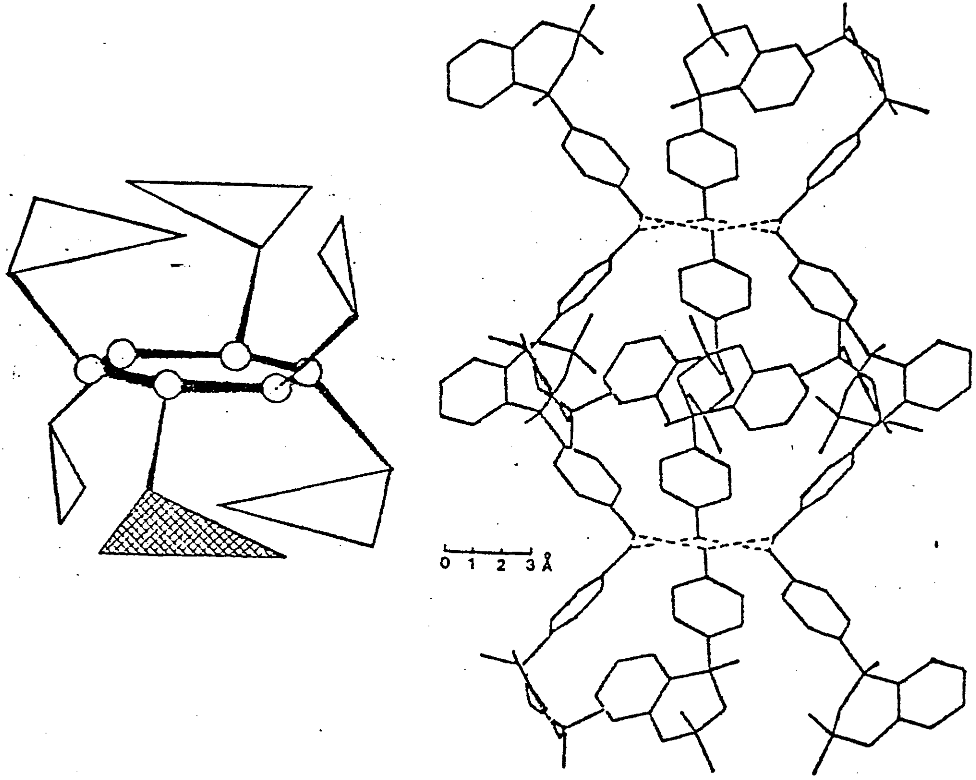


Figure 18 Schematic representation of one hexameric unit formed by Dianin's Compound and the packing found in unsolvated Dianin's Compound.

The structure of the adducts is isomorphous with the unsolvated form. The key feature of the open clathrate is the unit of six molecules linked via hydrogen bonds. The oxygen atoms form a distorted hexagon with the residues of the molecules alternately up and down from the plane of the hexagon. There is an array of these hexamer units aligned along the crystallographic c-axis, the interpenetration of the three-legged "cups" producing a series of cages. Since there is only one hydroxyl group per molecule there is no infinite framework as in the quinol clathrates.

The dimensions of the cage are illustrated in the section through the van der Waals surface (Figure 19).

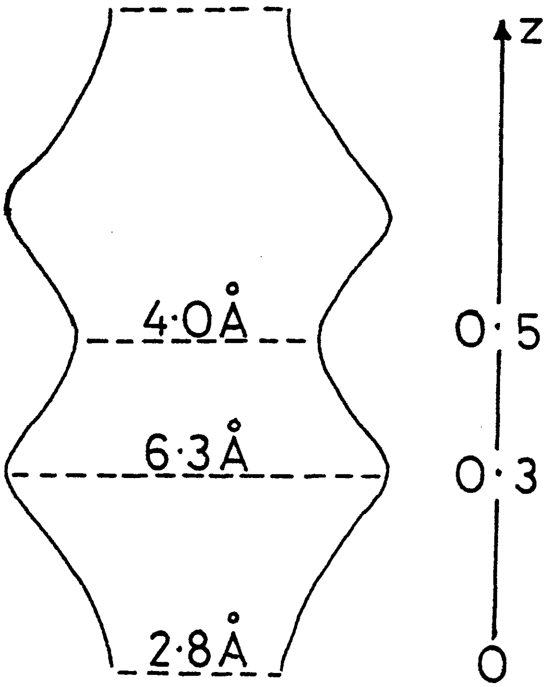


Figure 19 A section through the van der Waals surface of the cavity present in unsolvated Dianin's Compound. The length of the cage is 10.9Å.

The cavity is of an hour-glass shape imposed by one of the two geminal dimethyl groups, the one syn to the 4-hydroxyphenyl group. As can be seen from the table of guests, large molecules are fitted one per cage, to give a host to guest ratio of 6:1, while smaller guests are accommodated two per cage corresponding to a ratio of 3:1. Methanol has been quoted [107] as forming a 2:1 host to guest complex but a 3:1 ratio has since been established. [111] Higher host to guest ratios probably indicates that some of the cages are unfilled while the 1:1 adduct with piperidine is probably not an inclusion compound, but a loosely bound salt. The crystals are unstable, losing the "guest" in air unlike the clathrates which have remarkable stability - the sulphur hexafluoride adduct showing less than 0.5% decomposition after three years at normal temperatures and pressures. [112] The loss may have been due to the host sublimation rather than guest escape through the walls. The dimensions of the cage are not greatly affected by different guests, only slight expansion taking place for the chloroform clathrate. This is in contrast to the hydroquinone clathrates where a trellis effect allows adjustment depending upon the relative length and width of the guest. [113] In Dianin's Compound, it is generally the guest molecule which will be distorted if necessary. In the n-heptanol clathrate, the length of the cage is too short to accommodate the guest unless it adopts a gauche conformation at both ends of the molecule. [114] (Figure 20)

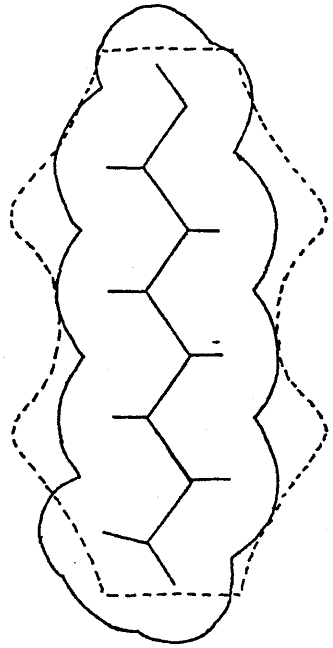


Figure 20 The relative size of an extended *n*-heptyl alcohol molecule within the normal cavity found in Dianin's Compound.

Like most inclusion compounds Dianin's Compound has found application in the separation of mixtures and as a matrix in which to study molecules under constraint. It has a drawback in that being a host of high molecular weight the amount of guest per weight of clathrate is small.

The constriction in the middle of the cage provides a barrier to certain guests and this has been used in a separation procedure. From an equimolar mixture of *n*-heptane and 3-methyl hexane the relative percentages of included guest were 89:11.[115] The generality of this result was established for C_5–C_7 linear hydrocarbons and the 3-substituted methyl isomers. In each case the steric interference of the waist allows selective inclusion of the straight chained alkane. A particularly impressive example is the separation of 2-methyl hexane in 99% purity from an equimolar mixture with 2,3-dimethyl pentane after only one recrystallisation from Dianin's Compound.

In the absence of X-ray data, information on changes in cavity shape brought about by host modification could be obtained from guest selectivities.

Studies on the motion of guests in the cages have been carried out using a number of spectroscopic techniques. Electron paramagnetic resonance, [116] proton magnetic resonance [117] and infra-red studies [103] have all been carried out. The cage has been employed as a matrix for studying radicals generated inside the cavity. They are produced by irradiation with X-rays; to produce Br_2 in the case of 1,2-dibromo-1,1-difluoro ethane, [118] or by γ-rays to give the $CH_3N.O_2H$ radical when nitroethane is the guest. [119]

The problem of low concentration which affects the spectroscopic studies is also a handicap in the application of Dianin's Compound as a trapping agent for radioactive gases. Only hydroquinone has found a general use in this area.[120] The sulphur hexafluoride clathrate has found application in the electrical industry, through controlled release of the guest, a gas of low dielectric constant.[121] Clathrates of some amines have been used as latent polymerising agents, the complexes being broken down by ultrasonic radiation.[122]

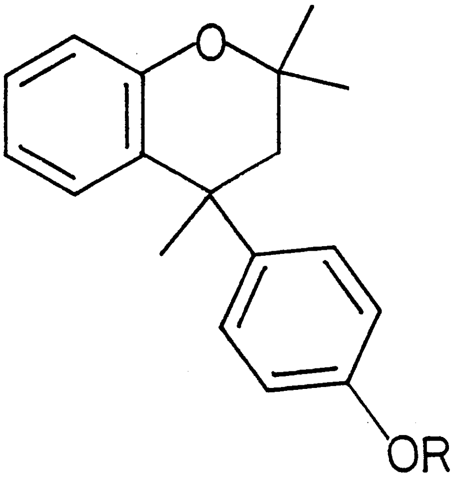
The three-dimensional protection of guests, compared to the less complete covering of other hosts is illustrated by the clathration of glycerol which was then protected from attack by hydrogen peroxide and lead tetra-acetate, though not from periodic acid. [123]

The β-cyclodextrin complex of glycerol did not provide the same degree of protection from the same reagents.

The structure of Dianin's Compound offers tremendous scope for modification, the only limitation being synthetic availability. Most of the possibilities have been studied recently by MacNicol and by Jacques.

(a) The hydrogen-bonding found in the hexameric unit of Dianin's Compound is fundamental to its ability to form inclusion compounds. Modifications to this function should have a substantial effect upon clathrate formation.

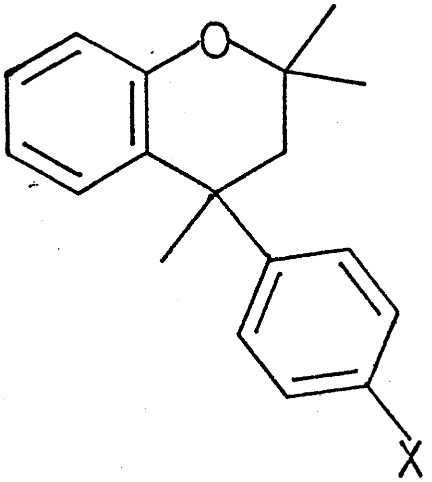
When the possibility of hydrogen-bonding is eliminated completely, then no directly analogous inclusion properties can be expected. Consequently, the molecules shown below do not form any adducts.



R	
CH_3	[49]
$-\underset{\underset{O}{\|}}{C}Ph$	[50]
$-\underset{\underset{S}{\|}}{C}NMe_2$	[51]

Two other functionalities capable of forming hydrogen-bonds are amines and thiols. The corresponding analogues (52) and (53) were prepared and studied. The amine undergoes spontaneous resolution,[124, 125] with individual crystals being made up completely of molecules of a particular enantiomer, the asymmetric centre being at C-4. No inclusion however takes place. One suggestion for the failure of this system to form an open structure may be that hydrogen bonding between the amine and the ring oxygen is preferred to the NH----N-- bonding required for the hexamer unit.

The thiol (53), when first prepared was found not to form inclusion compounds with a variety of solvents, the compound undergoing spontaneous resolution [125] as found for the amine (52).



X	
NH_2	[52]
SH	[53]

When the thiol (53) was recrystallised from carbon tetrachloride, however, a clathrate was obtained with a host to guest ratio of 3:1. Infrared measurements of the S-H stretching mode indicated an unusually short SH----S hydrogen bond. The crystals of the adduct did not have the stability of the parent phenol clathrates, noticeable decomposition taking place within a day.

The clathrate nature was confirmed when the X-ray structural analysis was carried out.[126] The structure (figure 21) shows the hexameric unit of the thiol analogous to Dianin's Compound itself.

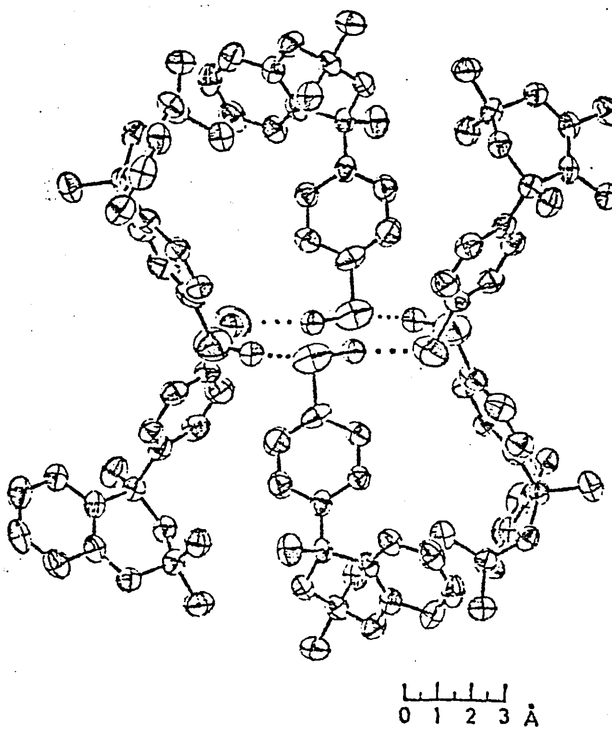
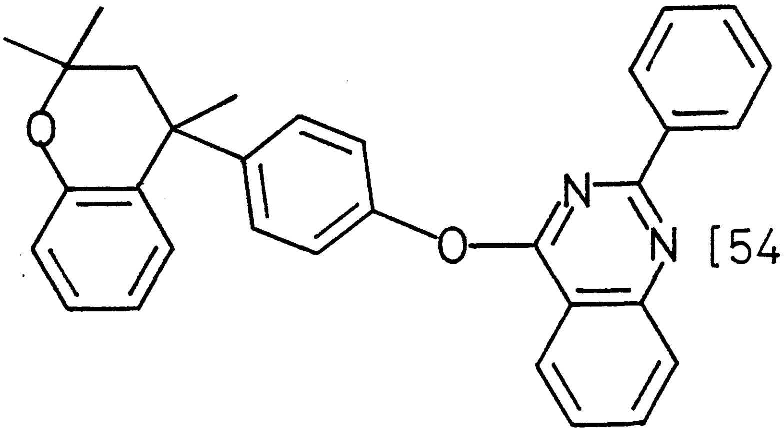


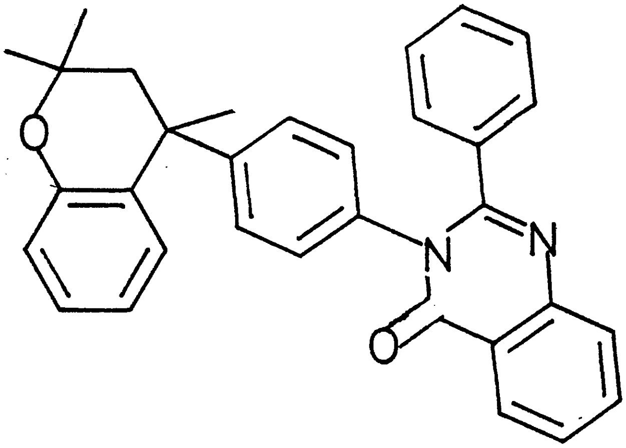
Figure 21 A general view of the hydrogen-bonded hexameric host unit of (53) in the CCl_4 clathrate.

The lack of stability of the clathrates may be a reflection of the relative weakness of the thiol hydrogen bond compared to the hydroxyl. The length of the cage is greater than in Dianin's Compound, the distance between the two hexameric units being 12.07Å against 10.94Å. Curiously, when very pure thiol is used, only unsolvated material is obtained. "Poisoning" the thiol with 2% of Dianin's Compound ensures the formation of a clathrate.[124]

Unlike the planned synthesis of the new host (53), completely unexpected were the two hosts (54) and (54a), prepared as intermediates in the synthesis of the amine (52).



[54]



[54a]

Whereas (54), was found to have only limited inclusion behaviour, the quinazoline host (54a) is a general inclusion host, forming adducts with a wide range of diverse solvents [127] (Table 3).

Table 3

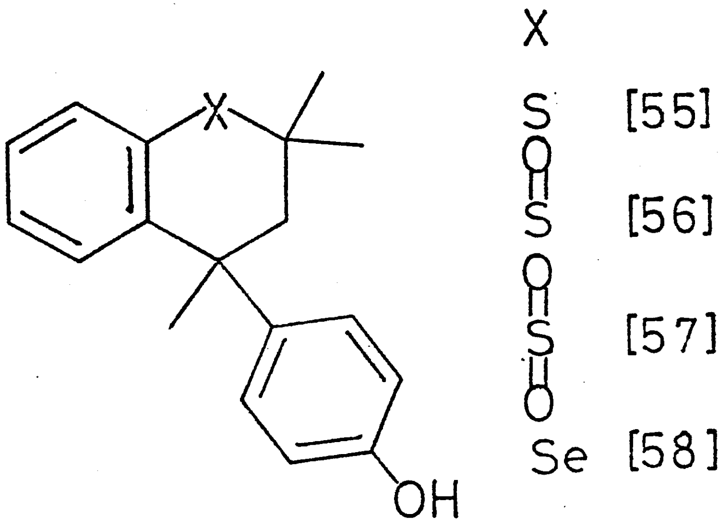
Reprepentative Inclusion behaviour of the quinazoline host (54a)

Guest	Mole Ratio of host:guest
cyclopropane	1:1
cyclooctane	2:1
benzene	1:1
t-butanol	1:1
acetic acid	1:1
carbon tetrachloride	1:1
t-butyl amine	2:1

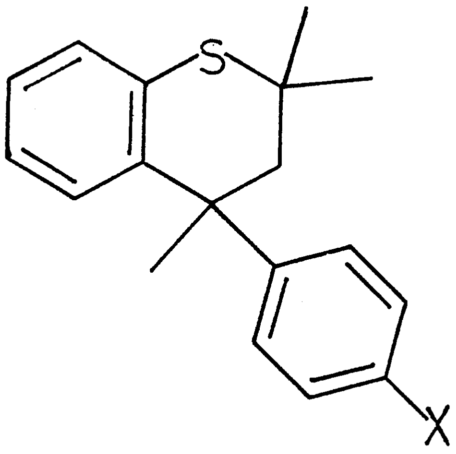
The closed nature of the cavity of (54a) was suggested by the survival of cyclopropane (b.p.-38°C) on heating its adduct at 45°C below 0.5mm Hg of pressure. X-ray structural analysis [128] confirmed the cage is indeed closed and hence the inclusion compounds of (54a) are true clathrates.

(b) The oxygen in the chroman ring does not appear to have an important function in the formation of the clathrates of Dianin's Coumpound. Modification at this position would not be expected to greatly alter its adduct forming ability.

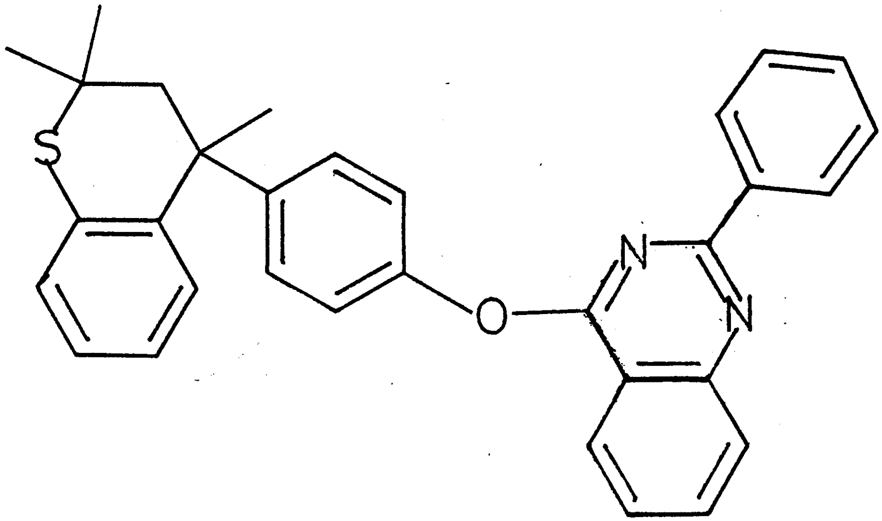
Compounds(55)-(58) have been prepared, the thiachroman [129] (55) and selenachroman [130, 131] (58) forming adducts but the sulphoxide [132] (56) and sulphone [130, 132] (57) failing to share these properties.



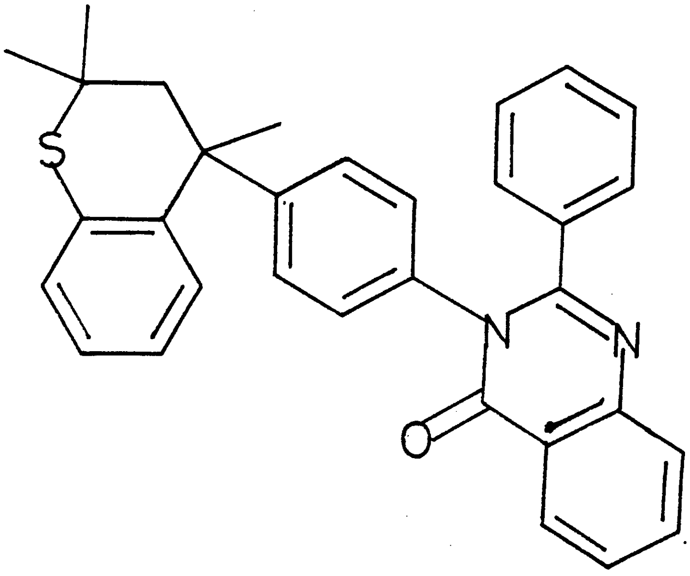
(55) appears to be the first example of a host of the closed-cage type which was deliberately prepared for that purpose. It shares a similar cavity goemetry to the parent and hence not surprisingly similar inclusion behaviour. This host was used to determine the absolute nature of the guest in a cage through X-ray analysis of the acetylenic alcohol $Me_3C.C\equiv C.CMe_2-OH$. [133] All the guest molecules adopt a staggered conformation. This is imposed upon the guest by the strict symmetry of the host structure which is $\bar{3}$.



X	
SH	[59]
NH_2	[60]



[61]



[62]

Other sulphur analogues have been prepared with differing results. Although both mono-sulphur compounds (53) and (55) form inclusion compounds no adducts have been found for the thiachromanyl thiol (59),[124] despite doping with 2% Dianin's Compound to promote clathrate formation.

The thiachromanyl amine (60) was prepared[124] with the hope that the removal of the strong NH---O interaction would allow the NH---N hydrogen bonding required for a hexameric unit to compete more favourably. No inclusion behaviour was observed.

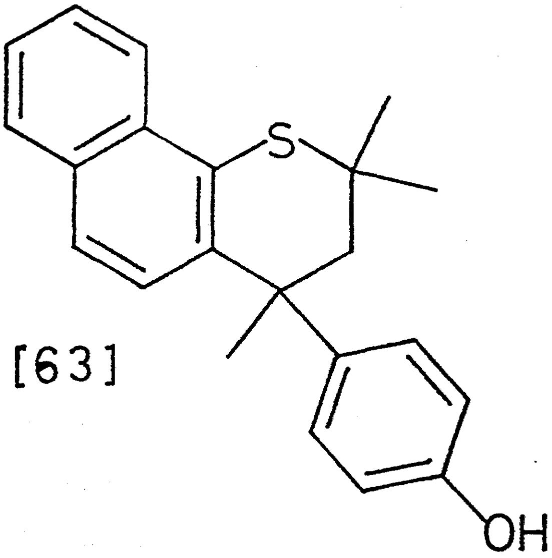
Lastly the two quinazoline derivatives (61) and (62) prepared[124] as intermediates in the route towards the amine show different behaviour. (61), the thio-analogue of the minor host (54) did not form inclusion compounds but (62) the analogue of the general host (54a) included a wide range of solvents similar to the parent.

The observations indicate that apparent minor modification does not automatically lead to new host systems. Clathrate formation is sensitive to changes in size, shape and polarity of the host system.

(c) The fused aromatic ring of the chroman lies on the outside of the column of cages in Dianin's Compound. Substitution of this ring would be expected to lead to interactions between the parallel columns affecting their packing.

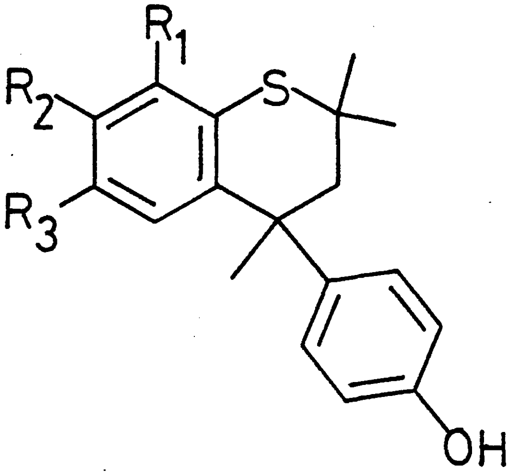
A study has been carried out on the thiachroman analogue of Dianin's Compound regarding the possible effects.

The addition of a fused benzene ring as in (63) leads to the removal of all inclusion properties, suggesting severe interference between the columns and a disruption of the normal packing arrangement.[134]



[63]

A more systematic approach involved substitution of a single methyl group into the aromatic ring. 6-methyl, (65), 7-methyl (66), and 8-methyl (67) analogues of (55) have been prepared and examined for changes with respect to the parent.



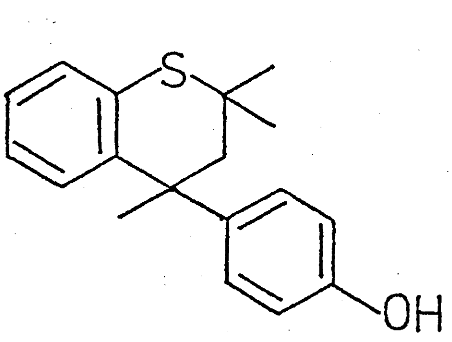
(65) $R_1=R_2=H$, $R_3=Me$

(66) $R_1=R_3=H$, $R_2=Me$

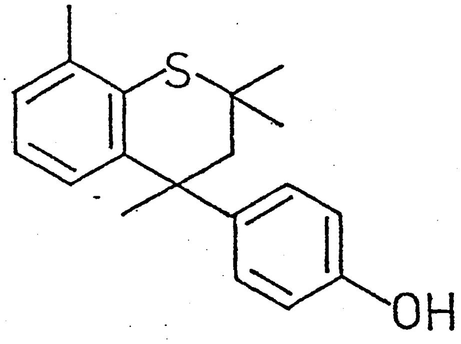
(67) $R_2=R_3=H$, $R_1=Me$

The 6-methyl (65), and 8-methyl (67) compounds do form inclusion compounds,[134] but whereas (65) is isomorphous with (55) having similar lattice parameters, (67) has a radically different cavity shape.[135]

A view of a section through the van der Waals radius of (55) and (67) shows how the hour-glass shape of the unsubstituted host has been modified to give a cavity of a "chinese lantern" type (Figure 22).



(55)



(67)

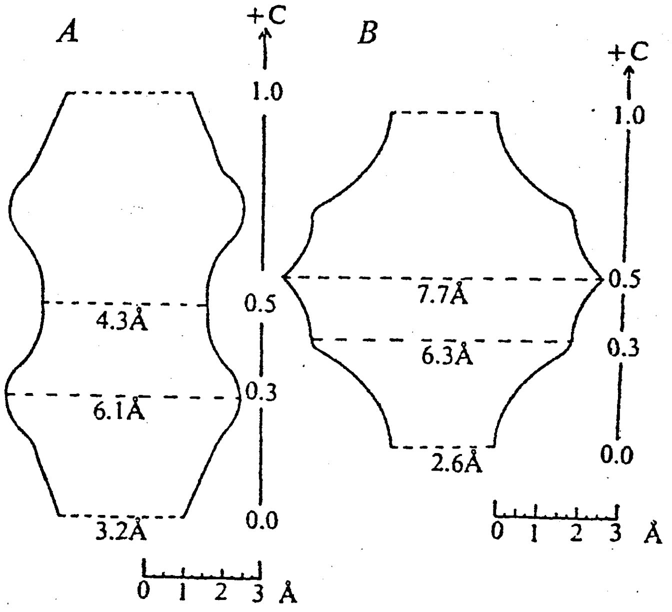


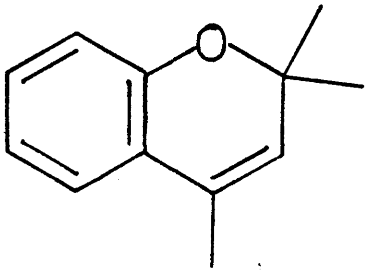
Figure 22 Section through the van der Waals surface of the cavity: A, for (55); B, for (67), representing the space available for guest accommodation.

Associated with this change in cavity shape is an alteration in the inclusion properties of the host. Particularly, selective inclusion from solvent mixtures is affected.

The addition of a methyl group to the 7-position, meta to the sulphur, leads to the loss of inclusion behaviour, a situation also found for the 7-methyl analogue of Dianin's Compound itself.[111] Curiously the 6-methyl compound also does not form inclusion compounds, contrasting with the situation found for (65). Substitution in the 5-position of both systems and in the 8-position of Dianin's Compound has yet to be carried out.

(d) Substitution of the 4-hydroxyphenyl group of Dianin's Compound has been carried out but with limited success.

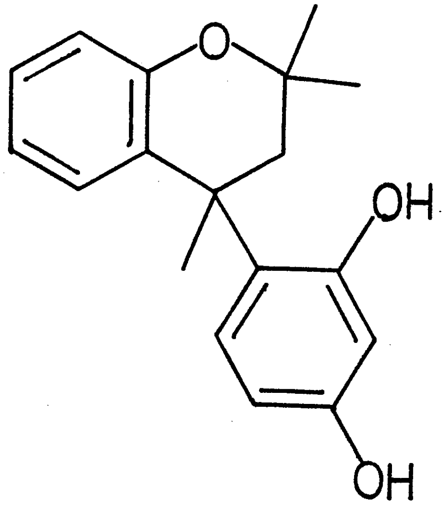
The first systematic study on the modification of Dianin's Compound involved the reaction of methyl phenols with 2,2,4-trimethyl chromene (68) in an attempt to produce new hosts. [107]



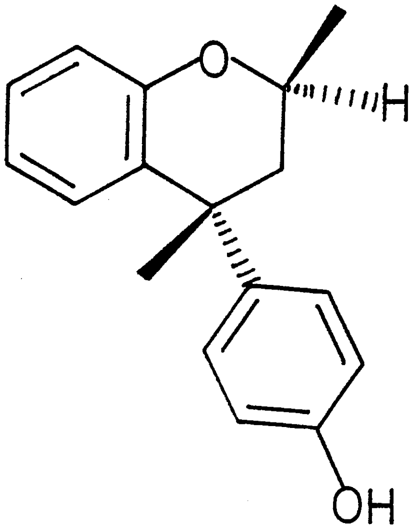
[68]

Ortho-cresol gave a crystalline homologue of Dianin's Compound but no adduct formation was observed. There is probably steric hinderance which interferes with the formation of the hydrogen-bonded hexamer. Meta- and para- cresol did not give phenolic products.

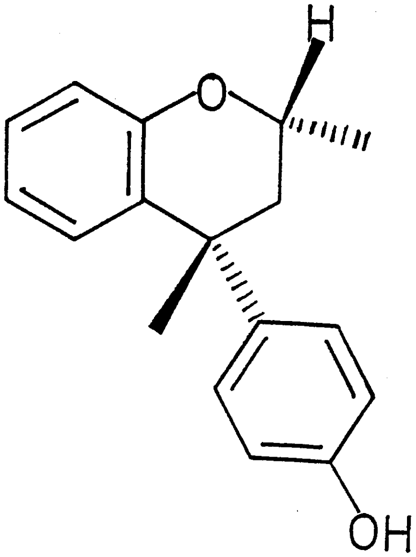
Reaction with catechol yielded products which would not crystallise, but, resorcinol reacted in good yield with the chromene to give 4-(2',4'-dihydroxyphenyl)-2,2,4-trimethyl chroman (69). This compound forms adducts with a variety of solvents including chloroform and acetone. [121]



[69]



[70]



[71]

(e) One of the most noticeable features of the hour-glass cavity, is the constriction which appears to divide the cage into two compartments. This waist is caused by six methyl groups, one of the geminal methyl groups from each of the six molecules forming the cage. It is the methyl group syn to the 4-hydroxyphenyl group which is responsible for this bottle-neck. Removal of this methyl substituent gives a new clathrate host [136] (70). The cavity shape found for the adducts has been determined [137] and compares remarkably well with that predicted by formal removal of the methyl group from the cavity of Dianin's Compound (Figure 23).

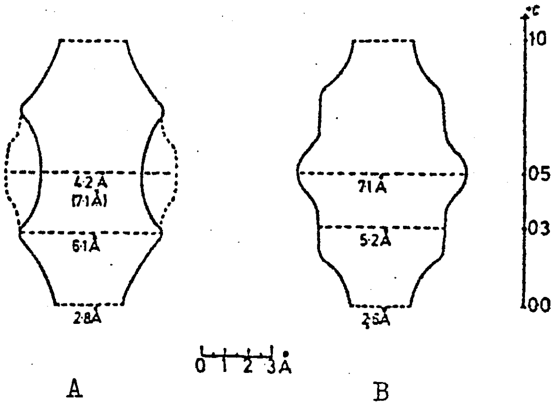


Figure 23 Section through the van der Waals surface of the cavity for A, Dianin's Compound (4) as chloroform clathrate, the curved broken lines represent the effect of formal removal of the waist methyl groups; B compound (70) as CCl_4 clathrate.

Collet and Jacques have synthesised the other 2-nor analogue (71) in which the methyl group <u>anti</u> to the aryl substituent is removed.[138] This compound is also an inclusion host, a host to guest ratio of 7:1 being found for the cyclohexane adduct.

The centre at position 4 in Dianin's Compound is asymmetric as in position 2 in the nor-methyl compounds (70) and (71). Chiral aspects of these systems will be discussed in a later chapter.

A summary of the work carried out on Dianin's Compound is represented schematically (Figure 24). A wide-range of inclusion behaviour has been observed, and the shape of the cavity has been altered <u>in a predictable manner</u>. Unexpected results are still obtained but they can later be rationalised. This is probably the classic example of clathrate engineering, showing the important role of X-ray analysis in elucidation of the effect of modification on the crystal structure and on clathrate formation.

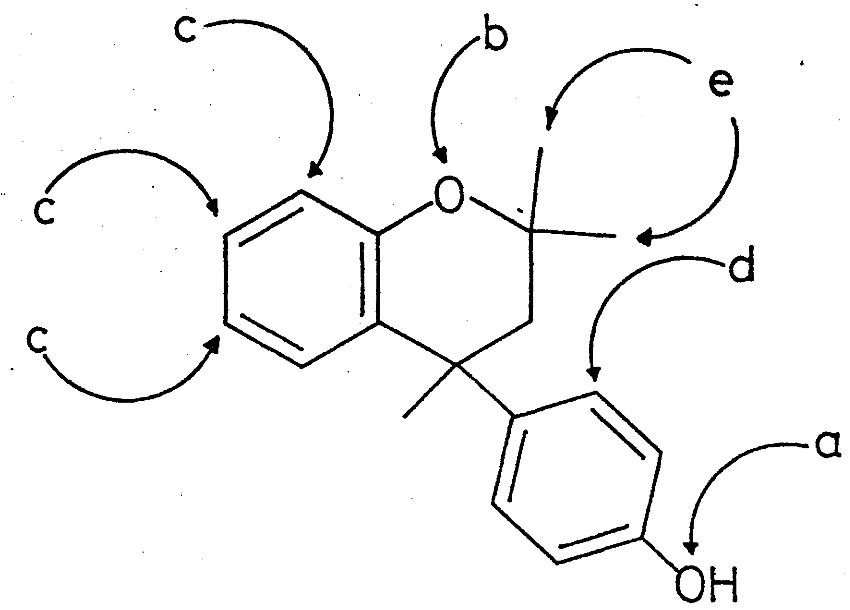


Figure 24 Summary of the modifications made to the structure of Dianin's Compound.

All previous examples of new hosts have been the result of structural modification of a known host system. A completely different concept however is the discovery of hosts not related structurally to an existing one. Those which have been found in the past are the results of chance observation. Recently however, the planned preparation of a group of compounds, not directly related to any host system, resulted in the discovery of a new series of clathrate inclusion hosts.

Analogy [139] between the hexagonal linkage of molecules in Dianin's Compound and the covalent structure of a benzene unit prompted MacNicol to prepare a number of hexasubstituted benzenes (figure 25). A number of such compounds had been prepared in the 1930's and had been found to retain solvents, [140] though the nature of inclusion compounds had yet to be established. A wide range of inclusion behaviour was found for a number of hexasubstituted molecules. Examples are presented in Table 4.

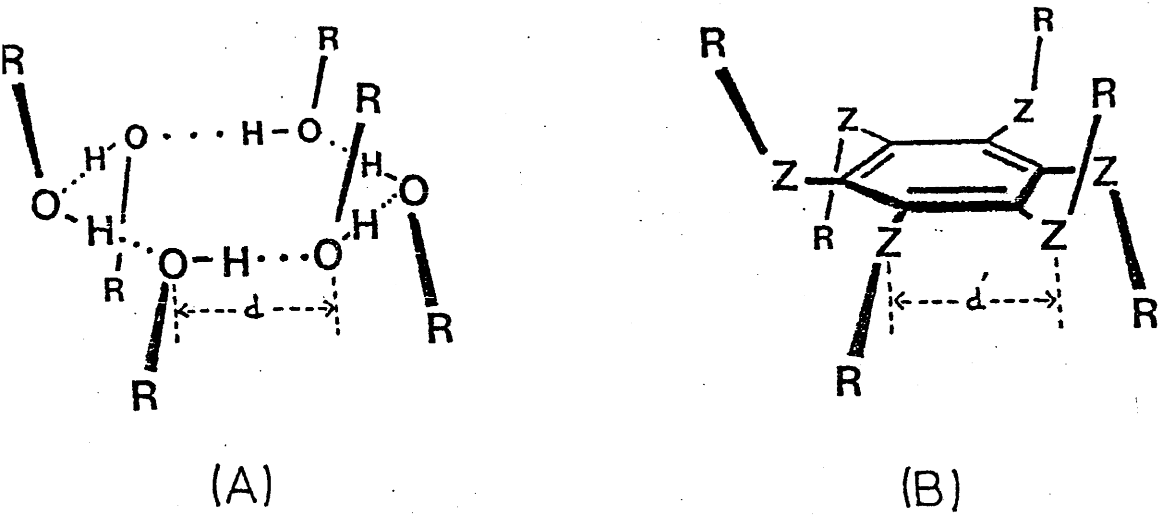
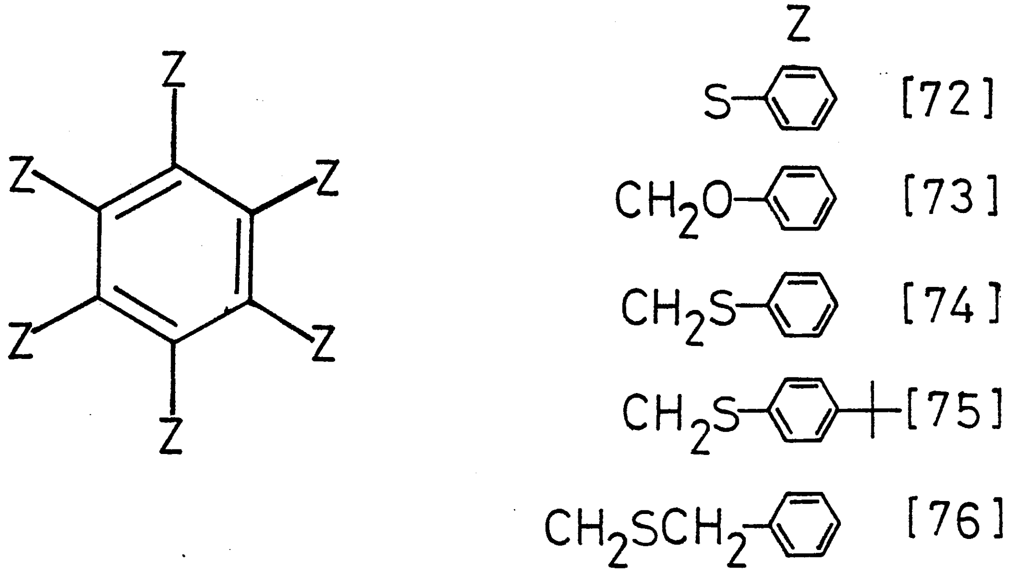


Figure 25 Comparison of the hexameric unit of hydrogen-bonded hydroxyl groups (A) and hexa-substituted benzenes (B).



[72]
[73]
[74]
[75]
[76]

Table 4

Representative Inclusion Compounds formed by hexahosts (72)-(76)

Host	Guest	Mole Ratio of host:guest
72	CCl_4	1:2
	CCl_3Br	1:2
73	toluene	1:2
74	toluene	1:1
75	cyclohexane	1:2
	toluene	1:2
	squalene	2:1
	hexamethyldisilane	2:1
76	cyclohexane	1:1
	acetone	1:2
	acetyl chloride	2:1

An X-ray structural analysis of the carbon tetrachloride adduct of hexaphenylthiobenzene (72) reveals that the crystals are trigonal with space group R$\bar{3}$, two molecules fitting into a three-dimensional cage i.e. a genuine clathrate structure.[141]

Guest selectivity[142] is found when a number of the hosts are recrystallised from an equimolar mixture of *ortho* and *para*-xylenes.

Whereas for hexakis (*p*-*tert* butylphenylthiomethyl) benzene (75) a guest composition of 95% *o*-xylene and 5% *p*-xylene is obtained, recrystallisation of hexakis (benzylthiomethyl) benzene (76) from the same xylene mixture gives an inclusion compound of guest composition 25% *o*-xylene and 75% *p*-xylene.

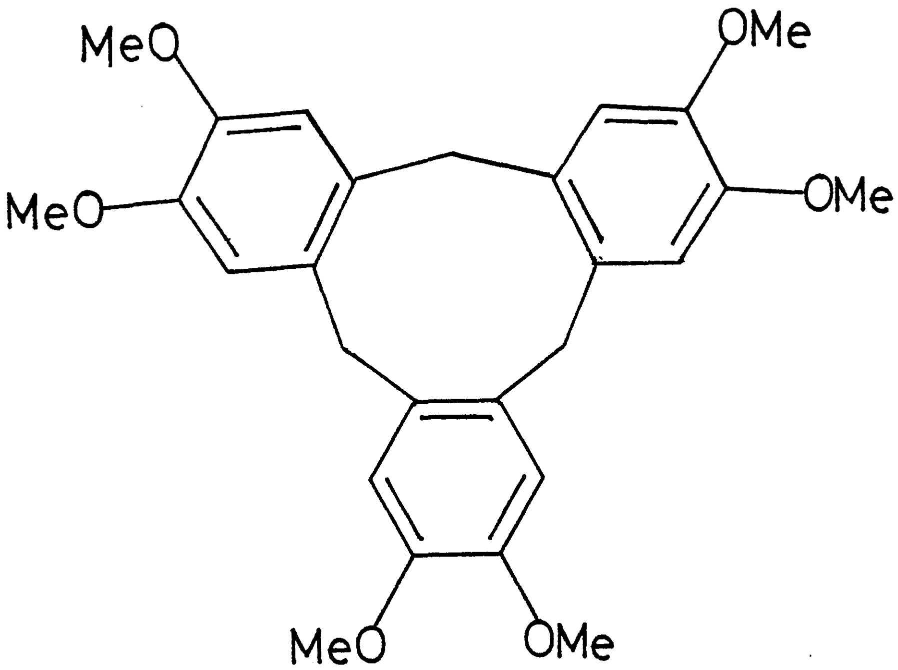
This reversal of selectivity found for (75) and (76) suggests that there is great scope for modifying the inclusion behaviour to produce a complete range of selectivities.

Chapter 3. Trigonal Symmetry

Although relationships between the various hosts may be made through the type of cavity found, there are few structural similarities between many of them. Several of the clathrate hosts are connected in that hydrogen-bonding is an intrinsic factor in their ability to form inclusion compounds. A structural relationship between 2-methyl naphthalene (43), deoxycholic acid (30), and urea (5), is absent, yet they all form channel-type adducts.

One feature, however, which appears frequently in both the molecular structure and crystal structure of inclusion compounds in general, is trigonal symmetry.

Among hosts already mentioned, a number possess trigonal symmetry including perhydrotriphenylene (31), triphenyl methane (32), tri-o-thymotide (3) and cyclotriphosphazenes (37).



[77]

Other molecules not possessing trigonal symmetry themselves crystallise in trigonal space-groups or display a high symmetry in their crystal structure, for example, hydroquinone (45) and Dianin's Compound (4).

Hexaphenylthiobenzene (72) exists in a conformation containing a three-fold axis of symmetry in its CCl_4 clathrate [141] (Figure 26).

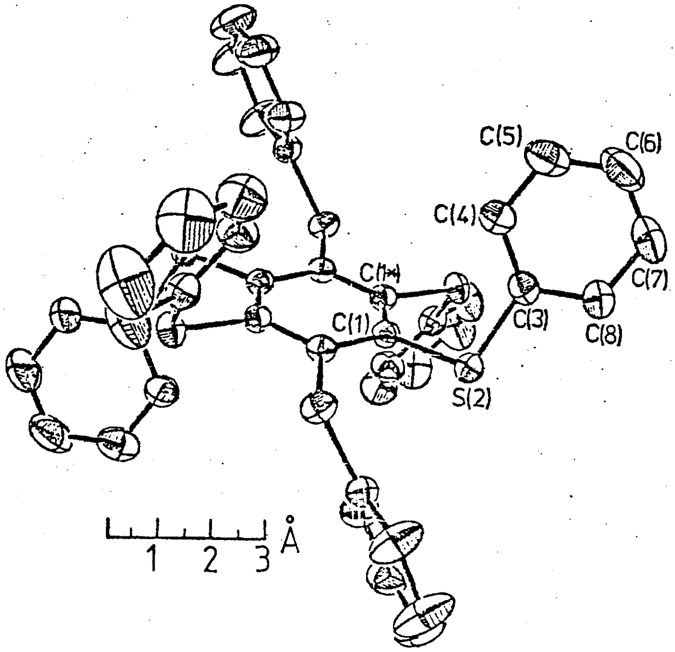
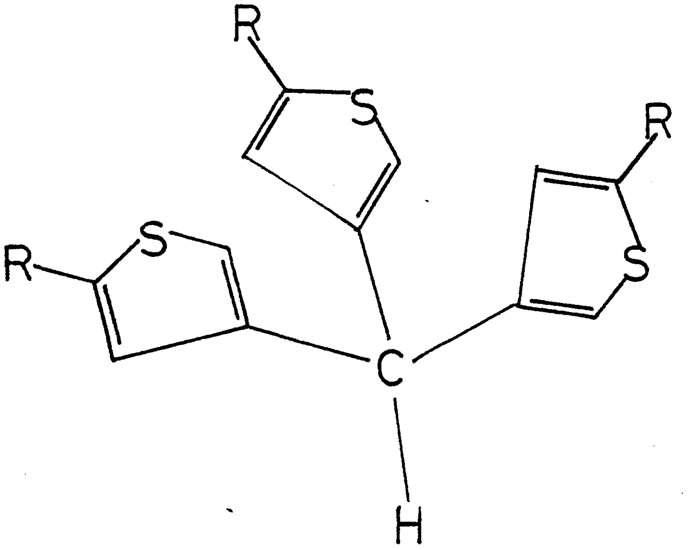


Figure 26 An ORTEP drawing showing a general view of the molecular structure of host molecule (72) in the crystal of the CCl_4 clathrate. (The hydrogen atoms are not shown.)

Cycloveratril (77) is an inclusion host [143] but the nature of the cavity is yet to be established. It exists in a crown conformation with C_{3v} symmetry.

Recently, a new host was discovered, apparently by chance, incorporating trigonal symmetry. Tris-(5-acetyl-3-thienyl) methane (78), prepared by the action of 2-acetylthiophene on chloroform in the presence of aluminium chloride, forms inclusion compounds with a very wide range of guests, for example, benzene, ethanol, acetone, ethyl acetate,nitromethane and pyridine, with a 2:1 host to guest ratio in each case. [144] No solvents were found which did not form adducts; in all 38 guests were tried. The nature of the cavity has yet to be determined.



R

$\overset{\|}{\underset{O}{C}}$Me [78]

CO_2Me [79]

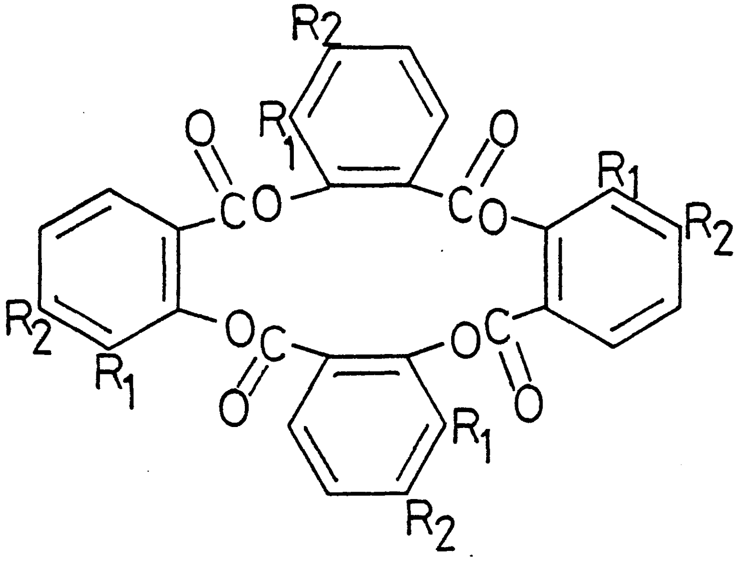
A number of analogues were prepared but only the tris-methyl ester (79), showed any inclusion behaviour.

On the basis of melting-point data, the author suggests that "three-legged" solvents are less favoured. The mesitylene adduct has a melting-point of 77-78°C compared to toluene, 109-110°C, m-xylene 97-98°C, p-xylene, 112-113°C and ethyl benzene 106-110°C.

Selective inclusion behaviour is also exhibited by (78), from an equimolar mixture of ortho and meta-xylene a guest composition of ca 5:1 is found in favour of the ortho isomer.

Tri-o-thymotide (3), is a rare example, in that it can crystallise in a different form to produce either a channel-type cavity or a cage. The length of the prospective guest usually decides which mode is adopted.[145] For molecules longer than 9.5Å, channel adducts are observed, but smaller guests are incorporated within a clathrate cage. Some guests on the borderline may crystallise in either form.

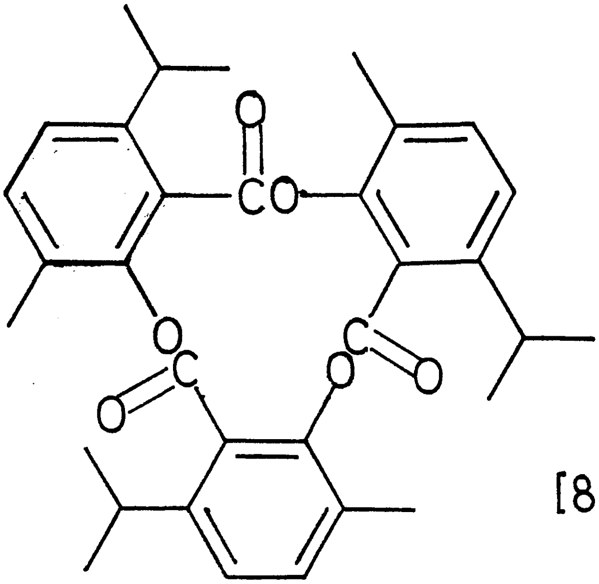
A large number of tri-o-thymotide analogues have been prepared and have been found to include solvents, but trigonal symmetry is not a necessary feature. Two examples, tetrasalicylide (80)[146] and tetra-o-cresotide (81)[147] have been known since the last century. Use of these hosts as chloroform purifying agent has been suggested on the basis of their selectivity for it as a guest. The tetra-m-cresotide (82) has been synthesised and is reported to form a 1:1 adduct with benzene.[148]



$R_1=R_2=H$	(80)
$R_1=Me$, $R_2=H$	(81)
$R_1=H$, $R_2=Me$	(82)

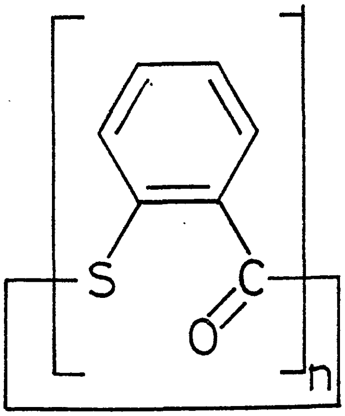
The corresponding di- and tri-salicylides[149] and o-cresotides[150] did not form inclusion compounds.

The closely related tri-o-carvacrotide (83) in which the methyl and isopropyl groups are in the reverse positions to that found in tri-o-thymotide has been studied but no complexes have been reported.[151]

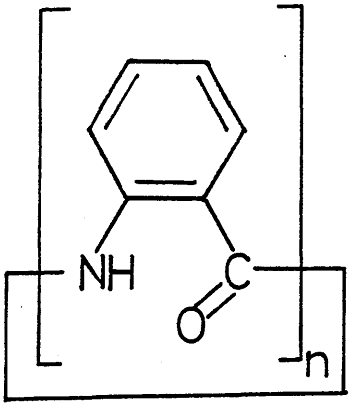


[83]

Sulphur and nitrogen analogues of the simple salicylides are known. A complete reversal of the behaviour found for the oxygen system is observed. The dimer (84) and trimer (85) both include benzene but the tetramer (86) does not.[152] Contrastingly the di- and tri-anthranilides (87) and (89) failed to form adducts.[153, 154]



n=2 (84)
n=3 (85)
n=4 (86)



n=2 (87)
n=3 (88)

For tri-o-thymotide, two conformations are found in solution,[155] corresponding to the symmetrical propeller and helical conformations schematically shown below (Figure 27).

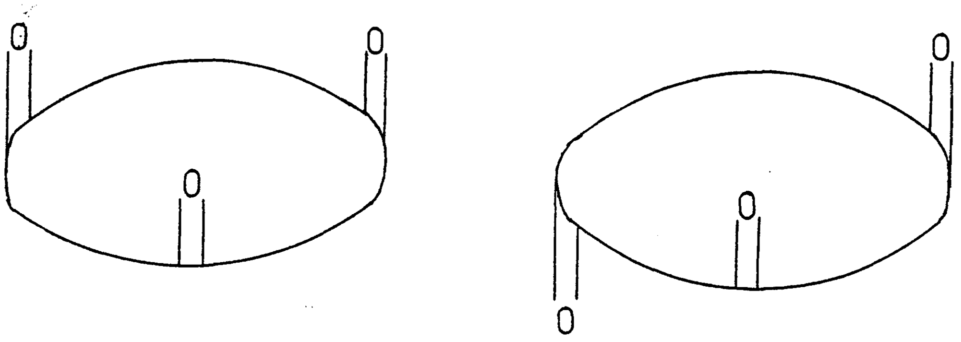
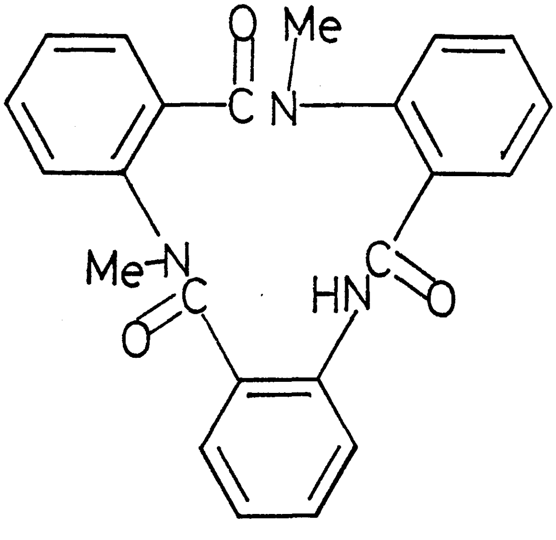


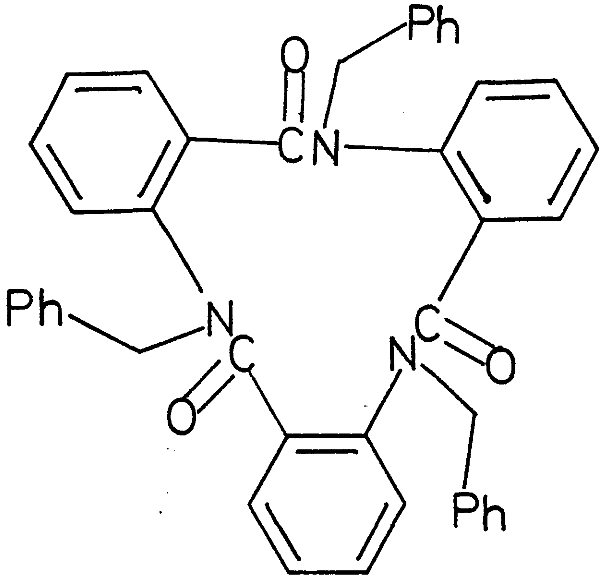
Figure 27 Solution conformations of tri-o-thymotide (3).

In both the cage and channel adducts of tri-o-thymotide, the propeller conformation is used.[156] This is not always true for its analogues, including N,N'-dimethyl-trianthranilide (89). The propeller conformation with pseudo-C_3 symmetry crystallises unsolvated, but the helical form with C_1 symmetry forms a 1:1 clathrate with ethanol.[157]



(89)

The trigonally-symmetric N,N',N''-tribenzyl trianthranilide (90), has also been reported to form a 1:1 complex with ethanol.



(90)

The cyclotriphosphazenes are general hosts where trigonal symmetry is evident in both the molecular and crystal structures. It is interesting to note that cyclotetraphosphazenes do not form inclusion compounds.[158]

Chapter 4. Chirality in Inclusion

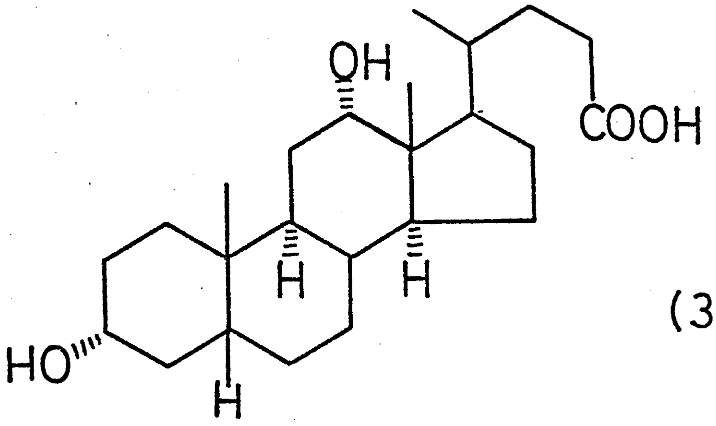
Much research has been directed towards the synthesis and properties of chiral inclusion compounds. There are two main reasons for the interest in this area.

(i) A greater understanding of biological systems is often gained by the study of models. Enzyme-substrate relationships for example involve many interactions which are of a host-guest nature, size and shape being of great importance. However, the essential requirement of enantiomeric selectivity is difficult to incorporate into most simple organic molecules. Inclusion complexes can provide excellent models for natural systems particularly if chiral discrimination can be incorporated into the host structure.

(ii) Separation procedures for optical isomers are limited. Unless diastereomers are formed, which can then be physically separated either through preferential crystallisation or by chromatographic means, there are very few methods through which the mirror-image forms may be isolated. Inclusion hosts capable of selectively binding or trapping one isomer in favour of the other would provide a method of separation which does not involve chemical modification of the chiral molecule. Once the resolved guest was released from the complex, the host could then be re-used for further separations.

Unlike synthetic materials, most naturally occurring compounds tend to exist in only one configuration and are an excellent source of chiral molecules.

The bile acid, desoxycholic acid (30) is an inclusion host found in one configuration and is optically active.



(30)

Of the other bile acids only apocholic acid (8, 14-dehydro-desoxycholic acid) shares the inclusion behaviour of (30).[159] Formation of the complexes is straightforward, the host and prospective guest being dissolved together in hot alcohol and allowed to cool slowly to crystallise the inclusion compound or "choleic acid".

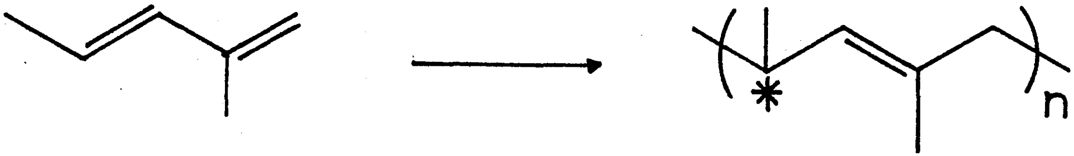
The formation of choleic acids has been used for the stabilisation of easily oxidised materials. Complexes of vitamins K_1 and K_2 are not only stable against oxidation, but also against chemical attack.[160] The vitamin adducts have been tested for activity which is found to be equal to that of the free vitamin, but having a greater stability. Many complexes of biologically active compounds have been prepared and tested, the earliest examples being the use of the camphor inclusion compounds of desoxycholic acid ("codechol") and apocholic acid ("camphochol").[161] A question mark over the usage of these pharmaceutical complexes, is the lack of information regarding the bioavailability of the drug, which is dependent upon breakdown of the adduct and where this takes place in the living system. Oral administration of a suspension of a salicyclic acid complex of desoxycholic acid led to a retardation in the excretion of the acid, compared to uptake as a solution, this due presumably to the stability of the choleic acid.[162]

It is expected that the choleic acids are stable at the very acidic gastric pH but would become increasingly unstable as its environment became more basic. Release of the guest would therefore be pH dependent.

The channel complexes of desoxycholic acid have been used for inclusion polymerisation. For example, 2,3-dichlorobutadiene forms a reasonably stable adduct with (30). γ-irradiation of the included monomer yields polymeric material of dominantly 1,4-<u>trans</u>-configuration.[163] Similar behaviour has been observed for other disubstituted butadienes.

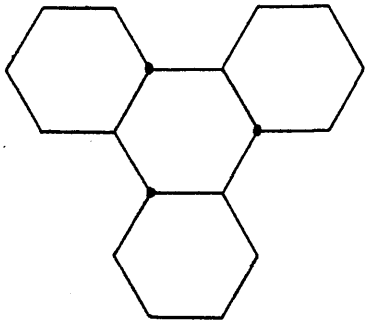
The polymerisation of prochiral monomers leads to the formation of optically active polymers. <u>Cis</u>-1,4-pentadiene is polymerised within the asymmetric channel to give a product whose specific rotation is -21°($\alpha_D$in toluene),[164] whereas <u>trans</u>-2-methyl penta-1,3-diene (91) affords a polymer of a much higher specific rotation.[165]

The degree of chirality may be dependent upon how tightly the host structure fits around the guest.



(91)

The first example of chiral inclusion polymerisation was carried out in the channels of resolved (*trans*-*anti*-*trans*-*anti*-*trans*) perhydrotriphenylene (PHTP) (31). The molecule does not possess a plane of symmetry, nor centre of inversion or improper axis and hence can exist in two enantiomeric forms. For each of the two configurations one rigid conformation exists (Figure 28)



(31)

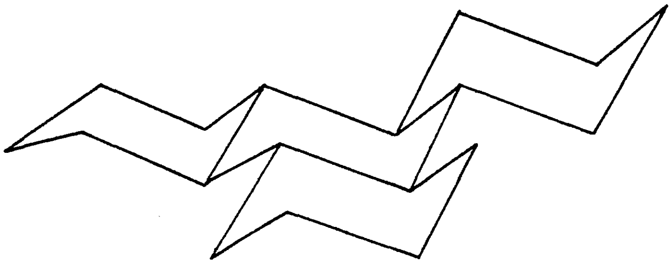


Figure 28 Conformation of *trans*-*anti*-*trans*-*anti*-*trans* perhydrotriphenylene (31).

Separation of the two enantiomers is however difficult. The lack of functionality and low reactivity of the compound thwarted attempts at resolution by various means. Farina and Audisio have succeeded in separating the two antipodes by the following method.[166] (Figure 29)

Treatment of PHTP with oxalyl chloride in carbon tetrachloride, initiated by benzoyl peroxide or UV light gives the acid chloride in low yield. Hydrolysis to the acid was followed by diastereomer formation using dehydroabietylamine. The salts were crystallised to constant optical rotation then the acid was regenerated. Resolved PHTP was then obtained by decarboxylation via the _tert_-butyl perester.

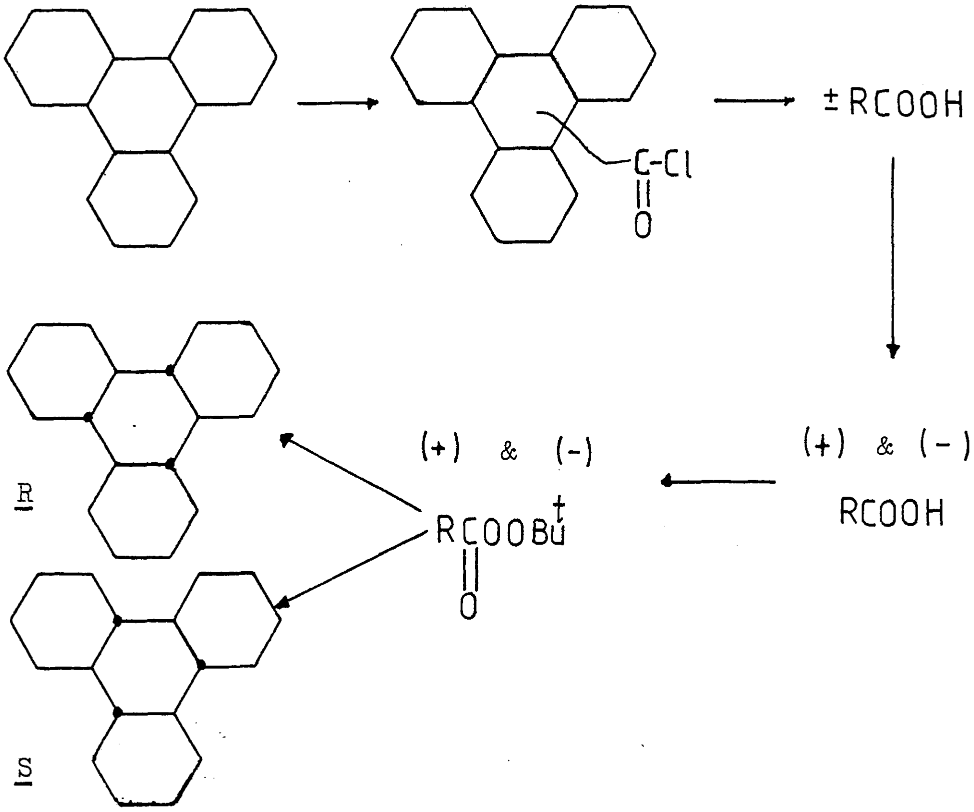


Figure 29 Procedure for the resolution of perhydrotriphenylene.

Optically active PHTP forms inclusion compounds, the size of the unit cell being the same as for racemic material, the space-groups are different, however, being $\underline{P}6_3$ and $\underline{P}6_3/\underline{m}$ respectively.

The polymerisation of trans-1,3-pentadiene was carried out in the presence of $\underline{R}(-)$-PHTP, but without prior formation of the inclusion compound.[167] The product was obtained as the polymer inclusion compound, which on release from the host was found to be of high chemical and steric purity though of low optical rotation.

The cyclodextrins are a series which show remarkable inclusion properties both in the solid state as channel inclusion compounds and as complexing agents in solution. They are large rings made up of 6, 7 or 8 D(+)-glucopyranose units, linked 1,4 to give respectively α, β and γ-cyclodextrin (Figure 30). Derived from natural materials they are optically active.

The complexes differ from most hosts in that the inclusion is due to a natural hole in the centre of the torus of sugar units, and are called unimolecular inclusion compounds because each guest molecule is bound by an individual cyclodextrin unit.

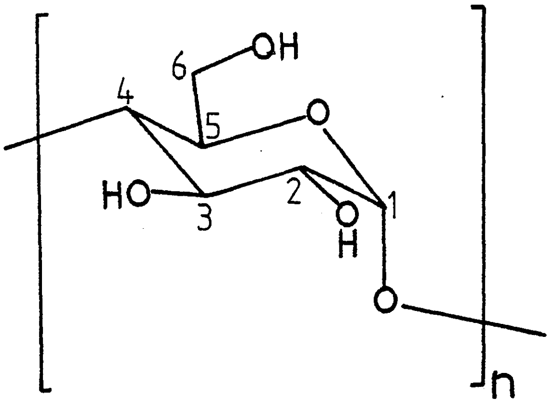


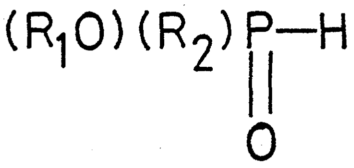
Figure 30 The 1,4-linked glucopyranose unit in the cyclodextrins.

Work on the cyclodextrins comprises a significant percentage of the total research into inclusion phenomena and many processes and applications have been patented. Consequently, the subject has been reviewed extensively, including a recent book by Bender and Komiyama.[168] The following discussion will be concerned only with their special properties as chiral hosts.

The diastereomeric interactions between cyclodextrins and the two enantiomers of a racemic guest would lead to an excess of that isomer which gave the most stable adduct being included. The difference in the binding energies is a measure of the degree of resolution obtainable.

Cramer and Dietsche [169] were the first to partially resolve some chiral compounds by this method, though the optical purity was low, ranging from 2% for the DL-menthyl ester of acetic acid to over 11% from cinnamic acid dibromide, via the crystalline complexes of β-cyclodextrin.

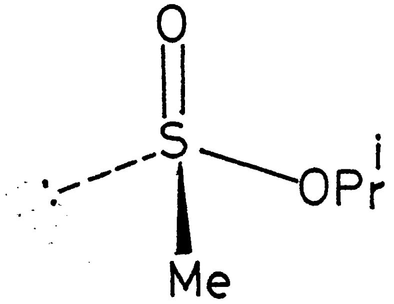
Other workers have applied the same method to the separation of enantiomers whose chirality is due to asymmetry at centres other than carbon. Benschop and van den Berg has described the resolution of a series of o-alkyl alkylphosphonates.[170]



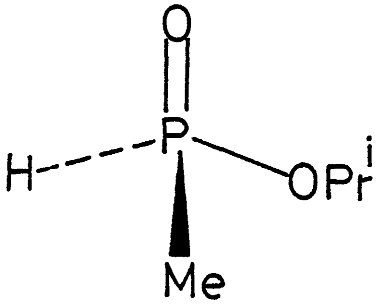
$$(R_1O)(R_2)\underset{\underset{O}{\|}}{P}-H$$

A maximum optical purity of 84% after three inclusion procedures was obtained when β-cyclodextrin was employed, R_1 = isopropyl, R_2 = CH_3.

Chiral sulphoxides were first examined in 1971 when optical purities of up to 14.5% were achieved.[171] Later work produced similar results for most alkyl benzyl sulphoxides.[172] However, an exceptional separation was obtained for isopropyl methane sulphinate (92) which is spatially very similar to the phosphonate which also gave the best separation. In both cases the S-isomer was preferentially included. This is probably due to the two molecules having the best fit within the cavity thereby being most sensitive to host-guest interactions.



S(-) (92)

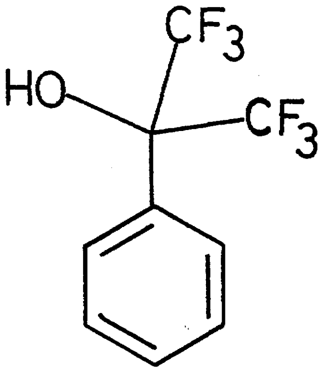


Microcalorimetric measurements have shown a small difference in the binding energy of the enantiomers of phenylalanine and α-methylbenzylamine. The results, for the solution complexes with α-cyclodextrin are in contrast to mandelic acid, amphetamine and phenyl trifluorcethanol for which no chiral discrimination was detected.[173]

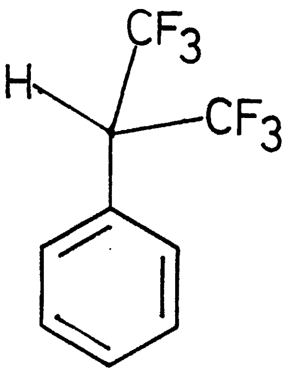
Since repeated recrystallisations from cyclodextrins produce only partial racemisations, their routine use by this method is limited. Similarly their solubility in water and aqueous alcohols prevents their extensive use as stationary phases for column chromatography. Crosslinking of the cyclodextrin units has solved the latter problem and these gels have been successfully used for the chromatographic separation of the enantiomers of mandelic acid esters.[174] For methyl mandelate, the cyclodextrin gel binds the L(+) isomer more strongly than the D(-) isomer. Initial fractions from the column were 100% D(-) isomer. This proves that a chiral discriminatory effect is present in solution for mandalates though magnification through multiple binding procedures is required for it to be observed. Separations by crystallisation procedures also involves lattice energies etc. which accounts for different results obtained in solution against those in the solid state.

Cyclodextrins have been employed as shift reagents in nuclear magnetic resonance studies. Addition of an excess amount of α-cyclodextrin to para-cymene in D_2O shows splitting of the aromatic signals in the ^1H n.m.r. spectrum.[175] The spectrum of adamantane has been expanded by the same method.

The chirality of the cavity has found application in this area for producing chemical shifts in the ^{19}F nmr spectrum of prochiral trifluoromethyl groups.[176]



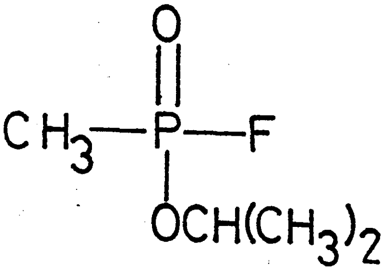
(93a)



(93b)

The normally single line for the $-CF_3$ groups in the proton noise-decoupled spectrum of (93a) shows marked splitting on addition of β-cyclodextrin. Similar behaviour is found for (93b), which is particularly significant as it lacks any functionality that might allow conventional shift reagents to be used.

Lastly, but probably of greatest importance, are those reactions which are catalysed in the prescence of cyclodextrins, in which one enantiomer reacts faster than the other. For example, the cleavage of chiral organophosphates is accelerated by α-cyclodextrin.[177] However, the more tightly bound S(+)-isomer of the fluoro compound (94) is less accelerated than the R(-)-isomer which does not form such a stable complex. It has been suggested that stereospecific interactions between the hydroxyl groups of the cyclodextrin ring and the chiral guests are responsible for the behaviour.



$CH_3-P(=O)(F)-OCH(CH_3)_2$

(94)

The reaction of hydrogen cyanide with <u>ortho</u>- or <u>para</u>-chlorobenzaldehyde normally would give racemic products under no external influence. In the prescence of α-cyclodextrin, optically active products are obtained (Figure 31), the reaction presumably being preceded by complex formation between the chlorobenzaldehyde and cyclodextrin.[178, 179]

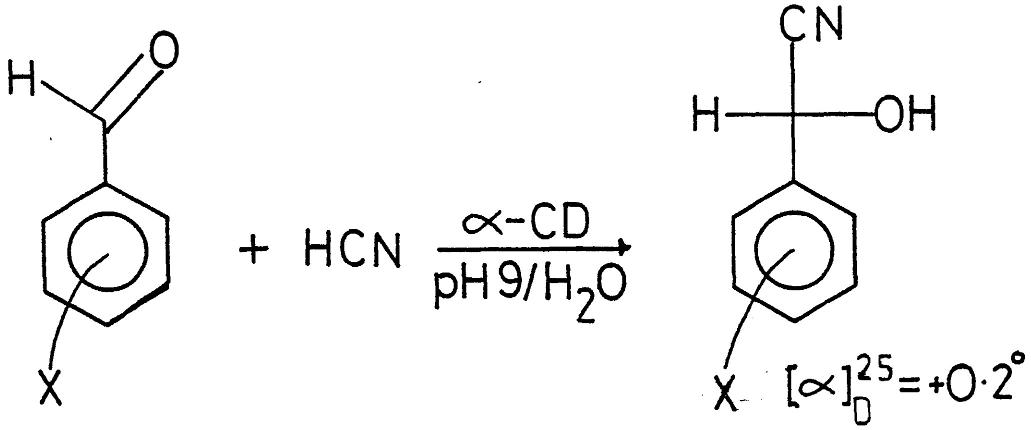
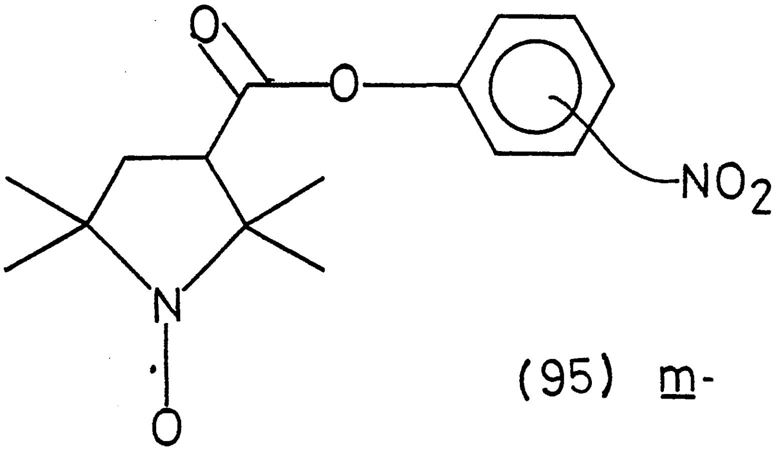


Figure 31 Optically-active products produced by cyclodextrin catalysis.

This behaviour has resulted in the application of cyclodextrins as enzyme models. The enantiomeric preference shown by α-cyclodetrin in the acylation step of the hydrolysis of 3-carboxy-2,2,5,5-tetra-methyl pyrrolidin-1-oxy-m-nitrophenyl ester (95), is comparable to that shown by α-chymotrypsin for the corresponding p-nitrophenyl ester (96). [180]

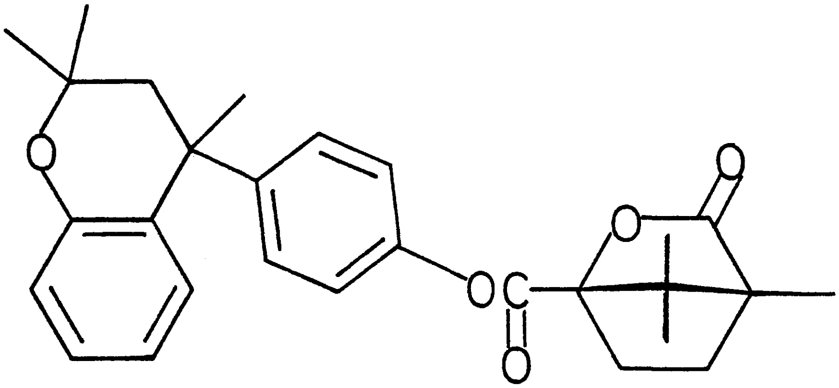


(95) m-

(96) p-

The versatile inclusion host, Dianin's Compound (4) is asymmetric at C-4, but the compound is synthesised as a racemate It had been proposed that resolution would provide an optically active host, potentially useful as a resolving agent. [181]

Resolved material was prepared by Brienne and Jacques via the camphanic acid ester (97). [182]

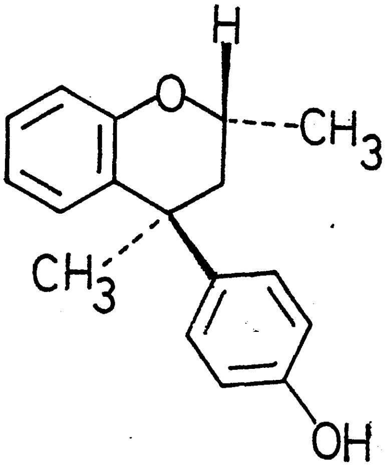


(97)

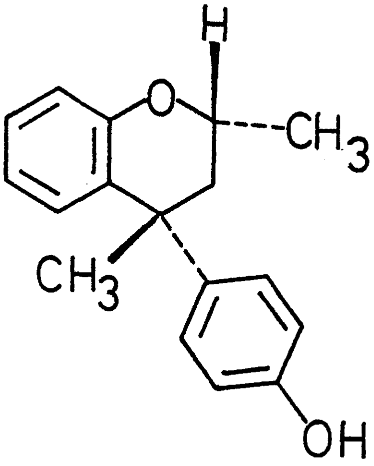
However the single enantiomer isolated, corresponding to S(–)-Dianin's Compound (4) failed to include either chiral or achiral guests. The cage in adducts of racemic Dianin's Compound is centrosymmetric with three molecules of one configuration and three of the opposite configuration, one set up and the other down, conforming with the $\bar{3}$ symmetry of the crystal structure. Unless both isomers are present inclusion will not take place.

Since the symmetry conditions prohibited the predicted behaviour, a different approach was adopted by Collet and Jacques which led to the preparation of "quasi-racemic" clathrates related to Dianin's Compound. [183]

Compounds (98) and (99) were prepared by an original synthetic route which allowed the absolute configuration shown to be established at C-2, the compounds being epimeric at C-4.



(98)



(99)

Curiously (98) gave a 2:1 adduct when recrystallised from carbon tetrachloride but the structure is unlikely to be of the normal cage type of Dianin's Compound. (99) crystallised unsolvated from cyclohexane or carbon tetrachloride.

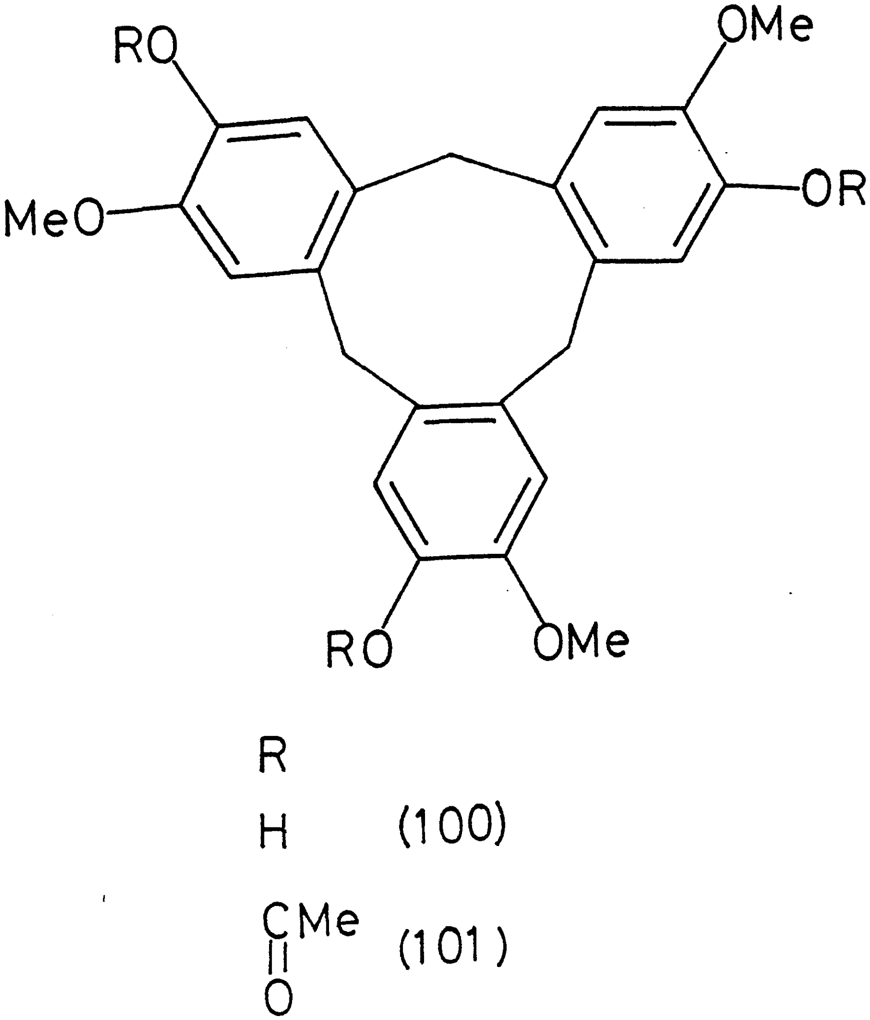
An equimolar mixture of (98) and (99) when recrystallised from carbon tetrachloride resulted in the formation of a clathrate with an overall host to guest ratio of 6:1 with the ratio of the two epimers being 1:1. Since both C-4 configurations were present the symmetry conditions are close to being upheld, but the resolution at C-2, although not preventing clathrate formation, introduces a chiral environment into the cage. These "quasi-racemic" clathrates were tested for chiral discrimination, but although recrystallisation from racemic ethyl-2-bromopropionate gave the 3:3:1 clathrate, less than 0.5% resolution was obtained.

Explanations for this lack of selectivity include disordering of the guest in the cage and the quasi-centrosymmetric shape of the guest itself.

The amine (52) and thiol (53) analogues of Dianin's Compound both undergo spontaneous resolution on recrystallisation from various solvents, [124] the latter only when unsolvated, single crystals being made up of one enantiomer only.

Cycloveratril (77), which exists in a crown conformation, does not undergo inversion up to 200°C in solution. Asymmetric analogues would therefore retain their optical integrity and perhaps yield chiral inclusion compounds.

Collet and Jacques prepared the interesting molecules (100) and (101), in optically active form.[184] Although optically stable, the compounds did not display any inclusion behaviour.



R

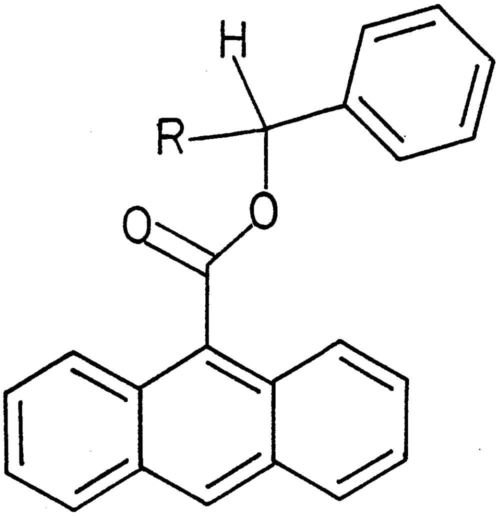
H (100)

$\mathrm{C(=O)Me}$ (101)

Clearly it is not sufficient merely to make chiral analogues of known achiral hosts and expect inclusion behaviour to be retained.

Aspects of symmetry are critically important in the formation of inclusion compounds. The chirality may prevent the compound from crystallising in those space-groups which are associated with the formation of open structures.

As planned preparation of chiral hosts has met with failure, it is even more interesting that a chiral inclusion compound has recently been discovered by chance. In the course of studies on the packing modes of racemic and enantiomeric materials, resolved molecules 1-phenyl-propyl 9-anthroate (102) and 1-phenyl-butyl 9-anthroate (103) were found to include n-hexane with a 6:1 host to guest ratio. [185]



R	
Et	(102)
Pr^n	(103)

The n-hexane complex of the propyl derivative (102) crystallises in a hexagonal space group with the host molecules adopting a helical arrangement along the six fold axis. The dimensions of the channels are similar to those of urea, and they have been suggested as a matrix for performing asymmetric synthesis, or for the resolution of chiral paraffins, though no work has been done in this area.

Tri-o-thymotide (3), when recrystallised in unsolvated form was found to be racemic.[186] Formation of adducts with chloroform, hexane or benzene produced single crystals, which on dissolving gave solutions showing optical activity, racemisation taking place rapidly however. Powell suggested that the chirality was due to hindrance to free rotation around the single bonds of the twelve-membered ring. The two enantiomorphic forms are related to each other as right- and left-handed three-bladed propellers. Powell achieved partial resolution of sec-butyl bromide using tri-o-thymotide.[187] Later, attempted resolution of bromochlorofluoromethane gave evidence of success but a lack of material prevented proof of resolution from being obtained.[188]

All hosts, mentioned to date, which have been used for studies towards chiral inclusion have themselves been optically active. It is the asymmetry of the host molecule itself which is responsible for the chiral elements of the cavity.

Curiously, urea (5) a flat molecule possessing symmetry planes has also been investigated for its ability to resolve racemic mixtures.[189-192] The urea molecules in the adduct structure are connected by hydrogen bonds to form helices which make up the walls of the channel. Depending on whether the helix is right or left handed allows the hexagonal lattice to exist in two mirror-image forms.

Recrystallisation of urea from a racemate can result in four possible combinations, with each of the isomeric lattices capable of including either of the two guest enantiomers. One pair of interactions will be energetically more favourable than the other, though this in itself would not constitute a method of separation as each pair contains both isomeric guests. One member of the pair of more stable combinations may be artificially induced to crystallise preferentially, though in certain cases it happens spontaneously. Isolation of the adduct before crystallisation is complete would then yield an excess of one enantiomer of the guest in the channels with its antipode in relatively minor excess in the liquid phase. When a pseudo-racemic mixture is used, where one enantiomer is in excess before the recrystallisation procedure, then further resolution is induced. Other methods of inducing the preferential adduct formation include seeding with crystals of the appropriate lattice form, crystallisation on asymmetric surfaces, by using chiral co-solvents and by displacement of a guest from a lattice of known configuration.

Schlenk has examined this phenomenon in great detail and has achieved partial resolutions for a large number of racemic and pseudo-racemic guest mixtures. He has also determined the absolute configuration of the optically laevorotatory lattice to be that possessing a right-handed helix of urea molecules.

For a series of α-substituted carboxylic acids he has determined that, with a few exceptions, the equivalent antipodes are selectively included by the same lattice.

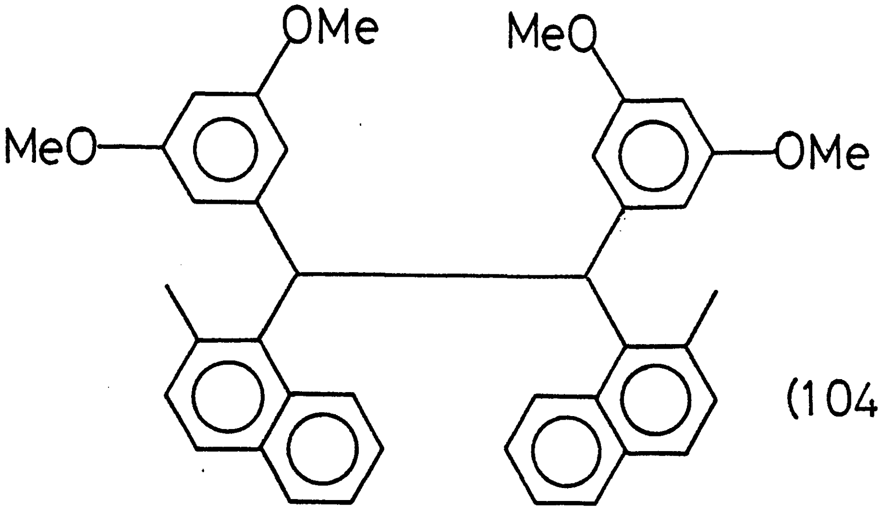
Two unusual applications of inclusion compounds to resolution procedures have been discovered.

Formation of complexes of the type $Ni(NCS)_2(\alpha\text{-arylalkylamine})_4.Ar$ is done quite simply by mixing a solution of nickel thiocynate with the stoichiometric amount of amine in the presence of the prospective aromatic guest, e.g. p-xylene.[193] The adduct crystallises and may be separated from the mother liquors. The same product is obtained when the diamine complex is reacted with two additional moles of amine. Normally the complexes will form as a racemate if both amine enantiomers are available, hence if the amine is rich in one isomer, it will be left behind in solution as indicated below.

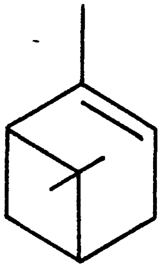
$$[Ni(NCS)_2dl]+ddl+Ar \rightleftharpoons [Ni(NCS)_2dldl].Ar+d$$

The procedure is only possible when partial resolution of the amine has already been carried out. Further optical enrichment is then obtained by this method.

The other procedure involves resolution of a racemic host by inclusion of a chiral guest. Recrystallisation of 1,2-bis(2-methyl-1-naphthyl)-1,2-bis(2,4,6-trimethoxyphenyl) ethane (104) from (+)α-pinene (105) gave a 1:1 inclusion compound.[194]



(104)



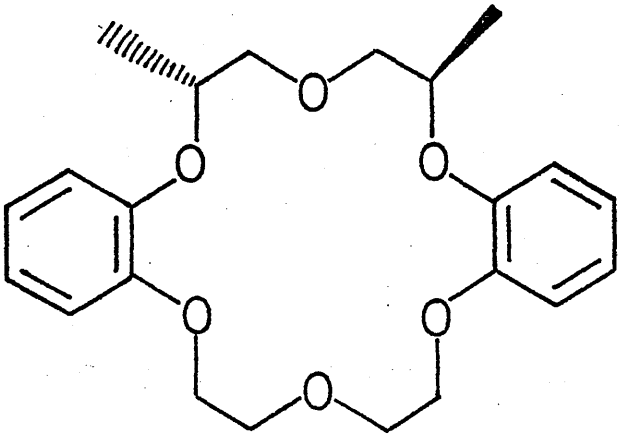
(105)

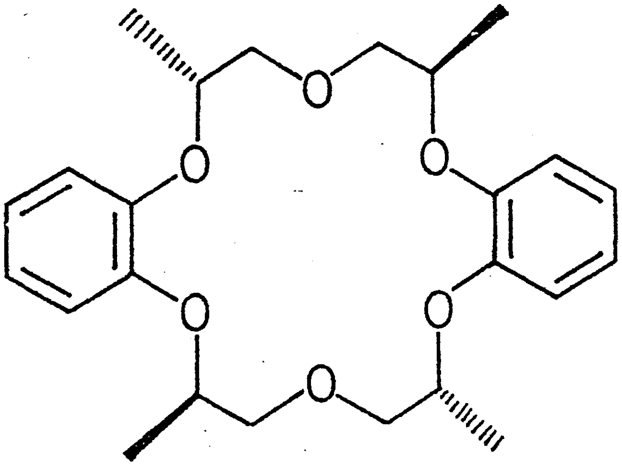
On removal of the pinene, a residual optical activity for the host was discovered. This result confirmed that the "ethane" derivative was of a dl configuration not meso. The degree of resolution was small and therefore not a viable method in this particular case. However, the principle could be applied to the resolution of other hosts, for example, perhydrotriphenylene or tri-o-thymotide.

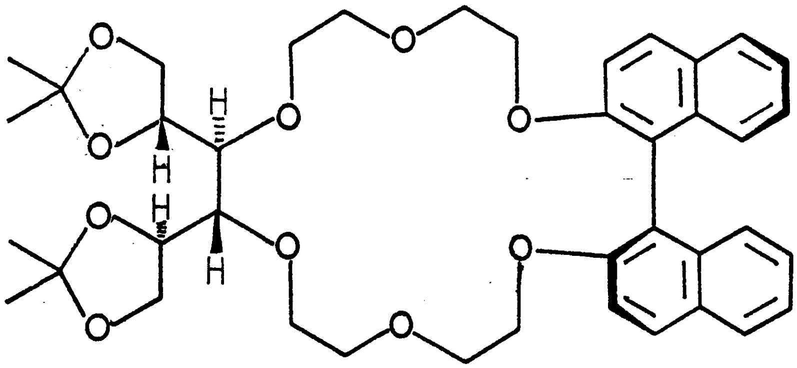
Unlike the cyclodextrins, whose chirality is a natural consequence of their preparation, the other main group of unimolecular inclusion hosts, the macrocyclic polyethers, or crown complexes, are completely synthetic and require any asymmetry to be specifically introduced.

Naturally occurring compounds have provided the chiral building blocks from which many of the crowns are derived. Starting from

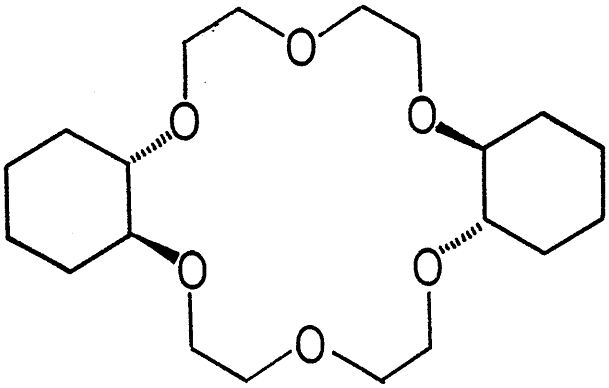
S-(+)- lactic acid the two chiral dibenzo-18-crown-6 molecules (106) and (107) have been prepared.[195] Other such molecules have been obtained using D-mannitol[196] (108), D-ω-ephedrine,[197] and S,S,-cyclohexane-1,2-diol (109)[198] as precursors. Inouye has recently published an improved synthesis of chiral crown ethers from L-tartaric acid (110).[199]


(106)

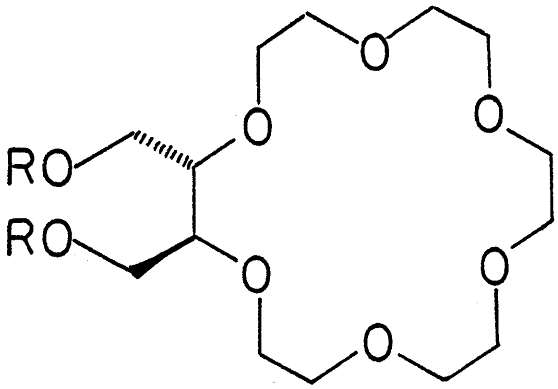

(107)



(108)



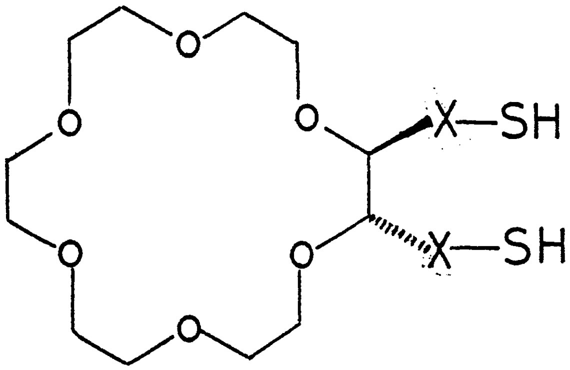
(109)



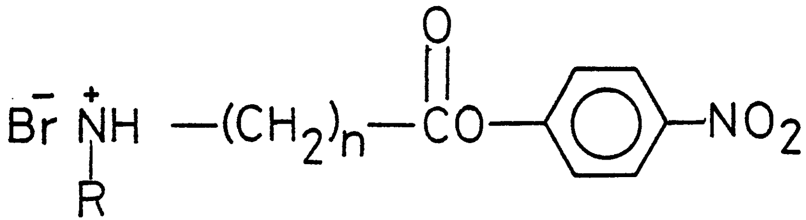
(110)

Koga has used appropriately functionalised chiral crown ether complexes (111) as enzyme models,[200] using the host cavity as a binding site for the substrate, and suitably positioned thiol groups as the catalytic site (Figure 32). The side-arms constitute regio-recognition sites, and may be systematically altered.

The models were designed to show regioselectivity in the reaction between the thiol containing crowns and complexed amino acid p-nitrophenyl ester salts (112).



(111)



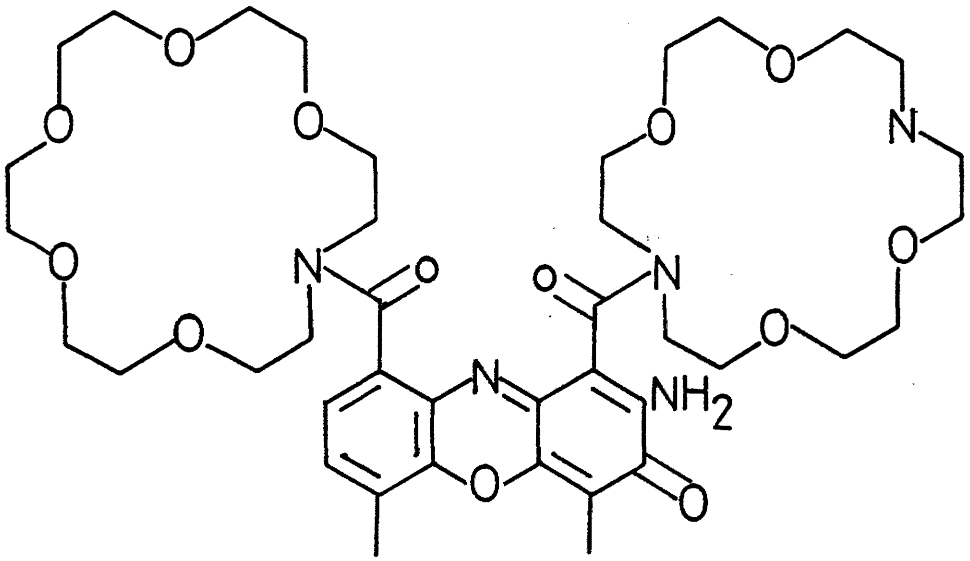
$\overset{-}{Br}\ \overset{+}{N}H(R){-}(CH_2)_n{-}\overset{O}{\overset{\|}{C}}O{-}C_6H_4{-}NO_2$

(112) a R=H
b R=Me

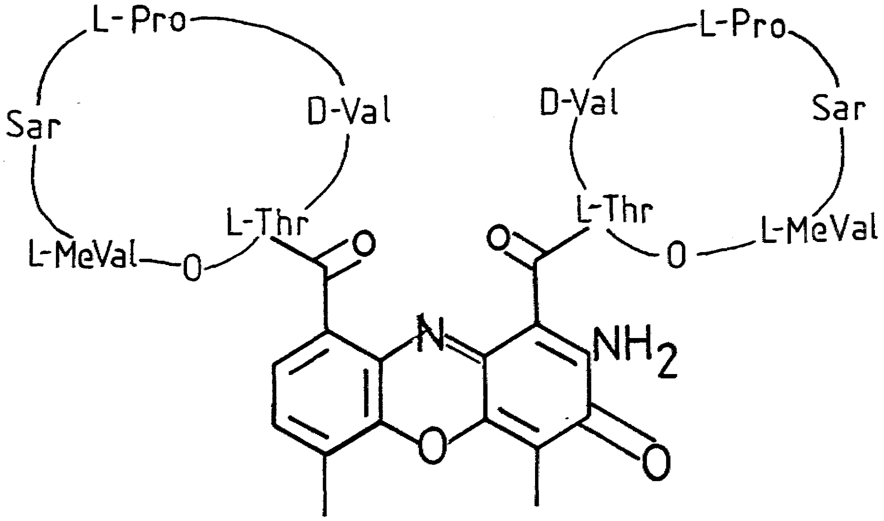
Figure 32 Thiol containing crown ethers as enzyme models.

Rate data for the release of p-nitrophenol was compared with their predictions using CPK molecular models. The rate for (112a) is much greater than for (112b) in the prescence of crown ether (111), due to less efficient complexation of the N-methyl salt compared to the unsubstituted molecule and therefore a lower concentration near the thiol groups. The feasibility of obtaining regioselectivity of attack was established for a series of crown ethers and amino ester salts.

Of interest are the cryptomycins (113),[201] prepared by Vogtle as analogues of the antibiotic actinomycins (114), in which the cyclopeptide groups are replaced by aza-crown ethers. It was hoped that the cryptomycins would perform similar functions to their naturally occurring counterparts including metal cation interactions.



(113)



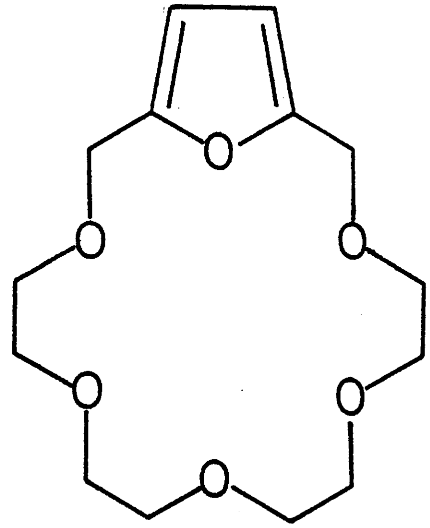
(114)

Promisingly cryptomycin-B does form orange crystalline complexes with alkali and alkaline earth metal salts. Elemental analysis of the sodium perchlorate complex shows that it is a monohydrate; the water if placed between the two rings would indicate a co-operative effect of the two aza-crown ether rings.

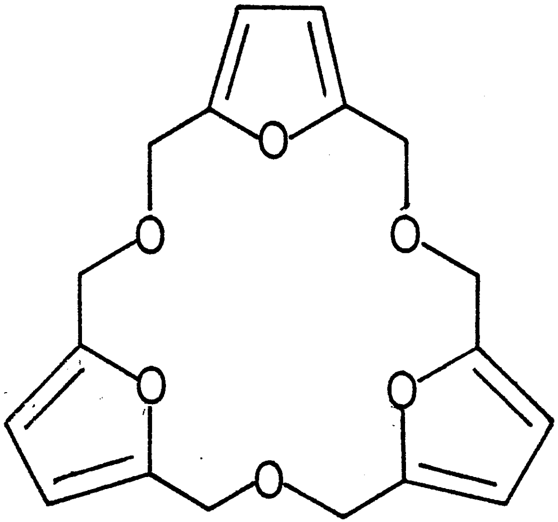
In tremendous contrast to the chance discoveries of inclusion behaviour, so frequently encountered, the programme of research carried out by Cram [1,44,202-214] stands out. Using the macrocyclic polyether as his basic framework and molecular models as a predictive tool, he has done much to remove the chance element from such work. He has designed an impressive range of host systems, incorporating many original structural units, capable of exhibiting high structural and chiral recognition towards guest molecules. A summary of his work provides an excellent means of presenting the advances made in the design of inclusion hosts.

In order to evaluate the complexing ability of one host in relation to another, Cram developed a scale [202] of binding potential based on the ability of the host to extract _tert_-butyl ammonium salts from water into chloroform. The scale is either quoted as the association constant, Ka, or as the free energy of association, ΔG^o.

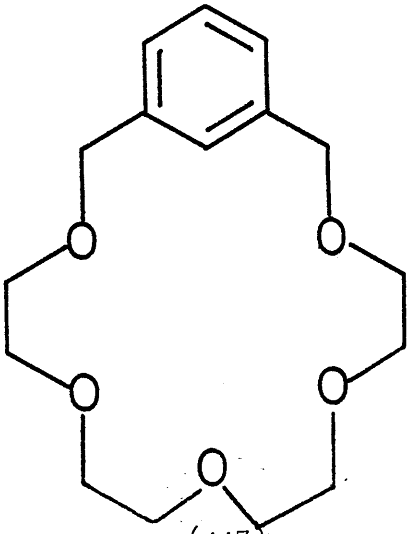
Examples of the new hosts he prepared and their corresponding association constants are illustrated overleaf (Figure 33).



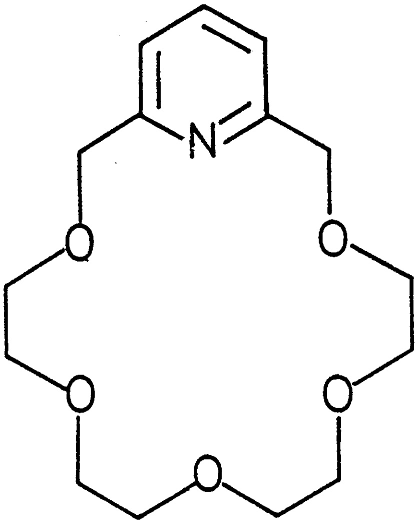
(115)
48,000



(116)
310



(117)
1,500



(118)
1,400,000

Figure 33 Crowns, prepared by Cram, possessing original structural units.

Among the new units he introduced into the macrocyclic ring were the furanyl (115) and (116), 1,3-xylyl (117) and pyridyl (118) moieties. The mono-pyridyl crown ether (118) was the only member of the series to have an association constant greater than that of 18-crown-6 itself, possibly due to a stronger hydrogen bond between nitrogen and the guest, but unfavourable $\ddot{N}$-----N^+ interactions act against additional pyridine rings.

Association constants for hosts containing the 1,3-xylyl unit were sensitive to substitution in the 2'- and 5'-positions. Occupation of the remote 5'-position affects the electron density of the system while a substituent in the convergent 2' position may either sterically hinder complexation, or provide an extra binding site (Figure 34).

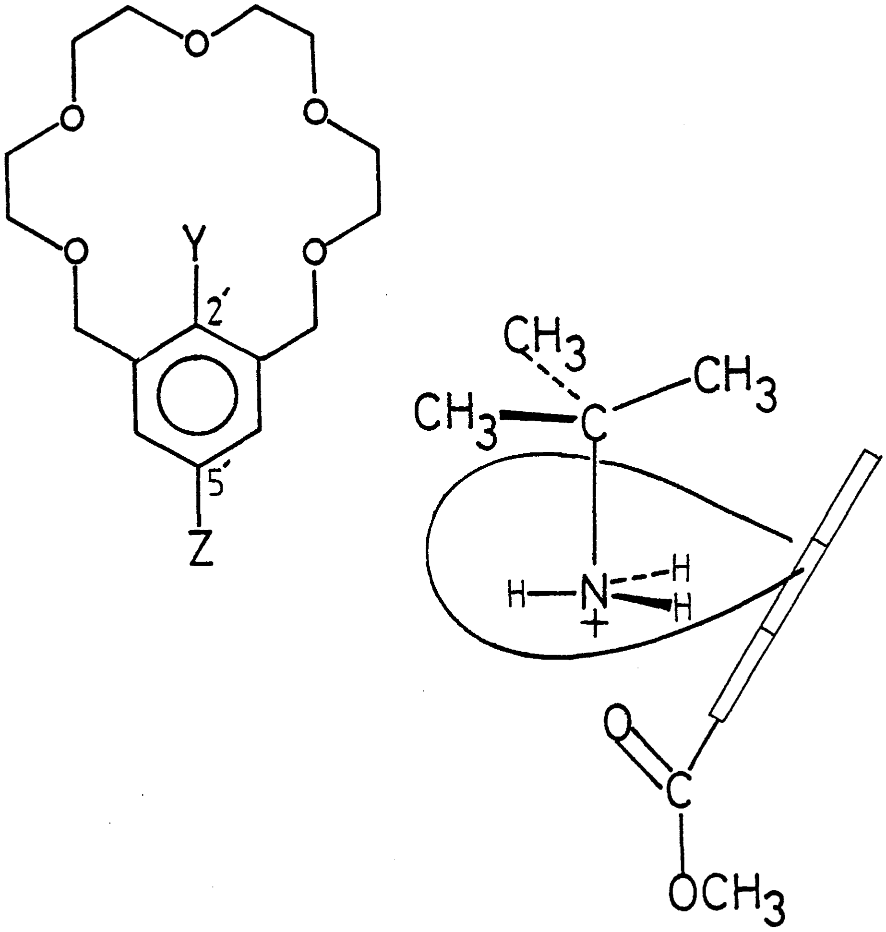


Figure 34 Extra binding site provided by 2'-substituent in crowns incorporating a 1,3-xylyl unit.

In order that a host may be able to show guest discrimination cavities must be designed in which steric barriers allow only specific molecules to form stable complexes. Systems must be devised such that parts of the molecules capable of imparting recognition properties converge upon the binding site. Cram, realising the importance of these concepts devised rigid units around which the polyether rings could be attached.

A number of hosts were prepared in which the rigid unit was formed by a substituted [2.2] paracyclophane. Of the 16 sites for substitution, eight are termed "semi-convergent" in one direction, with the other eight semi-convergent in the opposite direction (Figure 35).

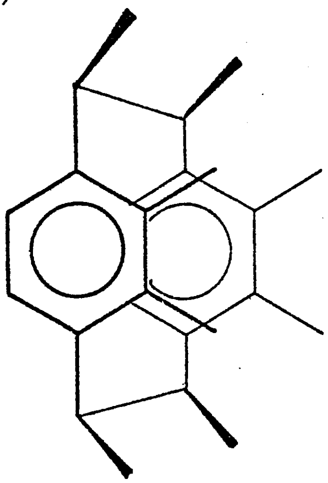
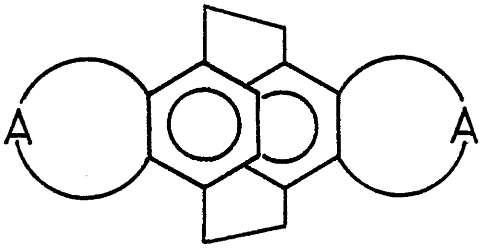


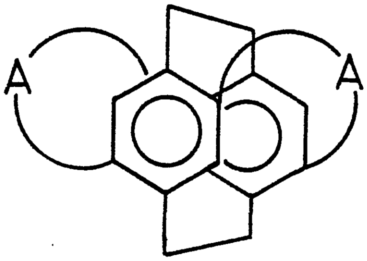
Figure 35 The [2.2] paracyclophane unit showing the eight semi-convergent sites for substitution.

This versatile unit provides the basis for more than one series of hosts, since different substitutions patterns are possible. The parent hosts (119), (120) and (121) were prepared and their complexing properties compared. Host (119) was found to be the most promising candidate for further investigation being the best binder, showing the highest structural recognition and being easiest to prepare. The molecule is also referred to as being sided as the two faces of the macrocyclic ring are now non-identical. (121) is also sided, but (120), although of the three the only one which is chiral, is non-sided.

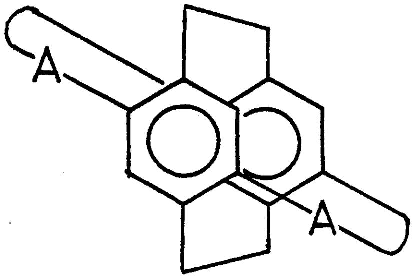
$A = O(CH_2CH_2O)_5$



(119)



(120)



(121)

Cram is investigating hosts of the type shown below with a view to obtaining chiral recognition of the enantiomers of racemates of general structure $LMSC\text{-}NH_3^{+}X^{-}$, where L, M and S are the large, medium and small substituents. The conformation of the predicted more stable complex (Figure 36) has the smallest substituent against the larger steric barrier, the medium substituent against the smaller barrier with the largest substituent having no steric barrier.

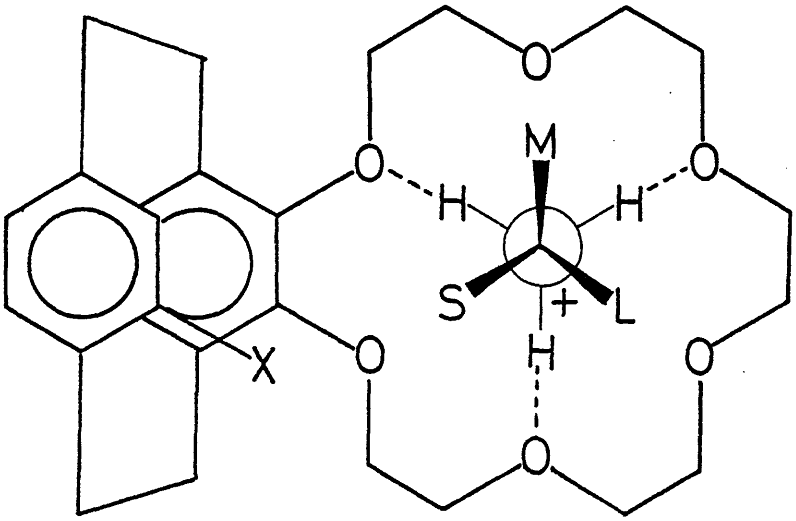
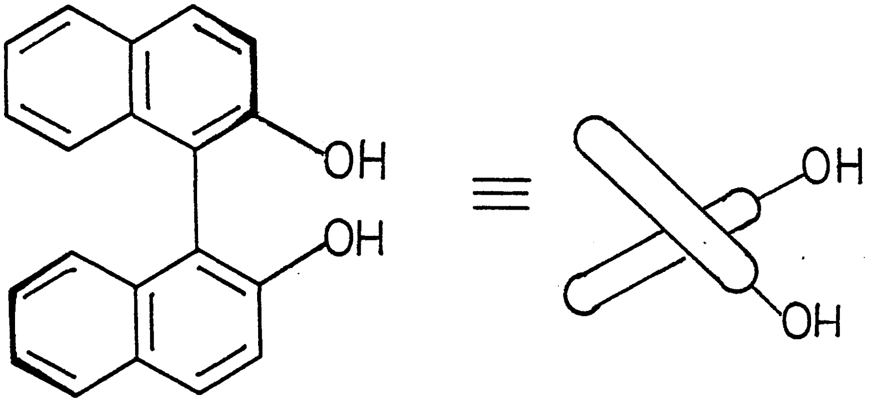


Figure 36. Model of paracyclophane host for exhibiting high chiral recognition towards LMSC-$NH_3^+X^-$ where L, M and S are the large, medium and small substituents.

By far the most studied hosts have been those possessing one or more 1,1'-dinaphthyl units with the macroring attached to the 2,2' positions via oxygen ether linkages. The unit, represented by a key starting material in the host syntheses, 2,2'-dihydroxy-1,1'-binaphthyl (122), possesses many useful structural properties.



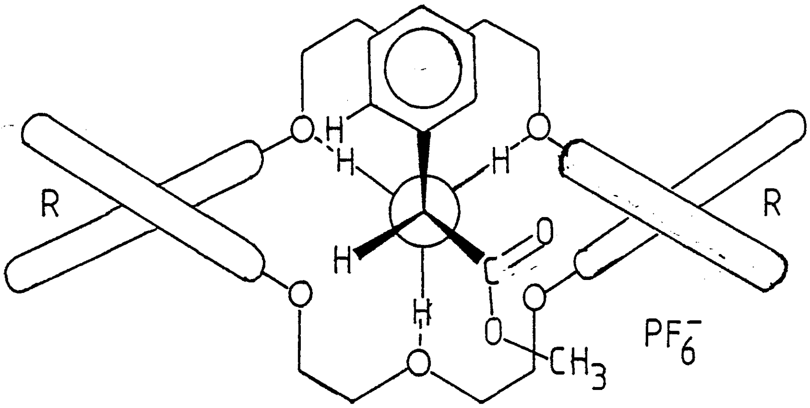
(122)

The binaphthyl unit is chiral, the naphthyl rings presenting potential chiral barriers towards appropriate guest molecules. The resolution of the building-block (122) may be carried out via the cinchonine salt, the absolute configurations of the enantiomers having been established by X-ray analysis. The units are optically stable under neutral conditions and under the reaction conditions required for the macrocycle synthesis. Many host molecules containing one, two or three binaphthyl units have been prepared in optically active form and tested for structural and chiral recognition.

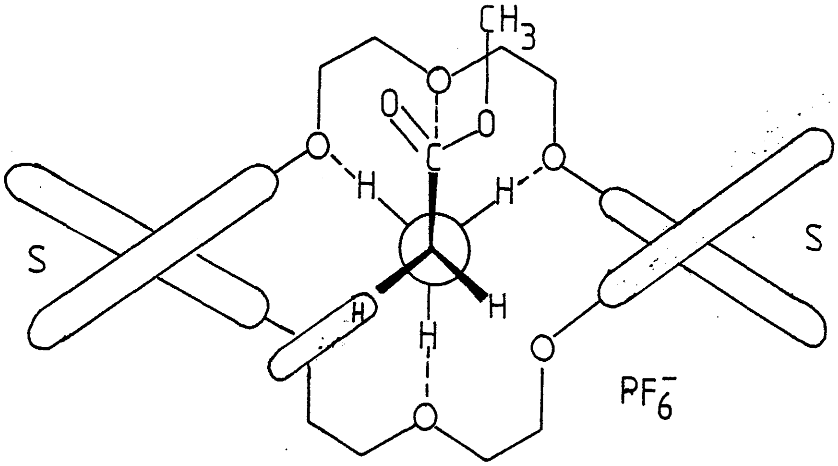
The gross properties of the macrocycles may be modified (e.g. solubility and spectroscopic properties) through substitution in the remote 6,6' positions. Substitution of the 3,3' positions will have direct effect upon the cavity itself, including extension of the chiral barrier.

Measurement of a host's ability to discriminate between enantiomers of a particular racemate is quantified through the enantiomer distribution constant (EDC), defined as the ratio D_A/D_B where D_A is the distribution constant between the organic layer and aqueous layer, after the extraction procedure, of the more complexed isomer, and D_B is that for the less complexed isomer.

The ability to predict which of the two mirror-image forms of the guest will be preferentially bound has been a very important aspect of Cram's work. For the bis-dinaphthyl host (123) two binding models for amino acid ester salts were employed (Figure 37), which could be distinguished from 'H nmr measurements.



three-point binding model

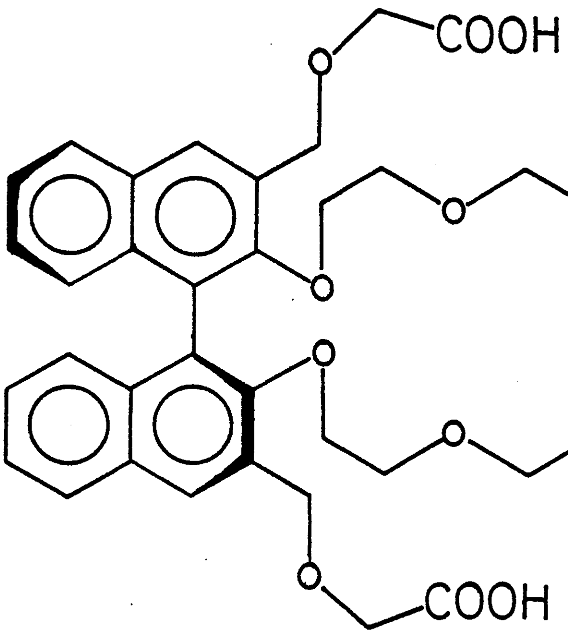


four-point binding model

Figure 37 The two binding models for host (123) with amino acid ester salts.

The enantiomer distribution constant (EDC) for (S,S)-(122) with the methyl ester of phenylglycine was 3. Extension of the chiral barrier by the addition of two methyl groups in the 3 and 3' positions of one of the binaphthyl units raised the EDC value to 12. For each case the three-point binding model appeared to be in operation.

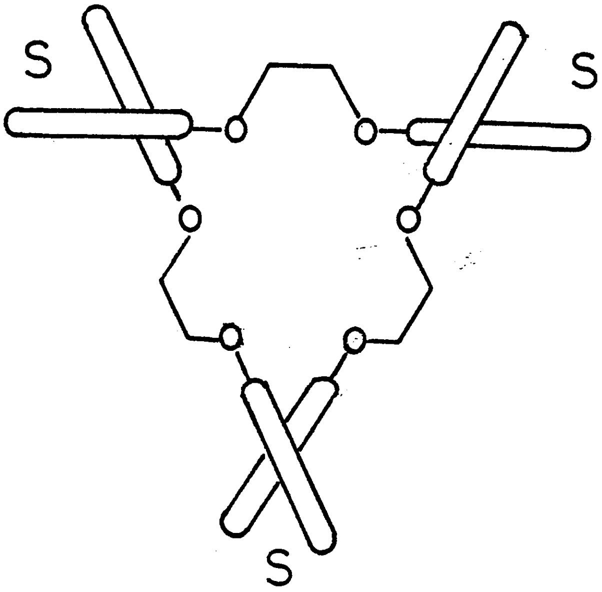
Molecular models suggested that the host (124) of the S-configuration would form a more stable complex with L-valine than D-valine, and this was confirmed in an extraction procedure.



(124)

However, the stability of that particular complex was applied in the opposite sense, that is, chiral discrimination displayed by L-valine towards racemic host (124). By careful manipulation of the organic and aqueous phases partially resolved host material having an excess of the (S)-configuration could be recovered.

Unlike the mono- and bis-dinaphthyl hosts, the macrocyclic structure (125), possessing D_3 symmetry did not complex any salts.



(125)

This was a disappointment to Cram who had had great expectations for these systems.

Total optical resolution by application of chiral crown ethers has been accomplished through chromatographic techniques, both liquid-liquid chromatography in which the mobile-phase is made up of optically pure hosts, and liquid-solid chromatography in which the stationary solid phase is a silica-gel bond host system.

Liquid-liquid chromatography using the bis-dinaphthyl host (126), with the enantiomeric amino ester salts in the water phase absorbed on a stationary solid phase, achieved almost base-line separation of racemic methyl phenylglycinate hexafluorophosphate salt (Figure 38). The more stable complex is eluted first, and agrees with that obtained for the traditional extraction procedure.

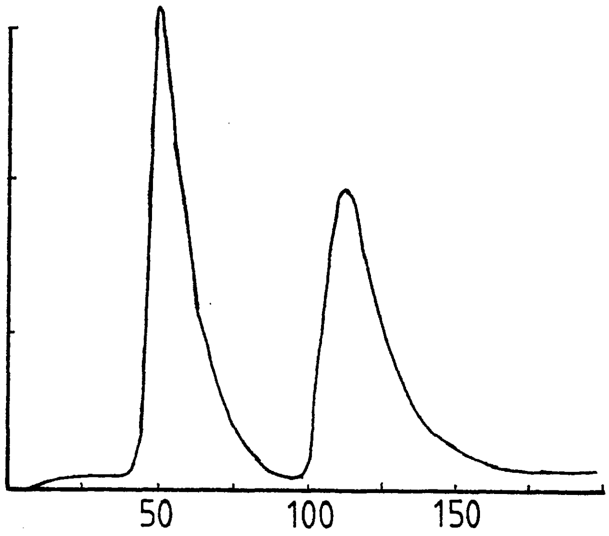
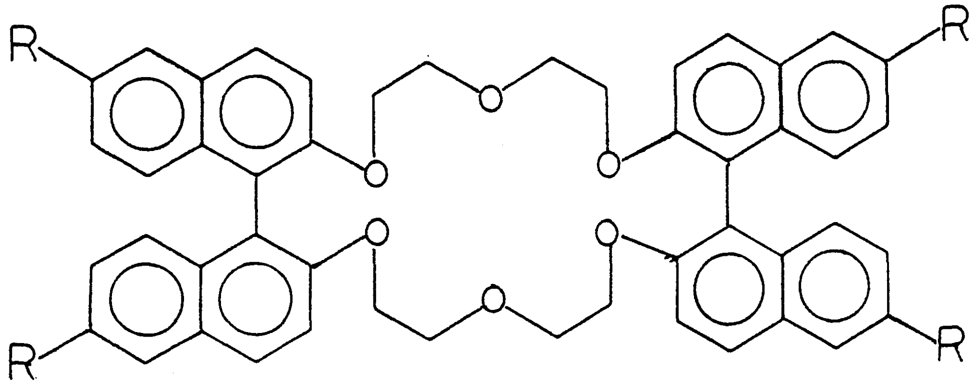


Figure 38 Optical resolution by chiral recognition in liquid-liquid chromatography employing (R,R)-(123).



R	
Br	(126)
Si–Cl	(127)

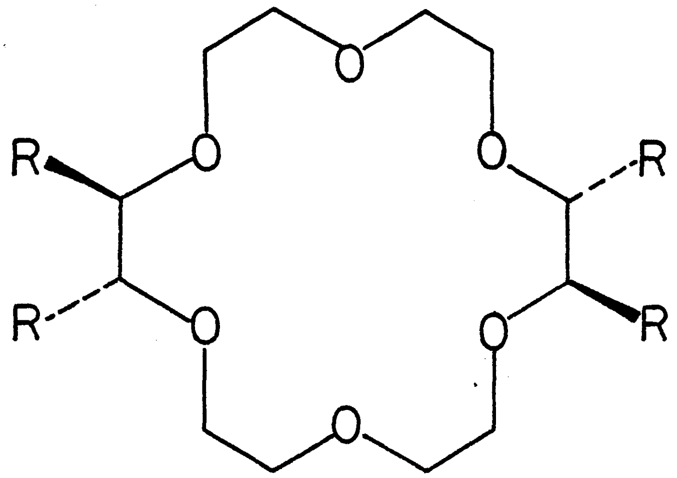
The second method involving liquid-solid chromatography utilised the tetrabromide (R,R)-(126), giving the tetrakis(dimethylchlorosilyl)-derivative (127) after lithiation and treatment with dichlorodimethyl silane. Treatment with silica gel, then dry methanol to convert the remaining chlorine substituents to methoxyl groups gave the host-bond gel.

The mobile phase consisted of solutions of primary amino-acid salts in organic solvents, with 18-crown-6 or alcohols as solubilisers. Base-line separation was achieved in a number of examples, the isomer forming the less stable complexes being eluted first. The effects of temperature, counterion, medium etc have all been carefully considered by Cram.

Most recently Cram has obtained chromatographic resolution by the covalent binding of hosts to polystyrene resins. Enantiomeric separations have been successfully carried out by this method for a series of amino acid and ester salts.

Apart from Cram, one of the leading researchers of chiral crown ethers has been Stoddart, who has developed a series of compounds whose asymmetry is provided by modified carbohydrates. L-threitol,[215] D-glucose,[216] D-galactose,[216] D-mannitol [205, 215, 115, 217] and L-iditol [218] have all been incorporated into macrocyclic polyether structures. The 18-crown-6 derivative incorporating a D-mannitol unit and a binaphthyl moiety has been formulated previously (108). It exhibited chiral recognition when complexing with racemic α-phenylethylamine salts under equilibrium conditions.

A chiral crown ether derived from two D-mannitol units, 1,2:1',2':5,6:5',6'-tetra-O-isopropylidene-3,3':4,4'-bis-O-oxydiethylenedi-D-mannitol (128) exhibits similar recognition properties with (*RS*)-α-phenylethylammonium hexafluorophosphate. Stoddart then synthesised the diastereomeric compound (129) from L-iditol to discover what effect the change in configuration at the four centres would have on the chiral recognition properties.



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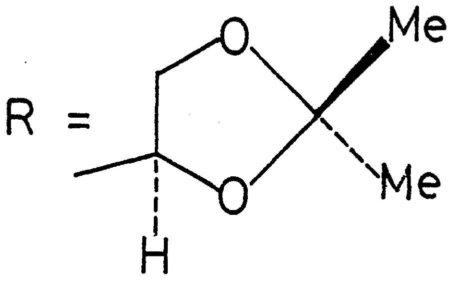
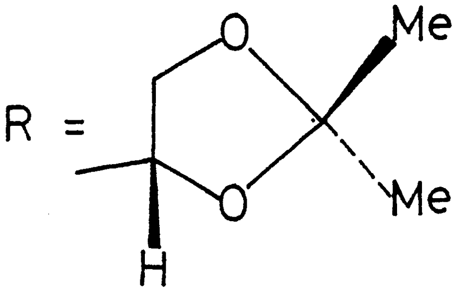


(129)



LL-(129) was found to form slightly stronger complexes with alkylammonium salts than DD-(128), but did not exhibit chiral recognition towards the HPF_6 salt of racemic α-phenylethylamine. However it did show enantiomeric differentiation with the perchlorate salts of (RS)-phenylglycine methyl ester. The D-mannitol based crown ether DD-(128) surprisingly did not show any chiral recognition towards this guest.

Both hosts showed a preference for the salt of the (R)- configuration in their respective cases. This has been accounted for by reference to the CPK space-filling model of the diastereomeric complexes, which indicate that the (S)-isomer, in the complex with LL-(129), experiences a greater steric barrier than the (R)-isomer (Figure 39).

Stoddart has reviewed his work to-date in a recent article.[219]

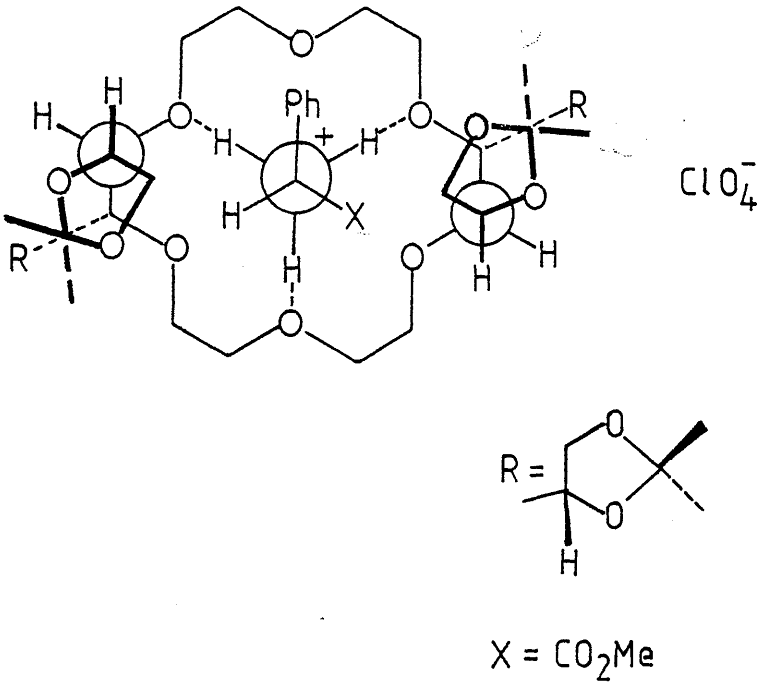


Figure 39 The complex formed by LL-(129) with the perchlorate salt of (R)-phenylglycine methyl ester.

From the chance observation of an unexpected side-product in 1967 to the total optical resolution of amino acid salts is a reflection of the explosion of interest surrounding the phenomenon of host-guest complexation.

Many workers, particularly Cram in the field of unimolecular hosts and MacNicol in multimolecular hosts, have succeeded in removing some of the "luck" element from the discovery of new systems which possess the remarkable property of molecular inclusion.

Superior separation procedures, asymmetric synthesis, working enzyme models, the control of drug release and the safe handling of toxic or reactive compounds are some of the advances made in the last ten years of inclusion chemistry, these areas also providing fertile ground for further research.

Results and Discussion

Chapter 5. Systematic modification of the hexahost skeleton

Opportunities for obtaining controlled changes in inclusion behaviour have, until recently, been hindered by the lack of suitable series of host compounds.

The series of inclusion hosts related to Dianin's Compound has been successfully studied. However, the family of compounds possessing a hexasubstituted benzene skeleton are more readily accessible, with an almost infinite range of modified systems available through alteration of the substituent.

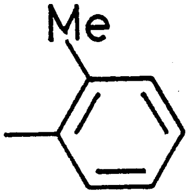
Adduct forming properties have been discovered for many of the simpler hexasubstituted benzenes, whose general structure may be represented as $C_6(Z\text{-}Ar)_6$, where variation in both Z, the "arm" or "leg" or chain, and Ar, the outer aromatic ring has produced new inclusion hosts.

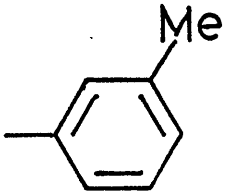
A more systematic study was undertaken to elucidate the effect of structural changes on inclusion behaviour. Alterations to the cavity geometry brought about by such changes are best studied by X-ray analysis, but owing to the time required for an extensive X-ray investigation of this type, effects were studied by comparison of the guests included and by selectivity experiments.

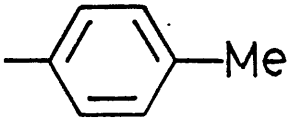
One of the most general hexahosts is hexakis (benzylthiomethyl) benzene (76), which forms adducts with a wide range of guests. A detailed study of the effect of substitution of the outer aromatic ring was carried out. Twelve analogues were prepared by reaction of the appropriate benzyl mercaptide with hexakis (bromomethyl)-benzene, $C_6(CH_2Br)_6$. The structures of these analogues are given in Figure 40.

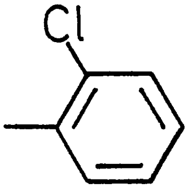
$C_6(CH_2SCH_2-Ar)_6$

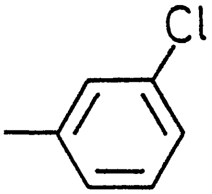
Ar

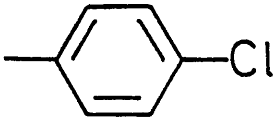

(130)


(131)

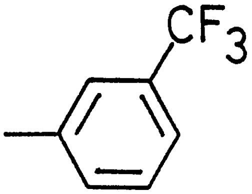

(132)

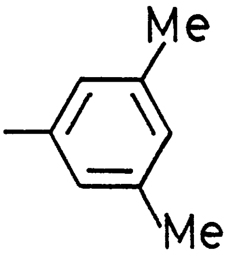

(133)

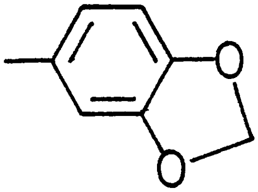

(134)

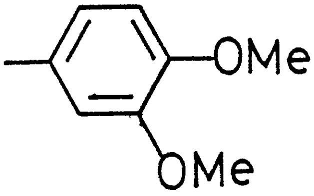

(135)

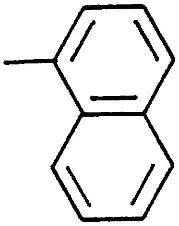
Ar


(136)


(137)


(138)


(139)


(140)

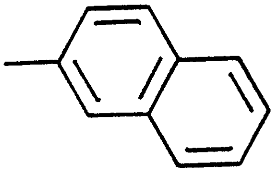

(141)

Figure 40 Twelve analogues of hexakis(benzylthiomethyl)benzene (76).

Inclusion experiments were carried out by recrystallisation of unsolvated material from the appropriate pure liquid. Problems of insufficient solubility were overcome by the use of sealed tubes for those solvents. The behaviour of compounds (76) and (130)-(141) is listed in Tables 5-18.

Table 5 gives some illustrative guests for the parent host (76). Substitution of each of the six outer aromatic rings with a single methyl group gives the new hosts (130)-(132). Whereas the *ortho*-methyl (130) and *para*-methyl (132) compounds show only relatively limited inclusion properties (Tables 6 and 7), the *meta*-methyl derivative (131), exhibits general inclusion behaviour similar to the parent. Subtle differences are found however in selectivity experiments. Like the unsubstituted host the *meta*-methyl host shows a preference for the *para*-isomer, on recrystallisation from an equimolar mixture of *ortho*-xylene and *para*-xylene, but improved selectivity of 15:85 against 25:75 is observed. Selective inclusion of the larger cycloalkanes from a ternary mixture of cyclo-pentane, -hexane and -heptane is also found. From a quaternary mixture of the three xylene isomers and ethyl benzene, there is no significant inclusion (<5%) of *meta*-xylene, but *ca*. 15% of the guest is ethyl benzene.

Variable rates of guest loss are found for the three hexamethyl hosts. The *ortho*-compound (130) loses solvent very rapidly, but both the *meta*- and *para*-derivatives form more stable adducts. For example, the dioxan-*para*-methyl (142) inclusion compound displays no apparent guest loss after 24 hours under vacuum.

A similar trend of inclusion behaviour was found for the three hexachloro-compounds (133)-(135), in which inclusion is again favoured by meta-substitution. The ortho and para-chloro inclusion compounds have unusual host:guest ratios, suggesting that the cavity geometry is different from that found for the parent host system (Tables 9, 10 and 11).

The very high guest content in the 1,4-dioxan adduct with hexakis(4-chlorobenzylthiomethyl)benzene (135) suggests the presence of spacious voids in the lattice of this inclusion compound.

These two series suggest that whereas ortho and para-substitution appears to have a disruptive effect upon the normal packing arrangement of the unsubstituted host, meta-substitution allows general inclusion properties to be retained. As a test of the sensitivity to meta-substitution, hexakis(3-trifluoromethylbenzylthiomethyl)benzene (136) was prepared. Although (136) formed adducts, the inclusion behaviour was not found to be as wide-ranging as for (131) and (134). This suggests that the size and polarity of the meta-substituent are important factors in the formation of inclusion compounds of this type.

A number of hexasubstituted benzenes possessing a more complex substitution pattern in the outer aromatic ring have also been prepared. The dodecamethyl compound (137), in which both meta-positions are substituted is a general inclusion host but disappointingly did not form an adduct with the equimolar mixture of ortho and para-xylenes.

Fusion of a methylenedioxy unit onto the 3,4-positions of each outer ring, as in (138), gives a new host having more general inclusion properties than the related host (139). Both exhibit ortho-xylene selectivity particularly (138) which forms an adduct of overall host to guest ratio of 3:2 with an ortho/para ratio of 80:20. Lastly the two compounds (140) and (141) were examined, these possessing a naphthalene ring in place of the monocyclic aromatic group. The α-naphthylmethane thiol derivative formed adducts, incorporating more guest than the simpler hosts (Table 16) consistent with the presence of a larger cavity in the former case. The β-naphthyl compound (141) also formed inclusion compounds.

To obtain definitive information on these inclusion compounds, an X-ray crystal structure analysis of the 1,4-dioxan adduct with the parent host hexakis(benzylthiomethyl)benzene (76) was undertaken.

The crystal used was an almost colourless near hexagon of approximate dimensions 0.97 x 0.72 x 0.36 mm; the crystal being sealed in the thin-wall glass capillary with a small amount of solvent to prevent crystal decomposition during data collection. Crystal data are given in Table 19.

The molecule is located on a crystallographic centre of inversion and is therefore constrained to be centrosymmetric (Figure 41). This situation may be compared with the exact three-fold symmetry found for the CCl_4 clathrate of hexaphenylthiobenzene, $C_6(SPh)_6$, (72). The sulphur atoms in the "legs" are situated alternatively above and below the plane of the central benzene ring. Torsion angles reveal approximate three-fold symmetry at the core of the molecule, but deviations become greater towards the outer parts. In each of the terminal phenyl groups half the ring atoms lie above the plane of the central benzene ring, while the other half lie below.

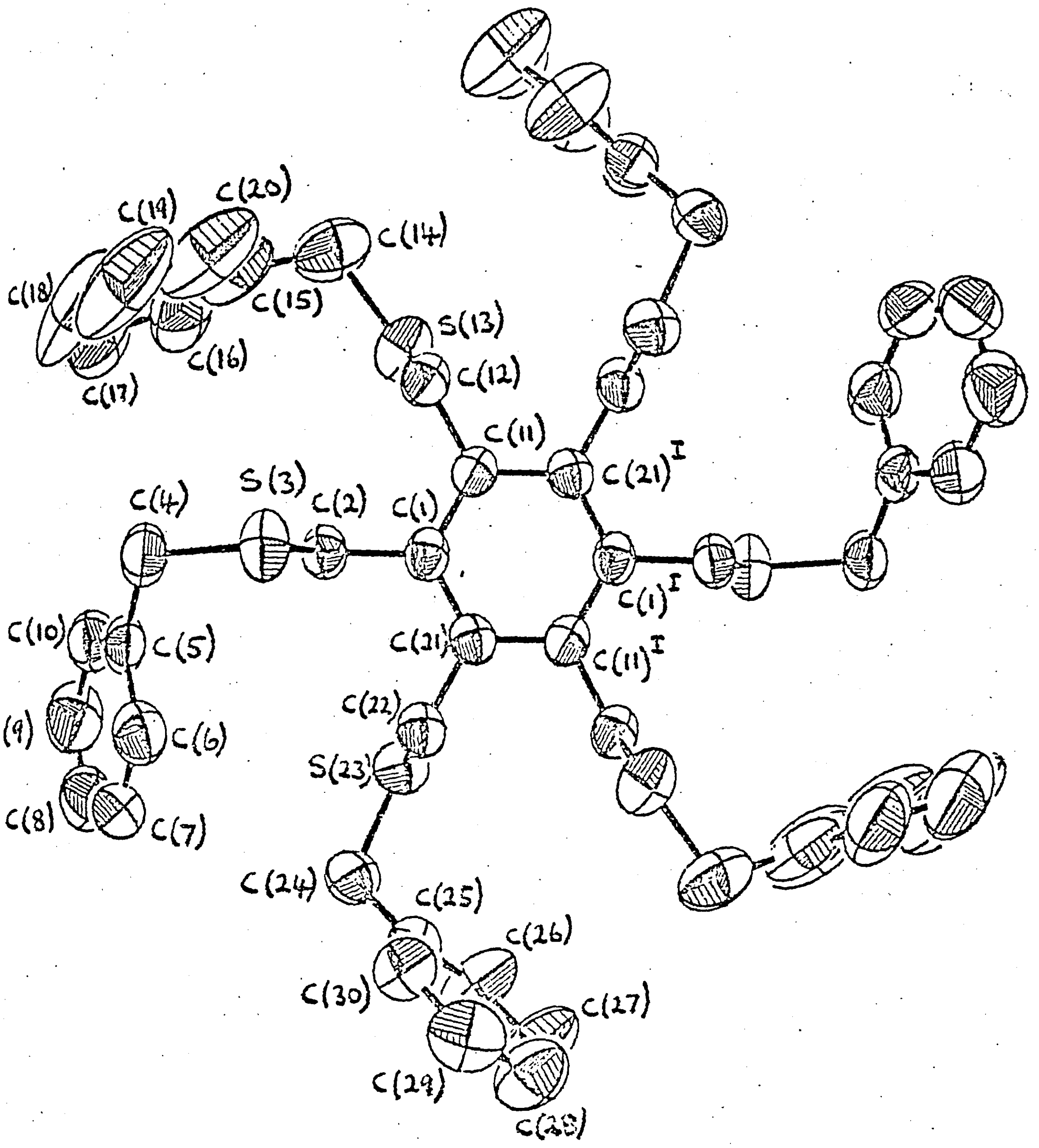


Figure 41 An ORTEP drawing showing a view normal to the plane of the central benzene ring of host molecule hexakis(benzylthiomethyl)-benzene (76) in its 1,4-dioxan clathrate. The hydrogen atoms have been omitted for clarity.

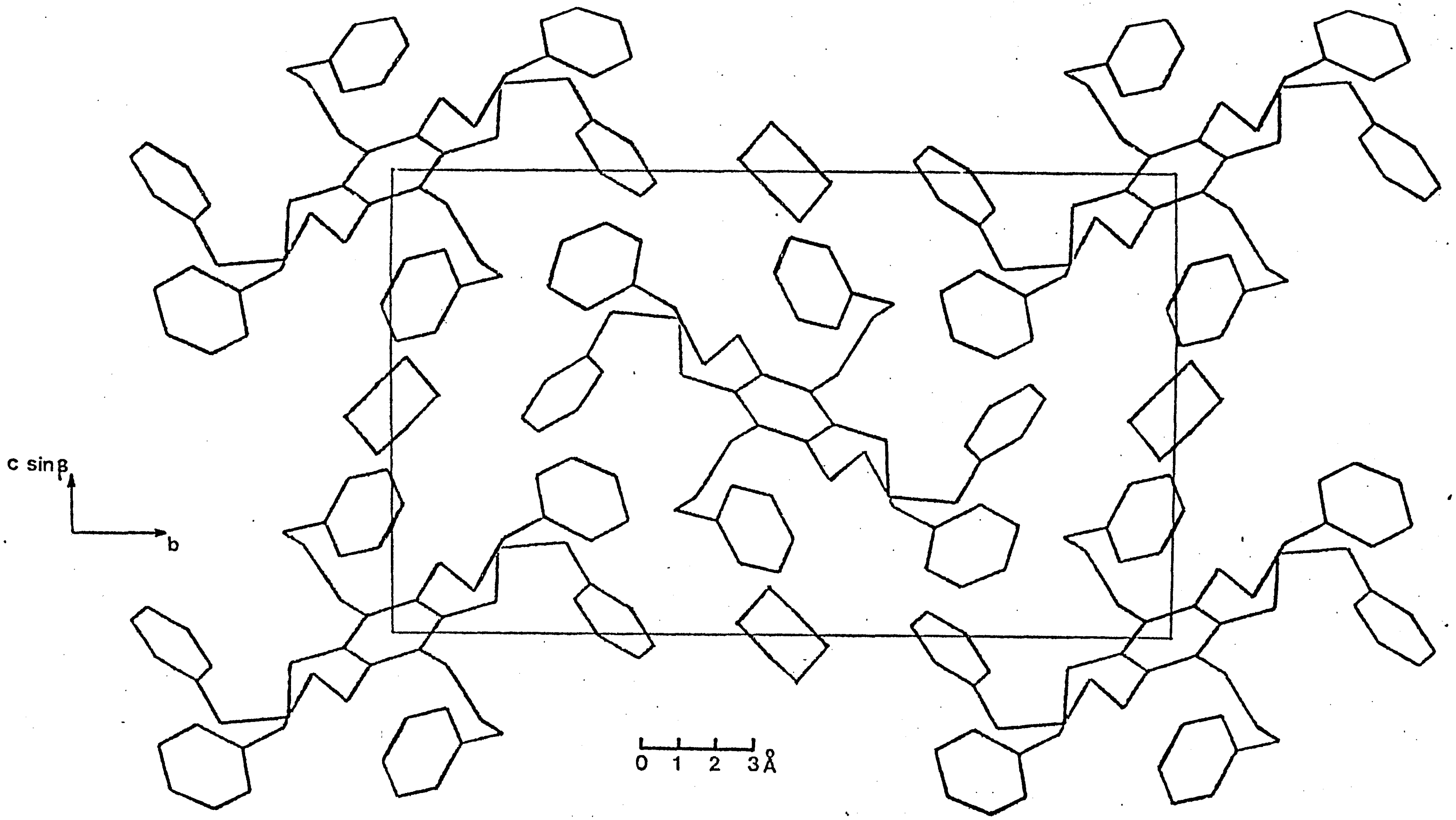
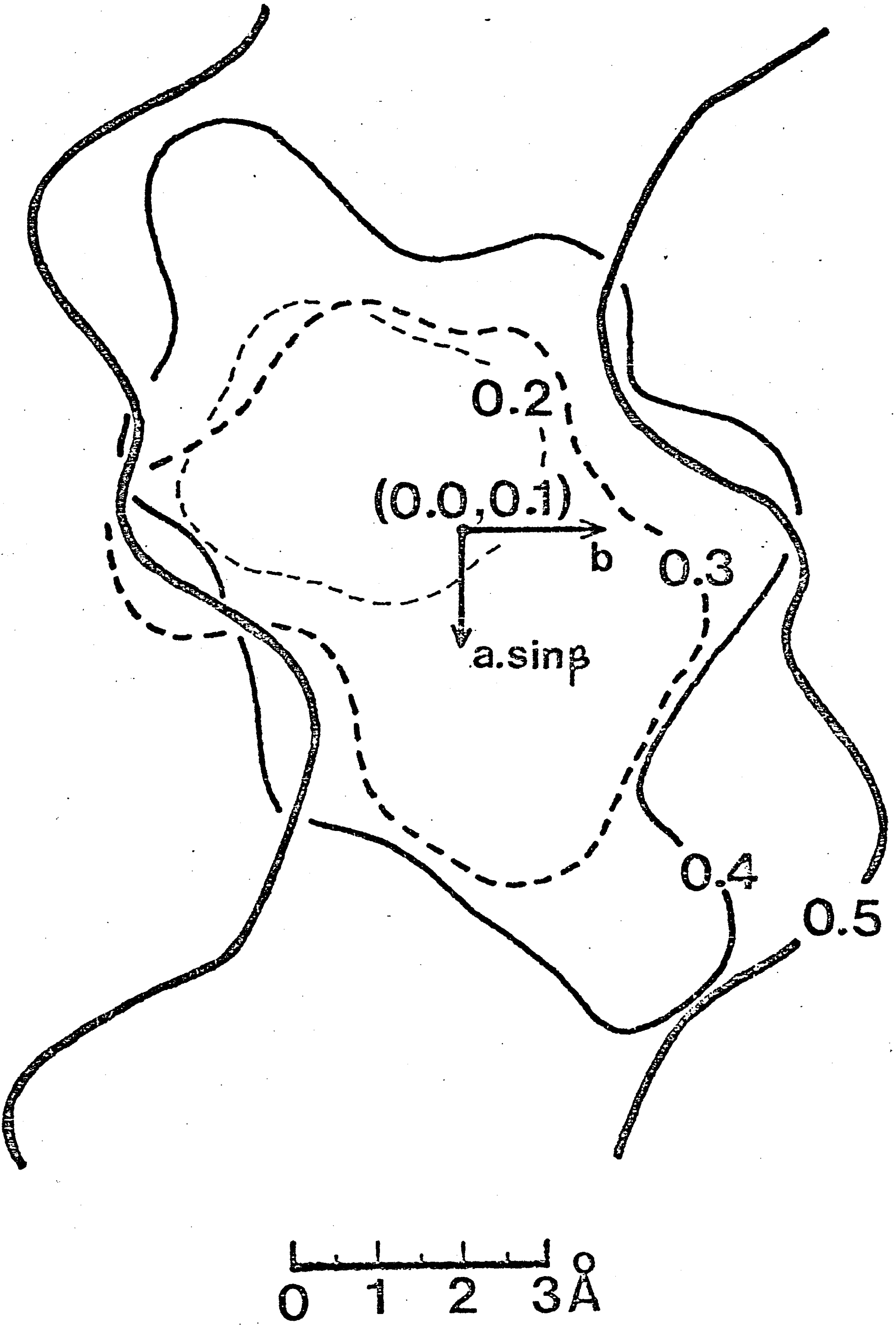


Figure 42 An illustration of host to guest packing in the crystal of the 1,4-dioxan clathrate of (76), as viewed along the a-axis.

Figure 43 The space available in the cage of (76), in cross-section at various fractional levels perpendicular to the c-axis. The contours shown represent only half the centrosymmetric cage.

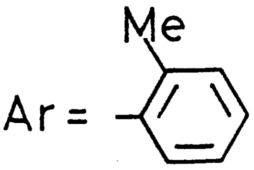


The host-guest packing arrangement in the crystal is illustrated in Figure 42, the host and guest molecules above and below these shown being directly superposed in this view. All the molecules are located at crystallographic centres of symmetry on the *bc* plane. The space available for guest accommodation may be appreciated from Figure 43 which shows the contours at fractional levels perpendicular to the *c*-axis, these sections representing only half the centrosymmetric cage. The cavity may be considered to be of a closed cage type, there being only a narrow interconnection between cages.

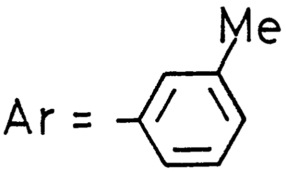
Table 19 gives a comparison of selected crystal data for hexakis(benzylthiomethyl)benzene (76) and the *meta*-methyl and *para*-methyl derivatives (131) and (132). Whereas the two general hosts (76) and (131) both form monoclinic adducts, the *para*-methyl compound forms solvated orthorhombic crystals from 1,4-dioxan with an approximate doubling of the unit cell volume.

Two other parent systems were examined briefly. The inclusion behaviour of hexakis(phenylthiomethyl)benzene (74) and three hexamethyl derivatives, (142)-(144) prepared from the corresponding thiocresols and hexakis(bromomethyl)benzene, is less clear-cut than in the previous case. (Tables 20 and 21).

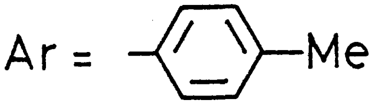
$C_6(CH_2S{-}Ar)_6$



(142)



(143)

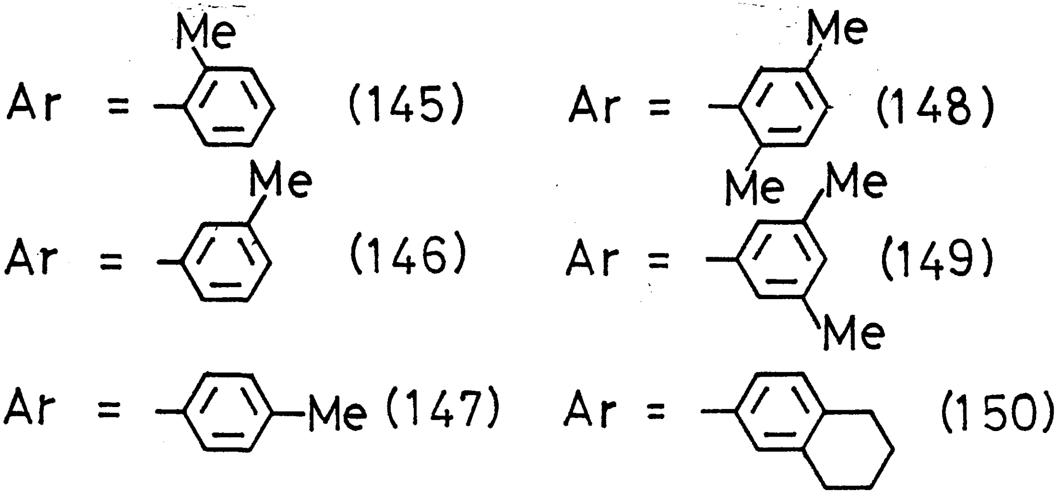


(144)

The unsubstituted host has not yet been the subject of an X-ray structural analysis and hence the nature of the cavity remains unknown. Of the three hexamethyl derivatives, only the meta-substituted compound (143) formed an adduct, with benzene.

Various derivatives of the host hexakis(phenoxymethyl)-benzene (73) have been synthesised.

$C_6(CH_2O—Ar)_6$

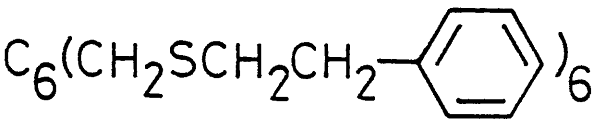


Again, of the three hexamethyl compounds, the meta-analogue (146) showed inclusion behaviour parrelleling most closely that of the parent (Tables 22 and 24). Interestingly the ortho-methyl compound (145) also forms an adduct with 1,4-dioxan. However, unsolvated material has also been recovered from this solvent in a separate experiment.

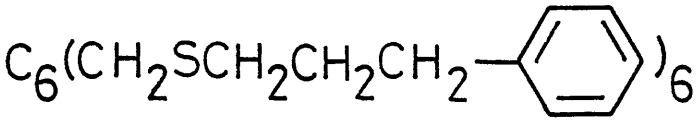
Two dodecamethyl hexasubstituted benzenes of this type showed contrasting behaviour. The compound (148) possessing an unsymmetrical relationship of methyl groups in the outer aromatic ring recrystallised unsolvated from a number of solvents but its isomer (149) having both meta positions substituted forms inclusion compounds (Table 25). The adduct with 1,4-dioxan displayed no significant guest loss after 24 hours under vacuum at room temperature. Raising the temperature to 60°C resulted in complete removal of the guest after 15 hours under vacuum.

In each case, substitution of the *meta*-position of the outer aromatic rings appears to be the most effective substitution pattern for retaining and modifying inclusion behaviour.

Hexaphenylthiobenzene (72) and hexakis(benzylthiomethyl)-benzene (76) have been established as forming clathrates and along with hexakis(phenylthiomethyl)benzene (74), these compounds comprise a series of hosts possessing 1, 2 and 3 atom units linking the central benzene ring and the outer aromatic ring. In order to discover where an upper limit to the length of the connecting arm exists above which *multimolecular* inclusion will not take place, the two compounds, hexakis(2-phenylethylthiomethyl)-benzene (151) and hexakis(3-phenylpropylthiomethyl)benzene (152) were synthesised, these having respectively four and five atom inter-ring chains.



(151)



(152)

Crystallisation of unsolvated (151) from a number of solvents has established inclusion behaviour for this, the first four-atom chain hexahost molecule (Table 26). The 1,4-dioxan adduct of (151) exhibits the same host-guest ratio, 1:1, found for the dioxan clathrate of hexakis(benzylthiomethyl)benzene (76). Common ratios are, however, not found in all cases, for example, (151) gives 1:2 adducts with both benzene and toluene, while its shorter chain counterpart (76) gives 1:1 adducts with these solvents. Interestingly compound (152), which corresponds to further chain extension compared with (151), has given no evidence of inclusion behaviour to-date, unsolvated material being obtained from cyclohexane, nitromethane and acetone. However, the high solubility of (152) has hindered the study of a wide range of potential guest molecules.

The further extended "octopus" molecules of Vogtle [33] have ion binding properties as have other hexasubstituted benzenes recently prepared by him. [220]

Table 5

Inclusion behaviour for $C_6(CH_2SCH_2$-$)_6$ (76)

Guest	Mole Ratio of host:guest[a]
Cyclohexane	1:1[b]
toluene	1:1[b]
1,4-dioxan	1:1[b]
acetone	1:2[b]
1,1,1-trichloroethane	1:1[b]
ethyl acetate	1:1[b]
acetyl chloride	2:1[b]
benzene	1:1
p-chlorotoluene	1:1
nitromethane	1:1

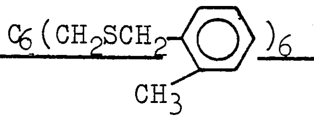
a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integral ratio.

b. From reference 124.

The following solvents were not included:

cycloheptane, cyclooctane, *n*-decane and ethanol.

Table 6

Inclusion behaviour for  $C_6(CH_2SCH_2\text{-}C_6H_4(CH_3))_6$ (130)

Guest	Mole Ratio of host:guest[a]
1,1,1-trichloroethane	1:1[b]

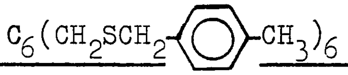
a. Determined by multiple integration of the 'H n.m.r. spectrum.

b. Variable ratios found in some experiments.

The following solvents were not included:

1,4-dioxan, benzene, nitromethane, acetone, toluene, furan and *para*-chlorotoluene.

Table 7

Inclusion behaviour for  $C_6(CH_2SCH_2\text{-}C_6H_4\text{-}CH_3)_6$ (132)

Guest	Mole ratio of host:guest[a]
1,4-dioxan	1:1
benzene	1:1[b]

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer .

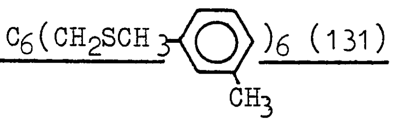
b. On one occasion unsolvated material obtained.

The following solvents were not included:

nitromethane, acetone, cyclohexane, 1,1,1-trichloroethane, toluene, anisole, furan, ethyl acetate and acetyl chloride.

Table 8

Inclusion behaviour for $C_6(CH_2SCH_3$-ring-$)_6$ (131)



$C_6(CH_2SCH_3\text{-}C_6H_4(CH_3))_6$ (131)

Guest	Mole ratio of host:guest[a]
1,4-dioxan	1:1
benzene	1:1
toluene	1:1
cyclohexane	1:1
o-xylene	1:1[b]
p-xylene	1:1
ethyl benzene	1:1
anisole	1:1
ethyl acetate	1:1
acetone	1:2
furan	1:2
nitromethane	1:2
1,1,1-trichloroethane	1:1
acetyl chloride	2:3

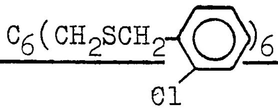
a. Determined by multiple integration of the ¹H n.m.r. spectrum and given to nearest integer.

b. Unsolvated material also obtained from this solvent.

The following solvent was not included:

m-xylene.

Table 9

Inclusion behaviour for  $C_6(CH_2SCH_2C_6H_4Cl)_6$ (133)

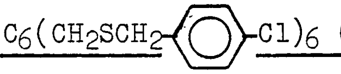
Guest	Mole ratio of host:guest[a]
nitromethane	1:3

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

toluene, 1,4-dioxan, acetone, furan, 1,1,1-trichloroethane, anisole, cyclohexane, ethyl acetate and benzene.

Table 10

Inclusion behaviour for  $C_6(CH_2SCH_2C_6H_4Cl)_6$ (135)

Guest	Mole ratio of host:guest[a]
1,4-dioxan	1:6 (1:8)[b]

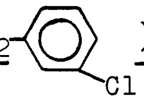
a. Determined by multiple integration of the 'H n.m.r. spectrum.

b. Variable guest ratio found, upper and lower limit.

The following solvents were not included:

benzene, nitromethane, cyclohexane and anisole.

Table 11

Inclusion behaviour for $C_6(CH_2SCH_2$  $)_6$ (134)

Guest	Mole ratio of host:guest[a]
cyclohexane	1:1
benzene	1:1
1,1,1-trichloroethane	1:1
1,4-dioxan	1:1
ethyl acetate	1:1
anisole	1:1[b]
toluene	1:1

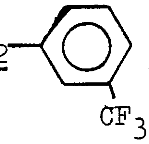
a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

b. A ratio of 1:2 also obtained in a separate experiment.

The following solvents were not included:

nitromethane and acetone.

Table 12

Inclusion behaviour for $C_6(CH_2SCH_2$  $)_6$ (136)

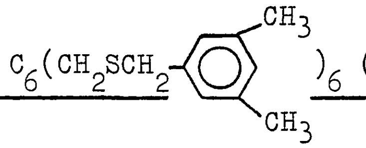
Guest	Mole ratio of host:guest[a]
anisole	1:1
toluene	1:1

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

1,4-dioxan, benzene, nitromethane, cyclohexane, 1,1,1-trichloroethane and ethyl acetate.

Table 13

Inclusion behaviour for  (137)

$C_6(CH_2SCH_2-C_6H_3(CH_3)_2)_6$ (137)

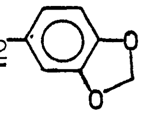
Guest	Mole ratio of host:guest[a]
benzene	1:1
anisole	1:1
cyclohexane	1:2
1,1,1-trichloroethane	1:2
1,4-dioxan	2:3

a. Determined by multiple integration of the ^{1}H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

acetone and toluene.

Table 14

Inclusion behaviour for $C_6(CH_2SCH_2$-  $)_6$ (138)

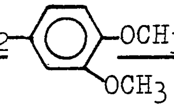
Guest	Mole ratio of host:guest[a]
benzene	1:1
fluorobenzene	1:1
toluene	1:1
anisole	1:1
ethyl acetate	2:3
1,4-dioxan	1:2
acetone	1:2
nitromethane	1:2
thiophene	1:2

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

1,1,1-trichloroethane, cyclohexane and *para*-chlorotoluene.

Table 15

Inclusion behaviour for $C_6(CH_2SCH_2$-  $)_6$ (139)

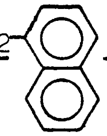
Guest	Mole ratio of host:guest
1,4-dioxan	1:4[a]

a. Determined by multiple integration of 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

toluene, benzene, nitromethane and anisole.

Table 16

Inclusion behaviour for $C_6(CH_2SCH_2$- ) (140)

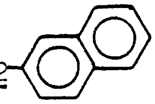
Guest	Mole ratio of host:guest[a]
1,4-dioxan	2:3
nitromethane	2:3
benzene	1:2
1,1,1-trichloroethane	1:1

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

toluene and cyclohexane.

Table 17

Inclusion behaviour for $C_6(CH_2SCH_2$-  $)_6$ (141)

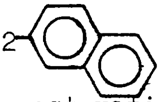
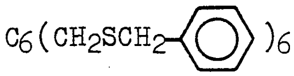
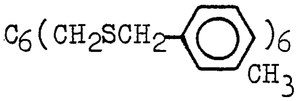
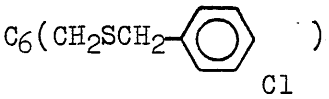
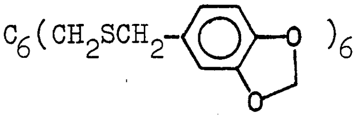
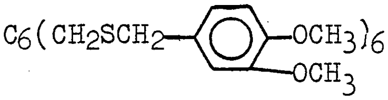
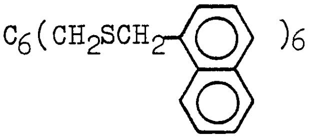
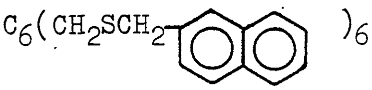
Compound (141), $C_6(CH_2SCH_2$-  $)_6$, formed an adduct with 1,4-dioxan with host:guest ratio of 1:1. Toluene was not included.

Table 18

Guest selectivity properties of hosts (76), (131), (134), (138), (139), (140) and (141), on recrystallistation from an equimolar mixture of *ortho*-xylene and *para*-xylene.

Host		Respective mole percentage of guest included[a]		Overall host: guest ratio
		o-xylene	p-xylene	
	(76)	25	75	1:1
	(131)	15	85	1:1
	(134)	55	45	1:2
	(138)	80	20	1:1[b]
	(139)	70	30	2:3
	(140)	70	30	2:3
	(141)	55	45	3:2

a. Determined by multiple integration of the ^1H n.m.r. spectrum and given to nearest 5%.

b. Variable host:guest ratios have been obtained due to rapid guest loss *in vacuo*.

The other related hosts did not form inclusion compounds with the same solvent mixture.

Table 19

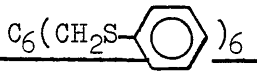
Some selected crystal data for Hexakis(benzylthiomethyl) benzene (76) and related molecules (131) and (132)

Host	Guest (host:guest ratio)[a]	Space Group	Lattice Parameters
(76)	1,4-dioxan (1:1)	$P2_1/c$ monoclinic	a = 10.542, b = 20.863, c = 12.496,Å β= 95.48°, z = 2(host), U = 2735.7Å^3
(131)	o/p-xylene[b] (1:1)	$P2_1/c$ monoclinic	a = 9.62 b = 15,45, c = 22.72Å, β= 111.0°, z = 2(host), u = 3152.6Å^3.
(132)	1,4-dioxan (1:1)	Pcab orthorhombic	a = 18.67, b = 14.18, c = 2322Å, z = 4(host), U = 6147.3Å^3.

[a] Ratio determined by 'H n.m.r. employing $CDCl_3$ as solvent.

[b] See text.

Table 20

Inclusion behaviour for  (74)[a]

Guest	Mole ratio of host:guest[b]
toluene	1:1
1,4-dioxan	1:2

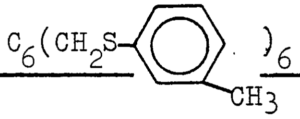
a. From reference 124.

b. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

cyclohexane, cyclopentane, tetrahydrofuran, tetrahydropyran and tetrahydrothiophene.

Table 21

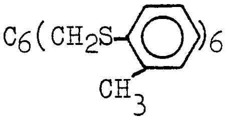
Inclusion behaviour for  (143)

Guest	Mole ratio of host:guest[a]
benzene	1:1

a. Determined by multiple integration of the 'H n.m.r. spectrum.

The following solvents were not included:

toluene, cyclohexane, acetone, xylene, or 1,4-dioxan.

Compound (142),  did not form an inclusion compound with either benzene, toluene, 1,4-dioxan, <u>para</u>-xylene or <u>ortho</u>-xylene.

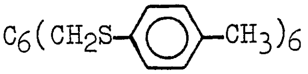
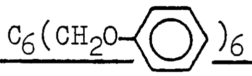
Compound (144), , did form an inclusion compound with either 1,4-dioxan, benzene, <u>ortho</u>-xylene or <u>para</u>-xylene.

Table 22

Inclusion behaviour for  $C_6(CH_2O\text{-}C_6H_4)_6$ (73)[a]

Guest	Mole ratio of host:guest[b]
toluene	1:2
1,4-dioxan	1:3
tetrahydrothiophene	1:1

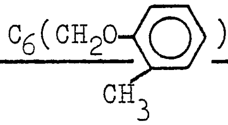
a. From reference 124.

b. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

cyclohexane, tetrahydrofuran, cyclooctane, tetrahydropyran, 1,1,1-trichloroethane and acetone.

Table 23

Inclusion behaviour for  $C_6(CH_2O\text{-}C_6H_4CH_3)$ (145)

Guest	Mole ratio of host:guest[a]
1,4-dioxan	1:2[b]

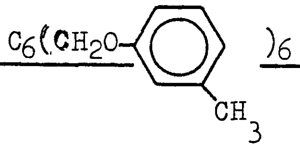
a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

b. Unsolvated material also obtained from this solvent.

The following solvents were not included:

benzene, toluene, cyclohexane, xylene, nitromethane and *tert*-butylbenzene.

Table 24

Inclusion behaviour for  (145)

Guest	Mole ratio of host:guest[a]
toluene	1:2
benzene	1:2

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

xylene, 1,4-dioxan and nitromethane.

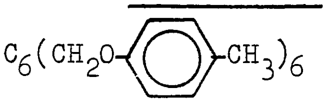
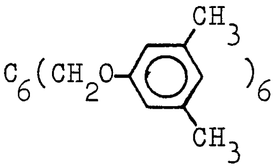
Compound (147),  did not form an inclusion compound with either toluene, xylene or dioxan.

Table 25

Inclusion behaviour for  (149)

Guest	Mole ratio of host:guest[a]
1,4-dioxan	1:2
benzene	1:2

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

toluene and xylene.

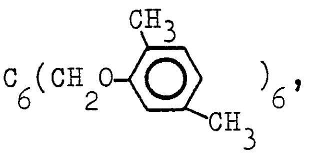
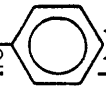
Compound (148), , did not form an inclusion compound with either toluene, acetone, xylene, benzene or cyclohexane.

Table 26

Inclusion behaviour for $C_6(CH_2SCH_2CH_2$–$)_6$ (151)

Guest	Mole ratio of host:guest[a]
benzene	1:2[b]
toluene	1:2[b]
fluorobenzene	1:2[b]
chlorobenzene	1:2[b,d]
bromobenzene	1:1[c]
iodobenzene	1:1[c]
1,4-dioxan	1:1[b]
1,1,1-trichloroethane	1:1[b,c]
tetrahydropyran	2:3[b]

a. Given to nearest integer.

b. Determined by multiple integration of 'H n.m.r. spectrum.

c. Determined by microanalysis for halogen.

d. Ratio of 2:3 obtained by microanalysis for halogen.

The following solvents were not included:

ethyl acetate, acetone, nitromethane, cyclohexane and *n*-decane.

Chapter 6 Trigonal Symmetry - A Key Design Feature for the Synthesis of New Inclusion Hosts

Much evidence in previous chapters has been placed upon the accidental or chance discovery of new inclusion compounds. With the notable exception of the hexahost analogy, described in Chapter 2, the only efficient method for the planned preparation of new inclusion hosts has been the modification of known systems. Fetterly [221] in 1964 stated that "the discovery of new multimolecular inclusion compounds has been and still is a matter of chance". In order to discover whether new inclusion compounds could be synthesised, which are not structurally related to any known examples, design features common to a number of existing hosts were examined.

In Dianin's Compound and the hexahosts the lattice structure contains a central core, of respectively a hydrogen-bonded and covalently bonded nature, with angular fragments or molecular residues which make up the walls of the cavity. The cyclotriphosphazene channels are produced in an analogous manner, though also possessing, in common with many other host systems, elements of trigonal symmetry in their molecular structure.

Employing these two design features, the model for a new inclusion host was constructed (Figure 44). Interaction between the host molecules might lead to the formation of an open lattice structure with discrete cages or infinite channels.

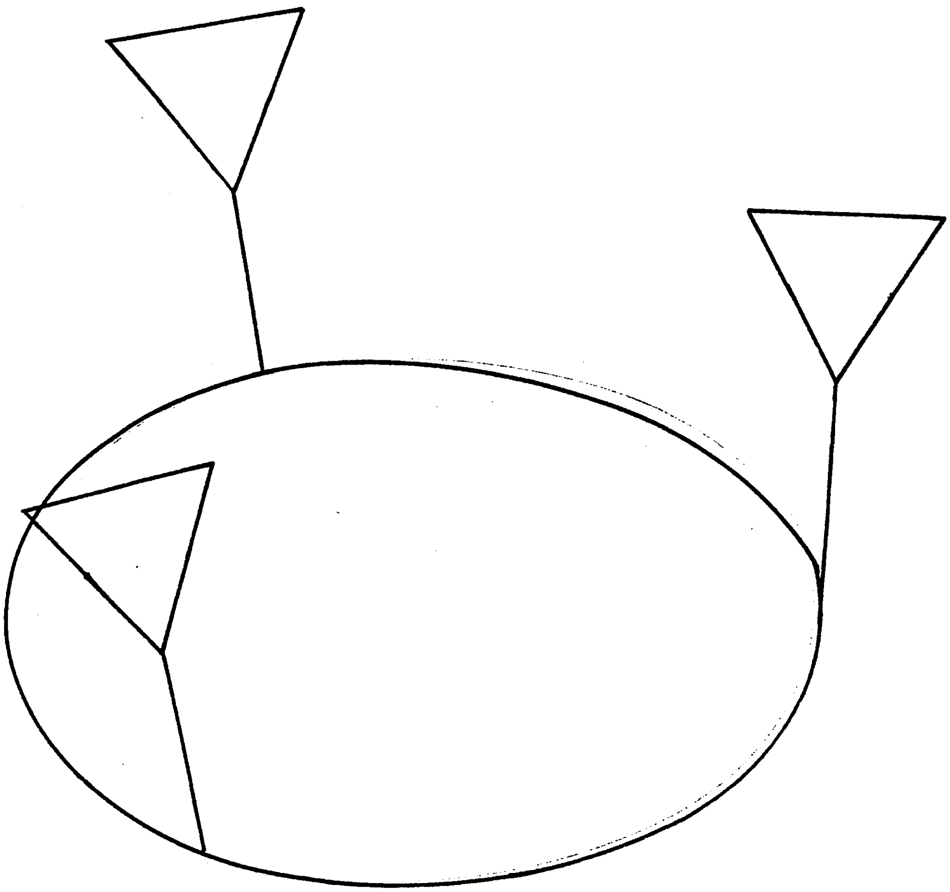
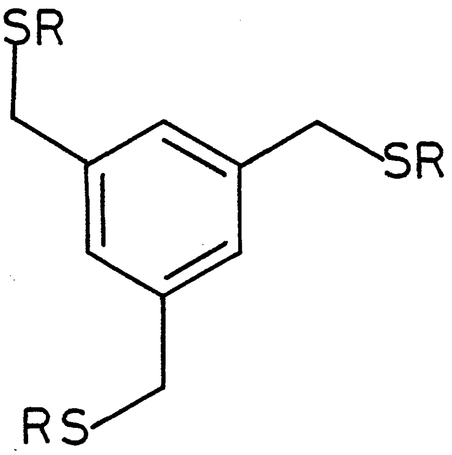
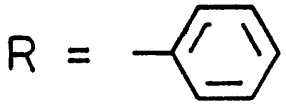


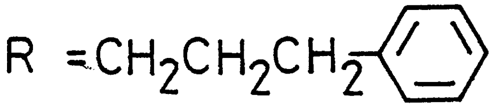
Figure 44 Model for an inclusion host incorporating trigonal symmetry as a key design feature.

A series of compounds incorporating both elements are those based upon a 1,3,5-tris-substituted benzene skeleton. With suitable substituents the molecules might be induced to adopt an open-packed structure. A literature search did not uncover any examples of adduct forming behaviour for systems of this type. Compounds (153)-(158) were prepared by the reaction of the sodium salt of the appropriate thiol with 1,3,5-tris(bromomethyl)benzene. The two molecules with the longest "legs" (156) and (157) were isolated as oils and resisted all attempts at crystallisation (see experimental).

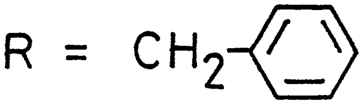




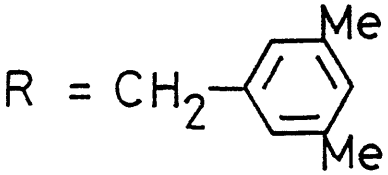
(153)



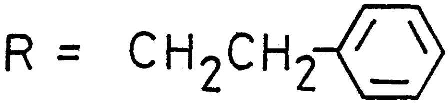
(156)



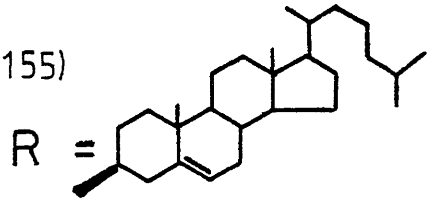
(154)



(157)



(155)

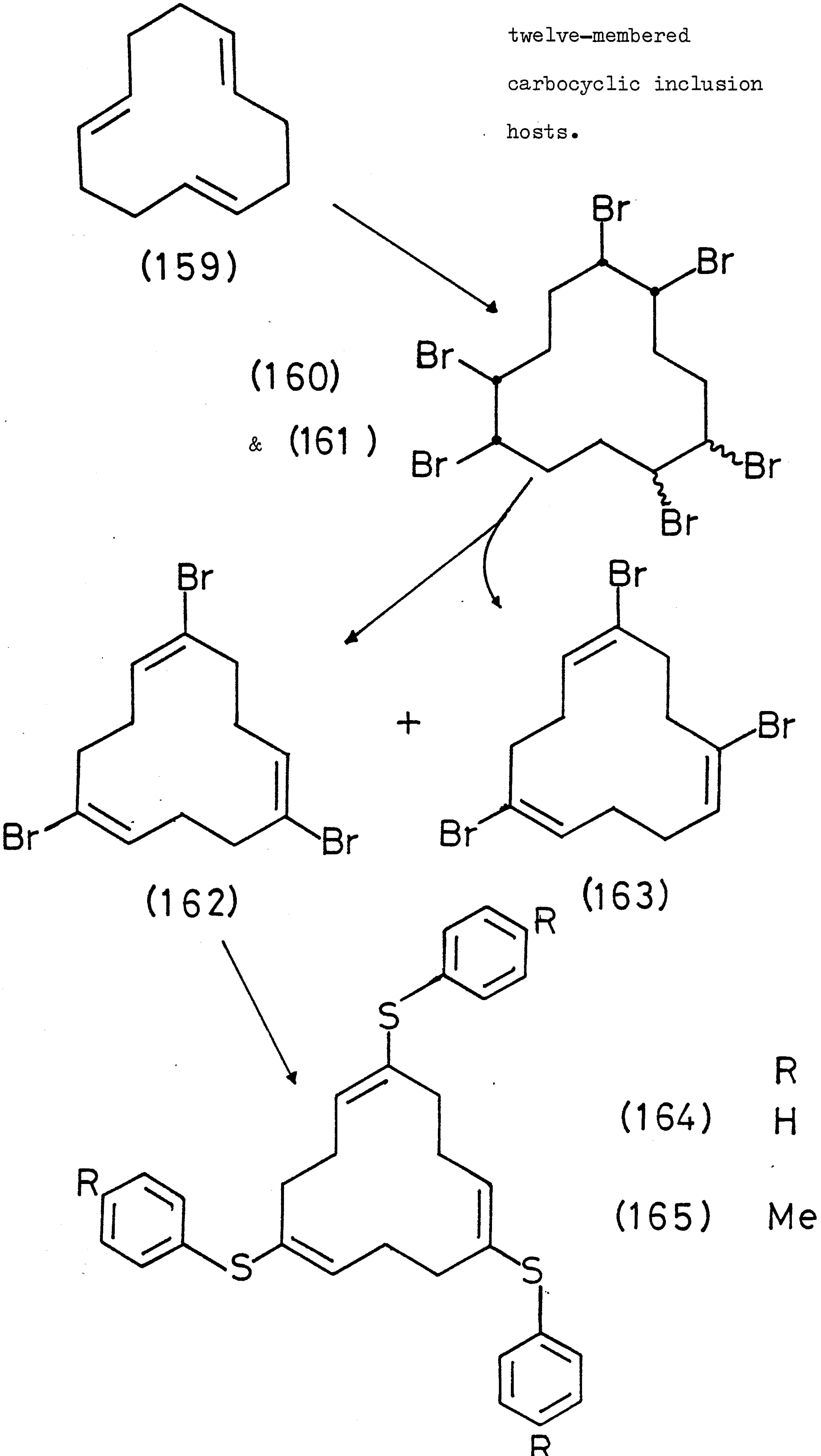


(158)

The remaining four tris-substituted benzenes were recrystallised from a number of solvents but did not form any adducts. Interestingly, related molecules prepared by Vogtle for ion-binding studies also failed to display any complexing properties in contrast to the behaviour of their hexasubstituted analogues.[220]

A second series of trigonal molecules was proposed based on a symmetrically substituted twelve-membered carbocyclic ring. This particular ring size is found in tri-o-thymotide (3) and in the naturally occurring metal-ion complexing agent enterochelin (17). The target compound, 1,5,9-tris(phenylthio)-cis,cis,cis-cyclododeca-1,5,9-triene (164) was synthesised by the route shown (Figure 45).

Figure 45 Synthesis of two novel twelve-membered carbocyclic inclusion hosts.



Bromination of trans,trans,trans-cyclododeca-1,5,9-triene (159) gave a mixture of two hexabromocyclododecanes (160) and (161). Three-fold dehydrobromination of the isomeric mixture of hexabromides gave the two all-cis trivinylbromides (162) and (163), on treatment with sodium ethoxide in ethanol. The desired crystalline symmetrical isomer (162), the minor product on a purely statistical basis, was separated chromatographically then reacted with copper (I) thiophenolate under standard conditions to give the target compound (164), substitution having occurred with complete retention of configuration.[222]

When the trisulphide (164) was recrystallised from cyclopentane an adduct was obtained with a host:guest ratio of 2:1. A preliminary indication that inclusion had indeed taken place was obtained from the melting-point behaviour of the adduct.

The needle-shaped crystals melted over a broad range, from 47-60°, but on maintaining a temperature of around 60° recrystallisation from the melt began to take place, the new crystals being much thicker than those of the original sample. This material then melted sharply at 99-100°. This behaviour is characteristic of inclusion compounds in which guest loss occurs at the first melting-point with subsequent recrystallisation of unsolvated material. Unsolvated crystals were obtained from methanol, having a sharp melting-point of 100-101°.

A second twelve-membered ring compound (165) was prepared using the copper salt of para-thiocresol in the reaction with the tribromide (162). This molecule proved to be a more general host than (164) forming adducts with both cyclic and acyclic guests. Interestingly, though cyclopentane is included, (165) fails to form an adduct when recrystallised from the linear *n*-pentane. The inclusion behaviour of these two novel hosts is given in Tables 27 and 28.

In a selectivity experiment the *para*-methyl host (165) showed a preference for cyclohexane when recrystallised from an equimolar mixture of the 5-,6- and 7-membered cyclic paraffins.

A closed-type cavity or severely constricted channel is suggested by the stability at room temperature of the adduct of (165) with the very volatile guest *tert*-butyl acetylene (b.p. 38-9°) which showed no significant guest loss after two hours under vacuum.

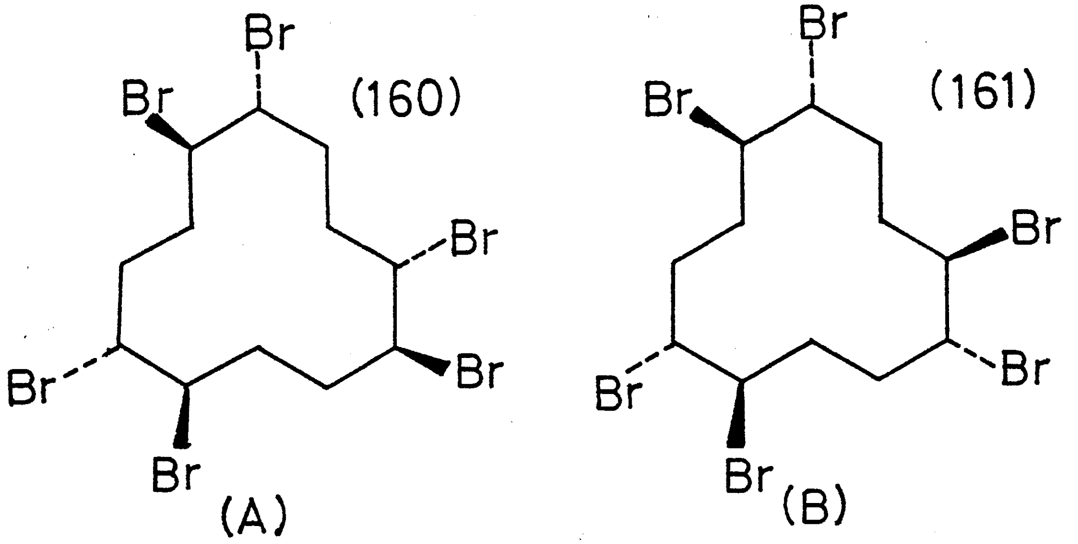
An X-ray crystal structure analysis has been initiated, some data having been obtained for the cyclopentane inclusion compound of 1,5,9-tris-(4-methylphenylthio)-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (165). The crystals are triclinic with hexagonal cross-section with space group *P*1 or *P*1; *a* = 6.26, *b* = 17.54, *c* = 14.48Å, $\alpha = 95.5^\circ$, $\beta = 91.2^\circ$, $\gamma = 95.7^\circ$.

Unfortunately, the preparation of further compounds of this type was hindered by the difficulty of obtaining the intermediate tribromide (162) of sufficient quantity and purity.

The hexabromocyclododecanes (160) and (161), intermediates in the synthesis of the two trigonal hosts, were themselves of great interest. They had been prepared previously by Untch and Martin[223] who had assigned isomeric structures to the solid and oil obtained. The solid isomer was incorrectly (see below) assigned to the more symmetrical structure while the oil was thought to correspond to the less symmetrical substitution pattern.

On repeating the procedure the reaction product from the bromination was obtained as a small amount of white solid, while the bulk of the material remained as a dark-brown glass. Addition of boiling benzene to the glass and cooling yielded a white crust which proved to be an adduct. The quantity of solid, isolated by repetition of this procedure, was greater than the statistically allowed value for the symmetrical isomer, contrary to the earlier report.

N.M.R. evidence and X-ray analysis of an adduct of the solid isomer proved that the structures of the solid and oil are (A) and (B) respectively (Figure 46).



(160) (161)

(A) (B)

Figure 46 Configurations of the two hexabromocyclododecanes (160) and (161); (A), the solid isomer; and (B), the liquid isomer.

The symmetrical liquid isomer was finally purified by repeated plate and column chromatography. The proton noise-decoupled ^{13}C n.m.r. spectrum shows two intense singlets at 34.8 and 58.1 δc, at 60° in d$_6$-acetone, with respect to T.M.S. In contrast, the ^{13}C spectrum of the solid isomer is more complex, consistent with the unsymmetrical configuration. An X-ray structural analysis of the 1:1 adduct of (160) with 1,4-dioxan confirmed the new assignments, though the molecule is severely disordered. Break-up of the solvated crystal also hindered data collection. The crystals are monoclinic with $\underline{a} = 9.30$, $\underline{b} = 18.773$, $\underline{c} = 14.306\text{Å}$, $\beta = 112.52^{\circ}$, $\underline{u} = 2307.2\text{Å}^3$ with four host and four guest molecules in the unit cell and space group $\underline{C}2/\underline{c}$ or $\underline{Cc}$.

The inclusion behaviour of the solid hexabromide host is given in Table 29, the adducts being unstable in air. As in the inclusion compounds of the other twelve-membered ring hosts, variable melting behaviour was found for solvated and unsolvated material. Unsolvated crystals, from cyclohexane, melted sharply at 181-182°, in contrast to the 1,4-dioxan adduct which melted over a broad range, from 80-94°.

A recent review[224] has reported that inclusion behaviour was observed for the hexabromocyclododecane in 1966, a 2:1 host: guest ratio being found for the benzene "clathrate". A 1:1 ratio has been established however for each of the adducts of (160) suggesting solvent loss in the above analysis.

Although the hexahost analogy has already established that molecules with no <u>direct</u> relationship to any known host can be found otherwise than by chance, the present trigonal <u>indirect</u> analogy has permitted the synthesis of new hosts with no structural relationship to any known system, other than three-fold symmetry. Hence this approach represents an important new extension of host design.

Table 27

Inclusion behaviour for 1,5,9-tris(phenylthio)-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (164)

Guest	Mole ratio of host:guest[a]
cyclopentane	2:1
cyclohexane	2:1
fluorocyclohexane	2:1
1,4-dioxan	2:1

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

methanol, methylcyclohexane, cycloheptane and cylcooctane.

Table 28

Inclusion behaviour for 1,5,9-tris(4-methylphenylthio)-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (165)

Guest	Mole ratio of host:guest[a]
cyclopentane	2:1
cyclohexane	2:1
fluorocyclohexane	2:1
methylcyclohexane	2:1
tert-butyl acetylene	2:1
2,2-dimethylbutane	2:1
2,3-dimethylbutane	2:1
diethyl ether	4:1
ethyl acetate	4:1

a. Determined by multiple integration of the 'H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

ethanol and *n*-pentane.

Selectivity Experiment

Guest	Respective mole percentages[a] of guest included	Overall host: guest ratio
33:33:33 cyclo-pentane/ -hexane/and-heptane	35:40:25	1:1

Table 29

Inclusion behaviour of 1,2,5,6,9,10-hexabromocyclododecane (160)

Guest	Mole ratio of host:guest[a]
benzene	1:1
1,4-dioxan	1:1
thiophene	1:1

[a] Determined by multiple integration of the ¹H n.m.r. spectrum and given to nearest integer.

The following solvents were not included:

cyclohexane, pyridine, fluorobenzene and toluene.

Chapter 7. Synthesis of a Chiral Hexahost Molecule

As previously described the hexasubstituted benzene skeleton has proved to be uniquely suitable for the production of new inclusion hosts. An extension of this idea has led to the synthesis of a chiral host. An alternative approach, employing the trigonally substituted twelve-membered ring system, was investigated: this was not fully developed owing to the difficulty in preparing the tribromide (162).

The six-fold substitution of hexakis(bromomethyl)benzene using a chiral nucleophile would produce the desired systems, but two possible draw-backs present problems. Firstly, the asymmetric centres in each chain will prevent crystallisation in those space-groups normally favoured by hexahosts due to the breakdown of the symmetry conditions. Secondly, because of the six-fold nature of the substitution process any optical impurity in the attacking nucleophile may be expected to have a serious effect on product purity. For example, a 95% optically pure reagent would give only 73.5% of the desired product on a purely statistical basis, making product isolation difficult.

To avoid this latter difficulty, an approach to hexasubstituted benzenes through catalytic trimerisation of acetylenes was attempted. Although successful for hydrocarbons,[225] some initial experiments using oxygen and nitrogen containing acetylenes were discontinued due to the difficulty in finding suitable catalysts.

Returning to the former substitution approach, an attractive source of chiral molecules of high optical purity is natural products and a number of experiments were tried using terpenoids and steroids as potential substituents. Cholest-5-ene-3β-thiol used in the preparation of the tris-substituted benzene (158) was reacted with hexakis(bromomethyl)benzene under standard conditions. After extensive chromatographic purification a small amount of pale yellow solid, spectroscopically compatible with a hexasubstituted product, was obtained. Low purity and very poor solubility prevented adequate examination of the compound's properties. Menthol and estrone were also employed as potential ligands, but did not yield hexasubstituted products. Thioestrone was prepared from estrone by the method of Newman and Karnes,[226] but formation of the copper salt, for reaction with the twelve-membered ring tribromide (162), could not be accomplished. Since synthetic results employing natural products were unproductive a route through a synthetically resolved nucleophile was devised. In Chapter 5 the generality of inclusion behaviour of hexahosts derived from benzyl mercaptans was established. Accordingly, the simplest chiral analogue α-phenylethanethiol appeared to be a promising candidate.

Resolved (+)-1-phenylethane thiol (170) was prepared by the method of Isola and co-workers[227] (Figure 47). This efficient method gives thiol (170) in optically pure form, as after purification of the diastereomer (168) no further reaction takes place at the asymmetric carbon. In contrast, many routes to chiral sulphur compounds rely upon the degree of SN_2 character present in the reaction of a sulphur bearing nucleophile with a resolved precursor. The thiol was assigned the R-(+)-configuration from the the depolarised Raman c.i.d. spectrum (Figure 48) this assignment being concordant with chemical correlation.[228]

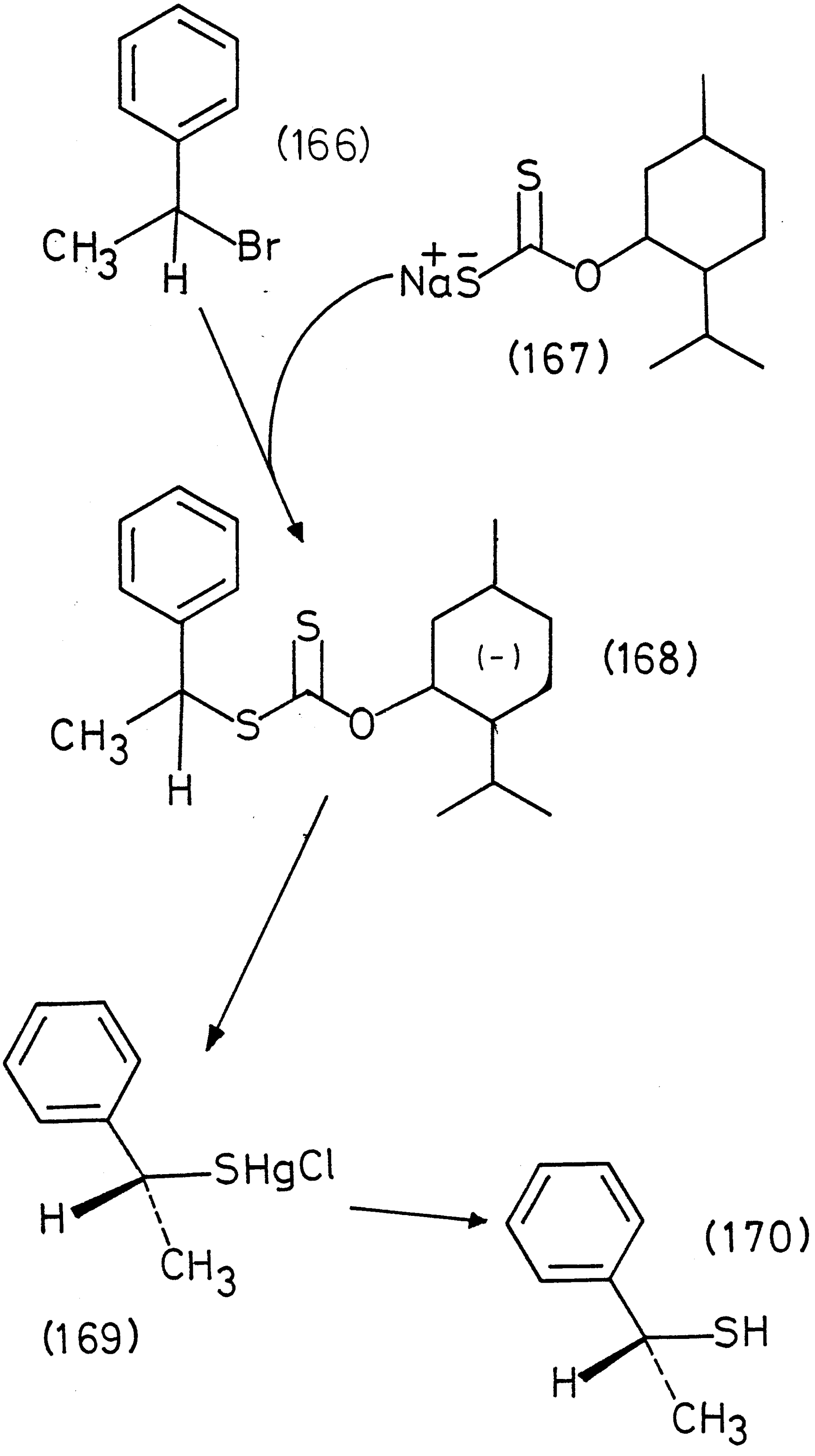


Figure 47 Synthesis of (R)-1-phenylethanethiol.

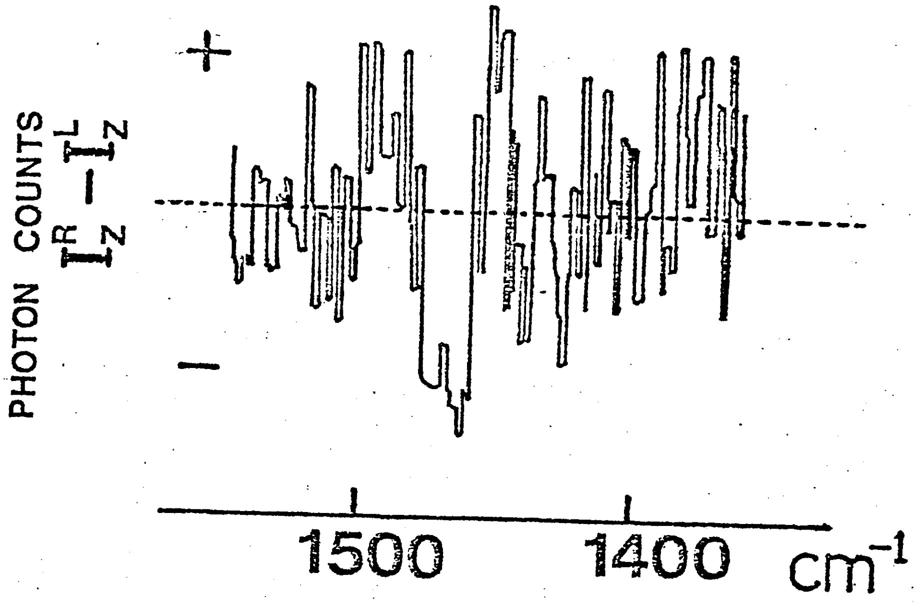
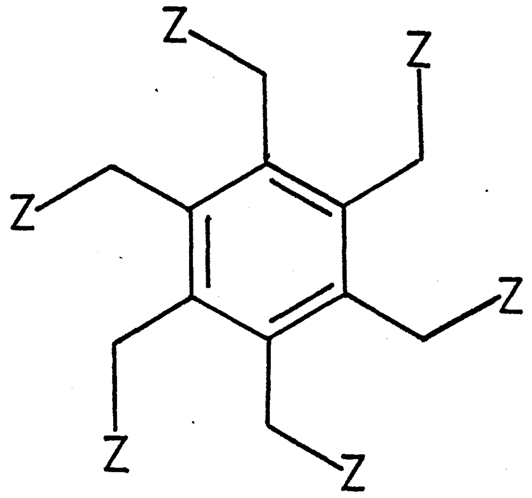


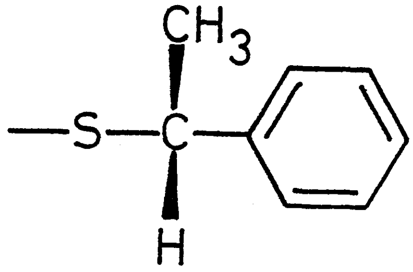
Figure 48 Part of the depolarised Raman c.i.d. spectrum of R-(170).

This R-(+)-1-phenylethane thiol (170) was reacted with hexakis(bromomethyl)benzene, $C_6(CH_2Br)_6$, in sodium ethoxide/ethanol, the thiol being kept in excess over base to minimise racemisation. The hexabromide had also been very finely powdered to reduce the reaction time. The hexasulphide (171) was of high optical purity, as indicated by the proton noise-decoupled ^{13}C n.m.r. spectrum, which shows only eight singlets (Figure 49).

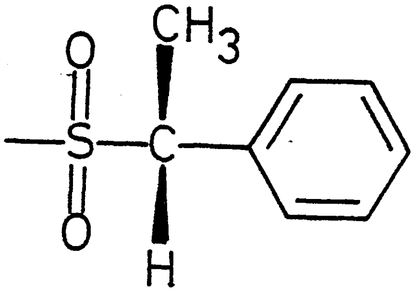
Hexakis(R-1-phenylethylthiomethyl)benzene (171) was recrystallised from a wide range of solvents; benzene, dioxan, t-butyl amine, ethyl acetate, isopropanol and piperidine, giving excellent crystals, but disappointingly no inclusion behaviour was observed.

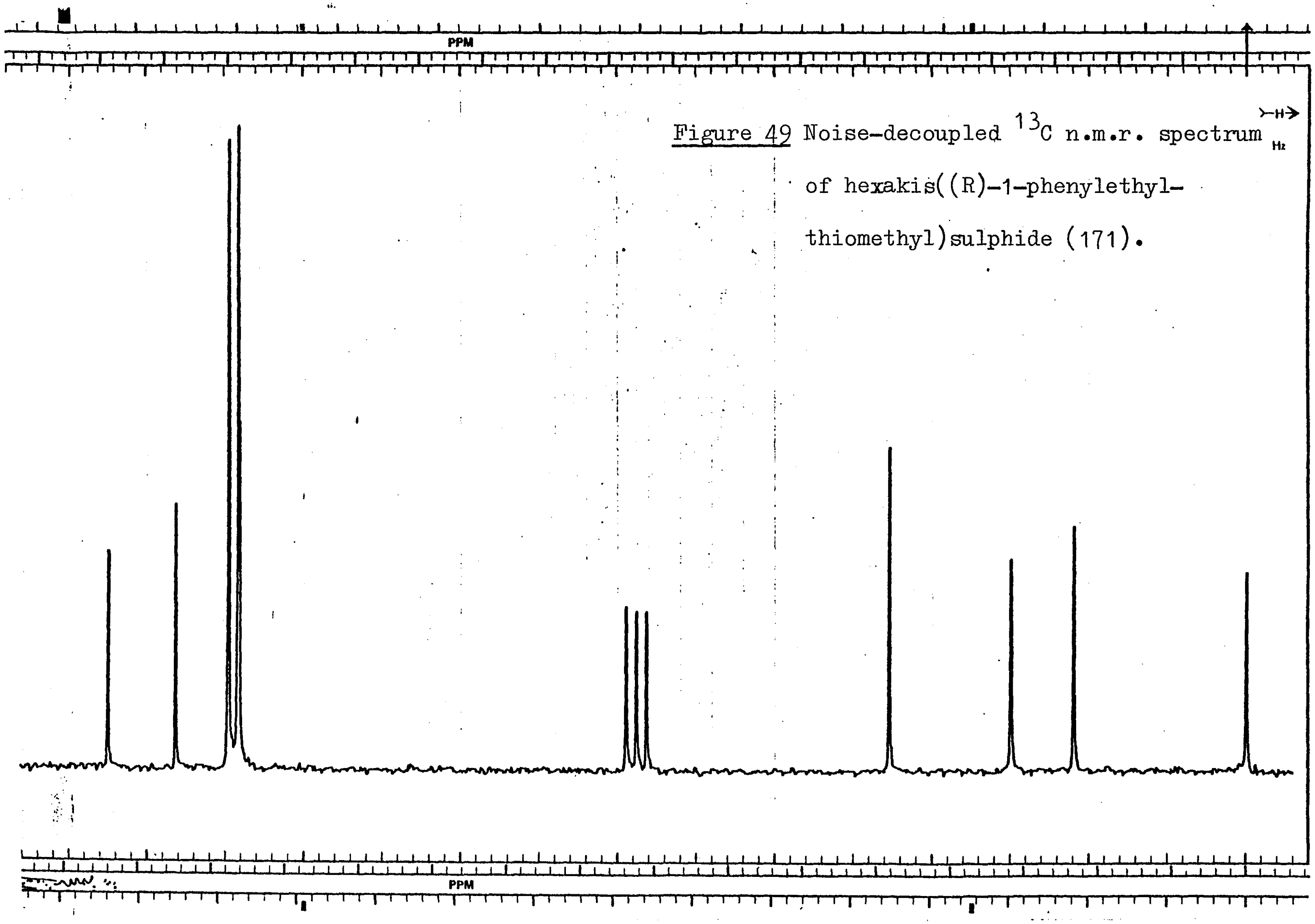


(171) Z =

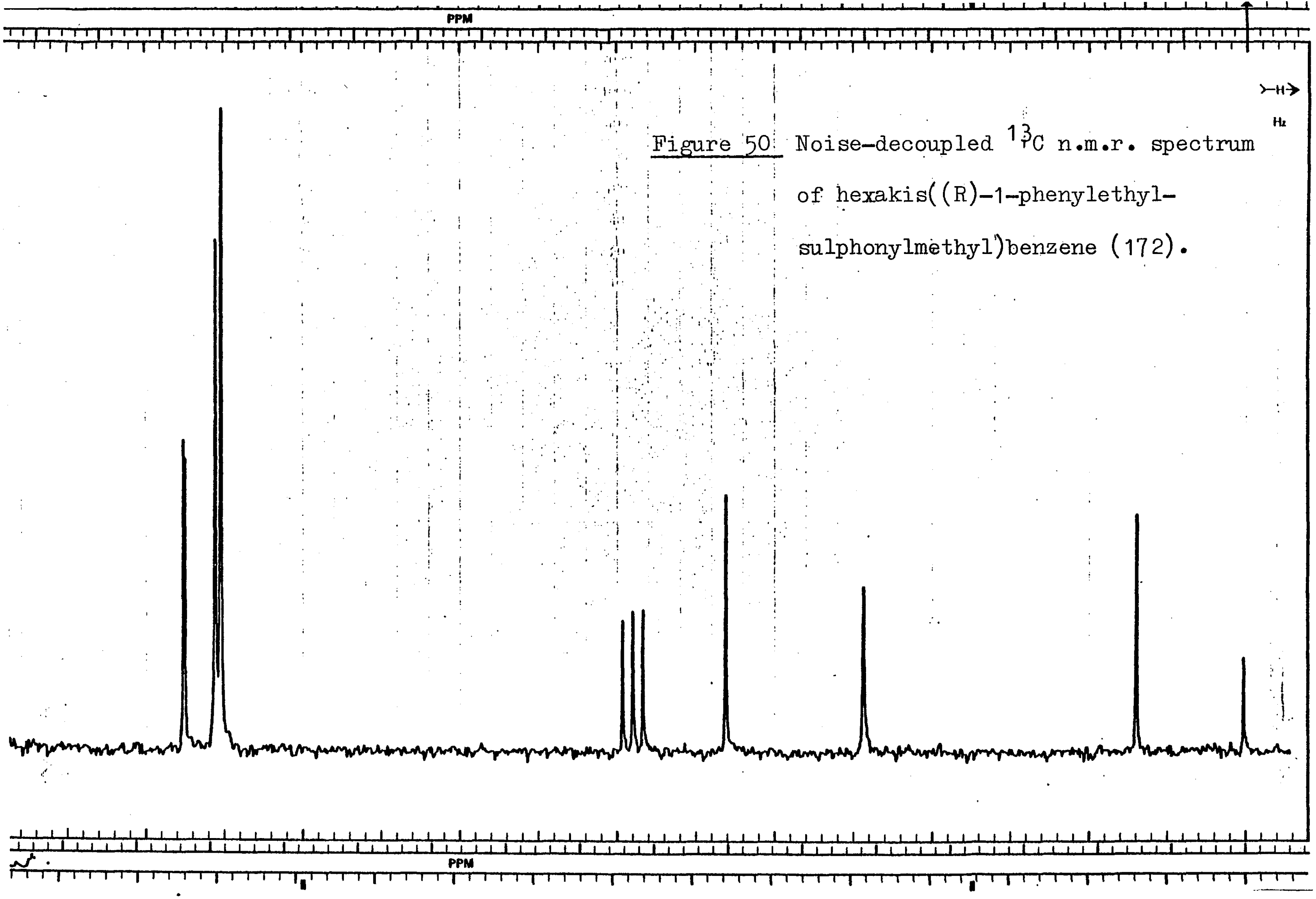


(172) Z =





<u>Figure 49</u> Noise-decoupled ^{13}C n.m.r. spectrum of hexakis((R)-1-phenylethylthiomethyl)sulphide (171).



<u>Figure 50</u> Noise-decoupled ^{13}C n.m.r. spectrum of hexakis((R)-1-phenylethyl-sulphonylmethyl)benzene (172).

Oxidation of the hexasulphide (171) using hydrogen peroxide in glacial acetic acid gave the hexasulphone (172) in high yield. Other hexasulphones, prepared by Backer over forty years ago,[229] had been very insoluble in most solvents, though some did include acetic acid direct from the reaction mixture. Interestingly, the presence of the six methyl groups α- to the sulphonyl groups greatly increases the solubility of the compound (172), compared to the related molecule hexakis(4-methylphenylsulphonylmethyl)-benzene which is almost completely insoluble in chloroform. The optical purity of hexakis(R-1-phenylethylsulphonylmethyl)benzene (172) was again established by ^{13}C n.m.r, only seven singlets being observed in the noise-decoupled spectrum, two of the aromatic signals being superposed (Figure 50).

On recrystallisation of (172) from acetic acid, an inclusion compound was formed, indicated by the clear crystals becoming opaque on standing in air. A host:guest ratio of 1:4 was established by multiple integration of the ^1H n.m.r. spectrum, employing $CDCl_3$ as solvent. Study of the carbonyl stretching band in the infra-red spectrum of the adduct showed that the acetic acid was present mainly in the form of the dimer (prominant band 1709 cm^{-1}) (Figure 51).

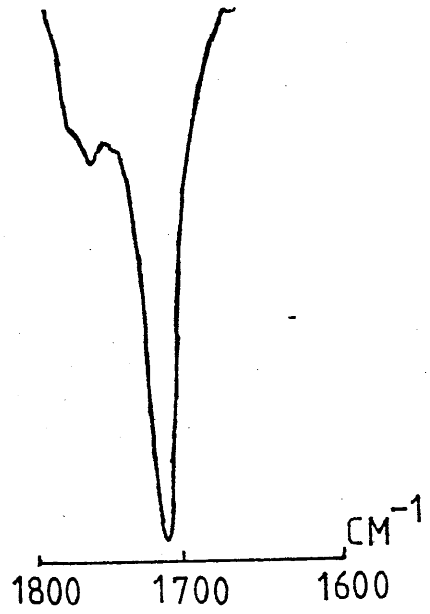


Figure 51 Part of the infra-red spectrum of the acetic acid adduct of (172) showing the dimeric nature of the guest.

The nature of the inclusion compound was finally elucidated by X-ray structural analysis of the crystalline adduct.

Crystal data: $C_{60}H_{66}S_6O_{12}$. $5(CH_3CO_2H)$, monoclinic, space group P21, Z = 2; a = 16.320, b = 13.870, c = 16.731Å, β = 106.47°.

(Figure 52) shows a view of the molecular structure of the host (172) and also illustrates the acetic acid guest molecules. In the host molecule the $-SO_2-$ moieties in the chains linking the central ring to the phenyl groups are situated alternately above and below the mean plane of the central benzene ring. This disposition of the "legs" of (172) is analogous to that found in hexakis(benzylthiomethyl)benzene (76) (see chapter 5).

The four acetic acid guest molecules appear as hydrogen-bonded dimeric pairs which are crystallographically independent. These discrete hydrogen-bonded units contrast with the infinite chains of hydrogen-bonded molecules found in the crystal structure of acetic acid [230] and in the 1:1 complex of deoxycholic acid and acetic acid.[231] Each dimer consists of two planar acetic acid

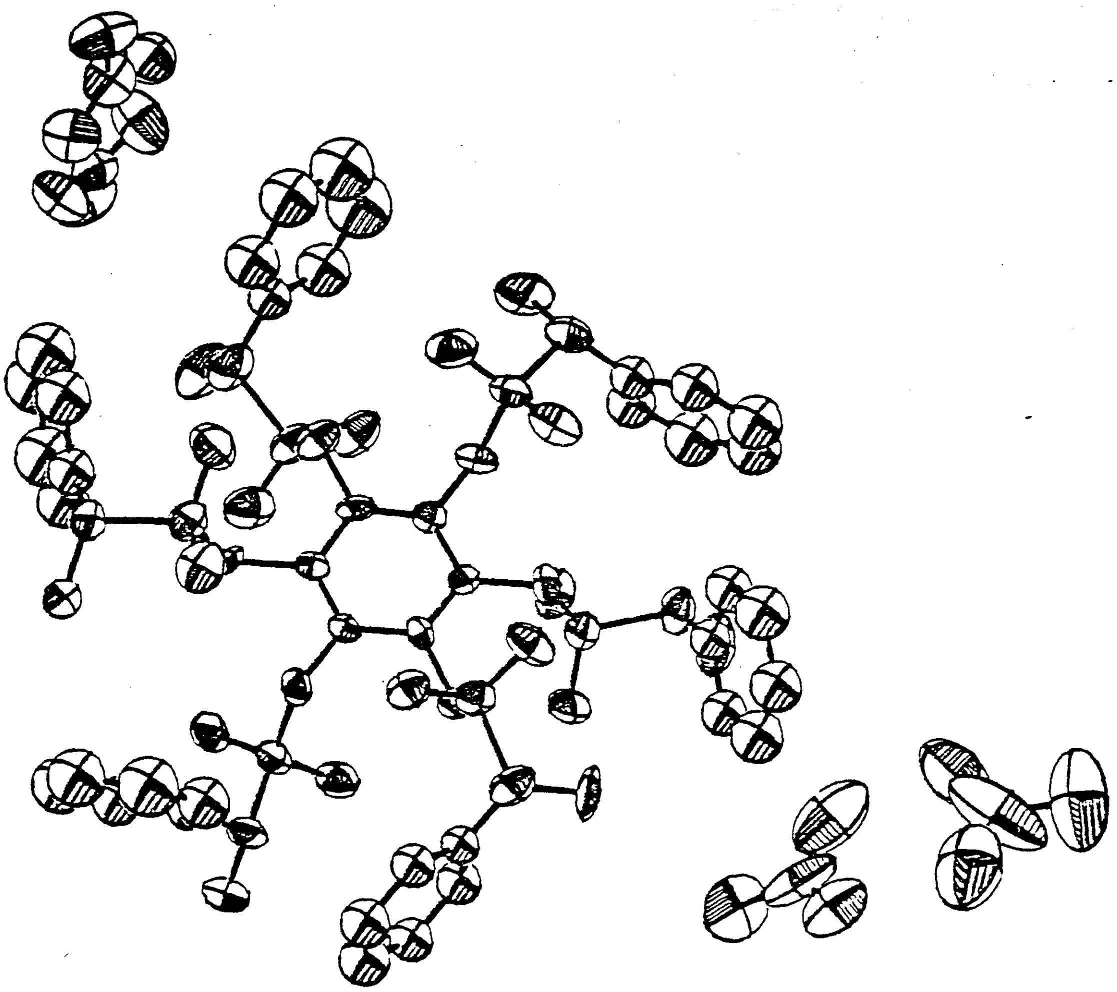


Figure 52 A view illustrating the hexakis(R-α-phenylethylsulphonylmethyl)benzene (172) host molecule and the two crystallographically independent acetic acid guest dimers. Hydrogen atoms have been omitted for clarity.

molecules whose mean planes intersect at an angle of approximately 18 degrees. The mean O....O distance is 2.62Å. This analysis constitutes the first direct observation of dimeric acetic acid.

Unsolvated (172), necessary for other inclusion experiments, could be obtained by recrystallisation from ethanol. From racemic *sec*-butylmethyl ketone crystalline material, of much poorer quality than obtained from acetic acid, was recovered. An inclusion compound with host:guest ratio of approximately 1:1 was obtained, but no evidence of chiral discrimination of the host towards the guest could be found. The hexasulphone (172) did not crystallise well from other racemic solvents, though only a small range of solvents have been investigated to-date. However, in the future, it is likely that significant optical resolution will be found for this, or related chiral hexahosts.

EXPERIMENTAL

'H n.m.r. spectra were recorded on Varian T-60, HA-100 and Perkin-Elmer R32 instruments with $CDCl_3$ as solvent and TMS as internal standard unless indicated otherwise. ^{13}C n.m.r. spectra were recorded on a Varian XL-100 machine. Mass spectra were recorded using A.E.I-G.E.C. MS12 and MS902 instruments. Infra-red spectra were recorded on Perkin-Elmer 225 and 580 instruments. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Melting-points were determined on a Kofler hot-stage apparatus and are uncorrected. Analytical T.L.C. was carried out using Kieselgel G(Merck) and for chromatographic columns Kieselgel G_{60}(Merck) was employed. Petrol refers to that fraction boiling between 60 and 80°C. Solvents were removed on a rotary evaporator at reduced pressure. Nitrogen and argon were passed through alkaline pyrogallol, to remove residual oxygen, and dried using silica gel traps, when necessary.

Abbreviations

s	singlet
d	doublet
t	triplet
q	quartet
m	multiplet
br.	broad

Hexakis(bromomethyl)benzene

This was prepared from hexamethylbenzene by the method of Backer.[232] The highly crystalline crude product, m.p. 295-296° (lit. 309-10°) was used for later experiments without further purification.

Hexakis(benzylthiomethyl)benzene (76)

Preparation of this compound was carried out by a previously described method.[233] Results of inclusion experiments on (76) are given in Tables 5 and 18.

Hexakis(2-methylbenzylthiomethyl)benzene (130)

To dry ethanol (80 ml) was added finely cut metallic sodium (1.00 g, 0.043 mol) under a dry, oxygen-free nitrogen atmosphere. After hydrogen evolution had ceased, 2-methylbenzyl mercaptan (5.87 g, 0.042 mol) was added, forming a homogeneous solution, followed immediately by finely powdered hexakis(bromomethyl)-benzene (3.0 g, 0.0047 mol) with vigorous stirring. After stirring under reflux for six hours, the reaction mixture was allowed to cool then added with stirring to ice/water (300 ml). The white precipitate was collected by filtration, washed with water, dilute aqueous sodium hydroxide, and more water till neutrality, then dried *in vacuo*. Recrystallistation from toluene gave (130) (3.96 g, 85.4%) m.p. 171-175° (Found: C, 73.70; H, 6.73. $C_{60}H_{66}S_6$ requires C, 73.57; H, 6.79%), ν_{max} (KBr) 3015, 2929, 1492, 1485, 1238, 765, 727 and 681 cm^{-1}, τ ($CDCl_3$) 7.71 (18H, s), 6.65 (12H, s, br), 6.45 (12H, s, br.) and 2.87 (24H, m). Results of inclusion experiments are given in Table 6.

Hexakis-(3-methylbenzylthiomethyl)benzene (131)

(131) was prepared by a similar method to (130), the reagents being: dry ethanol (100 ml), sodium (2.28 g, 0.099 mol), 3-methylbenzyl mercaptan (12.8 g, 0.093 mol) and hexakis(bromomethyl)-benzene (6.36 g, 0.01 mol). After the work-up described, drying *in vacuo* gave crude (131) (9.01 g, 91.9%), m.p. 130-133° (ex acetone 1:2) thick needles. (Found: C, 73.50; H, 6.57. $C_{60}H_{66}S_6$ requires C, 73.56; H, 6.79%), ν_{max}(KBr) 3020, 2920, 1610, 1487, 1227, 788 and 712 cm^{-1}, τ($CDCl_3$) 7.65 (18H, s), 6.69 (12H, s, br), 6.48 (12H, s, br.) and *ca*. 2.7-3.1 (24H, m). Results of inclusion experiments are given in Tables 8 and 18.

Hexakis(4-methylbenzylthiomethyl)benzene (132)

The same procedure was used as in the preparation of (130), the reagents used being; dry ethanol (100 ml), sodium (2.27 g, 0.099 mol), 4-methylbenzyl mercaptan (12.5 g, 0.09 mol) and hexakis(bromomethyl)-benzene (6.36 g, 0.01 mol). The standard work-up, followed by drying *in vacuo* gave (132), (9.13 g, 93%) m.p. 181-186° (ex dioxan 1:1). (Found: C, 73.3; H, 6.94. $C_{60}H_{66}S_6$ requires C, 73.56; H, 6.79%), ν_{max}(KBr) 3017, 2909, 1512, 1242, 824, 803, and 731 cm^{-1}; τ($CDCl_3$), 7.74 (18H, s), 6.71 (12H, s, br.), 6.51 (12H, s, br.), and 2.88 (24H, s). Results of inclusion experiments are given in Table 7.

Hexakis(2-chlorobenzylthiomethyl)benzene (133)

(133) was prepared in a similar manner to (130), the reagents being: dry ethanol (100 ml), sodium (2.30 g, 0.1 mol), 2-chlorobenzyl mercaptan (14.28 g, 0.091 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). The crude product contained some unreacted

hexakis(bromomethyl)benzene. Two recrystallisations from 1,4-dioxan gave (133) (6.0 g, 54.1%) m.p. 148–149° (Found: C, 58.56; H, 4.55; Cl 19.40. $C_{54}H_{48}Cl_6S_6$ requires C, 58.85; H, 4.39; Cl, 19.30%), ν_{max}(KBr) 1483, 1474, 1444, 1234, 1053, 1040, 758 and 732 cm^{-1}; τ(CDCl$_3$) 6.47 (12H, s, br.), 6.34 (12H, s, br.) and ca. 2.6–2.9 (24H, m). Results of inclusion experiments are given in Table 9.

3-Chlorobenzyl mercaptan

This was prepared by the method of Urquhart, et al [234] from 3-chlorobenzyl bromide via the isothiouronium salt. Distillation took place between 113 and 116°C at a pressure of ca. 15mm Hg. (lit.[235] 118 at 19 mm Hg).

Hexakis(3-chlorobenzylthiomethyl)benzene (134)

(134) was prepared in a similar manner to (130), argon being used in place of nitrogen and the reagents being: dry ethanol (60 ml), sodium (0.78 g, 0.03 mol), 3-chlorobenzyl mercaptan (5.01 g, 0.03 mol) and hexakis(bromomethyl)benzene (2.35 g, 0.0037 mol). The normal work-up procedure followed by drying in vacuo gave crude (134) (3.8 g, 92.8%), m.p. 163–165° (ex. 1,1,1-trichloroethane, 1:1) (Found: C, 58.97; H, 4.36; Cl, 19.33. $C_{54}H_{48}Cl_6S_6$ requires C, 58.85; H, 4.39; Cl, 19.30%), ν_{max}(KBr) 1598, 1574, 1479, 1433, 1200, 1077, 791, 781 and 692 cm^{-1}, τ(CDCl$_3$) 6.66 (12H, s, br.), 6.52 (12H, s, br.) and ca. 2.6–3.0 (24H, m). Results of inclusion experiments on (134) are given in Tables 11 and 18.

Hexakis (4-chlorobenzylthiomethyl)benzene (135)

(135) was prepared in a similar manner to (130), the reagents being: dry ethanol (100 ml), sodium (2.30 g, 0.1 mol), 4-chlorobenzyl mercaptan (14.28 g, 0.091 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). Recrystallisation from 1,4-dioxan gave solvated (135) (9.83 g, 88.7%, desolvated), m.p. 207-211° (ex benzene) (Found: C, 58.97; H, 4.36; Cl, 19.57. $C_{54}H_{48}Cl_6S_6$ requires C, 58.85; H, 4.39; Cl, 19.30%), ν_{max}(KBr) 1492, 1094, 1023, 1018, 836, 812 and 728 cm^{-1}, τ ($CDCl_3$) 6.68 (12H, s, br.), 6.59 (12H, s, br.) and *ca*, 2.6-2.9 (24H, m). Results of inclusion experiments on (135) are given in Table 10.

Hexakis(3-trifluoromethylbenzylthiomethyl)benzene (136)

(136) was prepared by a similar method to (130) with argon used in place of nitrogen and the reagents used were: dry ethanol (100 ml), sodium (1.17 g, 0.051 mol), 3-trifluoromethylbenzyl mercaptan (9.81 g, 0.051 mol) and hexakis(bromomethyl)benzene (3.60 g, 0.0057 mol). The normal work-up procedure followed by drying *in vacuo* gave crude (136) (6.89 g, 93.3%) m.p. 166-168° (ex benzene), (Found: C, 55.26; H, 3.80; S, 14.56. $C_{60}H_{48}S_6F_{18}$ requires C, 55.29; H, 3.71; S, 14.76%), ν_{max}(KBr) 1451, 1331, 1239, 1161, 1128, 1072, 810, and 701 cm^{-1}, τ (CDCL3) 6.66 (12H, s, br.), 6.52 (12H, s, br.) and *ca*. 2.4-2.7 (24H, m). Adducts of (136) are given in Table 12.

3,5-dimethylbenzyl mercaptan

This was prepared by a literature route,[236] which is essentially the method of Urquhart *et al*.[234] The product gave consistent physical and spectroscopic data.

Hexakis(3,5-dimethylbenzylthiomethyl)benzene (137)

(137) was prepared by a similar method as used for (130), except that argon was used in place of nitrogen and the reagents were: dry ethanol (80 ml), sodium (1.14 g, 0.05 mol), 3,5-dimethylbenzyl mercaptan (7.54 g, 0.05 mol) and hexakis-(bromomethyl)benzene (3.5 g, 0.0055 mol). Recrystallisation of the crude product from toluene gave (137) (5.01 g, 85.5%) m.p. 165–170° (Found: C, 74.52; H, 7.60. $C_{66}H_{78}S_6$ requires C, 74.53; H, 7.39%), ν_{max}(KBr) 3020, 2920, 1606, 1467, 1229, 850, 721 and 690 cm^{-1}, τ (CDCl$_3$) 7.71 (36H, s), 6.73 (12H, s, br.), 6.48 (12H, s, br.) and 3.15 (18H, s, br.). Inclusion compounds of (137) are given in Table 13.

Hexakis(3,4-methylenedioxybenzylthiomethyl)benzene (138)

(138) was prepared in a similar manner to (130), argon being used in place of nitrogen. The reagents used were dry ethanol (100 ml), sodium (1.51 g, 0.061 mol), 3,4-methylenedioxybenzyl mercaptan (9.91 g, 0.059 mol) and hexakis(bromomethyl)benzene (4.20 g, 0.0066 mol). Normal work-up procedure followed by drying *in vacuo* gave crude (138) (7.61 g, 99%), m.p. 169–180° (ex toluene 1:1) (Found: C, 61.95; H, 4.89; S. 16.3. $C_{60}H_{54}S_6O_{12}$ requires C, 62.15; H, 4.69; S, 16.59%), ν_{max}(KBr) 2888, 1501, 1488, 1444, 1256, 1039, 927 and 811 cm^{-1} τ(CDCl$_3$) 6.62 (12H, s, br.), 6.46 (12H, s, br.), 4.13 (12H, s), and *ca*. 3.15–3.25 (18H, arom, H). Tables 14 and 18 give results of inclusion experiments for (138)

Hexakis(3,4-dimethoxybenzylthiomethyl)benzene (139)

(139) was prepared in a similar manner to (130), except the use of argon in place of nitrogen. The reagents used were: dry ethanol (100 ml), sodium (1.35 g, 0.059 mol), 3,4-dimethoxybenzyl mercaptan (9.97 g, 0.054 mol) and hexakis(bromomethyl)benzene (3.80 g, 0.006 mol). After the normal work-up procedure, drying *in vacuo* gave (139) (7.28 g, 97%), m.p. 191-195° (ex toluene) (Found: C, 63.29; H, 5.92; S, 15.52. $C_{66}H_{78}O_{12}S_6$ requires C, 63.13; H, 6.26; S, 15.32%), ν_{max}(KBr) 1515, 1466, 1262, 1228, 1155, 1134 and 1028 cm^{-1}, τ($CDCl_3$) 6.66 (12H, s, br.), 6.47 (12H, s, br.), 6.23 (18H, s), 6.12 (12H, s) and *ca*. 3.1-3.3 (18H, m). Results of inclusion experiments on (138) given in Tables 15 and 18.

Hexakis(1-naphthylmethylthiomethyl)benzene (140)

(140) was prepared in a similar manner to (130), argon being used in place of nitrogen. The reagents used were: dry ethanol (100 ml), sodium (1.30 g, 0.057 mol), 1 -mercaptomethylnaphthalene (9.82 g, 0.056 mol) and hexakis(bromomethyl)benzene (4.01 g, 0.0063 mol). After the normal work-up procedure, drying *in vacuo* gave crude (140) (6.81 g, 90.3%) m.p. 197-202° (ex toluene 1:1) (Found: C, 78.58; H, 5.21. $C_{78}H_{66}S_6$ requires C, 78.35; H, 5.56%), ν_{max}(KBr) 3050, 1598, 1513, 1400, 1229, 802, 793 and 778 cm^{-1}, τ($CDCl_3$) 6.91 (12H, s, br.), 6.72 (12H, s, br.) and *ca*. 2.0-3.5 (42H, m). Results of inclusion experiments are given in Tables 16 and 18.

2-mercaptomethylnaphthalene [237]

This was prepared by a literature route starting from redistilled 2-methylnaphthalene. The bromomethyl naphthalene was obtained as a pure crystalline solid, in contrast to the oil previously obtained. Isothiouronium salt formation in ethanol followed by hydrolysis gave the thiol.

Hexakis(2-naphthylmethylthiomethyl)benzene (141)

(141) was prepared in a similar manner to (130), argon being used in place of nitrogen. The reagents used were dry ethanol (60 ml), sodium (0.4 g, 0.017 mol), 2-mercaptomethylnaphthalene (3.0 g, 0.017 mol) and hexakis(bromomethyl)benzene (1.21 g, 0.0019 mol). After the normal work-up procedure, drying *in vacuo* gave crude (141) (2.1 g, 92.3%) m.p. 194–198° (ex toluene), ν_{max}(KBr) 3057, 1600,1510, 1232, 819 and 751 cm^{-1}, τ($CDCl_3$) 7.11 (12H, s, br.), 6.68 (12H, s, br.) and *ca*. 2.1–2.9 (42H, m). A satisfactory microanalysis was not obtained for this compound. Results of inclusion experiments are given in Tables 17 and 18.

Hexakis(2-methylphenylthiomethyl)benzene (142)

To dry *n*-amyl alcohol (100 ml) was added sodium metal (2.2 g, 0.1 mol) under an atmosphere of dry oxygen-free argon. The sodium reacted slowly at room temperature but at 100° it reacted completely. 2-methylthiophenol (11.2 g, 0.09 mol) and hexakis(bromomethyl)benzene (6.36 g, o.01 mol) were then added in turn the reaction mixture then being stirred under reflux for six hours. On cooling the mixture was added to ice/water (500 ml). An extremely fine precipitate was obtained which was collected by filtration, washed with water, dilute aqueous sodium hydroxide and more water till neutrality. Drying *in vacuo* gave crude (142)

(8.81 g, 99%) m.p. 199–200° (ex 1,4-dioxan), (Found: C, 72.37; H, 5.91. $C_{54}H_{54}S_6$ requires C, 72.43; H, 6.08%), ν_{max}(KBr) 3064, 1590, 1470, 1458, 1381, 1066, 1048 and 747 cm^{-1}, τ($CDCl_3$) ca. 2.7–3.0 (24H, m), 5.81 (12H, s, br.) and 7.72 (18H, s).

Hexakis(3-methylphenylthiomethyl)benzene (143)

(143) was prepared by a similar method as used for (142), except that argon was used in place of nitrogen, and the reagents used were: dry *n*-amyl alcohol (100 ml), sodium metal (2.3 g, 0.1 mol), 3-methylthiophenol (11.2 g, 0.09 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mole). After the normal work-up procedure, drying *in vacuo* gave crude (143) (8.7 g, 97%), m.p. 132–133° (ex toluene), (Found: C, 72.60; H, 6.10; S, 21.31. $C_{54}H_{54}S_6$ requires C, 72.43; H, 6.08, S, 21.49%), ν_{max}(KBr) 2925, 1594, 1580, 1475, 772, 695 and 686 cm^{-1}, τ($CDCl_3$) 3.92 (24H, m) 5.70 (12H, s, br.) and 7.73 (18H, s).

Results of inclusion experiments are given in Table 21.

Hexakis(4-methylphenylthiomethyl)benzene (144) [140]

(144), a known compound, was prepared by the same method as used for (142). The standard work-up procedure followed by drying *in vacuo* gave crude (142) in 99% yield, m.p. 182–184° (ex toluene) (lit.183.5–184°) τ($CDCl_3$) AA'BB' system centred at 2.92 (24H, J 9Hz), 5.83 (12H, s, br.) and 7.70 (18H, s).

Hexakis(2-methylphenoxymethyl)benzene (145)

To dry redistilled diglyme (100 ml) was added sodium metal (2.07 g, 0.09 mol) and 2-methylphenol (9.73 g, 0.09 mol) under an atmosphere of oxygen-free dry nitrogen. After the sodium had reacted completely, at 100°, hexakis(bromomethyl)benzene (6.39 g, 0.01 mol) was added. The reaction mixture was stirred under reflux for

24 hours, then on cooling was poured into ice/water (250 ml). The very fine pink precipitate was collected by filtration, washed with water, dilute aqueous sodium hydroxide, and more water. Drying *in vacuo* gave (145) (7.99 g, 99%), m.p. 172–176° (ex toluene), (Found: C, 81.50; H, 6.97. $C_{54}H_{54}O_6$ requires C, 81.12; H, 6.81% MW 798) m/e 798, ν_{max}(KBr) 1606, 1493, 1240, 1191. 1124, 1054, 1012 and 750 cm^{-1}, τ($CDCl_3$) ca. 2.8–3.3 (24H, m), 4.74 (12H, s) and 7.89 (18H, s). Results of inclusion experiments are given in Table 23.

Hexakis(3-methylphenoxymethyl)benzene (146)

(146) was prepared in an analogous manner to (145), the reagents used being: dry diglyme (100 ml), sodium metal (2.07 g, 0.09 mol), 3-methylphenol (9.73 g, 0.09 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). The normal work-up and drying *in vacuo* gave (146) (7.8 g, 98%) m.p. 198–199.5° (ex toluene, 1:2), (Found: C, 80.92; H, 6.74. $C_{54}H_{54}O_6$ requires C, 81.12; H, 6.81%), No molecular ion, ν_{max}(KBr) 1612, 1587, 1491, 1290, 1269, 1248, 1156, 1031 and 775 cm^{-1}, τ($CDCl_3$) *ca.* 2.8–3.4 (24H, m), 4.84 (12H, s) and 7.79 (18H, s). Results of inclusion experiments are given in Table 24.

Hexakis(4-methylphenoxymethyl)benzene (147)

(147) was prepared by a similar method as used for (145), the reagents used being: dry diglyme (100 ml), sodium metal (1.07 g, 0.09 mol), 4-methylphenol (9.73 g, 0.09 mol), and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). The normal work-up procedure followed by drying *in vacuo* gave crude (147) (7.42 g, 93%)

m.p. 250-255° (ex toluene), (Found: C, 81.40; H,6.80. $C_{54}H_{54}O_6$ requires C, 81.12; H, 6.81% MW 798) m/e 798, ν_{max}(KBr) 1510, 1292, 1230, 1179, 1018, 820 and 800 cm^{-1}, τ($CDCl_3$) *ca*. 2.8–3.3 (24H, m) 4.83 (12H, s) and 7.73 (18H, s).

Hexakis(2,5-dimethylphenoxymethyl)benzene (148)

(148) was prepared by a similar method as used for (145), the reagents used being: dry diglyme (100 ml), sodium metal (2.3 g, 0.1 mol), 2,5-dimethylphenol (11.0 g, 0.09 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). The normal work-up procedure and drying *in vacuo* gave crude (148) (7.97 g, 90%) m.p. 195-196° (ex toluene), (Found: C, 81.75; H, 7.69. $C_{60}H_{66}O_6$ requires C, 81.59; H. 7.5% MW 882) m/e 882 ν_{max}(KBr) 1511, 1417, 1261, 1159, 1131, 1023 and 809 cm^{-1}, τ($CDCl_3$) *ca*. 2.9–3.4 (18H, m), 4.74 (12H, s, br.), 7.81 (18H, s) and 7.89 (18H, s).

Hexakis(3,5-dimethylphenoxymethyl)benzene (149)

(149) was prepared by a similar method as used for (145), the reagents used being: dry diglyme (100 ml), sodium metal (2.3 g, 0.1 mol), 3,5-dimethylphenol (11.0 g, 0.09 mol) and hexakis(bromomethyl)benzene (6.36 g, 0.01 mol). After only partial reaction of the sodium with the xylenol, a solid formed which prevented efficient stirring. Addition of more diglyme did not disperse the solid which is probably a sodium salt of the dimethylphenol. The hexabromide was added giving an immediate cloudiness and slow disappearance of the phenoxide salt. Normal work-up and drying *in vacuo* gave crude (149) in quantitative uield m.p. 235-240° (ex toluene), (Found: C, 81.73; H, 7.41. $C_{60}H_{66}O_6$ requires C, 81.59; H 7.53% MW 882) m/e 882 ν_{max}(KBr) 1616,

1598, 1324, 1298, 1171, 1156, 1068, 734, 729 and 688 cm^{-1}, $\tau(CDCl_3)$ *ca*. 2.3-2.5 (18H, m), 4.81 (12H, s, br.) and 7.78 (36H, s). Results of inclusion experiments are given in Table 25.

Hexakis(5,6,7,8-(4H)-2-naphthyloxymethyl)benzene (150)

(150) was prepared by a similar method as used for (145), the reagents used being: dry diglyme (100 ml), sodium metal (2.3 g, 0.1 mol), tetralol(-2-hydroxy-5,6,7,8-(4H)-naphthalene) (13.34 g, 0.09 mol) and hexakis (bromomethyl)benzene (6.36 g, 0.01 mol). As in the preparation of (149), a salt precipitated during the initial reaction between sodium and the phenol. The same procedure was adopted and the reaction was allowed to continue. After the normal work-up procedure, drying *in vacuo* gave crude (150) (9.1 g, 87%) m.p. 223-226° (ex dioxan/chloroform) (Found: C, 83.30; H, 7.33. $C_{72}H_{78}O_6$ requires C, 83.20; H, 7.56%) $\nu_{max}(KBr)$ 2930, 1616, 1502, 1249, 1230, 1159, 1121 and 1013 cm^{-1}, $\tau(CDCl_3)$ ca. 3.1-3.4 (18H, m), 4.84 (12H, s, br.), 7.34 (12H, m) and 8.24 (24H, m).

Hexakis(2-phenylethylthiomethyl)benzene (151)

To dry DMF (50 ml), under an atmosphere of dry, oxygen-free argon was added sodium hydride (1.2 g, 50 mmol) and 2-phenylethanethiol (7.4 g, 50 mmol). After hydrogen evolution had ceased, finely powdered hexakis(bromomethyl)benzene (3.5 g, 5.5 mmol) was added and the reaction mixture stirred at 95-100° C for 2½ h. On cooling, the mixture was poured into ice/water (300 ml), the resulting white precipitate being collected by filtration. Washing with water, dilute aqueous NaOH and more water, then drying *in vacuo* gave crude (151) (5.3 g, 98%) m.p. 87-87.5° (from ethyl acetate, unsolvated). (Found: C, 73.76; H, 6.90. $C_{60}H_{66}S_6$ requires C, 73.56; H, 6.79%), ν_{max}(KBr) 3031, 2932, 1498, 1454, 1428, 1230, 1224, 1214, 756, 736, 711 and 699 cm^{-1}, τ($CDCl_3$) 2.79 (30H, m), 5.93 (12H, s, br.) and 7.11 (24H, m). Results of inclusion experiments are given in Table 26.

Hexakis(3-phenylpropylthiomethyl)benzene (152)

(152) was prepared in an analogous manner to (151), the reagents used being: dry DMF (50 ml) sodium hydride (1.1 g, 45 mmol), 3-phenylpropanethiol (6.9 g, 45 mmol) and hexakis(bromomethyl)-benzene (3.2 g, 5 mmol). The normal work-up procedure gave crude (152) (4.8 g, 90%) m.p. 80-81° (from ethyl acetate). (Found: C, 74.76; H, 7.63. $C_{66}H_{78}S_6$ requires C, 74.52; H, 7.39%), ν_{max}(KBr) 3029, 2954, 2931, 1499, 1480, 1455, 751 and 700 cm^{-1}, τ($CDCl_3$) ca. 2.6-3.0 (30H, m), 5.95 (12H, s, br.), ca. 7.2-7.6 (14H, m) and ca. 7.8-8.3 (12H, m). (152) did not form inclusion compounds with cyclohexane, acetone and nitromethane.

1,3,5-Tris(bromomethyl)benzene [238]

This was prepared by the method of Vogtle, from mesitylene and N-bromosuccinimide. Several recrystallisations were required to give material of sufficient purity m.p. 93-94° from $CHCl_3$ (lit 94°C), τ($CDCl_3$), 2.68 (3H, s) and 5.57 (6H, s).

1,3,5-Tris(phenylthiomethyl)benzene (153)

To dry ethanol (25 ml), under an atmosphere of dry, oxygen-free nitrogen was added sodium metal (0.25 g, 11 mmol). After hydrogen evolution had ceased thiophenol (1.2 g, 11 mmol) was added, followed immediately by 1,3,5-tris(bromomethyl)benzene (1.0 g, 2.8 mmol). Stirring under reflux for 4 hours gave, on cooling, a white precipitate and a yellow oil. The precipitate (NaBr) was removed by filtration and the solvent removed from the filtrate under vacuum. The resulting oil was dissolved in chloroform, the solution then being washed with water, dilute aqueous NaOH and more water till neutrality, then dried over anhydrous $MgSO_4$. Removal of the chloroform gave an oil which was further purified by column chromatography over silica. Elution with cyclohexane/chloroform (50:50) gave pure (153), (0.93 g, 75%), m.p. 55-56° (from cyclopentane). (Found: C, 72.73; H, 5.46; S, 21.81. $C_{27}H_{24}S_3$ requires C, 72.83; H, 5.44; S 21.63%) m/e 444 (M^+) ν_{max}(KBr) 3050, 1596, 1583, 1481, 1439, 893, 733 and 691 cm^{-1}, $\tau(CDCl_3)$ 2.81 (15H, m), 2.96 (3H s) and 6.04 (6H, s).

(153) did not form inclusion compounds with cyclohexane, benzene, 1,4-dioxan, n-decane or methanol.

1,3,5-Tris(benzylthiomethyl)benzene (154)

To dry ethanol (20 ml), under an atmosphere of dry, oxygen-free argon, was added sodium metal (0.23 g, 10 mmol). After the hydrogen evolution had ceased, benzyl mercaptan (1.2 g, 10 mmol) and 1,3,5-tris(bromomethyl)benzene (1.0 g, 2.8 mmol) were added in turn. Stirring under reflux for 15 minutes, then cooling, gave a precipitate of NaBr and a pale yellow oil, as in the preparation of (153). Addition of the reaction mixture to ice/water (100 ml) gave an oil which solidified on standing. The off-white material was collected by filtration, washed with water, dilute aqueous NaOH and more water, then dried <u>in vacuo</u>. Recrystallisation, twice, from cyclohexane gave (154) (0.85 g, 62%), m.p. 61-62°, (Found: C, 73.96; H, 6.19. $C_{30}H_{30}S_3$ requires C, 74.03; H, 6.21%) <u>m/e</u> 486, ν_{max}(KBr) 3066, 3033, 1603, 1496, 1454, 1074, 728, and 698 cm^{-1}, τ($CDCl_3$) 2.73 (15H, s), 2.95 (3H, s), 6.42 (6H, s) and 6.47 (6H s). Unsolvated material was obtained from benzene, 1,4-dioxan, cyclohexane or n-decane.

<u>1,3,5-Tris(2-phenylethylthiomethyl)benzene</u> (155)

A similar procedure to that used for (154) was adopted, the reagents being dry ethanol (20 ml), sodium metal (0.23 g, 10 mmol), 2-phenylethanethiol (1.38 g, 10 mmol) and 1,3,5-tris(bromomethyl)-benzene (1.0 g, 2.8 mmol). The colourless oil, produced on addition to ice/water (100 ml), did not solidify. It was dissolved in chloroform and the solution washed with water, dilute aqueous NaOH and more water and dried over anhydrous $MgSO_4$. Removal of the chloroform gave an oil which was further purified by column chromatography (SiO_2, chloroform/petrol (33:67)) and by prep. T.L.C. (SiO_2, chloroform/petrol (50:50) to give (155), a viscous oil, in good yield. (Found: <u>m/e</u> 528.1973. $C_{33}H_{36}S_3$ requires 528.1979) ν_{max}(thin film) 3030, 2919, 1604, 1498, 736 and 700 cm^{-1}, τ($CDCl_3$) <u>ca</u>. 2.6-3.0 (18H, m), 6.36 (6H, s) and <u>ca</u>. 7.0-7.6 (12H, m).

1,3,5-Tris(3-phenylpropylthiomethyl)benzene (156)

An identical procedure to that used for (154) was employed, except that the reagents used were: dry ethanol (20 ml), sodium metal (0.23 g, 10 mmol), 3-phenylpropanethiol (1.52 g, 10 mmol) and 1,3,5-tris(bromomethyl)benzene (1.0 g, 2.8 mmol). Work-up and chromatograhpic purification gave (156) as a colourless oil, in good yield. (Found: m/e 570.24484. $C_{36}H_{42}S_3$ requires 570.24484) ν_{max} (thin film) 3029, 2926, 2860, 1604, 1498, 1455, 1236, 747 and 700 cm^{-1} $\tau(CDCl_3)$ ca. 2.6-3.0 (18H, m), 6.38 (6H, s), 7.35 (6H, t), 7.61 (6H, t) and 8.14 (6H, m).

1,3,5-Tris(3,5-dimethylbenzylthiomethyl)benzene (157)

(157) was prepared by a similar method as used for (154), the reagents used being: dry ethanol (20 ml), sodium metal (0.25 g, 0.01 mol), 3,5-dimethylbenzyl mercaptan (1.7 g, 0.01 mol) and 1,3,5-tris(bromomethyl)benzene (1.0 g, 0.003 mol). Aqueous work-up and recrystallisation from ethyl acetate gave (157) (1.1 g, 77%), m.p. 65-66°, (Found: m/e 570.24482. $C_{36}H_{42}S_3$ requires 570.24484) ν_{max}(KBr) 3020, 2912, 1603, 1465, 1453, 1421, 871, 852, 832, 749, 704 and 689 cm^{-1}, $\tau(CDCl_3)$ 2.92 (3H, s), 3.12 (9H, s, br.), 6.44 (6H, s), 6.48 (6H, s) and 7.75 (18H, s).

Unsolvated material was obtained from acetone, toluene, benzene and n-decane.

1,3,5-Tris(Cholest-5-ene-3β-thiomethyl)benzene (158)

This was prepared in an analagous manner to (154), reflux however being prolonged to four hours, and the reagents used being: dry ethanol (20 ml), sodium metal (1.12 g, 0.005 mol), Cholest-5-ene-3 -thiol (1.97 g, 0.005 mol) and 1,3,5-tris(bromomethyl)-

benzene (0.5 g, 0.0013 mol). Aqueous work-up and repeated recrystallisation from methylene chloride/cyclohexane gave (158) in good yield m.p. 189–192° (ex methylene chloride/n-decane), Found: C, 81.95; H, 11.16; S, 7.10. $C_{90}H_{144}S_3$ requires C, 81.75; H, 10.97; S, 7.27%) ν_{max}(KBr) 2927, 2895, 2864, 1600, 1460, 1433 1382, 1375 and 1366 cm^{-1}, τ($CDCl_3$) 2.86 (3H, s), 4.76 (3H, m), 6.29 (6H, s, br) and ca. 7.5–9.5, complex spectrum (132H). Unsolvated material obtained from, methylene chloride, n-decane/ methylene chloride and cyclohexane/chloroform.

1,2,5,6,9,10-Hexabromocyclododecane (160) and (161) [223]

To trans,trans,trans-cyclododeca-1,5,9-triene (159), (88.5 g, 0.55 mmol) in glacial acetic acid (350 ml) was added bromine (312 g, 1.74 mol) over a period of four hours, with continuous stirring, and cooling using an ice bath. Aqueous work-up extraction using ethyl acetate gave a high yield of the hexabromide as a dark oil. By freezing a toluene solution of the isomeric mixture a pale yellow solid (41 g) m.p. 170–178° was obtained, the remainder of the reaction product remaining as a dark glass (see Chapter 5). Recrystallisation of the solid hexabromide from cyclohexane gave pure (161) m.p. 181–182° (lit. 178–179°).

The inclusion behaviour of (161) is given in Table 29.

1,5,9-Tribromo-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (162) [223]

The isomeric mixture of tribromides (162) and (163) was obtained in good yield by treatment of the hexabromocyclododecanes (160) and (161) with sodium ethoxide in ethanol, as described in the literature. The pale yellow oil was treated chromatographically but gave very poor separation of the two isomers under a variety of conditions. Small amounts of very pure symmetrical tribromide (162) were obtained, m.p. 115-117° from *n*-hexane (lit. 116-117°).

1,5,9-Tris(phenylthio)-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (164)

Cuprous thiophenolate (2.19 g, 0.013 mol), prepared by the method of Adams,[239] redistilled quinoline (14 ml) AnalaR pyridine (1.4 ml) and 1,5,9-tribromo-*cis*,*cis*,*cis*-cyclododeca-1,5,9-triene (162), (1.12 g, 0.003 mol) were placed in a glass tube which was evacuated then sealed. The tube was immersed in a Wood's metal bath and heated at 170-184° for six hours. While the reaction mixture was still warm, the tube was opened and the dark brown mixture added to 5M hydrochloric acid (40 ml) in ice/water (100 ml). The mixture was brought to pH6 by addition of dilute Na_2CO_3 when the pale yellow precipitate was collected by filtration. Washing with water, dilute NaOH and more water till neutrality yielded a brown solid. Extraction of the solid using chloroform, employing Soxhlet apparatus, followed by column chromatography of the isolated material (silica, 4:1 petrol/ethyl acetate) gave a yellow oil. Addition of cyclohexane produced a white fibrous solid which was then recrystallised from methanol to give pure (164) (0.49 g, 36%) m.p. 100-101°C, (Found: C, 74.25; H, 6.40;

S, 19.65. $C_{30}H_{30}S_3$ requires C, 74.01; H, 6.21; S, 19.75% MW 486), m/e 486, ν_{max}(KBr) 2976, 1581, 1478, 1466, 1438, 1022, 874, 740, 734 and 690 cm^{-1}, τ($CDCl_3$) 2.79 (15H, m), 4.16 (3H, m) and ca. 7.4-7.8 (12H, m). Results of inclusion experiments are given in Table 27.

1,5,9-Tris(4methylphenylthio)-cis,cis,cis-cyclododeca-1,5,9-triene (165)

(165) was prepared in a similar manner to that used for (164) the reagents being: cuprous 4-methylthiophenolate (1.93 g, 0.010 mol), redistilled quinoline (12 ml), AnalaR pyridine (1.2 ml) and 1,5,9-tribromo-cis,cis,cis-cyclododeca-1,5,9-triene (162) (0.92 g, 0.002 mol). Using a similar work-up procedure and chromatographic purification, recrystallisation from ethanol gave (165), (0.37 g, 30%) m.p. 99-100°, (Found: C, 75.15; H, 6.92. $C_{33}H_{36}S_3$ requires C, 74.95; H, 6.86% MW 528), m/e 528, ν_{max}(KBr) 2951, 1614, 1492, 1469, 1018, 811 and 805 cm^{-1}, τ(CS_2) AA'BB' quartet; 2.89 (6H, d, J 8Hz) and 3.01 (6H, d, J 8Hz), 4.32 (3H, m) and ca. 7.6-7.8 (21H, m).

Results of inclusion experiments are given in Table 28

R-(+)-1-phenylethanethiol (170) [227]

This was prepared from 1-phenylethyl bromide (166) [240] and (-)-sodium O-menthyl dithiocarbonate (167) [241] via (-)-O-methyl S-1-phenylethyl dithiocarbonate (168) and (+)-1-phenylethylthiomercury chloride, following the method of Isola. The resulting thiol had physical and spectroscopic properties consistent with literature data, $[\alpha]_D^{25}$ =+ 87.8° (c = 1.33, ethanol), (lit. $[\alpha]_D^{25}$ = +91.7 (c = 6.17, abs. ethanol).

Hexakis(R-1-phenylethylthiomethyl)benzene (171)

To dry ethanol (30 ml), under an atmosphere of dry, oxygen-free argon, was added sodium metal (0.20 g, 0.009 mol). After hydrogen evolution had ceased, R-(+)-1-phenylethanethiol (170), (1.3 g, 0.009 mol) was added, followed immediately by finely powdered hexakis(bromomethyl)benzene (0.66 g, 0.001 mol). After stirring under reflux for 10 minutes the reaction mixture became homogeneous. After 1 hour reflux, the mixture was cooled then added to ice/water (150 ml). The white precipitate was collected by filtration, washed with water, dilute aqueous NaOH, and more water, then dried *in vacuo* to give crude (171) (0.89 g, 88%), m.p. 137-138° (from benzene). Found: C, 73.70; H, 6.65; S, 19.62. $C_{60}H_{66}S_6$ requires C, 73.57; H, 6.79; S, 19.64% ν_{max}(KBr) 3030, 2967, 2925, 1492, 1453; 1030, 766 and 699 cm^{-1}, τ($CDCl_3$) 2.70 (30H, m), 6.37 (6H, q, j 7Hz), AB quartet; 6.33 (6H, d, J_{AB} 11Hz) and 6.52 (6H, d, J_{AB} 11Hz)and 8.49 (18H, d, J7Hz), ^{13}C n.m.r. (proton noise-decoupled, 106 K transients) showed only 8 singlets δ_c($CDCl_3$) 21.8, 29.7, 45.1, 127.1, 127.2, 128.4, 135.2 and 143.9, $[\alpha]^{25}_{D}$ =+135.6°(c = 0.19, $CHCl_3$).

Hexakis(R-1-phenylethylsulphonylmethyl)benzene (172)

Hexakis(R-1-phenylethylthiomethyl)benzene (171) (0.22 g, 0.2 mmol) was added to a solution of hydrogen peroxide (2.2 ml) in glacial acetic acid (22 ml). The mixture was stirred under reflux for 2 hours then cooled, and added to ice/water (250 ml).

No precipitate was obtained*, the mixture then undergoing freeze-drying to give crude (172) as a white powder (0.24 g, 91%), m.p. 255-260, decomp., (from acetic acid, desolvated in vacuo), ν_{max}(KBr) 3008, 2985, 1497, 1458, 1314, 1236, 1137, 1123, 786 and 777 cm^{-1} ($CDCl_3$) 2.61 (30H, s), AB quartet; 5.31 (6H, d, J_{AB} 16Hz) and 5.40 (6H, d, J_{AB}16Hz), 6.49 (6H, q, 7Hz) and 8.48 (12H, d, 7Hz), ^{13}C n.m.r. δ_c($CDCl_3$) 13.6 (q), 48.0 (t), 65.4 (d), 129.0 (superposed d), 129.7 (d), 133.6 (s), 133.8 (s). A satisfactory microanalysis was not obtained for this compound.

*In one run a precipitate was obtained, which was collected by filtration, washed with water, then dried in vacuo to give (172).

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SYNTHESIS AND INCLUSION PROPERTIES OF TWELVE-MEMBERED CARBOCYCLIC HOSTS

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SYNTHESIS AND INCLUSION PROPERTIES OF TWELVE-MEMBERED CARBOCYCLIC HOSTS

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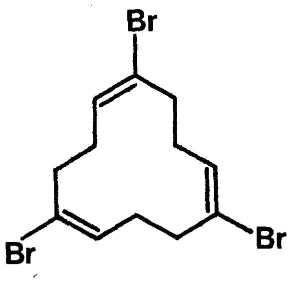
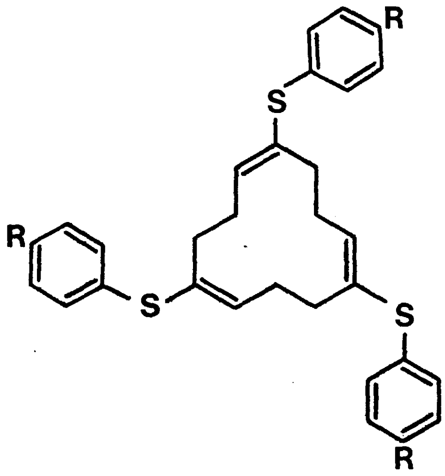
Trigonal symmetry is a feature encountered in the structures of certain hosts possessing the ability to form crystalline inclusion compounds in which the enclosing structure is consolidated by van der Waals forces alone.[1] Important hosts of this type are tri-*o*-thymotide,[2] perhydrotriphenylene,[3] cycloveratril,[4] triphenylmethane,[5] cyclotriphosphazenes,[6] and members of the hexa-host family.[7] Incorporating trigonal symmetry as a useful design feature, we have synthesised the twelve-membered carbocycles (IIa) and (IIb), and these molecules prove to be novel hosts capable of forming stable molecular inclusion compounds with volatile guest species.



(I)



(IIa); R=H

(IIb); R=Me

References

1. Only in certain cases, however, does the individual host molecule attain exact threefold crystallographic symmetry in its inclusion compounds (see, e.g. ref.7), though trigonal (or hexagonal) lattice symmetry is often present, as for host structures involving hydrogen bonding (see, e.g. ref.8).
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12. The liquid isomer, (IV), shows two equally intense singlets at 34.8 and 58.1 δ_c, in the noise-decoupled ^{13}C n.m.r. spectrum (in acetone-d_6 at 50°). A conformational study of (III) and (IV) will be the subject of a future publication.

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HEXAKIS(BENZYLTHIOMETHYL)BENZENE: STRUCTURE OF THE 1,4-DIOXAN CLATHRATE AND PROPERTIES OF RELATED HOSTS

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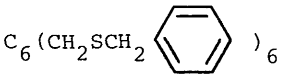
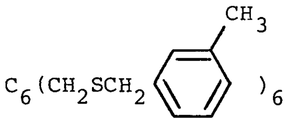
The use of analogy[1-3] has led to the discovery of a series of inclusion hosts[4] based on a hexa-substituted benzene skeleton. We now report the results of an X-ray study of the 1,4-dioxan clathrate of hexakis(benzylthiomethyl)-benzene[1] (I) which has a three atom CH_2SCH_2 linkage between each side-chain aromatic ring and the central core of the molecule. Also briefly described are the varying inclusion properties of the related molecules (II), (III), and (IV), which were prepared[5] by reaction of hexakis(bromomethyl)benzene, $C_6(CH_2Br)_6$, with the appropriate aralkyl mercaptan in NaOEt/EtOH.

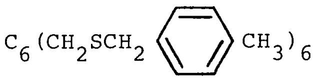
(I)



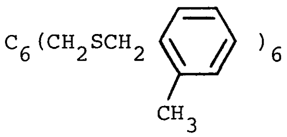
(III)



(II)



(IV)



The dioxan adduct of (I) crystallises in the monoclinic space group *P*2_1/*c* with two host and two guest molecules in the unit cell (Table). The structure was solved by direct methods employing 2495 independent diffractometer data (using a Lindemann capillary to inhibit solvent loss), and refined to a final *R* value of 0.045. All the hydrogen atoms have been located and allowed for; full details of the structural analysis will be published elsewhere.

Figure 1 shows a view looking directly onto the central benzene ring of the host molecule. The molecule is located on a crystallographic centre of inversion and is thus constrained to be centrosymmetric. Although (I) lacks the exact three-fold symmetry found for a clathrate[3] of hexaphenylthiobenzene, $C_6(SPh)_6$, the 'legs' of this molecule still point alternately above and below the plane of the central benzene ring. Figure 2 illustrates the host to guest packing in the crystal, the host and guest molecules above and below those shown being directly superposed in this view. All the host and guest molecules are situated at crystallographic centres of symmetry on the *b c* plane. The chair-shaped dioxan guest molecule is accommodated in a closed cage and no short host-guest contacts have been found.

percentages included by (III), 85%:15%, may be compared with the corresponding values of 75%:25% found[2] for the parent (I). Work on related hosts is underway.

We thank the S.R.C. for support.

Table Some Selected Crystal Data for Hexakis(benzylthiomethyl)-benzene (I) and Related Molecules

Host	Guest (host:guest ratio[†])	Space Group	Lattice Parameters
(I)	1,4-dioxan (1:1)	$P2_1/c$ monoclinic	a = 10.542, b = 20.863, c = 12.496Å, β = 95.48°, Z = 2(host).
(II)	1,4-dioxan (1:1)	$Pcab$ orthorhombic	a = 18.67, b = 14.18, c = 23.22Å, Z = 4(host).
(III)	p/o-xylene[§] (1:1)	$P2_1/c$ monoclinic	a = 9.62, b = 15.45, c = 22.72Å, β = 111.0°, Z = 2(host).

[†] Ratio determined by ^1H n.m.r. employing $CDCl_3$ as solvent.

[§] Crystals prepared by recrystallisation from an equimolar mixture of ortho and para-xylene; a marked selectivity for the para-isomer is found (see text).

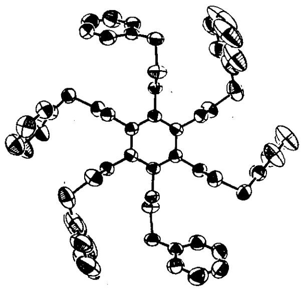


Figure 1. An ORTEP drawing showing a view normal to the plane of the central benzene ring of host molecule hexakis-(benzylthiomethyl)benzene (I) in its dioxan clathrate. The hydrogen atoms have been omitted for clarity.

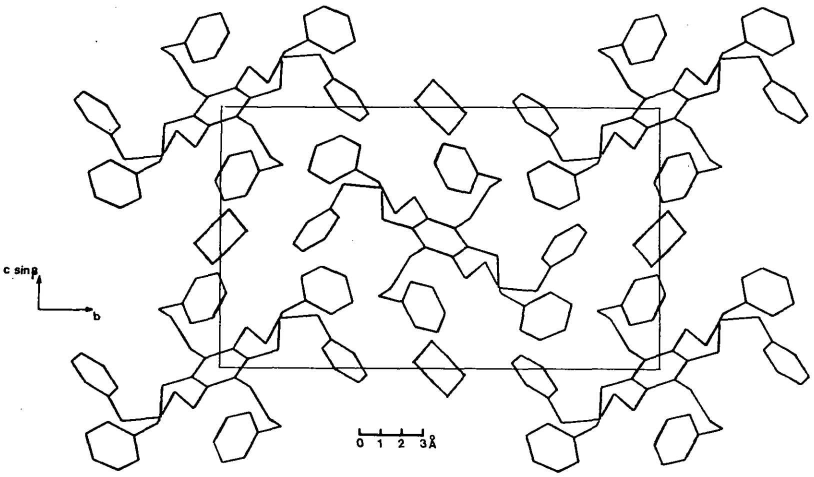


Figure 2. Host to guest packing in the dioxan clathrate of (I), as viewed along the a-axis.

Among the compounds related to (I) which have been studied are the methyl derivatives (II), (III), and (IV). The para-derivative (II) forms orthorhombic crystals of an adduct with 1,4-dioxan (see Table). In contrast to the ortho-derivative (IV), for which inclusion behaviour has not been observed, the meta compound (III) behaves similarly to the parent (I) including a wide range of guest molecules. For example (III) forms inclusion compounds with cyclohexane (1:1), acetone (1:2), benzene (1:1), furan (1:2), 1,4-dioxan (1:1), ethyl acetate (1:1), anisole (1:1), ethyl benzene (1:1), and p-xylene (1:1), the host to guest ratio being indicated in each case. Interestingly, when (III) is recrystallised from an equimolar mixture of para and ortho-xylene a marked preference for the para-isomer is found;[6] the relative isomer

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