THE DESIGN AND SYNTHESIS OF NEW CLATHRATE COMPOUNDS

by

DEREK RENNIE WILSON B.Sc.

being a thesis submitted for the degree of Doctor of Philosophy in the Faculty of Science of the University of Glasgow.

October, 1976.

ERRATA

1. Page 53, line 3: "for" should read "by".

2. Page 102, line 6: "Sommerlet-Hauser" should read "Sommelet-Hauser".

3. Page 111, line 21: "collaborration" should read "collaboration".

ACKNOWLEDGMENTS

I should like to express my sincere gratitude to my supervisor, Dr. David D. MacNicol for his expert advice and guidance during the course of this work.

In addition, I should like to thank the Science Research Council for maintenance during the last three years and Professor G.W. Kirby for providing the opportunities and facilities for research in this department.

I am also indebted to the technical staff, especially Mr. J. Gall and Dr. D.J. Rycroft for n.m.r. spectra, Mrs. F. Lawrie and her staff for i.r. spectra, Mr. A. Ritchie for mass spectra and Mrs. W. Harkness for microanalyses.

I should also like to convey my sincere thanks to Dr. A.D.U. Hardy for undertaking all the X-ray investigations and to Dr. I.C. McNeill for thermogravimetric differential thermal analyses.

Finally, I am grateful to my colleagues for their interest and helpful suggestions and to Mrs. Margaret McInnes for typing this thesis.

CONTENTS

(i)/

SUMMARY

A comprehensive review of clathrate inclusion compounds is given. Following this orientating survey, a study of the role of hydrogen bonding in clathrate formation is described, the host chosen for structural modification being Dianin's compound, 4-p-hydroxyphenyl-2,2,4-trimethylchroman. Replacement of the hydroxyl function by the mercapto group gives a new host, which is isomorphous with Dianin's compound, and has sextets of thiol molecules linked by hydrogen bonds involving their SH groups, such that the sulphur atoms form a hexagon. On the other hand, replacement of the OH group of Dianin's compound by the NH_2 group gives an amine which undergoes spontaneous resolution on recrystallisation, without inclusion of solvent. The wide-ranging inclusion properties of 3-p -(2,2,4-trimethylchroman-4-yl)-phenyl-2-phenyl-4(3H)-quinazolinone have been studied, important classes of guest being cycloalkanes, cyclic ethers, halides and ketones and aromatic molecules. In the case of the methylcyclohexane adduct, two guest molecules reside in each large closed cavity formed in the crystal host lattice. A thia-analogue of this versatile host has also been investigated.

A new rationale for the design of clathrate inclusion compounds, whose structures are not directly related/

related to any known host, is described. This approach, based on analogy is distinct from the earlier idea which depends on making judicious modifications to known hosts. Thus a series of hexa-substituted benzenes which incorporate the same symmetry and overall dimensions as the hydrogen-bonded hexameric units found in the clathrates of phenol, hydroquinone and Dianin's compound have been prepared. No less than twelve "hexa-hosts" have been discovered and shown to exhibit a wide range of inclusion behaviour. The crystals of the carbon tetrachloride adduct of hexaphenylthiobenzene are isomorphous with the above hydrogen-bonded hosts' clathrate structures. Furthermore, the substantial selective inclusion behaviour towards mixtures of isomeric hydrocarbon solvents observed for these hosts is of potential commercial interest.

The Dance of the Solids

"Textbooks and Heaven only are ideal,
Solidity is an imperfect state.
Within the cracked and dislocated real,
Nonstoichiometric crystals dominate.
Stray atoms sully and precipitate;
Strange holes, excitons, wander loose; because
of Dangling bonds, a chemical Substrate
Corrodes and catalyses - surface Flaws
Help Epitaxial Growth to fix adsorptive claws".

John Updike,
from Midpoint and Other Poems
(New York : Alfred A. Knopf, 1968, p.20)

INTRODUCTION

1. General description of inclusion compounds [1-17]

A very few compounds out of the many millions known exhibit the interesting and unusual property of molecular inclusion. An inclusion compound may be defined as a unique form of chemical complex in which one molecule is enclosed within another molecule or a network of other molecules. The enclosed molecule is termed the guest and the enclosing moiety the host. The distinguishing feature of this kind of complexation is that no chemical bonding is required between the components. The main criterion is simply that the guest be of suitable size and shape to fit into a cavity within a solid structure formed by host molecules although dipolar interactions between host and guest may sometimes be involved.

The guests may be accommodated in the host structure in three types of voids, corresponding to the classes,

(i) layer

(ii) channel

(iii) cage

In the first type of structure, there is alternation of discrete layers of host and guest molecules and such/

such complexes are known as intercalation compounds, typified by graphite and clay minerals.

Compounds with channel type cavities are called inclusion compounds, the same as for this general class of molecular compounds.

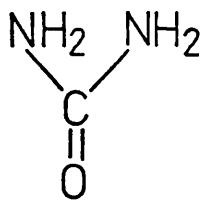
The term clathrate is reserved to describe the fascinating case where the host component includes the guest in closed holes or cages.

Inclusion compounds have been known since 1811 but it was only in the 1940's when Powell examined the clathrates of hydroquinone in single crystal X-ray analyses that their nature was understood. Other hosts, many of which had lain buried in the literature came to light and several have been examined by X-ray crystallography. Details of cavity type and dimensions as well as the types of bonding holding the host molecules together are derived from this powerful method.

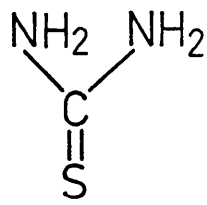
The molecular structures of the most important hosts are presented in tables (I) - (III). Tables (IV) - (VI) indicate the approximate cavity size, representative guests and references,preferably to review articles for each host.

Table (1)

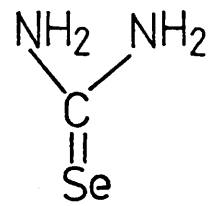
The molecular structure of channel-type inclusion compounds.



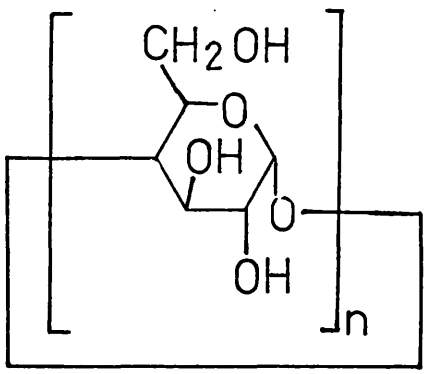
urea (1)



thiourea (2)



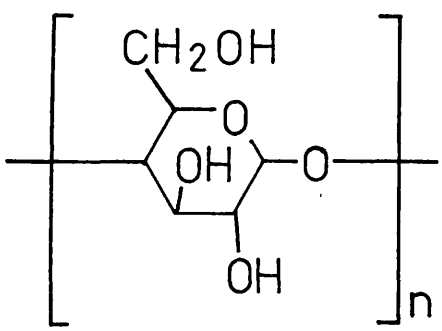
selenourea (3)



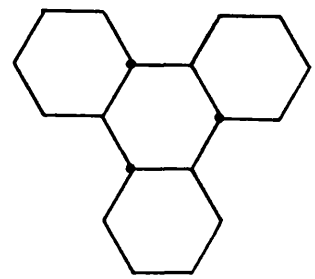
n = 6, α-cyclodextrin (4)*

n = 7, β-cyclodextrin (5)

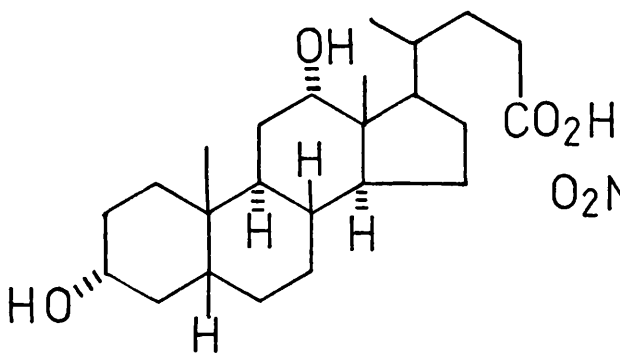
n = 8, γ-cyclodextrin (6)



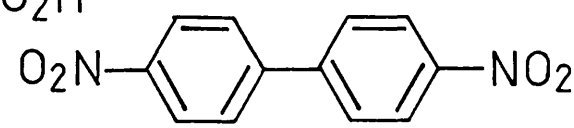
amylose (7)



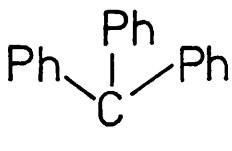
perhydrotriphenylene (8)



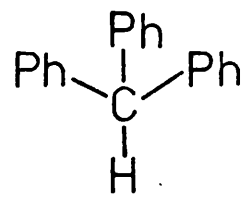
deoxycholic acid (9)



4, 4'-dinitrobiphenyl (10)

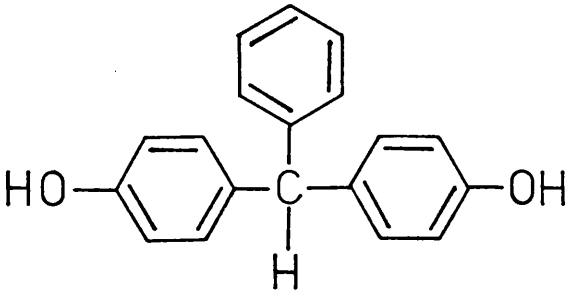


"triphenylmethyl" (11)

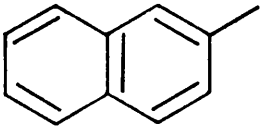


triphenylmethane (12)

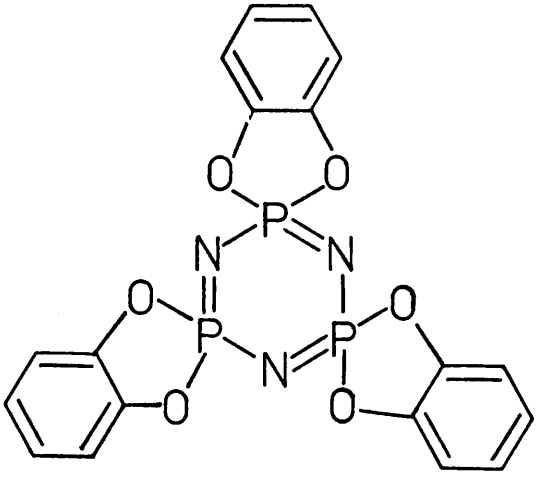
Table (1) continued



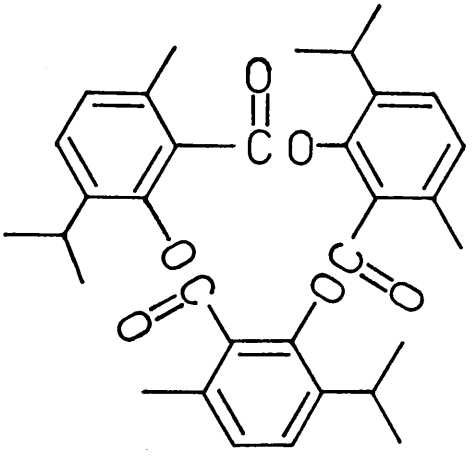
4,4'-dihydroxy-triphenylmethane (13)



2-methylnaphthalene (14)



tris-o-phenylenedioxy-cyclotriphosphazene (15)

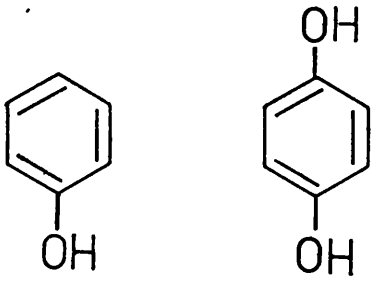


tri-o-thymotide (16)*

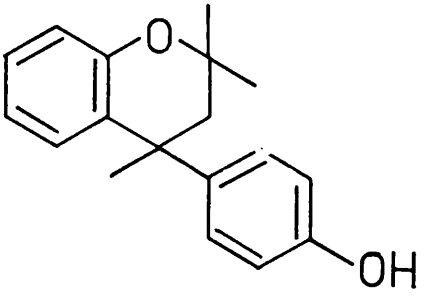
* cage-type cavity also known.

Table (11)

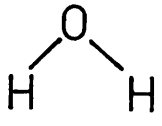
The molecular structures of cage-type inclusion compounds.



phenol (17) hydroquinone (18)



Dianin's compound (19)



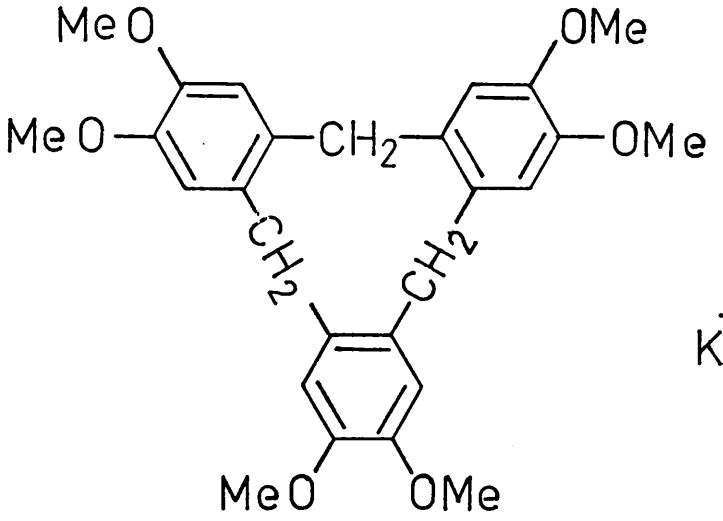
water (20)

$Ni(NH_3)_2Ni(CN)_4$

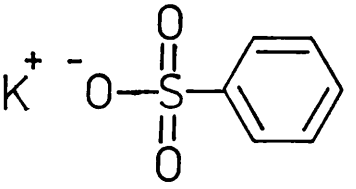
"Hofmann type" (21)

Table (111)

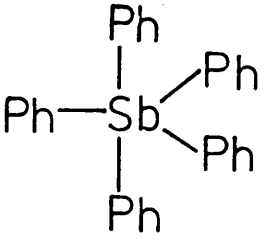
The molecular structures of inclusion compounds whose cavity type is unknown.



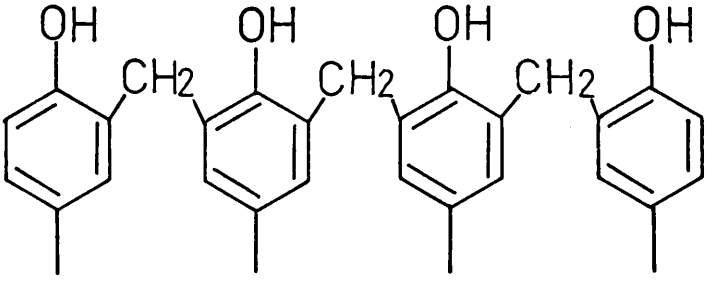
cycloveratril (22)



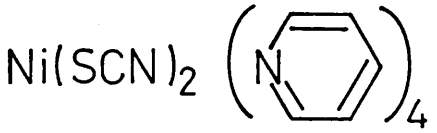
potassium benzene sulphonate (23).



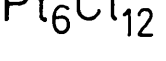
pentaphenyl antimony (24)



p-cresol-novolak tetramer (25)



"Werner complexes" (26)



platinum (11) chloride (27)

Table (IV)

Channel-type inclusion compounds.

Compound	Host	Guest	Channel diameter (A^{o})	References
1	urea	n-octane	5.2	18, 19
2	thiourea	cyclohexane	6.1	18
3	selenourea	camphor	6	20
4	α-cyclodextrin	$(I_2)_n$	6	21 - 24
5	β-cyclodextrin	naphthalene	8	21 - 24
6	γ-cyclodextrin	anthracene	10	21 - 24
7	amylose	n-butanol	6	24
8	perhydrotriphenylene	cyclohexane	6	25

Compound	Host	Guest	Channel diameter (A°)	References
9	deoxycholic acid	n-undecane	5 - 6	26, 27
10	4,4'-dinitrobiphenyl	biphenyl	5	28
11	"triphenylmethyl"	hexane	6	29
12	triphenylmethane	aniline	6	30
13	triphenylmethane derivatives	heptane	6	31
14	2-methylnaphthalene	n-hexane	6	32
15	cyclotriphosphazene derivatives	benzene	4.5 - 10	33, 34
16	tri-o-thymotide	cetyl alcohol	5	35

Table (V)

Cage-type inclusion compounds or clathrates.

Compound	Host	Guest	Cage diam. (A^{o})	Reference
17	phenol	CS_2	4.5	36
18	hydroquinone	SO_2	4	1 - 17
19	Dianin's compound	SF_6	complex	37
20	Water	Cl_2, $(^{i}amyl)_4\ N^{+}F^{-}$	5-6.6	38
21	diamminenickel (11) tetra-cyanonickelate (Hofmann type)	benzene	5	39
16	tri-o-thymotide	ethanol	-	35
8	α-cyclodextrin	Kr, I_2	-	40

Table (VI)

Inclusion compounds whose cavity type is unknown.

Compound	Host	Typical guest	Reference
22	cycloveratril	CS_2	41
23	potassium benzene sulphonate	cyclopentane	42
24	pentaphenyl antimony (arsenic)	cyclohexane	43
25	p-cresol-novolak tetramer	dichloroethane	44
26	di-isocyanato-tetrakis-4-methyl-pyridine nickel (Werner type)	xylene, methanol	45
27	hexaplatinum dodecachloride	benzene, $CHCl_3$	46

It is readily appreciated that the range of structures is diverse, however there are some features common to several hosts. Hydrogen bonding is very important and widespread as exemplified by clathrates of phenol (17), hydroquinone (18), Dianin's compound (19), water (20), deoxycholic acid (9), the ureas (1) - (3) and the cyclodextrins (4) - (6). Hydrogen bonding often gives rise to extremely stable clathrate formation. Both Dianin's compound and hydroquinone include inert gases, there being no loss of guest till the melting point of the host. For argon, this is more than 300° above the normal boiling point. However, hydrogen bonding is not a necessary condition, for in several cases the host structure is held together solely by van der Waals attractive forces, the same as is present in every type of molecular compound. Tri-o-thymotide (16), cycloveratril (22) and all hydrocarbon hosts (8), (11), (12) and (14) are in this category. Molecular symmetry is another important feature. Trigonal or hexagonal symmetry seems to be especially favoured as is apparent from the molecular structure of perhydrotriphenylene (8), triphenylmethane (12), tri-o-thymotide (16), cycloveratril (22), the cyclotriphosphazenes (15) and α-cyclo-dextrin (4). Moreover, X-ray analyses have revealed that hexagonal or trigonal symmetry is present in the clathrate crystal/

crystal structure of the ureas (1) - (2), phenol (17), Dianin's compound (19), amylose (7) etc., a feature not immediately obvious from their molecular structures.

In order to illustrate the bonding properties and uses of inclusion compounds four hosts have been selected for detailed discussion, namely

(i) Dianin's compound

(ii) Simple phenols

(iii) tri-o-thymotide

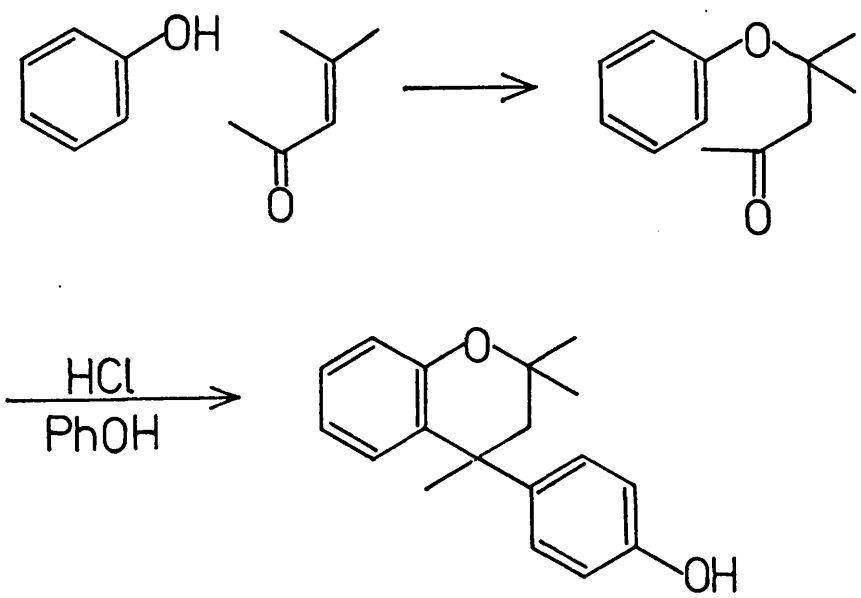
(iv) cyclodextrins

Once these parent hosts had been discovered, research workers wondered if it would be possible to modify the basic host structure and still maintain clathrating ability and if so, how the properties of the new potential hosts could compare with the parent. This is also discussed in the following chapters in relation to the four chosen hosts.

2. Dianin's compound and related systems.

(i) Dianin's compound

This particularly interesting host (19), 4-p-hydroxyphenyl-2,2,4-trimethylchroman was prepared as long ago as 1914 by the Russian chemist, Dianin by the route shown below. [47]



(19)

It received no further attention until Baker and McOmie [48] reinvestigated it in 1955, in the light of Powell's relatively recent work on clathrates, especially hydroquinone.[49] It was shown that an extensive range of guests could be clathrated to give very stable adducts.

Powell/

Powell and Wetters[50] undertook a crystallographic examination of several of these adducts and unsolvated material. All of these exhibited similar crystalline forms and possessed the same unit cell dimensions namely $\underline{a}$ = 27.0A° and $\underline{c}$ = 11.1A°, referred to hexagonal axes. The space group was determined as $R\bar{3}$, the same as that for hydroquinone clathrates. Crystal packing considerations suggested that three assemblies of six mutually hydrogen - bonded molecules could be arranged in the unit cell with satisfactory intermolecular contacts. The complex of six molecules has a form roughly resembling an hour-glass, the top and bottom of which are comprised of hexagons of hydrogen - bonded hydroxyl groups with alternate molecules pointing up and down to confer cup-like geometry (figure 1). In the crystal these complexes are piled directly above each other with their symmetry axes parallel to the $\underline{c}$ -axis. The authors also suggested that the cavities are closed by strong van der Waals bonding between one complex and its neighbour or that adjacent but non-bonded extremities of the two complexes may become entangled.

The/

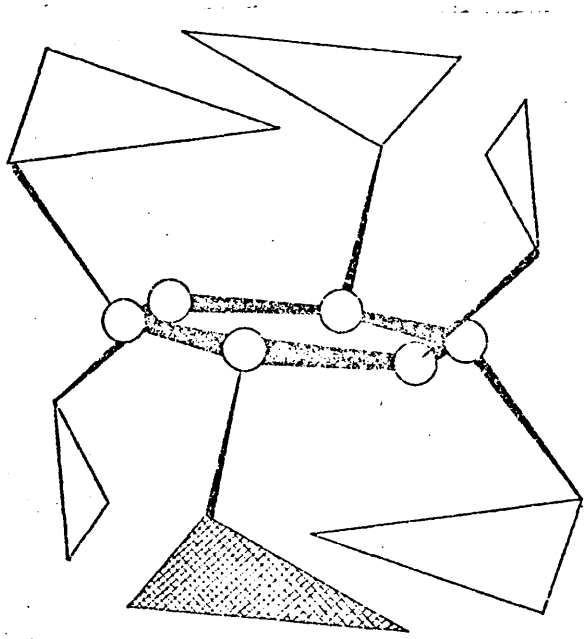


Figure 1

Schematic representation of one hexameric unit formed by Dianin's compound. Circles are OH groups. Lines pointing up or down from the hexagon of hydrogen-bonded OH groups are the links to the rest of the molecule which is denoted by a triangle. The shaded triangle is closest to the observer from whom the lines taper.

(H.M. Powell and B.D.P. Wetters, Chem. and Ind., 1955, 256).

The molecular structure of Dianin's compound was proved unequivocably in 1956 by repetition of the degradative oxidation [51] and by a rational unambiguous synthesis. [52] An impressive list of over fifty guests of diverse functionality and molecular size was presented and the host : guest ratio quoted for each case. Many exhibit a ratio of 6 : 1 i.e. each cage contains one guest molecule, but often seven or more host molecules are required for each guest molecule probably indicating that some of the cages are unfilled. Clathrates are formed with argon, [48] sulphur dioxide and ammonia highlighting the extremely tight retention of guest species. A 1 : 1 adduct is formed with piperidine but the crystals are very unstable, losing solvent rapidly in air. The crystals do not possess trigonal crystalline form and the adduct is probably a loosely bound salt. Dianin's method of synthesis of (19) was simplified and the reaction time reduced ten-fold to four days. Much more recently, a new cyclising agent was reported [53] namely $H_3PO_4.BF_3$ containing 37% BF_3. The yield is 50% after five days at room temperature. The parent host can also be obtained in high purity from/

from bisphenol A (2, 2-bis- (p - hydroxyphenyl) - propane) manufacture by-products by treatment with sodium hydroxide. [54]

The preparation of the sulphur hexafluoride clathrate of Dianin's compound was described in 1960. [55 56] This material has found application in the electrical industry on account of the low dielectric constant of the guest. This clathrate is remarkably stable, there being less than 0.5% decomposition after three years at room temperature and atmospheric pressure. The guest appeared to be lost by sublimation of the host rather than by diffusion through the cage walls, for instance. Evidence that the guest free form of Dianin's compound also possessed the hydrogen - bonded hexameric unit was derived from density measurements.

About this time, great scientific and industrial interest had been aroused by the inclusion of gaseous radioactive fission products in hydroquinone. Mock et al. tested twenty compounds for incorporation of inert gases but found that p-fluorophenol and and hydroquinone were the only hosts to trap significant amounts of gas in their solid state structures. Dianin's compound was considered to have/

have the major disadvantage that the percentage weight of the rare gas would be very small because of the high molecular weight of the host. [57]

A further application of Dianin's compound is the use of its diethylamine clathrate as a developer for the production of heat sensitive copying sheets. [58] At normal temperatures, the amine is tightly retained but on heating the guest escapes and reacts with an indicator, effecting a colour change.

The use of inclusion compounds as storage agents has been cleverly exploited by Johnson. [59] The adducts of various hosts with amines and peroxides are used as latent polymerising agents for epoxy and urethane resins. Clathrates of (19) with o-dimethylaminomethylphenol, imidazole and 1, 3,-propanediamine are employed. Ultrasonic radiation is employed to break down the host lattice and hence release the reagent, in addition to conventional heating. The $(CF_3SO_2)\ CH_2$ and phenylisocyanate clathrates of Dianin's compound have been used as latent curing catalysts in cationic polymerisations. [60]

Another/

Another property of Dianin's compound is the protection of included guest molecules from oxidation. For example, glycerol was protected from attack by hydrogen peroxide and lead tetra-acetate but not periodic acid.[61] However oxidation of glycerol included in β - cyclodextrin did proceed indicative of the more open structure affording less shelter than one with a closed cage-shaped cavity.

The great stability of clathrates in addition to the fact that interactions between host and guest molecules are small has encouraged a wide range of thermodynamic and other physical studies to be carried out on guests in the clathrate phase. Accordingly, Davies and Child[62] examined the infra-red spectrum of various substances included in Dianin's compound. The relatively small proportion of guest is a disadvantage since the guest absorptions are either weak or unobservable, the exception being the carbonyl stretching bands of carboxylic acids. Evidence that acetic acid molecules were not dimerised in the doubly occupied cavities was obtained. However later dielectric relaxation studies [63] revealed that the/

the guest was completely dimerised. A more recent dielectric relaxation study was performed by Cook et al.[64] on the ethanol, chloroform and n-heptanol clathrates. For the chloroform clathrate, there was evidence for strong interaction between guest molecules in the same cage, approximately half the cages containing two molecules of $CHCl_3$. For the other two cases relaxation was achieved by a combination of rigid body and internal rotations.

The first complete single-crystal X-ray analysis of Dianin's compound was undertaken in 1970 when Flippen, Karle and Karle[65] established the crystal structures of the ethanol and chloroform clathrates. Their results in agreement with the preliminary work of Powell and Wetters revealed that six molecules are held together by hydrogen bonding between hydroxyl groups (OH ••• O = 2.85 A^{o}) to form a large complex in which alternate molecules point up and down. The complexes are stacked directly above each other with their symmetry axis parallel to the c - axis to form infinite columns. A cage is produced when two of these complexes line up together with one hexagon of hydrogen-bonded oxygens forming the floor of the cage and the next hexagon of hydrogen-bonded oxygens, one unit cell away in c forming the ceiling of the cage. The hour glass shape

is/

is conferred on the cavity by the gem-dimethyl groups protruding into the void giving rise to a waist at $Z \sim 0.5$. The cage is much larger than that of hydroquinone clathrates, being about $11A^{o}$ in length and $6.2A^{o}$ wide at its point of maximum extension at $Z \sim 0.3$ and $Z \sim 0.7$.

This cage structure apparently persists regardless of the guest clathrated although slight expansion can occur to accommodate larger guests as exemplified by the slightly larger cell dimensions found for the chloroform adduct, paralleling the cavity lengthening observed in the acetonitrile clathrate of hydroquinone.[66] Further evidence of slight cage distortion comes from an X-ray study of the n -heptanol clathrate.[67] A consideration of the van der Waals radii suggests that this guest is able to fit through the waist, but appears to be too long to be accommodated within the cage. Flippen and Karle demonstrated that both ends of this normally extended molecule adopt a gauche configuration in order to be included.

An analysis of unsolvated Dianin's compound has shown that the molecule has a crystal structure similar to that of its clathrates, the hour-glass shaped cavity being/

being preserved with only minor alteration in its dimensions [68] (figure 2). A section through the van der Waals surface of the cavity is illustrated in figure 3. [68]

Molecular inclusion compounds have long been recognised as potential selective agents capable of effecting separations, difficult or impossible by conventional methods. An early patent described the isolation of n -heptane from mixtures of C_7 hydrocarbons by clathration in Dianin's compound. [69] For example, from a 50:50 mixture of n-heptane and 3-methylhexane 89% of the normal paraffin was included and 11% of the branched isomer. This work was extended after the full X-ray crystal structure was known. The most noticeable feature of the results is that linear hydrocarbons C_5- C_7 are readily included and that paraffins containing one or more methyl groups at C_3 are almost totally rejected, since inclusion would invoke steric repulsion around the waist of the cavity. The selectivity pattern for olefins is again dominated by molecular shape, cis- and trans - hept - 3 - enes being most readily included on account of their small cross sectional area midway along the carbon skeleton. Many hydrocarbons with similar boiling points are difficult to separate by distillation and since they contain no useful functional group the preparation of derivatives is impossible. Such cases are obvious candidates/

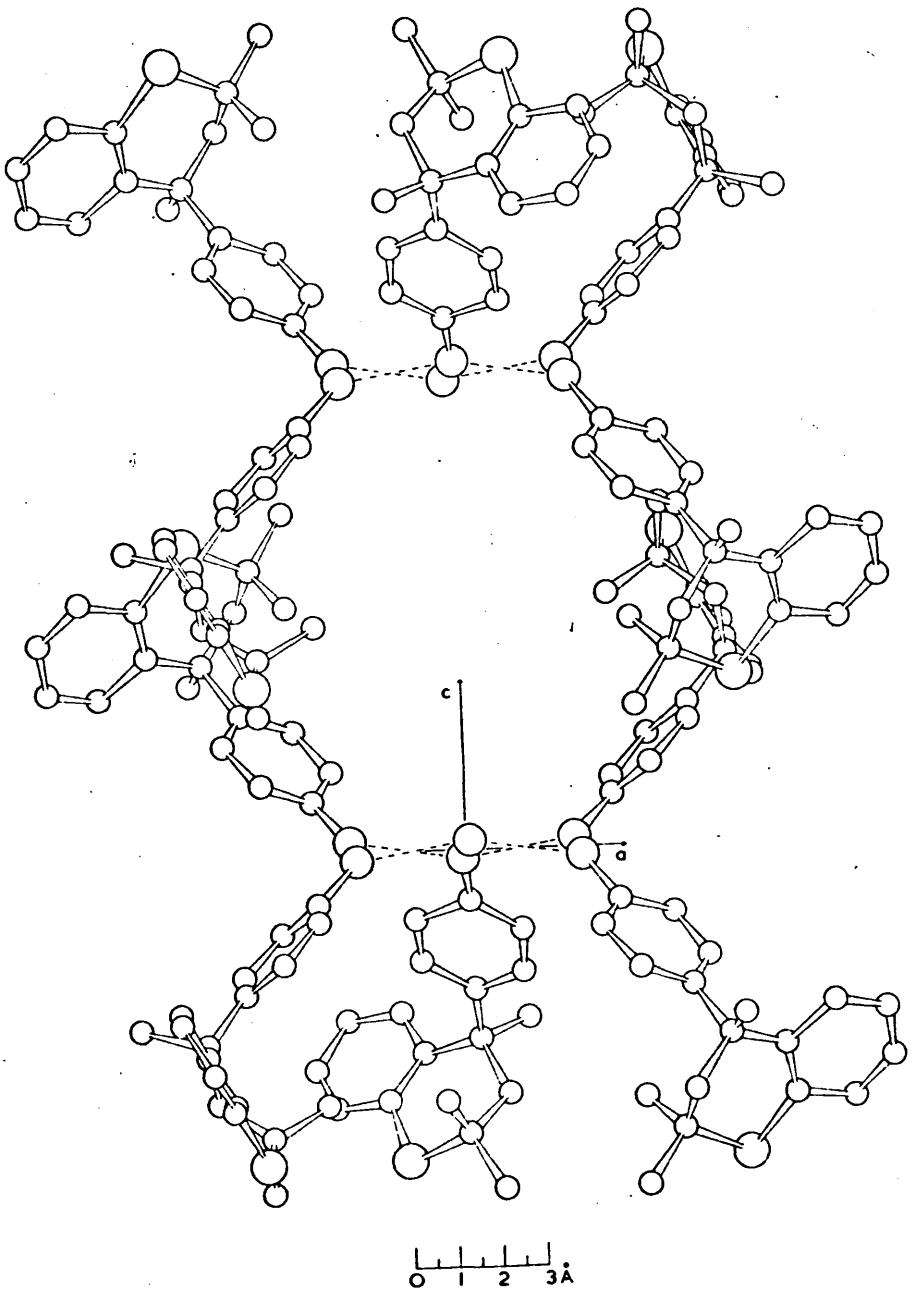


Figure 2

The packing of unsolvated Dianin's compound as projected on (010). Two molecules of the host which lie directly above and below the cavity as viewed in this direction have been excluded apart from their hydroxyl oxygen atoms.

(F.B. Wilson, Ph.D. Thesis, University of Glasgow, 1971).

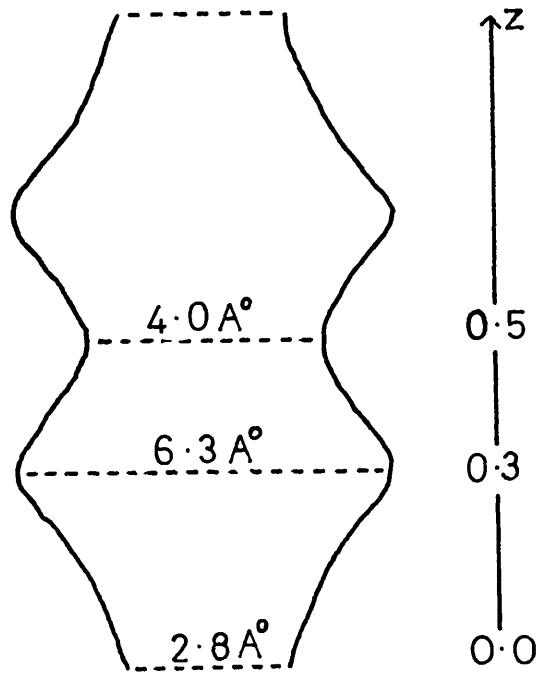


Figure 3

A section through the van der Waals surface of the cavity present in unsolvated Dianin's compound. The length of the cage is 10.9A°.

(F.B. Wilson, Ph.D. Thesis, University of Glasgow, 1971).

candidates for separation by clathration. A particularly attractive example is an equimolar mixture of 2-methylhexane (b.p. 90.05°) and 2, 3-dimethyl pentane (b.p. 89.78°) from which 99% of the former can be recovered in a single clathration with Dianin's compound. It was also established that the host unit cell dimensions vary only slightly according to the guest component. [70]

Electron paramagnetic resonance has been employed to characterise the motion of guest molecules and to estimate the magnitude of the energy barriers which hinder these motions. A clathrate is formed betwen Dianin's compound and di-t-butylnitroxide, [71] the odd electron of this guest providing a useful probe of its behaviour inside the host lattice. Two different radicals were present. One was found to be accommodated in one half of the cavity with a methyl residue of one t-butyl group protruding into the waist of the hour-glass shaped cage. The energy barrier to rotation was determined at 2.3 kcal mol^{-1}. The nature of the other species' environment was not definitely determined.

Later Gregoire and Meinnel [72] studied the temperature dependence of linewidth and the second moment in the proton magnetic resonance spectra, and obtained enthalpies of activation for movement of the included molecules pentafluorotoluene, bromobenzene and bromo-durene in Dianin's compound/

compound of 2.15, 2.3 and 1.7 keal mol^{-1} respectively.

Kispert and Pearson [73] further demonstrated that Dianin's compound could serve as a matrix for studying free radicals. They X-irradiated the clathrate of 1, 2 - dibromo - 1, 1-difluoroethane at 77°K and observed the $Br_2^{\cdot -}$ radical by E.P.R. spectroscopy. The radical was located as lying parallel to the c-axis.

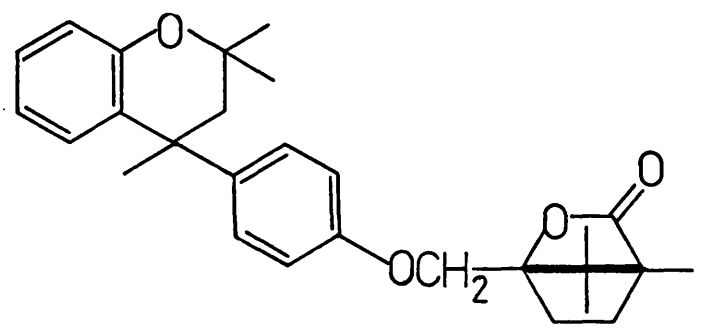
A Russian team has γ-irradiated the nitromethane and nitroethane clathrates of (19) in acetone at 77° - 260°K and probed the outcome by E.P.R. spectroscopy. For nitroethane, the radical $MeN.O_2H$ was confirmed and its temperature dependence studied. [74] The adducts of diethyl ether, methanol, ethanol, 1, 3-dioxolane, benzene, benzene-D_6, aniline, pyridine, acetophenone and nitrobenzene have also been γ-irradiated at 77°K. [75]

Dianin's compound has been suggested as a suitable host for the observation of transitions between two rotational sublevels of the same vibrational state, in small organic molecules, for example chloroform. [76]

Meinnel and co-workers described the crystallogenesis of large crystals of the bromobenzene clathrate of Dianin's compound for proton magnetic resonance studies. The crystals were found to grow along the c-axis of the rhombohedral/

rhombohedral system.[77]

In view of the fact that Dianin's compound is chiral in the 4-position of the chroman ring, Wilen[78] thought that resolved Dianin's compound would form clathrates with chiral cavities and would therefore be useful in resolution of racemic mixtures. Brienne and Jacques[79] have resolved the host by crystallisation of the diastereomeric camphamates (28) and



(28)

subsequent hydrolysis of the isolated pure diastereomer. Resolved Dianin's compound was found to possess an $[\alpha]_{578}^{25}$

of/

of -24° and melted at 140°, 17° below the racemic host. No clathrate formation has been found with either chiral or achiral guests. The consequence of an $R\bar{3}$ space group for synthetic Dianin's compound is that the three alternate molecules of the host which point up from the hydrogen-bonded hexagon of hydroxyls must possess the same chirality (say R) and the other three molecules which point down must be of the S configuration to satisfy the symmetry operation requirements. The space group for resolved Dianin's compound is not quoted but obviously it cannot be $R\bar{3}$, a space group that seems to be specially favoured as regards clathrate formation.

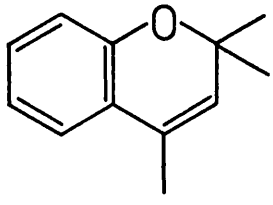
Very recently Barrer and Shanson [80] have described the zeolitic sorption by Dianin's compound for various guest species. They point out that the crystal topology of Dianin's compound is the same whether or not guest molecules occupy the cavities as in the zeolites. 1:1 compositions were claimed with argon and methane, surprisingly high in view of the fact that three host : one guest is the highest ratio known to date. It might be that some of the guest is trapped interstitially and not truly clathrated. The bona fide clathrates of this/

this host are stable till their melting points, i.e. the guest cannot escape until the host structure is broken down, so it seems unlikely that the guest can enter without similarly rupturing the hydrogen-bonded network.

No one can explain why Dianin's compound forms clathrates since after all, its discovery was purely a matter of chance. Powell[8] identified hydrogen bonding and bad packing of awkwardly shaped molecules as being important. It would obviously be very instructive to study analogues of the parent host to ascertain whether clathrate-forming properties would be retained and if so, how the cavity shape would alter.

(ii) Structural modification of Dianin's compound

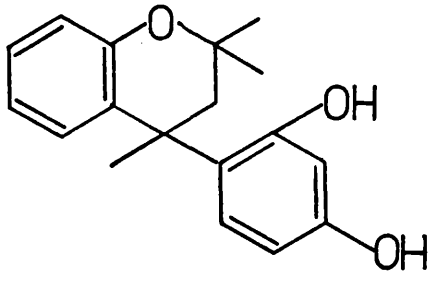
Baker et al [51] were the first researchers to deliberately set out to see if new hosts could be found, similar to the parent host. They condensed various substituted phenols with 2, 2, 4-trimethylchromene (29).



(29)

With m - and p - cresol, the chromene yielded non phenolic resins, probably cresol ethers, but o-cresol gave a phenolic crystalline homologue of Dianin's compound (19), which formed no complexes with solvents. Catechol also combined with the chromene but the product could not be crystallised and gave no adducts.

Johnson [59] condensed resorcinol with (29) to give a good yield of 4 - (2', 4' -dihydroxyphenyl)-2,2,4-trimethylchroman (30).



(30)

This compound is a new host, forming adducts with acetic acid, chloroform, ethyl acetate, ethanol, octane, ether and acetone, and host to guest ratios are quoted for each solvent.

A systematic study of structural modification of Dianin's compound was instigated in Glasgow in 1969. Three approaches were adopted initially.

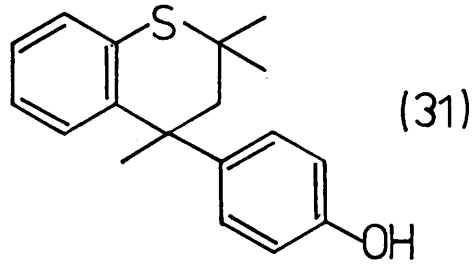
(a) Changing the ring hetero atom.

(b) Functionalisation of the carbon skeleton.

(c) Altering the hydrogen bonding moiety.

(a) Substitution of the ring hetero atom

The first advance in this direction was the synthesis of the thia analogue of Dianin's compound, 4-p-hydroxyphenyl-2,2,4-trimethylchroman (31).[81]

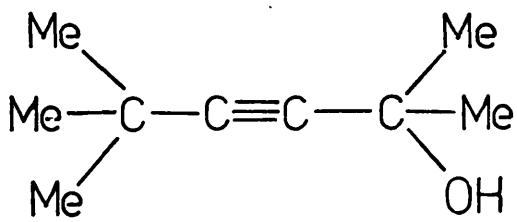


(31)

This molecule was found to form clathrates with all the organic solvents tried and as before, the host : guest ratio was dependent on the size of the guest molecule. For fairly small molecules such as acetone and ethanol, the ratio is 3:1 whereas for larger molecules such as toluene and p-xylene the ratio is 6:1. Subsequent X-ray analysis[82] showed crystals of the ethanol clathrate to be isomorphous with the guest free form of (31) and with the clathrates of Dianin's compound (19). The basic feature of the structure is the linking of the hydroxyl groups of six molecules by a network of hydrogen bonds such that the oxygen atoms form a distorted hexagon of side 2.9A°, and the space group is again $R\bar{3}$.

MacNicol/

MacNicol and F.B. Wilson [83] have successfully used this host in the first unambiguous determination of the orientation, conformation and dimensions of a guest molecule within the cavity of an organic clathrate, the guest being 2,5, 5-trimethylhex-3-yn-2-ol (32.)



(32)

The acetylenic unit was found to be colinear with the c-axis, the triple bond fitting neatly into the cavity waist leaving a tetrahedral unit in the upper and lower halves of the cage (figure 4). The staggered conformation imposed on (32) by the van der Waals surface of the cavity may be taken as an example of a "lock and key" type interaction in which the conformation of the guest molecule is governed by the host.

The internal rotation of the formyl group in benzaldehyde clathrated in this host (31) has been studied by MacNicol. [84] The measured barrier height is/

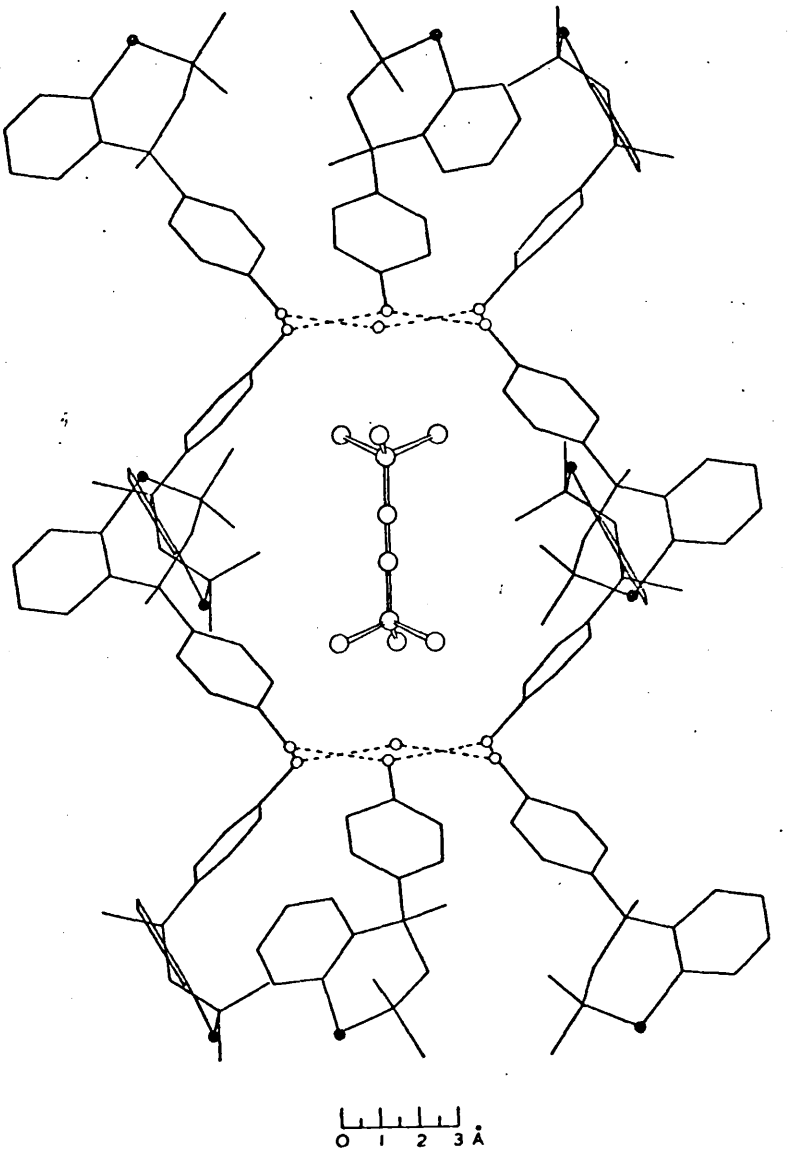


Figure 4

The structure of (31) projected along the a-axis showing the guest molecule (32) within the cavity. Two molecules of (31) which lie directly above and below the cavity as viewed in this direction have been excluded apart from their hydroxyl oxygen atoms.

(D.D. MacNicol and F.B. Wilson, Chem. Comm., 1971, 786).

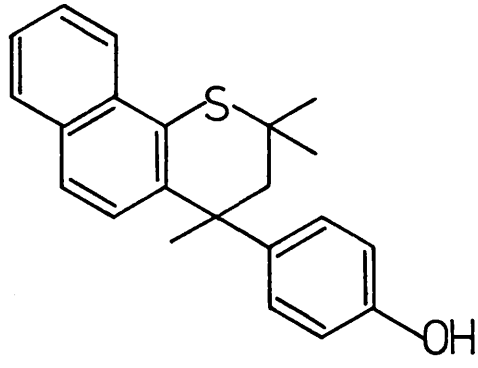
is greater than that found for the molecule in the vapour phase suggesting that there is increased double bond character in the bond linking the aldehyde group to the benzene ring. This corresponds to increased π-electron delocalisation in clathrated benzaldehyde arising from interaction with the host molecules comprising the cage wall. Additionally, the similarity between clathrate and liquid phase barriers is significant since an individual molecule in a host lattice approximates to many theoretical models of solution.

Clathration has also been employed as a safe method for handling the extremely toxic dimethylmercury [85]. A 6:1 clathrate is formed with (31) corresponding to single occupancy of the clathrate voids. This clathrate is very convenient for preparing solutions of known concentration in dimethylmercury, preweighed quantities of the adduct merely being dissolved in the appropriate solvent.

The sulphoxide and sulphone derivatives of (31) exhibit no propensity for including solvents and crystals of both do not have $R\bar{3}$ space group symmetry. [86] The corresponding selenium compound, 4 - p - hydroxy-phenyl - 2,2, 4-trimethylselenachroman has also been prepared and clathrate properties observed [87].

(b) Substitution of the carbon skeleton

Several derivatives of thiadianin's compound (31) have been prepared and an interesting spectrum of behaviour vis-à-vis clathrate formation has been observed.[88] Compound (33) which possesses an additional bulky fused benzene ring crystallises unsolvated from a range of solvents.

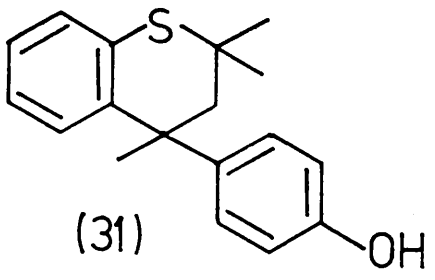


(33)

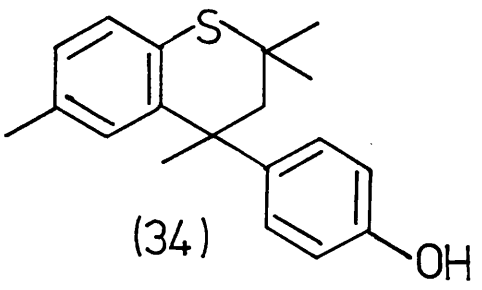
The structures, space group, unit cell dimensions for derivatives of (31) with a methyl group in the 6, 7, or 8 positions (compounds (34),(35) and (36) respectively) are compared with those for (31) itself in table VII.(34) is isomorphous with (31) with very similar lattice parameters implying fairly similar cage structures. Where the extra methyl group is meta to the sulphur atom (35) no clathrate/

Table (VII)

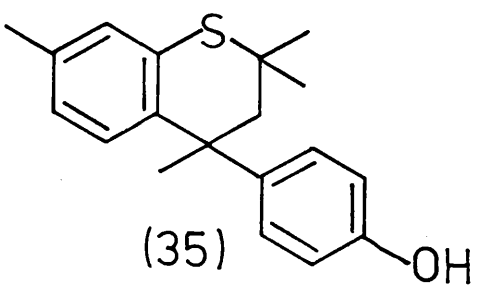
Comparison of crystal data for compounds (31) and (34) - (36).



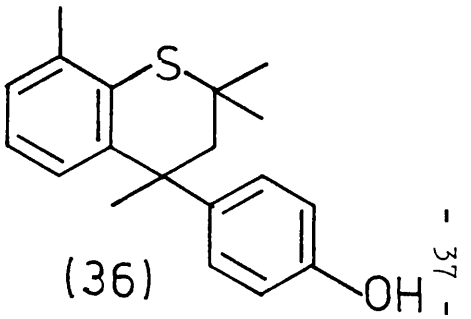
(31)



(34)



(35)



(36)

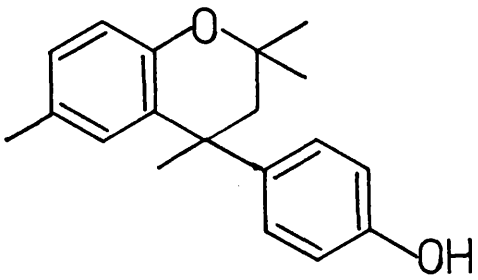
	(31)	(34)	(35)	(36)
Space group	$R\bar{3}$	$R\bar{3}$	$P2_12_12_1$	$R\bar{3}$
Lattice parameters	$\underline{a}$ = 27.81 $\underline{c}$ = 10.9	$\underline{a}$ = 29.32 $\underline{c}$ = 10.82		$\underline{a}$ = 8.23 $\underline{c}$ = 33.63 A^{o}
Guest	ethanol	cyclopentane	-	cyclooctane
Host : guest	3 : 1	6 : 1	-	4.5 : 1
Reference	82	88	89	90

clathrate-forming properties are observed. Instead, the unsolvated material is found to crystallise in the enantiomorphous space group $P2_12_12_1$, i.e. spontaneous resolution has occurred.[89] Long chains of molecules parallel to the y-axis are held together by OH...S hydrogen bonding with an OHS angle of about 160°. When a methyl group is introduced ortho to sulphur, the crystal structure of compound (36) is markedly altered, though still maintaining the ability to form stable inclusion compounds. Shortening of the c-dimension, referred to a hexagonal system of axes to $8.23A^{\circ}$ for the cyclooctane clathrate (host : guest ratio = 4 : 1) implies that this structural modification has effected a fundamental change in the dimensions and shape of the cavity. Consistently a marked difference between the selective clathration properties of (31), (34) and (36) is found towards an equimolar mixture of cyclopentane, cyclohexane and cycloheptane, again reflecting the altered cavity shape of (31).

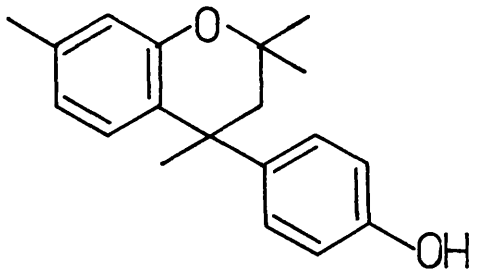
A full X-ray crystal structural analysis of the cyclooctane clathrate of (36) has been performed and the marked change in the cavity shape is most readily appreciated by comparing their van der Waals surfaces.[90] (see/

(see figure 5). In (31) the cavity has a pronounced waist, which is formed by six gem-dimethyl groups protruding into the cage. In (36) however, this waist has been eliminated, the hour-glass surface of (31) being converted into a "chinese lantern" shape.

Dianin's compound itself (19) has been substituted in a similar way. Compounds (37) and (38) have been prepared but no clathrating properties were observed in either case.[89]

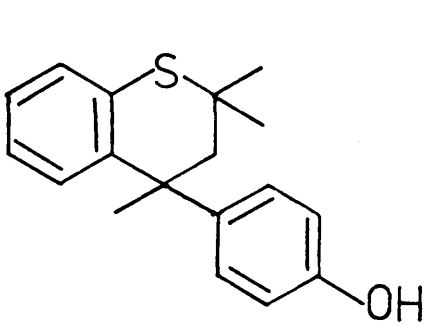


(37)

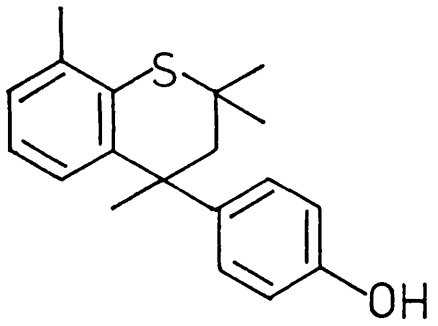


(38)

As will be recalled, the X-ray analysis of Dianin's compound (19) reveals how the gem-dimethyl groups of the six molecules comprising a cage form a constriction at about Z = 0.5. Obviously if this waist could be removed without collapse of the entire framework, a much larger cavity would result. 4-p-hydroxyphenyl-2,4,-dimethylchroman (39) has been prepared and it/



(31)



(36)

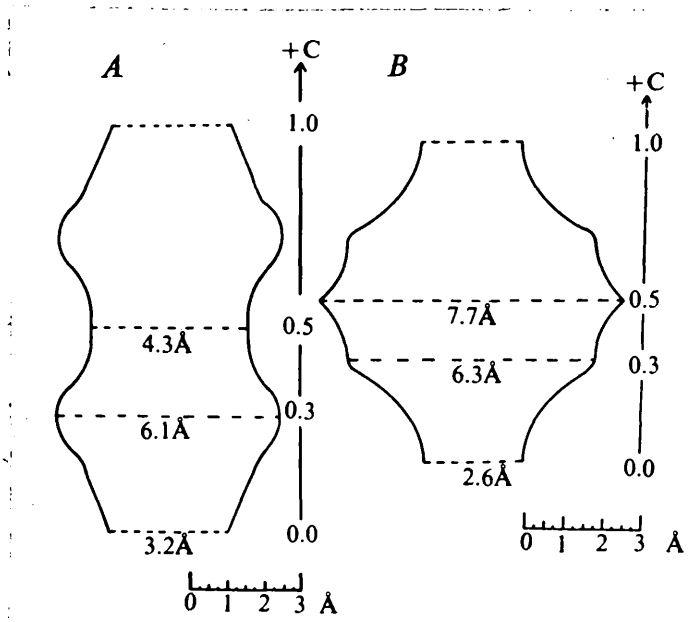
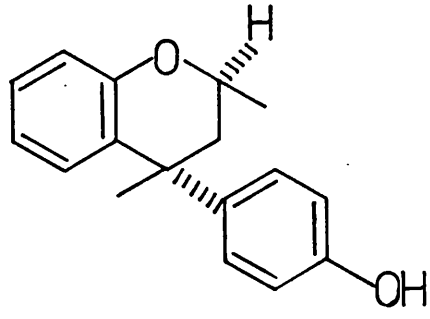


Figure 5

Section through the van der Waals surface of the cavity for (31) and (36).

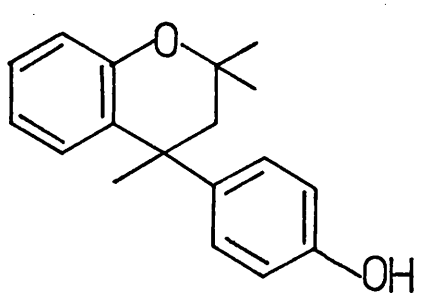
(D.D. MacNicol, A.D.U. Hardy and J.J. McKendrick, Nature, 1975, 256, 343).

it established that cyclohexane and carbon tetrachloride are included.[91]

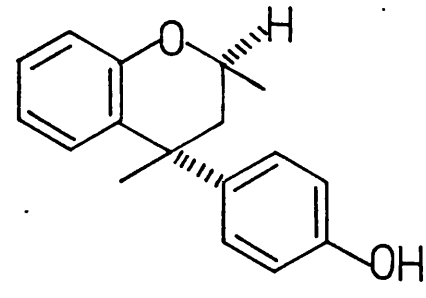


(39)

An X-ray analysis of the carbon tetrachloride clathrate determined the space group as $R\bar{3}$ and revealed a marked change in cavity shape. A formal removal of a gem-dimethyl group was made from Dianin's compound (19) and the resultant generated cavity compared with that determined for (39) by experiment. As can be seen from figure 6, the agreement is very close.



(19)



(39)

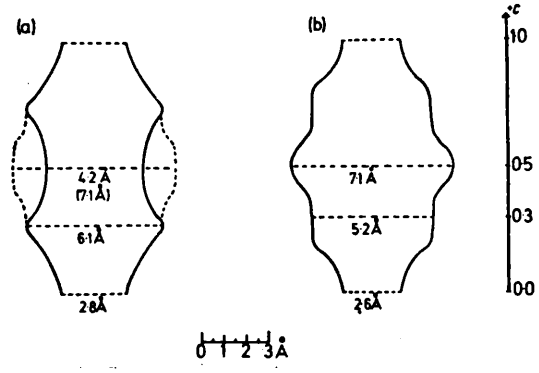


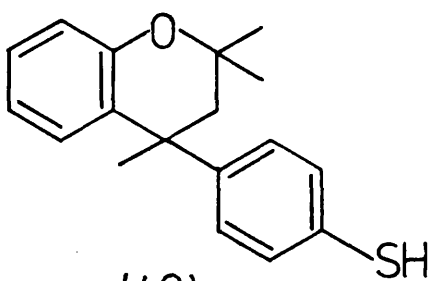
Figure 6

A section through the van der Waals surface of the cavity for : (a) Dianin's compound (19) as chloroform adduct; the curved broken lines represent the effect of the formal removal of the waist methyl groups. (b) compound (39) as the CCl_4 clathrate.

(A.D.U. Hardy, J.J. McKendrick and D.D. MacNicol, J.C.S. Chem. Comm., 1976, 355).

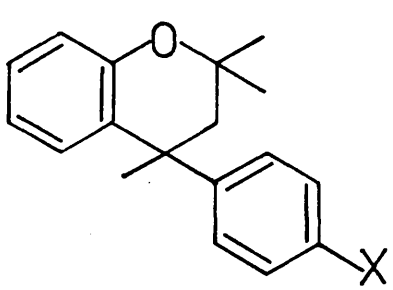
(c) Alteration of the hydrogen bonding moiety in Dianin's compound.

In view of the seemingly essential structural role played by the hydroxyl group in Dianin's compound, in forming the hydrogen-bonded hexamer unit, it should be interesting to determine the effect of altering the hydroxyl group. In a preliminary study of the corresponding thiol (40) no inclusion of solvent was observed. However, new results for this compound are presented in the discussion section.



(40)

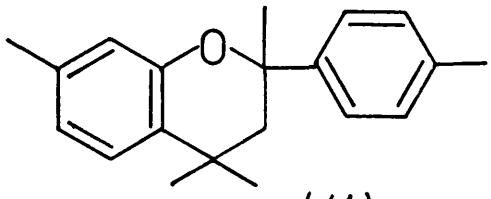
The methylether and several other derivatives of (19) where the possibility of hydrogen bonding has been eliminated not surprisingly do not form clathrates. A selection is presented below.



X	Reference
OMe	47, 52
$OCPh$ (=O)	47
$OCOMe$ (=O)	89
$SCNMe_2$ (=O)	89

(iii) Flavans and other chroman-type systems

There are many references throughout the literature reporting the formation of adducts of other types of molecules, incorporating the chroman ring system, with organic solvents. They have not been so widely studied however and no crystal structure determination has been carried out. Typical of the molecules involved is (41), 2'-hydroxy-2,4,4,7,4'-pentamethylflavan which had been reported [92] to form a 1:1 adduct with diethylether in 1908 but its molecular structure was not proven till 1951 [93].



(41)

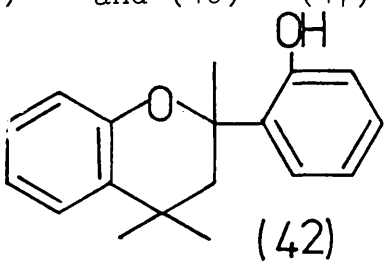
Niederl et al [94] observed that the crystalline ether adduct lost its solvent of crystalliation on standing in air and the host withered away to a glassy liquid. Addition of ether to this liquid regenerated the crystalline complex. The formation of the solid ether adduct renders isolating and purification much simpler [95]. It

was/

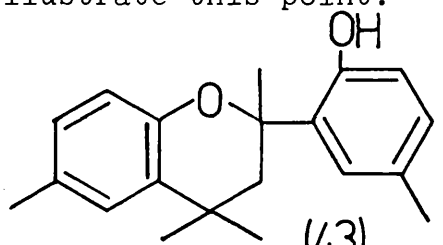
was suggested that the ready crystallisation of the unsolvated glassy liquid in contact with ether could be used as the basis of a delicate and specific test for diethylether. [96] Baker er al. [93] presented positive proof for the flavan structure and in an accompanying publication [97] reported details of the many crystalline adducts formed by (41). 1:1 complexes are formed with several ethers and ketones, with amines being particularly favoured, thus suggesting that salt formation may play some part behaviour reminiscent of the 1:1 adduct of piperidine [51] with Dianin's compound (19). 2-idopyridine, normally an unstable compound was greatly stabilised by inclusion in this host compound. (41), like Dianin's compound is chiral through this time at position 2. An attempt to resolve (41) by adduct formation with (-) coniine (2-n-propylpiperidine) was not successful.

The following year, many other flavans were prepared and shown to form complexes with amines and ethers again suggesting that there is some special feature of the flavan nucleus. Much more extensive substitution of the basic structure could be tolerated unlike/

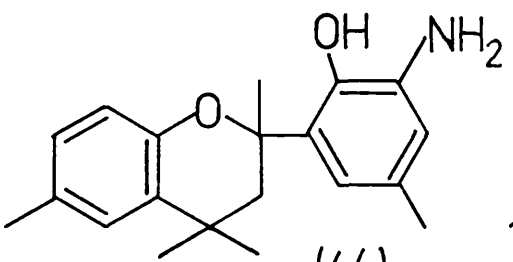
unlike Dianin's compound where often the slightest change thwarts all inclusion ability. Molecules (42) - (45) [98] and (46) - (47) [99] illustrate this point.



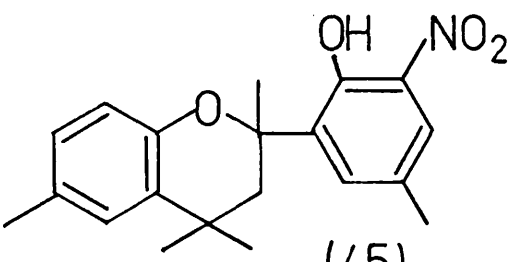
(42)



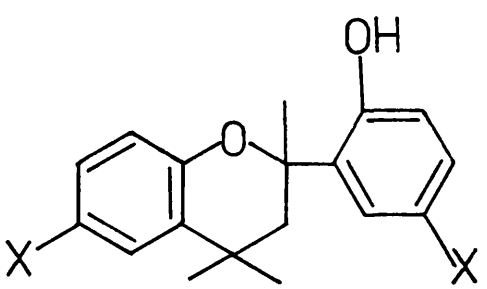
(43)



(44)



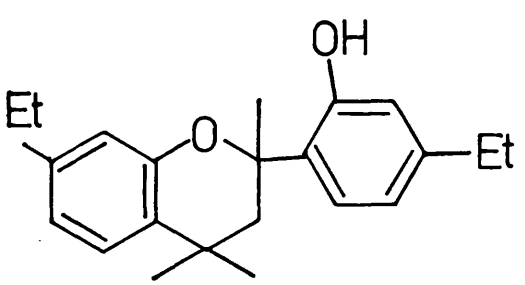
(45)



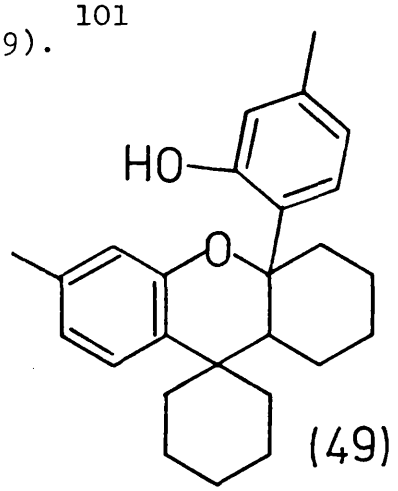
X=Br, (46)

X=Cl, (47)

The pronounced preference of these compounds to include amines has been exploited as an aid for the isolation and purification of synthetic pyrimidines.[100] Further similar hosts are (48) and (49).[101]

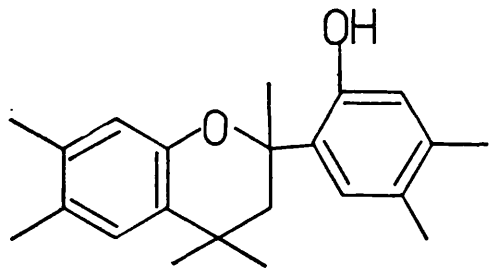


(48)



(49)

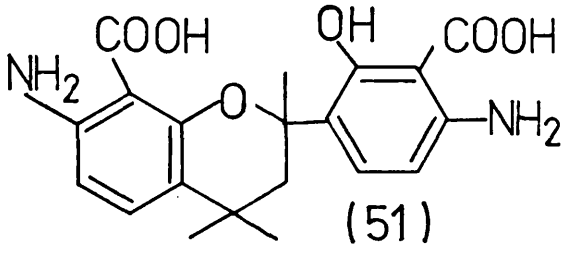
Lawton [58] employed the amine addition compounds of (41), (43), (48), (49) and (50) as developers for the



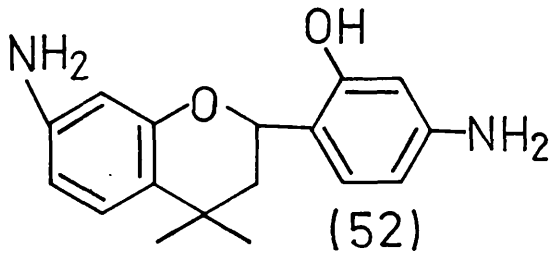
(50)

production of heat sensitive copying sheets. Similarly, the morpholine adduct of (42) is employed as an image recording material. [102]

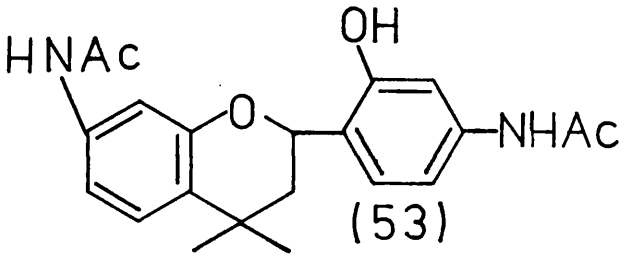
A Japanese team has condensed several diversely functionalised phenols with acetone to afford (51) - (55), all of which form a monoetherate.[103]



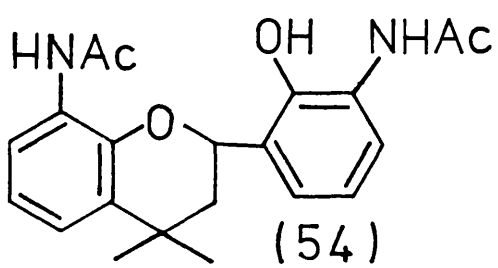
(51)



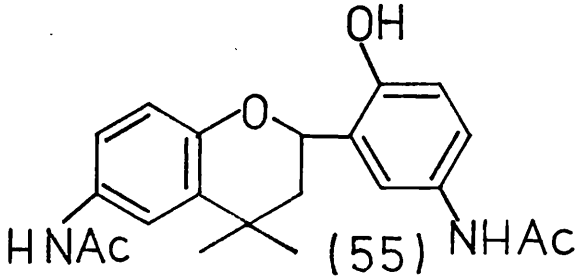
(52)



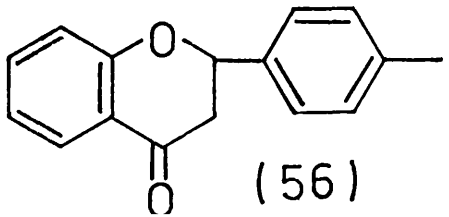
(53)



(54)



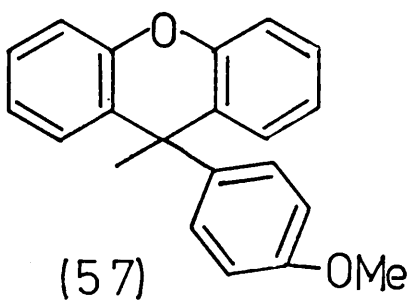
(55)



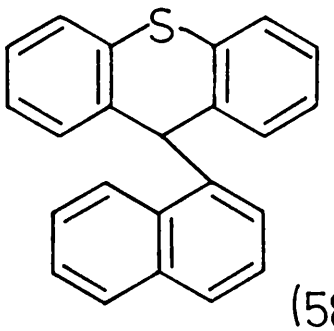
(56)

Cramer [104] observed the formation of a benzene adduct with 4'-methylflavone (56) No details about the nature of this adduct are known. He also discovered that a very large number of substituted flavones and coumarins formed blue addition compounds with iodine [105, 106].

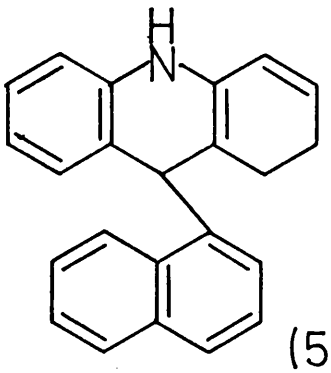
Several xanthenes,[107] thioxanthenes [108] and acridines [109], for example (57) - (59) form adducts with benzene and merit further study because of their similarity to Dianin's compound (19).



(57)



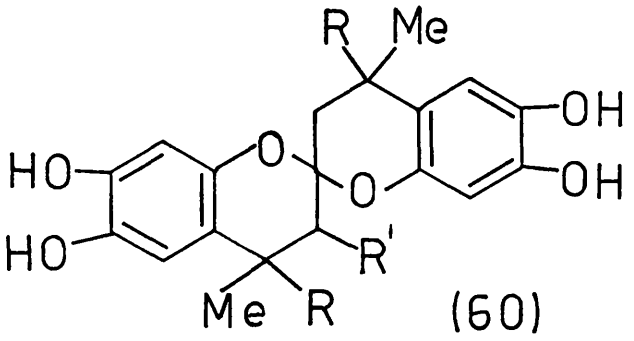
(58)



(59)

Finally, spirochromans have been used for the separation of relatively straight chain aliphatic hydrocarbons/

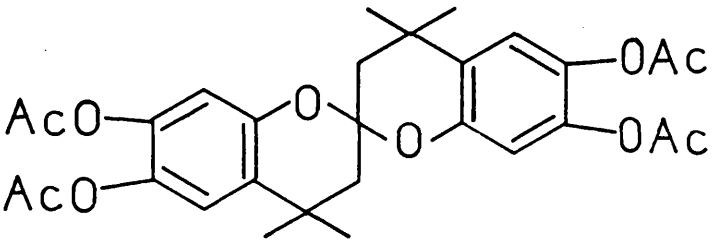
hydrocarbon mixtures.[110] Chromatographic sorption employing the pure chroman as the absorbent is effective for separating iso-octane and n-heptane. One of the molecules used is (60).



(60)

R = n-hexyl

R' = n-pentyl



(61)

A similar molecule (61) has been reported to form a 1:1 complex with acetic acid [95].

3. Simple phenols

Several very simple phenols have been found to form inclusion compounds. Not surprisingly, as is the case for Dianin's compound (19), hydrogen bonding is paramount.

(i) Phenol itself

The initial observation of inclusion behaviour for phenol itself was made only in 1935 by Terres and Vollmer [111] who were examining the solubility of petroleum and tar constituents such as phenol in liquid H_2S. A compound $2C_6H_5OH.H_2S$ was indicated. Nikitin, who had earlier prepared the clathrates of the inert gases with water, tested phenol as a host for the ideal gases. Very little sorption of radon by phenol at -120° was observed [112] but combination of radon with phenol did occur from an isomorphous solid solution of phenol - H_2S [113]. A compound Rn.2PhOH was indicated. The xenon phenol clathrate could only be prepared when seed crystals of the H_2S clathrate were present. [114] The yellow-green SO_2 clathrate of phenol was prepared in 1951 and it was found that the cubic crystals readily lost the guest and reverted to the hexagonal form.[115]

In/

In a more thorough study of the H_2S-phenol system at various pressures and temperatures, the only compound indicated was H_2S . $3C_6H_5OH$, and not H_2S . $2C_6H_5OH$. [116] The host to guest ratio of the SO_2 clathrate was reassessed as 3:1 and the temperatures at which the dissociation pressure equals one atmosphere are quoted in the table below [117] for several guests.

Table (VIII)

Dissociation temperatures for phenol clathrates when pressure equals one atmosphere.

Guest	CO_2	Xe	HCl	H_2S	HBr	SO_2
T (^oC)	- 10.3	4	5.8	25.3	28.5	39

The first crystal structure studies of phenol clathrates was undertaken in 1954.[118] The space group was determined as C_3^4 or C_{3i}^2 ($=R\bar{3}$) and the number of molecules in the unit cell established as twelve. The full crystal structure analysis of phenol clathrates was determined by Stackelberg et al. [119, 120] The principal feature of the structure is the linking of the hydroxyl groups of six molecules of phenol creating a hexagon of hydrogen-bonded oxygen atoms with alternate phenyl groups pointing up and down. Another similar/

similar unit packs directly on top of this and the phenyl groups enmesh leaving a small cavity of about $4.5A^{o}$. The unit cell is rhombohedral (space group $R\bar{3}$) and at each of the eight corners of the rhombohedron is situated one of the above twelve phenol molecule units with a small cavity in between. Within this rhombohedron there remains an elongated cage, about $15A^{o}$ long (see figure 7). The long cage can accommodate four molecules of HCl or HBr but only two molecules of CS_2. HCl, HBr, SO_2, CO_2 etc. can fit into the small cavity as well but the large CS_2 molecule cannot. Air may be trapped in the smaller cavity of the CS_2 clathrate. New guests listed were: Hl, H_2Se CO, COS, CS_2, CH_3Br, CH_2Cl_2, CHF_2CH_3, and $FCH = CH_2$. Lahr and Williams [121] studied the $Ar.4C_6H_5OH$, $Kr . 4 C_6H_5OH$ and $Xe .3 C_6H_5OH$ compounds and concluded that the rate of formation and decomposition was diffusion controlled. Allison and Barrer [122] found that the clathration of Kr, Xe, CH_4, C_2H_4, C_2H_6 and CO_2 by phenol did not obey Langmuir's isotherm whereas the quinol clathrates with Xe, Kr and CH_4 did. In a kinetic study of clathration by phenol it was found that the uptake of guest molecules was promoted by shaking the host with steel ball bearings. It was discovered that there was an initiation time for uptake of guest molecules which was pressure dependent but/

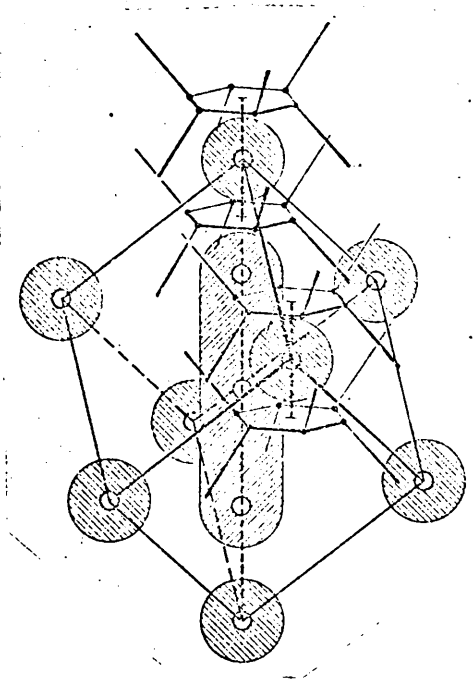


Figure 7.

The rhombohedral unit cell of phenol inclusion compounds showing the two types of cavities which are shaded. The hexagons (shown for only two corners) represent the ring of oxygen atoms of six hydrogen-bonded hydroxyl groups, and the line radiating from each corner indicates the phenyl residue.

(M.v. Stackelberg, A. Hoverath and C. Scheringer, Z. Elektrochem., 1958, 62, 123).

but temperature independent [123].

The only reported commercial use for inclusion compounds of phenol is for improving oxidation stability and rust resistance of fuels and lubricants. [124]

(ii) Fluorophenols

The most conservative structural change possible for phenol is the substitution of one of the aromatic hydrogens for fluorine. Several Russian workers have examined all three possible fluorophenols for clathrate formation.

Mock et al [57] found that 1% argon was retained by p-fluorophenol and suggested that this complex was of the clathrate type. Kazankin et al [125] studied the absorption of xenon and krypton by p-fluorophenol and in both cases, a clathrate was found with six host to one guest as the maximum possible composition. Clathrates are also formed with H_2S, SO_2, CH_3Br, C_2H_4 and C_2H_6, and a cavity size of 5-5.3A^{o} was indicated. [126] A 3:1 maximum composition for the argon clathrate was suggested from a study of the argon - p-fluorophenol - carbon tetrachloride system. 35.5% of the cavities were filled and Langmuir's isotherm for localised absorption was obeyed. [127] p-fluorophenol has been employed as a clathrating agent for gaseous/

gaseous mixtures whose components have van der Waals radii less than or equal to 2.7A.[o] [128]

A clathrate compound of m-fluorophenol with xenon is also known but this is very unstable having a melting point of 6.1[o] under 25 atmospheres of guest.[129]

Even o-fluorophenol forms a clathrate with xenon, but like meta compound, only under a large guest pressure. [130]

(iii) Miscellaneous phenols

Several other substituted phenols have been found to form clathrates. p-Chlorophenol for example forms a 3:1 clathrate with H_2S, but the dissociation pressure at room temperature is several atmospheres. Some radon is also included from a Rn/H_2S guest mixture. [131]

Xenon forms a 6:1 clathrate with p-cresol but this is very unstable, the vapour pressure of Xe being 25 atmospheres at 25°C. [132] Krypton and Xe/Rn mixture also form isomorphous clathrates with p-cresol. [133] The melting points of the HCl, HBr, HI, H_2S, Kr, Xe and CO_2 clathrates of p-cresol fall in the range 28-40°. The dissociation pressures at 10° vary from 158mm. for HI, 905mm. for HCl to 24000mm. for CO_2 so the clathrate stability is very guest dependent. No molecule larger than 5.1A° in diameter forms a clathrate with p-cresol. [134]

No less than nine dimethyl - and trimethylphenols have been reported to form molecular complexes with simple alcohols. It is/

is suggested that these are of the clathrate type. [135]

SO_2 was found to form unstable complexes with pyrogallol and catechol but whether these are clathrates remains to be seen. [136]

The crystal structures of the adducts of HBr with phloroglucinol and orcinol have still not been determined, 66 years after their initial isolation. [137]

(iv) Hydroquinone or quinol (18)

By far the best known and most extensively studied clathrate host is the diphenol, hydroquinone or quinol. It was the elucidation of the crystal structure of the β-quinol adduct with SO_2 that prompted Powell [49] to coin the word "clathrate". Only a brief description of the crystal structure, the various academic uses and practical applications will be presented here.

As in the clathrates of Dianin's compound (19) and phenol (17), the hydroxyl groups of six hydroquinone molecules are linked by hydrogen bonding so that the oxygen atoms form an almost planar hexagon from which alternate aromatic residues point up and down from the oxygen atoms. The hydroxyl groups at the para position of these aromatic rings are similarly hydrogen-bonded thus forming an infinite cage in three dimensions. However, the space-filling of this arrangement is very ineffective and such large gaps are left that it is possible to insert a second identical framework, displaced vertically between the top and bottom hexagons (figure 8). Although the two frameworks approach/

138

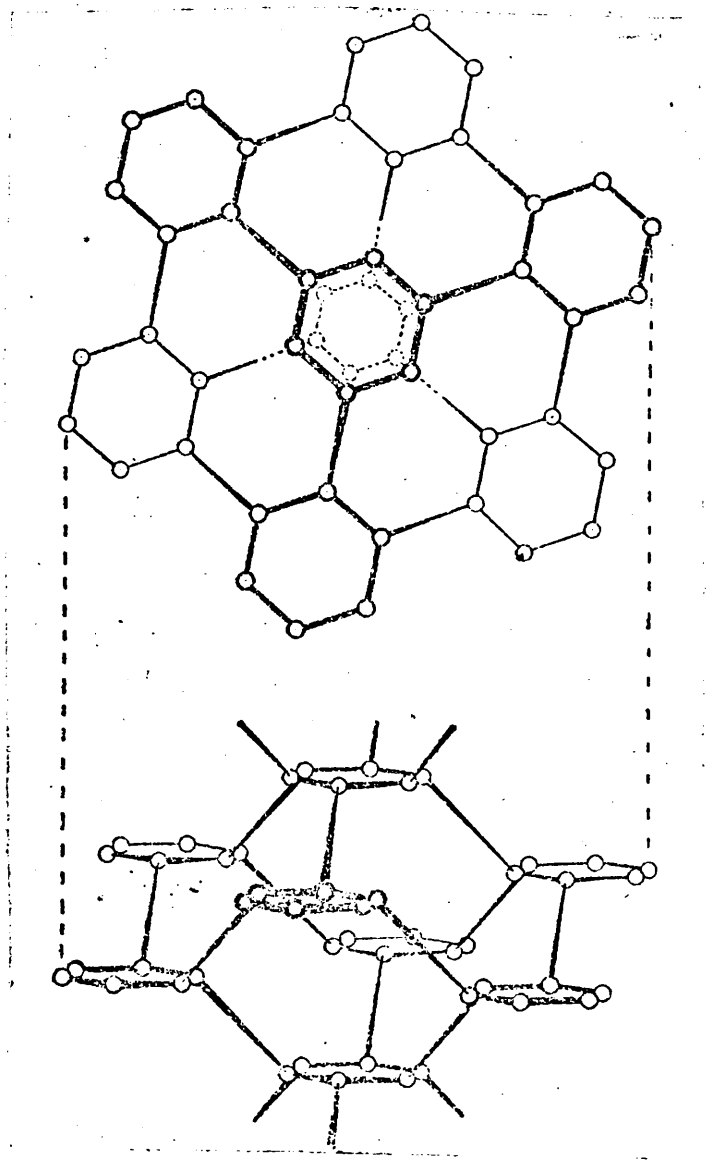


Figure 8. Manner of hydrogen bonding of hydroquinone molecules.

Above: Each regular hexagon denotes six hydrogen bonds between oxygen atoms. Hexagons at different levels are denoted by different line thickness. The tapered lines, representing the O-O axis of a hydroquinone molecule, show the method of linking to form an infinite three dimensional cagework. Each taper points downwards from the observer.

Below: Perspective drawing corresponding to the above.

(D.E. Palin and H.M. Powell, J. Chem. Soc., 1947, 208).

approach to give normal van der Waals contacts, there remain between the two networks cavities of sufficient size to contain a small molecule at normal unlinked distances from the surrounding atoms. (figure 9.) These spaces are bounded by hexagons of oxygen atoms of the two different equivalent frameworks on the top and bottom of the cavity and by the aromatic rings on the sides. It is in these nearly spherical cavities of about 4.2A^{o} in diameter that the trapped molecules are located. Only molecules compatible with this dimensions can form clathrates. With two large molecules such as ethanol, a different crystal modification results. Similarly helium cannot be clathrated since it is small enough to diffuse through the cage walls. The limiting composition, corresponding to 100% occupancy of the cages is three molecules of host to one of guest. No less than 35 guests have been included in hydroquinone, all of which are listed below with a reference in table (IX). Almost every clathrate is isomorphous with the space group $R\bar{3}$ and the unit cell parameters are very similar for different guests. Acetonitrile, whose length is longer than that compatible with the undistorted host lattice is however included. Marked lengthening of the/

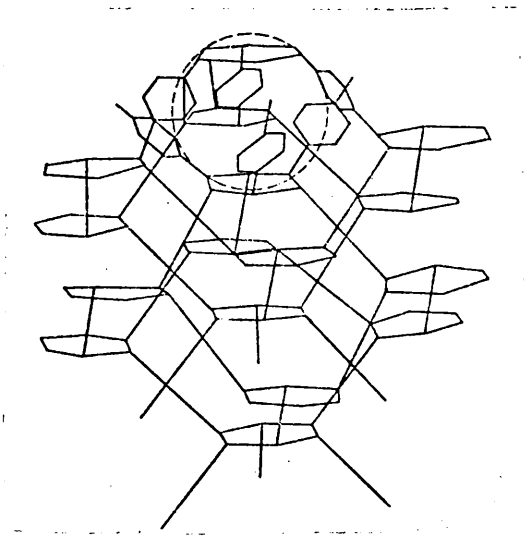


Figure 9

Representation of the interpenetration of two similar hydrogen-bonded cageworks each identical with that shown in Figure 8. Benzene rings are shown by small hexagons in the upper part of the figure but are omitted elsewhere for clarity. The larger hexagons represent hydrogen bonds. The roughly spherical space between the two cageworks is outlined by the dotted line. (D.E. Palin and H.M. Powell, J. Chem. Soc., 1947, 208).

Table (IX)

Hydroquinone clathrates

Guest	Reference	Guest	Reference
H_2S	139	C_3H_8	149
SO_2	140	N_2	150
HCN	141	CO	151
HCO_2H	141	CH_3Br	152
HCl	142	Ne	153
HBr	137	NF_3	154
CH_3OH	143	CH_3F	155
C_2H_2	144	CHF_3	155
CO_2	144	S_2O	156
CH_3CN	144	H_2 Se	157
Ar	145	HCHO	158
Kr	146	CH_3CHO	158
Xe	147	C_2H_4	158
O_2	148	C_2H_6	159
NO	148	COS	159
CH_4	149	Me NC	159
CH_3Cl	149	Me SH	159
N_2O	149		

the c-axis dimension occurs and the space group is lowered in symmetry to the non-standard space group C3. Also atypically, the guest is readily lost at room temperature and atmospheric pressure, highlighting the instability brought about by the host lattice distortion. [160]

The clathrates of hydroquinone have been the subject of study for very many branches of spectroscopy and miscellaneous physical measurement. Only a few selected examples are described.

The statistical mechanics for the motion of guest molecules in the clathrate voids, based on the Lennard-Jones chemical potential model has been derived by van der Waals. [161] The heat capacity and entropy of argon in its clathrate with five different percentage occupations of the cavities were in good agreement with those predicted on the basis of the Lennard-Jones model. [162] Similar measurements for the methane clathrate indicated that the rotation of the guest was almost unrestricted as low as 150°K. [163] The magnetic susceptibility of the diradical oxygen in its hydroquinone clathrate was found to be almost the same as the gas phase value, and this was interpreted as evidence for very little host/

host-guest interaction.[164] Kazankin [165] studied clathration isotherms for krypton and xenon sorption by hydroquinone. Langmuir's isotherm satisfactorily explained krypton sorption but xenon sorption was anomalous, since beyond a certain pressure of guest, the uptake of guest declined.

In an examination of the thermal decomposition of several quinol clathrates, McAdie [166] found that for symmetrical guests, the temperature and enthalpy for clathrate decomposition increases as the molecular volume of the guest increases but for unsymmetrical guests which cause distortion of the cavities, the temperature and enthalpy decreases as the amount of distortion increases.

When acetonitrile clathrate crystals were X-irradiated at liquid nitrogen temperature, e.p.r. spectroscopy was employed to demonstrate the presence of cyanomethyl radicals and to show that there is rapid rotation of the radicals parallel to the c-axis even at $77^{o}K$. [167]

The rigid quinol lattice has been employed as a matrix for studying the Mossbauer effect of gaseous atoms [168, 169] Both ^{85}Kr and ^{129}Xe clathrates have been examined.

The/

The anistropy of the ^{19}F chemical shift of trapped methyl fluoride in the quinol lattice has been demonstrated in a single crystal study. The C-F bond was found to be aligned parallel to the trigonal crystal axis and the frequency recorded was the highest when the c-axis of the crystal was parallel to the field. [154]

P.M.R. studies of some single crystals of hydroquinone clathrates revealed two types of signal, firstly broad signals as expected for molecules included in clathrate voids but also thin spectral lines which were attributed to liquid guest molecules trapped in large holes during crystallisation. [170]

Even pure nuclear quadruple resonance spectra 150 have been recorded for $^{14}N_2$ in β-quinol below $25^{\circ}K$. The results indicated that the axes of the trapped molecules oscillate around the trigonal crystal axis of the host structure.

Far infra-red spectra of H_2S, H_2Se and the corresponding deuterated clathrates suggested that rotation of the encaged molecule was nearly free. [157] However a similar study of the sulphur dioxide clathrate/

clathrate revealed that the translational and rotational vibrations of SO_2 were restricted even at room temperature. [171]

In dielectric relaxation experiments, it was found that the absorption for the HCl clathrate was almost independent of temperature, and even at $88^{\circ}K$, the guest rotated freely. This was rationalised by the fact that the HCl molecule is so small that there is some free volume in the cavity.

Finally Davies et al.[172] obtained evidence for C-Br bond compression in the methyl bromide clathrate from Raman studies.

(v) Practical applications of the quinol clathrates

Several practical applications of the quinol clathrates have been reported, taking advantage of the great stability of the adducts under normal conditions.

Powell [173] found that the inert gases could be obtained in an exceptionally pure state by release from the appropriate quinol clathrate. When the gas is required, the clathrate crystals are simply placed in a solvent which dissolves the host and thus allows escape of the guest.

Probably the best known use of hydroquinone clathrates is the use of the ^{85}Kr complex as a pollution monitor and a thickness gauger. The clathrate of this β-emitting gas has been described as the safest form of radioactivity. For example, ozone causes oxidation of the host thereby damaging the host lattice and allowing some guest molecules to escape. Using a suitable counting arrangement, one molecule of ozone in a billion can be detected.[174] Similar methods for SO_2 and fluorine [175] have been described. The ^{85}Kr clathrate can also be used to give surface coatings permanent luminescence.[176] It has also been suggested that waste radioactive noble/

noble gases from nuclear power stations could be stored safely as their quinol clathrates. [177]

The methyl bromide clathrate has been employed as a fumigant for the control of soil nematodes [152] and the use of inclusion compounds of hydroquinone and other hosts as agents for improving the oxidation stability and rust resistance has been described by Cover. [124]

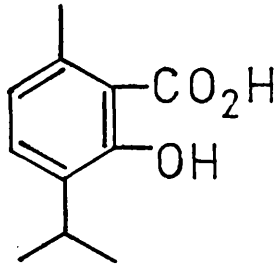
(vi) Simple phenol derivatives with modifications to the hydroxyl group.

It is highly significant that for anisole, thiophenol, aniline, p-aminophenol, p-phenylenediamine etc., where a formal substitution has been made for the hydroxyl groups of simple phenol hosts, no inclusion properties have been observed to date. This is probably mainly as a result of the weaker strength of SH···S and NH···N hydrogen bonding.

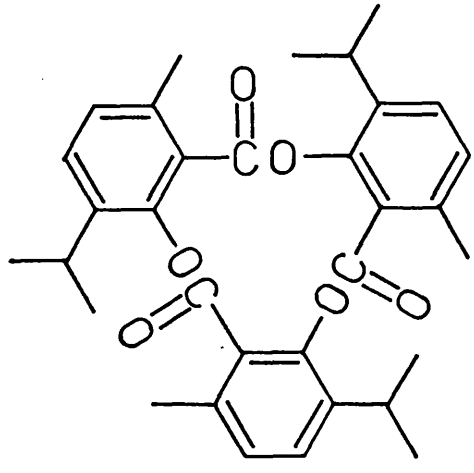
4. Tri-ortho-thymotide and related systems.

(i) Tri-o-thymotide itself.

Inclusion compounds are very rare but those which can crystallise with two type of cavities are even rarer. Tri-o-thymotide (16) is one of only two hosts to display this behaviour. It differs from Dianin's compound (19) in the respect that there is no hydrogen bonding functionality, yet the van der Waals forces holding the host structure together still lead to a very stable structure capable of retaining volatile guest species. This host was first prepared by dehydrative cyclisation [178] of o-thymotic acids (62).



(62)



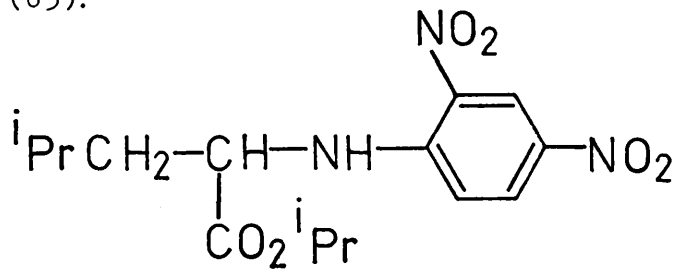
(16)

Thorough characterisation was achieved forty three years later in 1952 [179] and the ready inclusion of solvent/

solvent observed. An unsolvated form of (16) could be obtained by methanol crystallisation but if seed crystals were present, the methanol adduct was formed. The inclusion compounds of (16) melt over a wide range and the initial decomposition temperature varies from guest to guest, indicative of a van der Waals bound host, unlike the hydrogen-bonded Dianin's compound where a melting point range of 1^{o} is the norm and all decomposition temperatures are almost the same. It was found that the ethanol adducts of (16) required thirteen hours heating at 160^{o} and 1mm. and then six hours at 178^{o} to effect removal of all the guest. Other guests did not require such long heating periods again suggesting that the guest molecules affect the stability of the host structure.

By X-ray analyses, [180] the unsolvated host was found to be a racemate but every adduct was found to be spontaneously resolved. The activation energy for racemisation was estimated as 16kcal. mol^{-1} with the half time being 12.4 mins. at 10^{o} in solution. It was thought that the optical activity arose from hindrance to free rotation about single bonds in the twelve-membered ring, with the host molecules crystallising as either left - or right - handed three bladed propellors. Several different space groups for different adducts/

adducts of (16) were noted again illustrating the guests' influence on the host's packing. The lattice parameters were observed to vary considerably even within a series of adducts with the same space group.[181] Molecules longer than 9.5A° always crystallise in the channel form and smaller molecules normally crystallise in the cage type of cavity, although some guests, especially those near the crossover point, can crystallise in either form. Recently, it was reported[182] that (16) formed an inclusion compound with the very large molecule (63).

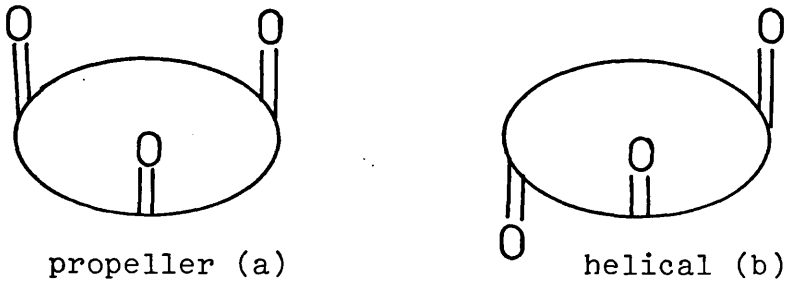


(63)

Whether this is a channel type structure or some completely new arrangement has not been determined.

N.M.R. studies have proved to be of great importance to the understanding of the ring inversion processes and the attendant consequences for (16). By studying the temperature dependent spectra of the host[183] evidence was derived for two conformations in solution, the propeller (a) and the helical conformations (b) both/

both of which are chiral and are schematically drawn in figure 10.

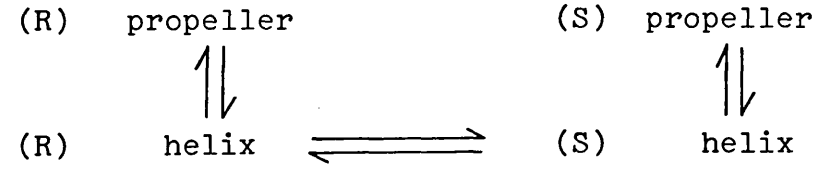


propeller (a) helical (b)

Figure 10

Solution conformations of tri- o -thymotide (16) (c.f. W.D. Ollis and I.O. Sutherland, Chem.Comm., 1966, 402).

The activation energy for racemisation was estimated as 22.2 kcal mol. $^{-1}$ In both channel and cage type clathrates, the host molecules were found to be in the propeller conformation, [184] this being established by low temperature n.m.r. studies, circular dichroism and absorption spectra. Further n.m.r. studies [185] enabled elucidation of the mechanism of racemisation in solution and this is shown below.



Final proof for the propeller conformation only, in the solid state has come from full X-ray structural determinations/

determinations. [186, 35] This conformation is found in the empty orthorhombic form as well as the two inclusion compound forms. Slight deviations from perfect C_3 symmetry required for the propeller conformation have been observed. [35]

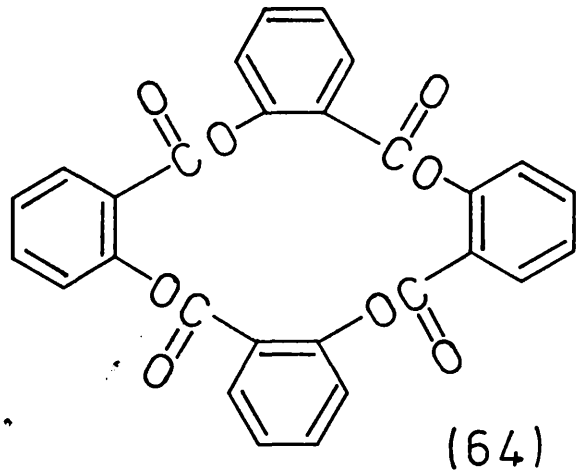
The observation of spontaneous resolution of (16) prompted Powell to attempt resolution of a racemic mixture by adduct formation. [187] Partial resolution of sec-butylbromide was thereby achieved. Similarly Hargreaves and Modarai [188] attempted resolution of bromchlorofluoromethane by complexation with (16). However it did not prove possible to obtain the active haloform in sufficient quantity to prove resolution.

The tri-o-thymotide menthol inclusion compound has been employed as a flavouring agent for tobacco, the menthol not being released until the tobacco is smoked. [189] Inclusion compounds of (16) and other hosts have found application as anti-oxidants for fuels and lubricants. Among others, tri-o-thymotide inclusion compounds' crystal lattice has been used to orient small aliphatic compounds in the external field in high resolution n.m.r. studies. [190] Guest selectivity properties [191] have also been examined and it is found that/

that cyclic hydrocarbons are preferred over linear ones and that from a mixture of xylenes, p-xylene is clathrated preferentially. Another interesting study is that of Wu et al., [192] who observed motional narrowing in the ^{19}F n.m.r. of the 1,1,1-trifluoro-2-chloro-2-bromoethane - tri-o-thymotide clathrate. Free rotation of the CF_3 group was observed about its C_3 axis at temperatures as low as 108°K. The self radiolysis of clathrates containing tritium-labelled molecules has been described by Ciranni et al [193, 194]. 9, 10-Di-T-methylstearate in (16) and other hosts was the case under investigation.

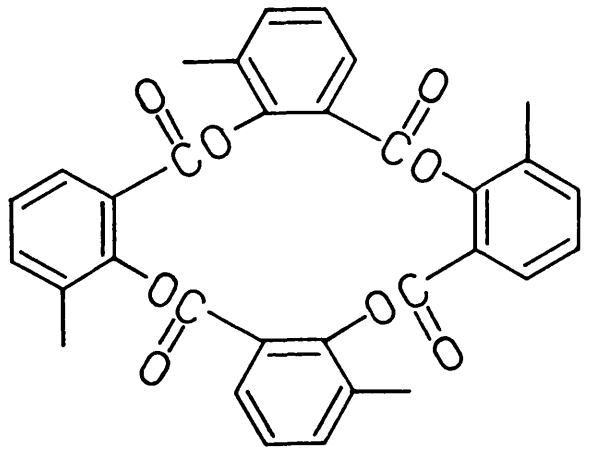
(ii) Analogues of tri-o-thymotide (16)

Several molecules similar to (16) have been found to include solvents but no crystal structures have been carried out to determine their nature. One of the best known is tetrasalicylide (64) which crystallises with two molecules of chloroform. [195]



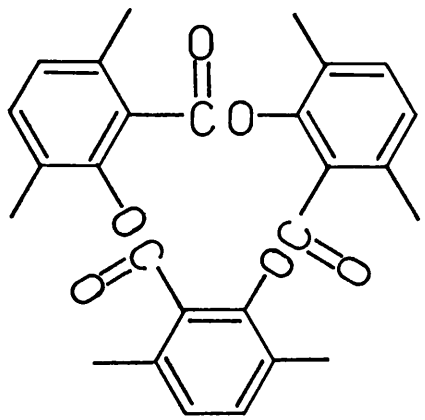
(64)

The use of this adduct and that of tetra-o-cresotide (65) to prepare very pure chloroform was suggested in 1892 [196] indicating that the inclusion of chloroform is fairly specific.

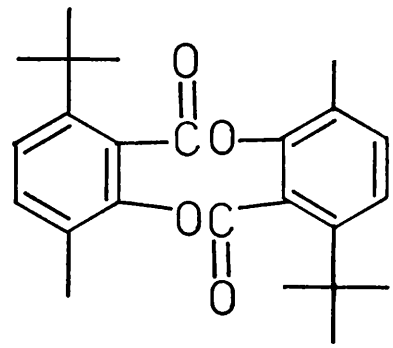


(65)

Baker et al. [197] found that the chloform was not lost until the adducts of either the cresotide (65) or salicylide (64) was heated to 100° at 1 m.m. Interestingly, the corresponding di-and tri- o -cresotides [198] and the di-and tri-salicylides [197] showed no inclusion ability. Tetra-m-cresotide, similar to (65) has been reported to form a 1:1 adduct with benzene. [199] Several other compounds were synthesised to test for clathrate formation, e.g. (66) and (67) but none included any solvents. [200]

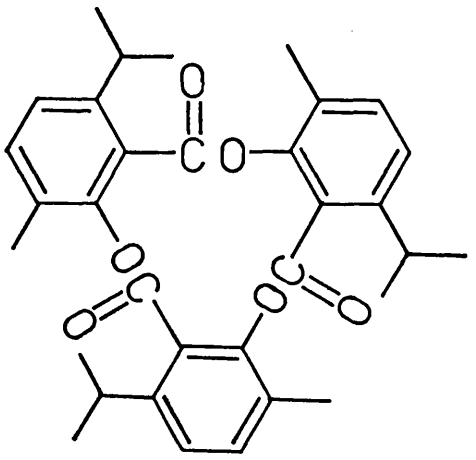


(66)



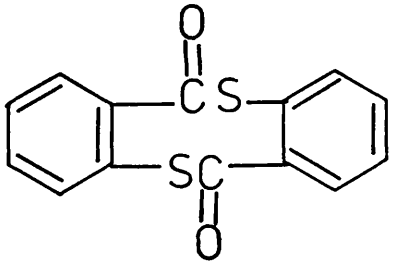
(67)

Tri-o-carvacrotide (68) similar to (16) except that the methyl and isopropyl groups positions are reversed was prepared and studied by n.m.r. [201] Propeller-helix conformational processes were observed but no clathrates were formed.

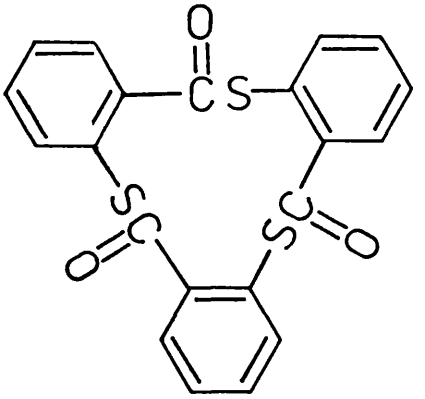


(68)

Di-, tri- and tetra-thiosalicylides have been prepared and the dimer (69) and trimer (70) both include benzene tightly. [202] This behaviour is in stark contrast with the salicylides themselves where only the tetramer includes chloroform.

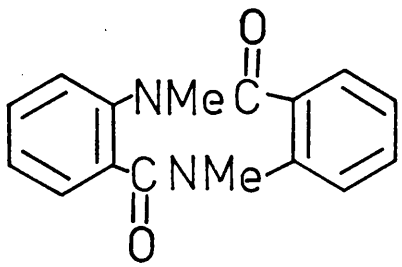


(69)

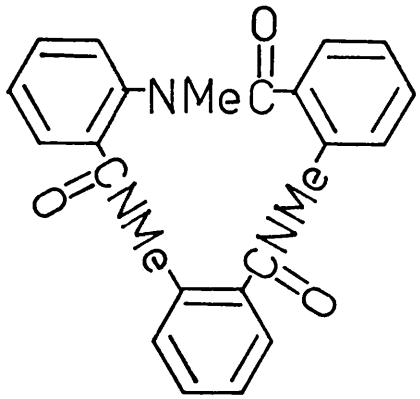


(70)

The corresponding di-[203] and tri-[204] anthranilides (71) and (72) respectively, were disappointingly not found to include solvent.

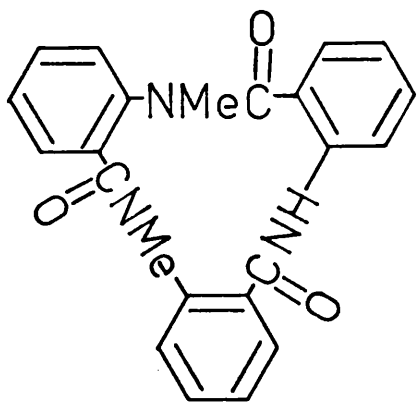


(71)

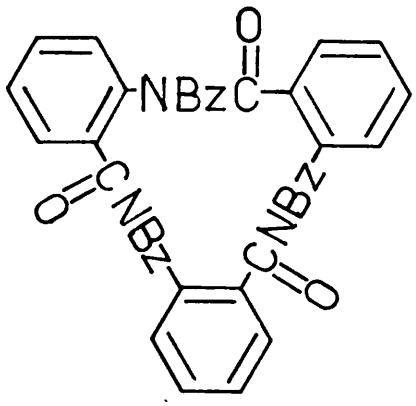


(72)

Interestingly the trimer crystallised in the helical conformation unlike the other salicylides, but in solution, there is about 5.5% of the propeller conformation present. [205] It has been found that both the helical and propeller conformational isomers can be separately isolated in the solid state in the case of N,N'-dimethyl-trianthranilide (73). Both conformers have completely different melting points. The same holds for N,N',N''-tribenzyltrianthranilide (74). The propeller form with C_3 symmetry melts from 260 - 3° whereas the helical form with C_1 symmetry melts from 134 - 144° and forms a 1:1

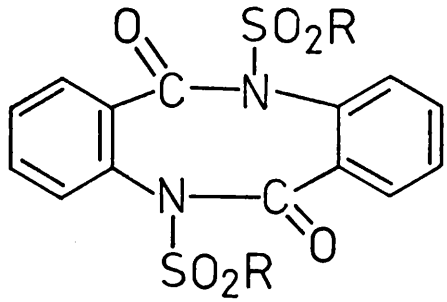


(73)



(74)

clathrate with ethanol. [206] Three other dianthranilides have been reported [203] to form 1:1 adducts with chloroform namely compounds (75) - (77).

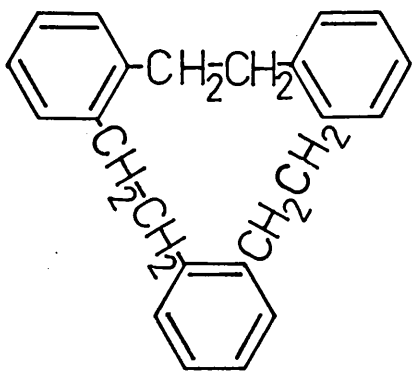


R = phenyl (75)

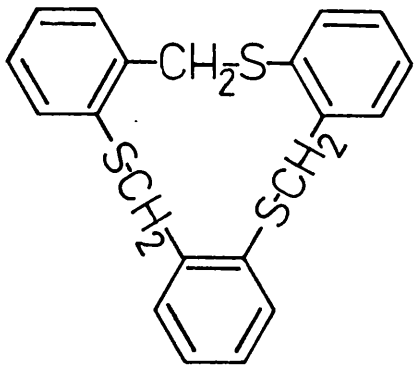
R = p-tolyl (76)

R = β-naphthyl (77)

Compounds such as (78) [207] and (79) [208] still encompassing a twelve-membered ring, do not form clathrates but are interesting from a dynamic n.m.r. point of view.



(78)



(79)

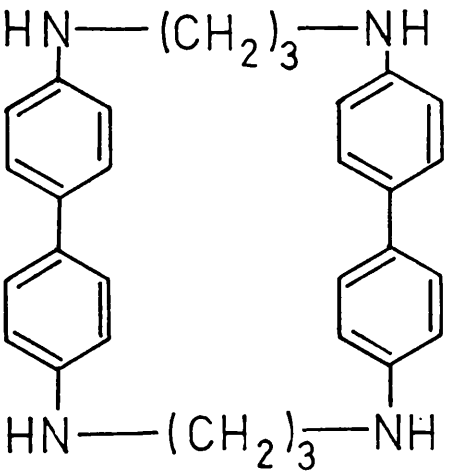
A recent X-ray analysis has revealed [209] that (79) crystallises in the helical conformation with space group $P2_1/n$.

5. Monomolecular inclusion compounds.

(a) Introduction

In all the previous cases discussed, several molecules of the host are required to form the inclusion compound crystal lattice. However a few cases of monomolecular inclusion compounds i.e. where a single molecule embodies a cavity into which a guest molecule may fit have been recognised.

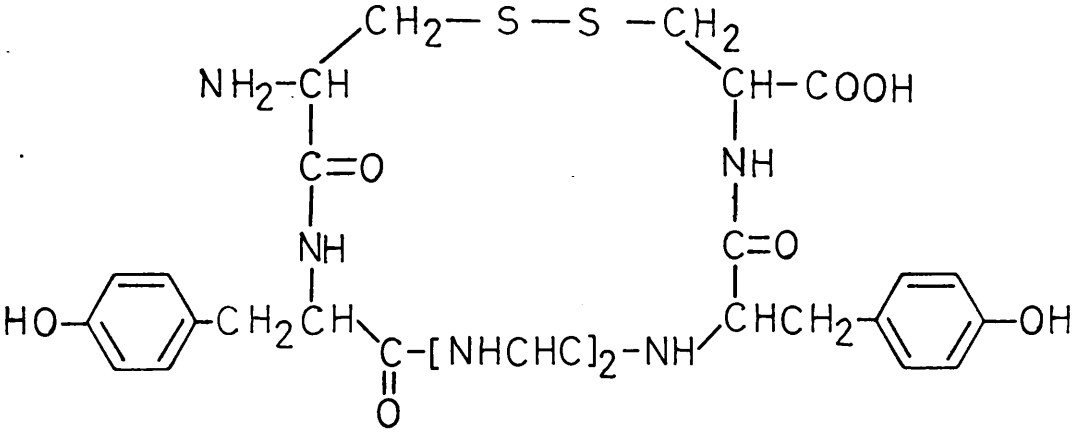
The simplest molecule in this category is bis - N, N'-trimethylenebenzidine (80) and the corresponding tetramethylene analogue.[210]



(80)

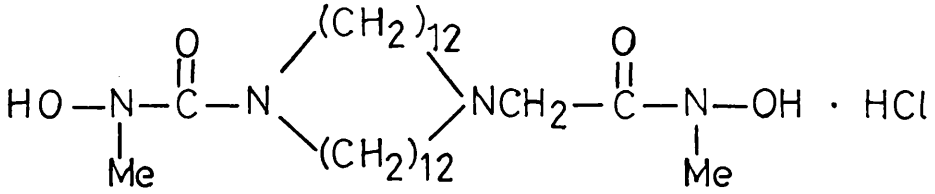
Benzene and dioxan can both be included but the guests are lost when the crystals are dried under vacuum.

Lautsch and Gunther have described the inclusion compound of quinone with the complex macrocyclic disulphide (81).[211]



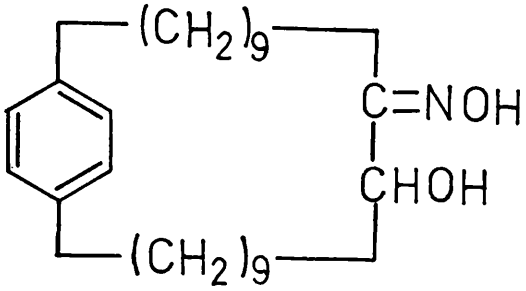
(81)

Another interesting compound (82) has been described as a reactive enzyme model molecule. [212]



(82)

Nucleophilic and metal ion acceleration of ester hydrolysis have been observed in the presence of (82) in solution. It is suggested that the binding site may be the hydrophobic internal cavity of 5.6A° in diameter formed by the aliphatic chains. A similar example is the paracyclophane (83) which possesses a hydrophobic cavity of 6.5A° in diameter which again functions as the binding site for the substrate. [213]



(83)

By far the most widely studied molecules in this class are the Schardinger dextrins (4) - (6). Currently more papers and patents are appearing concerning these hosts than all the rest put together. These hosts are discussed in detail in the next sections.

Related to the cyclodextrins is polymeric amylose (7) one of the major components of starch. It consists of long unbranched chains of α- (1, 4) -glucose units, the same building block as for the cyclodextrins. This normally non-crystalline material can crystallise in an infinite helix with a channel remaining in the centre, capable of accommodating a wide range of guest molecules [24, 214] such as simple alcohols, terpene alcohols, ketones, cresols, pyridine, nitrobenzene, but best known of all, iodine. The blue addition compounds of iodine formed with crude starch is largely due to its amylose component although amylopectin, the isomeric branched constituent of starch also forms an iodine complex.

(b) Cyclodextrins (4) - (6)

(i) General

The cyclodextrins have been the subject of a number of excellent reviews, namely those by French [21] Thoma and Stewart [22], Cramer and Hettler, [215] and Griffiths and Bender [23]. Accordingly, emphasis will be placed on recent developments.

The cyclodextrins are a homologous series of compounds, consisting of different numbers of D (+)-glucopyranose units, α-(1,4) linked to give large ring compounds. The best known compounds are the so-called α, β and γ-cyclodextrins comprising 6, 7 and 8 glucose units respectively, disposed in a torus-shaped ring which encompasses a cavity in the centre of 6, 8 and 10A$^{\circ}$ respectively, capable of including a vast range of guest molecules. The molecular structure [216] of α-cyclodextrin (4) is displayed in figure 11.

An alternative name for α-cyclodextrin is cyclohexaamylose and corresponding names are used interchangeably for β- and γ-cyclodextrins too. For brevity C.D. will be used in this thesis to denote cyclodextrin.

The C.D.s are produced by the action of Bacillus macerans amylase on potato starch. The mixture of/

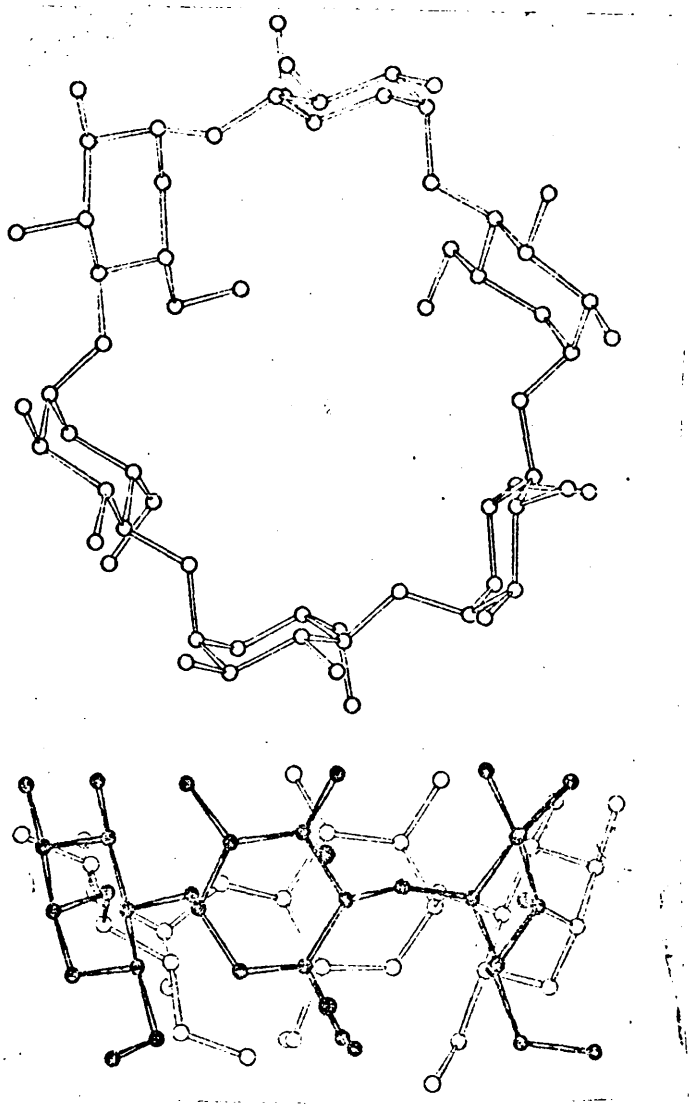


Figure 11

The molecular structure of ∝-cyclodextrin.
Above : plan view, below : end-on view.
(P.C. Manor and W. Saenger, Nature, 1972, 237, 392).

of α, β and γ-isomers so formed are readily separated by selective adduct formation [217]. For example α-C.D. forms an adduct with chlorine but β-C.D. with its larger channel-type cavity does not form an adduct with chlorine but does with bromine. Iodine is the only halogen guest suitable for γ-C.D. The three isomers can also be separated chromatographically.[218] It is particularly interesting that the yield of β-C.D. for example, over α-and β-C.D. can be greatly increased during the enzymic preparation in the presence of a suitable selective precipitant such as toluene. [219]

It was established fairly recently by p.m.r. infra-red [220] and O.R.D. studies [221] that in solution, the glucose molecules are in the chair conformation. This has important consequences since from molecular models, it is readily appreciated that the cavity interior is lined by glucosidic oxygen atoms and is not hydrophobic hydrocarbon as was once thought.

(ii) Crystal structure of inclusion compounds

Recent X-ray analyses have confirmed that the same holds good for the solid state. Full crystal structural analyses have been conducted on α-C.D. only. The α-C.D..I_2.$4H_2O$ complex was found to be orthorhombic with space group $P2_12_12_1$ and to possess a cage type cavity in which the iodine molecule is accommodated/

accommodated. A "herring-bone" arrangement of the C.D. molecules results in closed cage formation; [222] (see figure 12). The α-C.D. .Kr.$5H_2O$ structure was found to be similar [223] as was the p-iodoaniline trihydrate complex with α-C.D. The three water molecules were located as lying in a different kind of cage intermolecularly whereas the p-iodoaniline is accommodated intramolecularly like iodine and krypton. [224] However a continuous channel type of structure is also found in which the α-C.D. molecules stack directly on top of each other instead of the previously described half-staggered arrangement. Notlemeyer and Saenger [225] solved the crystal structure of $(\alpha\text{-C.D.})_2 Li\ I_3.I_2.8\ H_2O$ and $(\alpha\text{-C.D.})_2\ Cd_{\frac{1}{2}}\ I.2I_2.26H_2O$ adducts very recently. The former is triclinic with space group P1 and the latter tetragonal with space group $P4_22_12$, the difference arising from the slightly different arrangement of packing of the infinite columns of torii; (see figure 13). The iodine in the Li^+ case is accommodated as polyiodide chains running through the columns with a slightly staggered conformation of the guest. The water molecules are located between the columns intermolecularly.

Although full crystal structural analyses have not been conducted on β- and γ-C.D., a continuous channel arrangement, similar to that of the polyiodide inclusion compounds of α-C.D. is indicated. Evidence for/

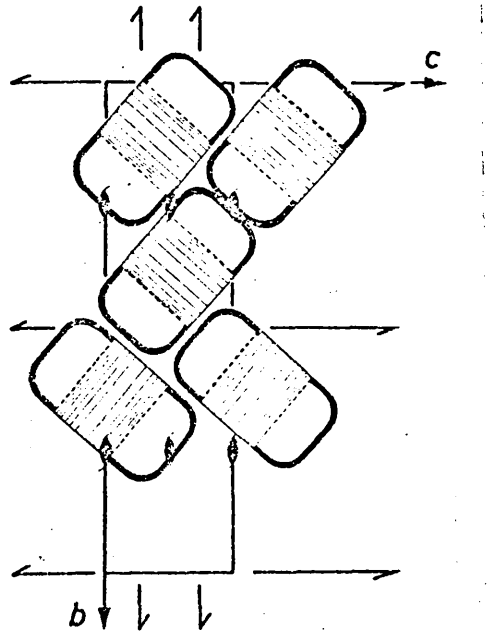


Figure 12

Schematic packing diagram of ∝-cyclodextrin adducts for small molecular guests looking along the crystallographic axis.

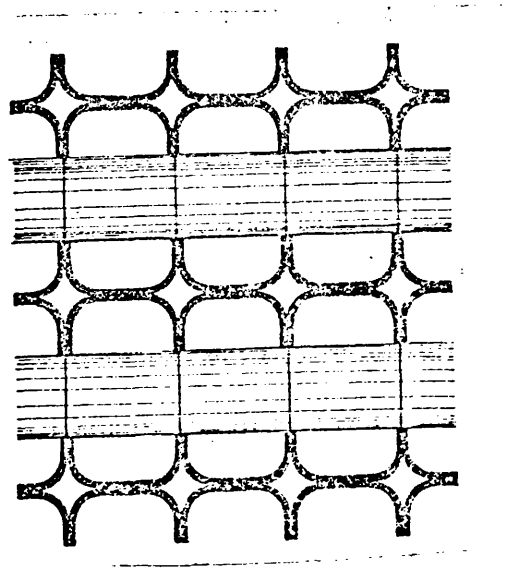


Figure 13

The packing scheme for ∝-cyclodextrin adducts with large molecular guests. (R.K. McMullan, W. Saenger, J. Fayos and D. Mootz, Carbohydrate Res., 1973, 31, 37).

for this was obtained from X-ray powder photograph studies of the n-propanol adducts of γ-C.D. [226] and from the fact that volatile guests such as the ideal gases are not retained by β-or γ-C.D.

Hamilton et al.[227] reported the space groups and cell dimensions for various β-C.D. inclusion compounds. The space groups vary remarkably with respect to the guest and the extent of hydration, as table (X) shows.

Table (X)

Space group data for various β-C.D. inclusion compounds.

Guest	Space group
none	$P2_1$
1-adamantane carboxylic acid .16H_2O	C1
1-adamantane carboxylic acid .15H_2O	P1
m-bromobenzoic acid	C2
m-t-butylphenol	$C222_1$
phenylmercuric acetate	$P22_12_1$

(iii) Solution phenomena

Normally when an inclusion compound is dissolved in a solvent, the host structure breaks down releasing the guest. The cyclodextrins however, possess permanent ring/

ring-shaped cavities which are capable of including guest molecules in aqueous solution. [228] Cramer [229] observed that several dyes such as crystal violet and methylene blue in β-C.D. solution give stronger blue colours than solutions at the same dye concentrations in water or glucose solution. Absorption spectra showed an enhancement of the peak near 600 mμ and sometimes a shift towards longer wavelengths. This was attributed to the high electron density. of the interior surface of the cyclic dextrin which acts as a Lewis base towards the included molecule. MacNicol [230] has employed α-C.D. in D_2O solution as a shift reagent for hydrocarbons such as p-cymene and adamantane, further demonstrating that inclusion occurs in solution. Absorption spectra indicate that on complex formation with C.D.s, acetylacetone and furoin tautomerise to the easily oxidisable enol forms. The rate of oxidation was doubled in the presence of α-C.D. and trebled with β-C.D. [229]

(iv) Enantiomeric properties

Since the cyclodextrins are optically active compounds, being composed of D-glucose units, the preferential inclusion of one of the antipodes of a racemic mixture might be expected. Cramer et al.[231] showed that insoluble β-C.D. inclusion compounds formed with/

with several racemates, are enriched 3-12% in one of the stereo-isomers e.g. for the ethylester of mandelic acid. O-alkyl-alkylsulphinates were obtained in up to 70% optical purity by β-C.D. inclusion compound formation. [232] Addition of HCN to 2 - or 4 - chlorobenzaldehyde in the presence of α-C.D. gave rise to optically active cyanohydrins, which on saponification produce optically active mandelic acids [233]. In a similar inverse experiment, the hydrolysis of ethyl-4-chloromandelate in the presence of β-C.D. produced at 50% completion a mixture of partially resolved product and partially resolved starting material. [233]

(v) Catalytic properties

The greatest interest in cyclodextrin inclusion compounds lies in their parallel with enzyme-substrate complexes. It is found that many reactions can be retarded, accelerated or even have their course altered catalytically in the presence of cyclodextrins for which the explanation is always that it is the result of inclusion in the cyclodextrin cavities. Three main types of catalysis may operate. These are:

(a) Covalent catalysis

(b) Microsolvent effect catalysis

(c) Conformational or orientational catalysis

(a)/

(a) Covalent catalysis

In this case the key step is nucleophilic attack by a cyclodextrin hydroxyl group or alkoxide ion on the suitably orientated reactive guest molecule, thus forming a covalent bond between host and guest with concomitant expulsion of a leaving group from the guest. A fairly early example is the decarboxylation of phenylmethylcyanoacetic acids, the rates of which are increased in the presence of cyclodextrins [234] with acceleration factors ranging from 1-15. The mechanism proposed in 1965 is strikingly similar to those invoked for enzyme-mediated reactions; see figure 14.

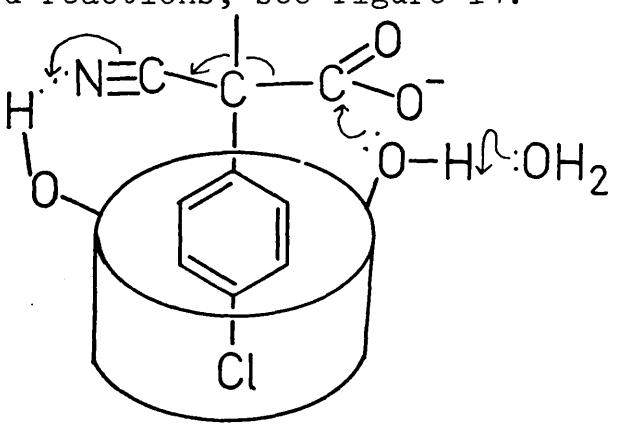


Figure 14.

Mechanism of catalysis of decarboxylation by cyclodextrin. (F. Cramer and H. Hettler, Naturwissensch, 1967, 54, 625.)

The system can be treated kinetically according to Michaelis-Menten theory. However, later work [235] (q.v.) indicated that the catalysis was not covalent in nature but microsolvent derived.

Pyrophosphates/

Pyrophosphates are cleaved at pH12 in the presence of C.D.s at high catalytic rates. [236] The mechanism is depicted below in figure 15.

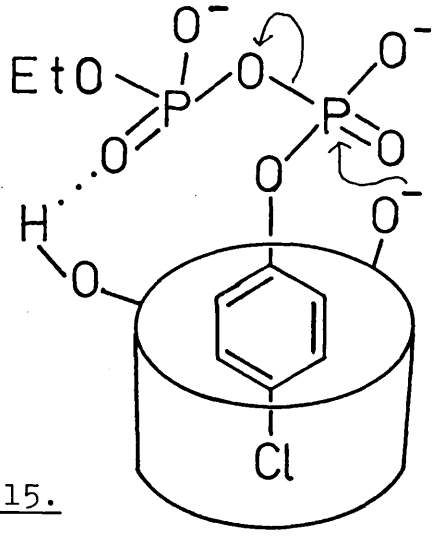


Figure 15.

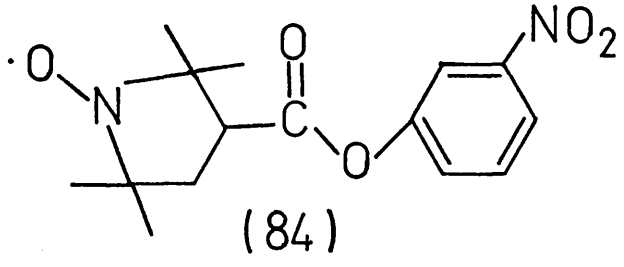
Mechanism of phosphate transfer caralysis by cyclodextrin. (F. Cramer and H. Hettler, Naturwissensch., 1967,54, 625).

It is well known that the hydrolysis of substituted phenylacetates follows the normal Hammett relationship between the log of the rate constant and the appropriate substituent constant. However, when the hydrolysis solution contains either α-or β-C.D. very large and variable accelerations are found with pseudo first order rate constant corresponding to the appearance of the phenol [237] The accelerations do not follow a Hammett relationship since steric effects are now paramount. Hydrolysis of m-substituted ester are enhanced relative to p-substituted ones and the meta/para specificity decreases as the size of the C.D. cavity increases/

increases. This suggests that there is a specific rate accelerating interaction between the secondary hydroxyl groups of the C.D. and the carbonyl group of the included ester.

β-C.D. has also been studied as a model for the alkaline hydrolysis of penicillin derivatives. Rate enhancements of 20-90 fold were observed and the key step was again suggested as the attack of a host hydroxyl group on the β-lactam carbonyl group.[238]

Flohr et al.[239] have reported the observation of enantiomeric specificity in the reaction of α-C.D. with 3 - carboxy - 2,2,55 - tetramethylpyrrolidine - 1 - oxy - m - nitrophenylester (84), a spin label for identifying enzyme-substrate interactions.[240] The enzyme specificity is only slightly less than that

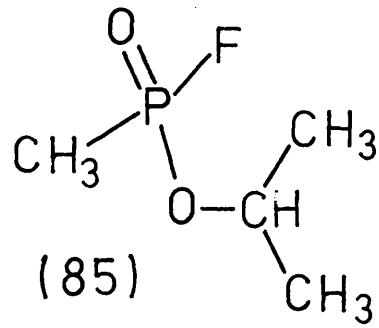


(84)

observed for the chymotrypsin catalysed hydrolysis of the p-nitrophenyl analogue.[241] Significantly, no enantiomeric specificity is observed in the reaction of (84) with β-C.D. with its larger cavity, consistent with the idea that specificity is derived from tight binding/

binding of the substrate. [240]

The reaction of α-C.D. with chiral organophosphorous substrates such as sarin (85) is a further example of exceptionally high induced enantiomeric specificity. The (R) isomer reacts faster



(85)

than the (S) isomer and it was established that the reactions involve intracomplex nucleophilic attack on phosphorous by an ionised α-C.D. hydroxyl group, thus releasing fluoride at an accelerated rate. [242]

The mechanisms of the cycloamylose catalysed rates of hydrolyses of diphenyl carbonate and structurally analogous phosphonates were compared by Brass and Bender [243]. Both involve nucleophilic attack by a hydroxyl group of β-C.D. Remarkably a kinetic acceleration of at least 10^4 is indicated in the catalysed hydrolysis of bis -(p-nitrophenyl)-methylphosphonate, which is similar to rate enhancements associated with the formation of cyclic phosphates from nucleoside diesters. The mechanism of the second step is/

is shown in figure 16.

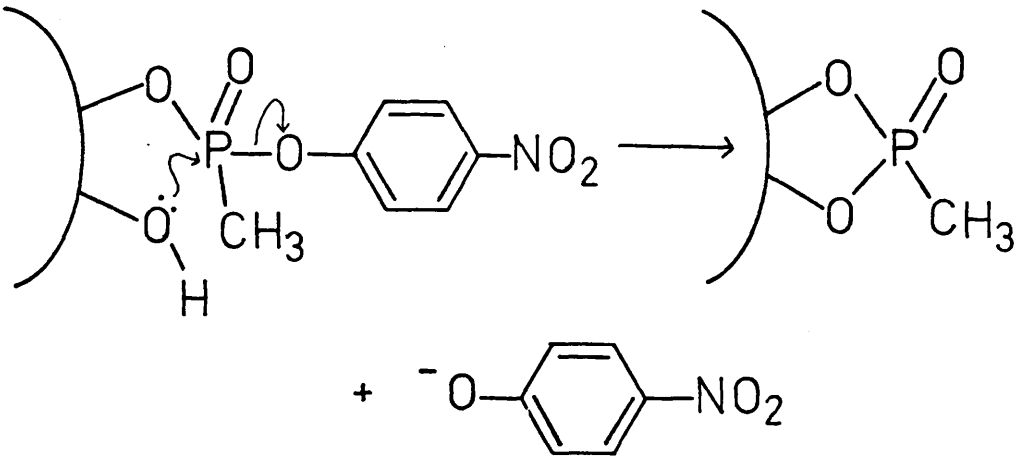


Figure 16.

Cyclodextrin catalysed hydrolysis of methylphosphonates. (H.J. Brass and M.L. Bender, J. Amer. Chem. Soc., 1973, 95, 5391).

(b) Microsolvent effect catalysis

The manifestation of non-covalent catalysis as a microsolvent effect is illustrated by the work of Straub and Bender [235], who reinvestigated and extended Cramer and Kampe's work [234], on the decarboxylation of phenylcyanoacetic acids. Unlike the previously discussed cases, the rate accelerations are approximately independent of both size and position of the phenyl ring substituent, and pH independent. The final piece of evidence for the microsolvent effect is that the rate accelerations imposed by β-C.D. could be achieved in a macroscopic solvent such as 57.5% propan-2-ol/water. Similar results were obtained for the β-C.D. catalysed hydrolysis of aryl sulphates. [244]

(c) Conformational catalysis

Accelerations or decelerations may be imposed by the cyclodextrins on the rate of an intramolecular reaction of account of the conformational restrictions imposed by the fixed dimensions of the cavity. For example, Matsui et al [245] found that the benzidine rearrangement of hydrazobenzene was retarded by C.D.s. It was proposed that the substrate was located in the cavities which either restricted the large conformational change of the substrate necessary for reaching a sandwich-type transition state or by lowering the concentration of the diprotonated hydrazobenzene by means of the void alaklinity of the host. Interestingly, cyclohexanol, previously known to form an inclusion compound with C.D. serves as an inhibitor, since the retardation is diminished with increasing cyclohexanol concentrations.

The rates of decarboxylation of several unionised β-ketoacids such as substituted benzoylacetic acids are accelerated six-fold by β-C.D. but α-C.D. depresses the rate. [246] This has been explained by assuming that the smaller α-C.D. cavity cannot accommodate the cyclic transition state necessary for acidic/

acidic decarboxylation (figure 17.)

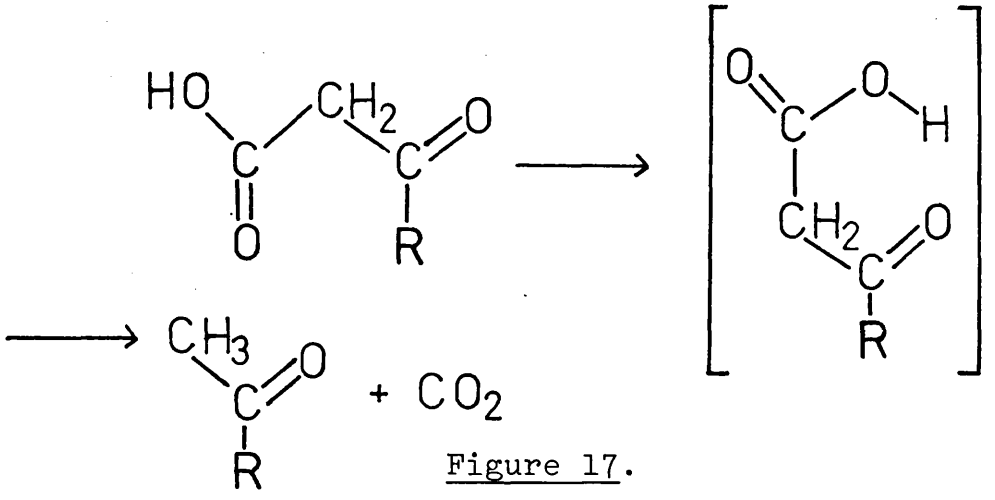


Figure 17.

Acid-catalysed β-ketoacid decarboxylation.

(T.S. Straub and M.L. Bender, J. Amer. Chem. Soc., 1972, 94, 8881).

Another beautiful example is the intramolecular transesterification shown below (figure 18) which is accelerated by α-C.D. this time but decelerated by β-C.D. [247] The intramolecular transesterifaction occurs 10^5 times faster than the intermolecular transfer of the trimethylacetyl group to surrounding water molecules.

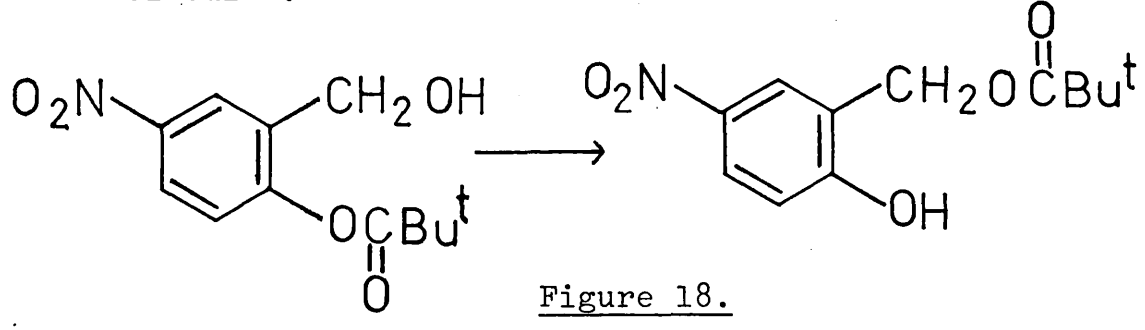


Figure 18.

Intramolecular transesterification.

(D.W. Griffiths and M.L. Bender, J. Amer. Chem. Soc., 1973, 95, 1679).

Van der Jagt et al. [248] studied the rates of formation of cyclic anhydrides from monoesters of 3-substituted glutaric acids (figure 19) and found that the rate varied dramatically with the 3-substituent. Both the catalysed and uncatalysed reactions showed the same pH dependence so the geometry of the binding must determine the reactivity.

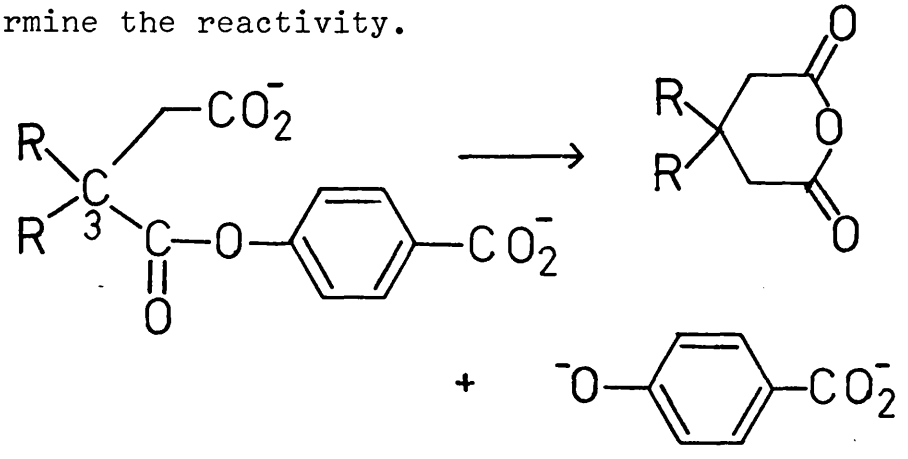


Figure 19.

Cyclic anhydride formation.
(D.L. Van der Jagt., F.L. Killian and M.L. Bender, J. Amer Chem. Soc., 1970, 92, 1016).

There are two magnificent examples of pertubation of reaction courses effected by C.D. conformational catalysis. The first is the reaction of anisole with hypochlorous acid. In the uncatalysed reaction, 40% o-chloroanisole is produced but the ortho chlorination was completely suppressed in the presence of α-C.D. [249] Figure 20 displays a schematic diagram of the anisole inclusion/

inclusion complex showing the effective shielding of the o- and m-positions.

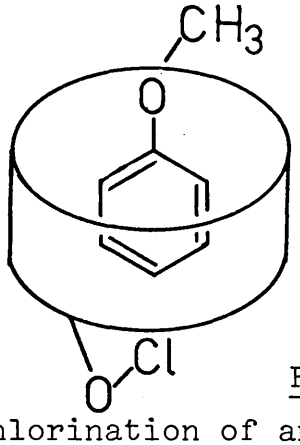
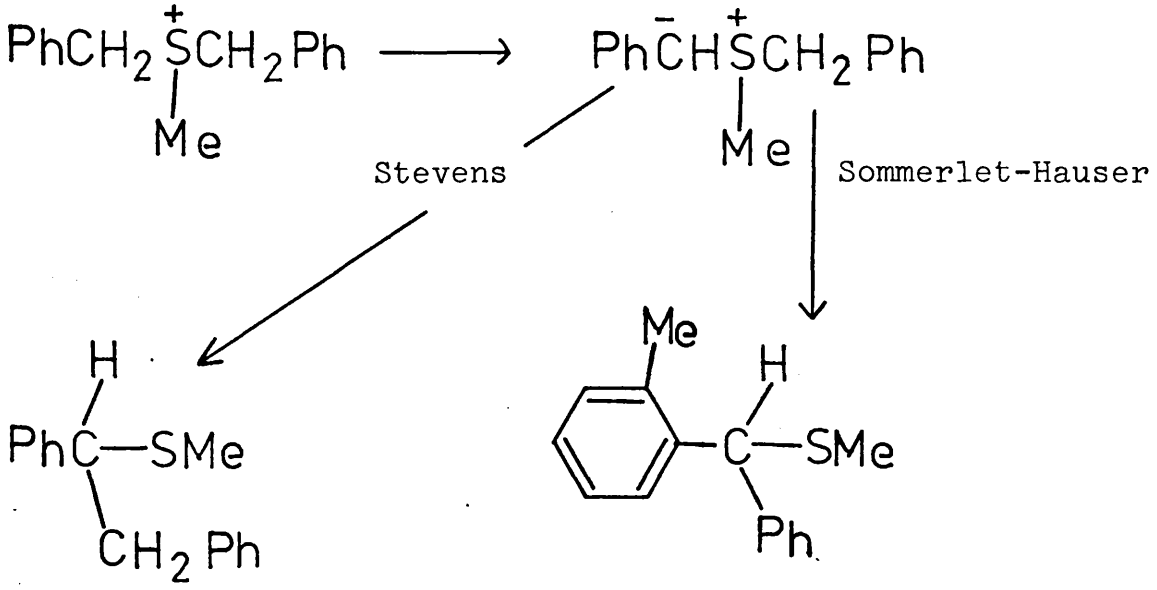


Figure 20.

∝-C.D. catalysed chlorination of anisole.

(R. Breslow and P. Campbell, Bioorganic Chem., 1971, 1, 140).

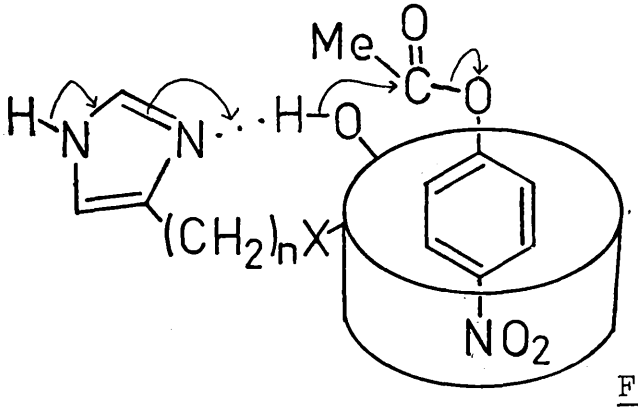
The second particularly intriguing example is the rearrangement of sulphonium ylides. Normally the Stevens rearrangement product predominated with a minor amount of Sommerlet-Hauser product being formed. In the presence of β-C.D. the reverse is observed. [250]



(vi) Derivatives of the cyclodextrins

Since the cyclodextrins possess an intrinsic cavity, derivativisation should not be expected to result in loss of clathrating properties, either in solution or in the solid state unless most of the secondary hydroxyl groups on the inside of the torus were substituted by larger groups.

French [21] reported a "foolproof" preparation of cyclodextrin acetate and observed that solvent was included but lost slowly on standing in air. More recently, it has been found that cyclodextrins furnished with imidazole groups have a high catalytic effect upon the hydrolysis of p-nitrophenylacetic acid esters at pH 7.5 and serve as a remarkably good model for the enzyme chymotrypsin: [251] (see figure 21).



X = O or NH

n = 1 or 2.

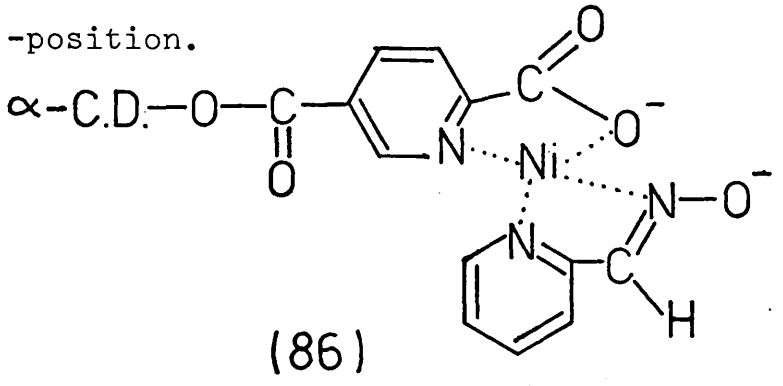
Figure 21.

Catalytic hydrolysis by imidazole-bearing C.D.s.

(F. Cramer and H. Hettler, Naturwissensch., 1967, 54, 625).

Breslow/

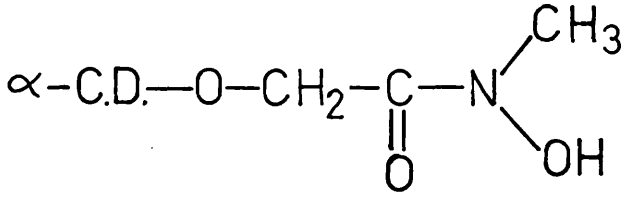
Breslow and Overman [252] synthesised an elegant artificial enzyme combining a metal catalytic group (86) comprising an α-C.D. derivative, mono-substituted in the 6 -position.



(86)

10^3 rate enhancements over the uncatalysed rates for the hydrolysis of nitrophenylesters were obtained.

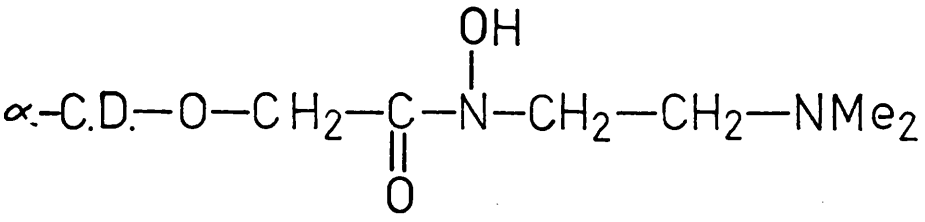
The N -methylhydroxamic acid derivatives of α-C.D. (87) has also been prepared. Kinetic specificity for p-nitrophenylacetate over the meta isomer was observed the reverse of that found for α-C.D. itself. [253] In a similar study, the catalytic power of (88) as



(87)

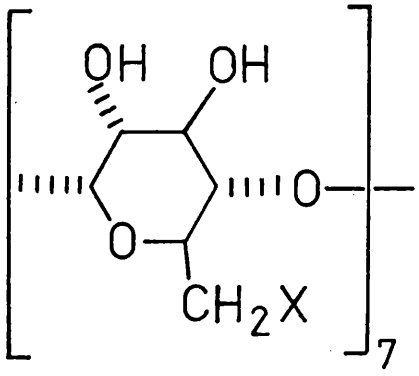
regards ester hydrolysis was greater than for α-C.D. itself. In addition, optical selectivity for the hydrolysis of (R) - and (S) - acetylphenylalanine nitrophenylesters/

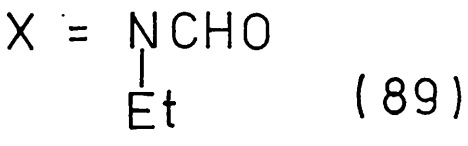
nitrophenylesters was observed but this was in the opposite sense to that encountered with the unsubstituted C.D. [254]



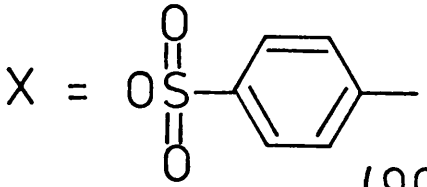
(88)

By careful heptakis substitution of the 6-position of β-C.D., Emert and Breslow [255] were able to create a hydrophobic floor at the base of the β-C.D. torus, composed of seven substituents. The purpose of this was to bring about stronger binding of substrate to host since without the floor the torus is open to solvent molecules at both ends. Indeed, 1-adamantane carboxylic acid was found to be an excellent inhibitor for compounds (89) and (90) and all others prepared.





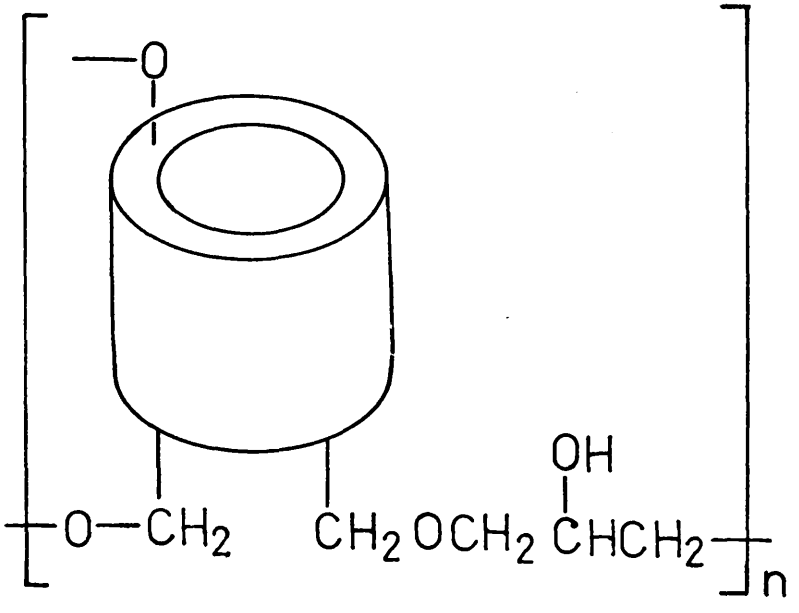
(89)



(90)

Bender et al. [256] synthesised the mono-3-histamine derivative of α-C.D. which proved to be a better model for/

for chymotrypsin since the rate enhancements for ester hydrolysis could be achieved at enzyme-operating pH's unlike previously described results. As a final example, Breslow [257] who had earlier studied the anisole chlorination reaction with α-C.D. [249] compared the same reaction with the 2, 6-dodecamethylether and the epichlorohydrin polymer of α-C.D. (91). Both still gave 99% p-chloroanisole, much the same as for α-C.D. itself.



(91)

(vii) Selected practical uses of the cyclodextrins

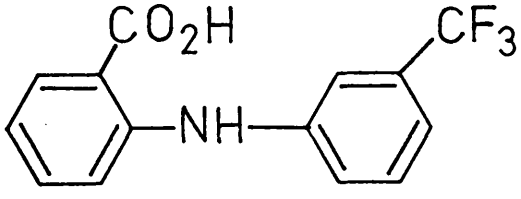
Cyclodextrins and their inclusion compounds have amazingly diverse uses as will be seen presently. An early report described the use of cyclodextrin acetates as the stationary phase in the G.L.C. of fatty acid esters.[258] α- C.D. has been employed as an indicator for the paper chromatography of lipids[259] The chromatogram is developed by spraying first with α-C.D. and then with iodine, the compounds showing up against the background α-C.D. is also useful as a separating agent for o-, m - and p-cymene. From an approximately 1:1:1 mixture, 97% pure p-cymene was obtained by steam distilling the crystalline adduct.[260]

The nitroglycerine inclusion compound of β-C.D. is used as an explosive or as a pharmaceutical, probably as a heart stimulant.[261] The chloropicrin adduct of β-C.D. is used as a bactericide and insecticide[262] and clathrates of various pyrethroids prove more effective against cockroaches than the guest compounds in their free state.[263] Rather mundane uses are exemplified in the use of the CO_2 clathrate of α-C.D. as a baking powder[264] and of aminoethyl derivatives of C.D.'s as paper size agents.[265]

The/

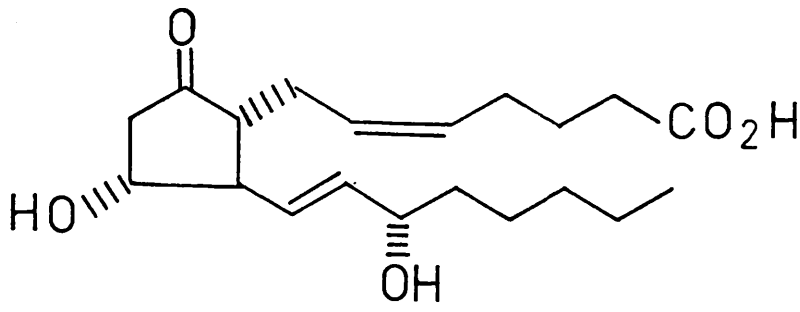
The cavities of the cyclodextrins also afford protection to hydroperoxides [266] coenzyme A [267] and fatty acids for example, the latter being preserved against oxidation even in a pure oxygen atmosphere. [268]

Currently much of the great interest in the cyclodextrins arises from their pharmaceutical applications. For example, stable clathrates of 1-butyl-1-nitrosourea, a useful anti-tumour agent are formed with α- and β-C.D.s. [269] Significantly, the inclusion compound of flufenamic acid (92) is water soluble unlike the drug itself. [270]



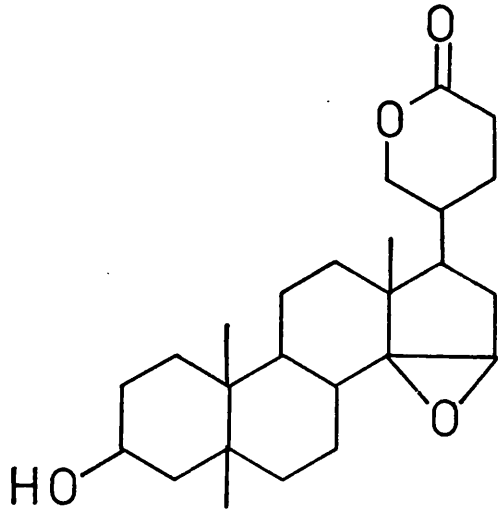
(92)

The silver-sulphadiazine - β -C.D. compound [271] is effective in treating burns and infected wounds. Prostaglandin E_2 (93) is greatly stabilised by formation of the α- and β -C.D. inclusion compounds. [272] Whereas after 30 hours at 106° 30% of the free prostaglandin remained intact, under the same conditions, 90% of (93) as its inclusion compound still remained.



(93)

The β-C.D. inclusion compound of (94), a bufadienolide derivative, was found to be more stable, less toxic and more effective than the free reagent. [273]



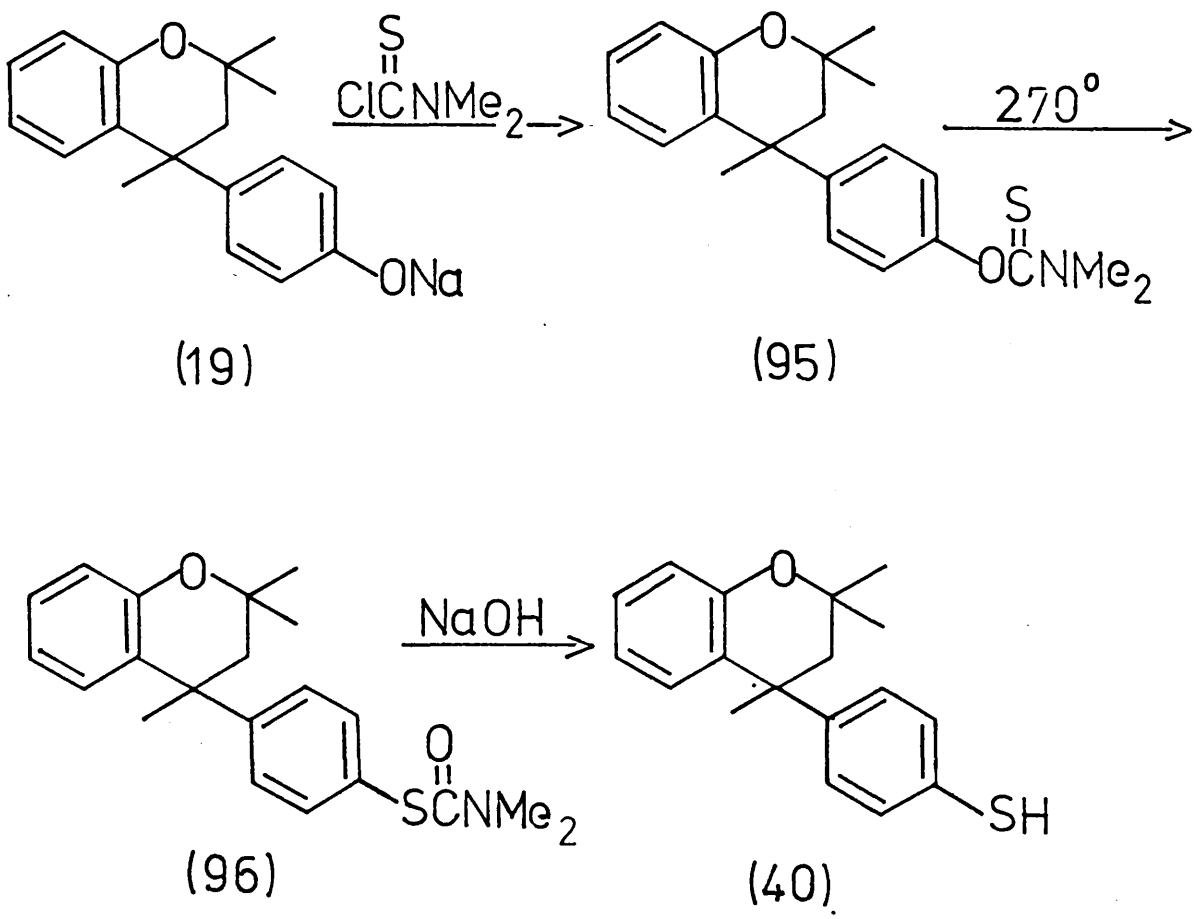
(94)

Finally, instead of including expensive drugs in the cyclodextrins, researchers have attempted to prepare derivatives of cyclodextrins which would be pharmacologically active themselves. For example, the hexakis - (6 - amino - 6 - deoxy) - α-C.D. compound exhibits significant anti-tumour activity [274] while the hexakis - (9 - adenyl - 6 - deoxy) - α-C.D. and corresponding β-C.D. compound are cholesterol - reducing agents. [275]

RESULTS AND DISCUSSION

1. Modification of Dianin's compound

The essential rôle of the OH function in consolidating the hexameric units in Dianin's compound has been described in the introduction. When the hydrogen bonding moiety is removed, no clathrates are formed but what about the case where the hydroxyl group is altered but hydrogen bonding possibilities preserved? In a preliminary study [89], the thiol (40) was prepared [276] via scheme 1 in Glasgow but no inclusion ability observed.

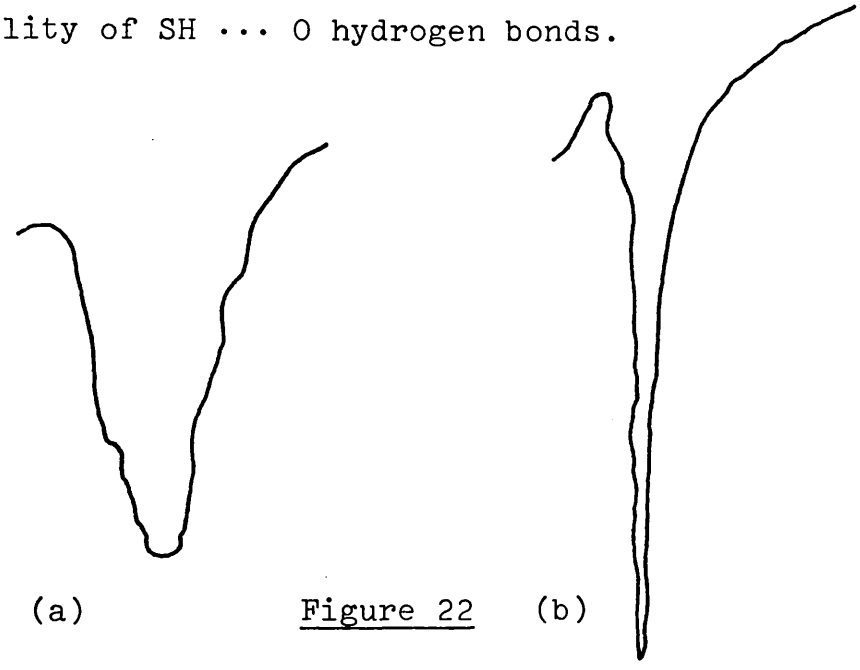


Scheme 1.

In the present work however, when (40) was recrystallised from carbon tetrachloride, a clathrate was formed with a host : guest ratio of 3:1. [277] The nujol mull infra-red spectrum of very lightly ground crystals has a broad (S-H) band (figure 22a) at 2506 cm. $^{-1}$, $\Delta\nu_{\frac{1}{2}}^{a}$ of 70 cm $^{-1}$ whose position and width is compatible with unusually short SH ••• S hydrogen bonds. [278] This may arise from a "supported hydrogen bond" effect [279] such that the overall potential energy minimum results in a reduced S •••• S distance. These crystals are not particularly stable and after one day's standing, the faces become powdery, indicative of solvent loss. The crystals melt over a wide range from 40 - 80°, and are trigonal with space group $R\bar{3}$ and lattice constants $\underline{a}$ = 26.898A° and $\underline{c}$ = 12.022A° when referred to hexagonal axes, so hexagons of S atoms are definitely present. However, taken with the above infra-red evidence, hexagons of mutually hydrogen-bonded thiol groups are almost certainly present. Ultimate proof of this is being sought in an X-ray structural analysis being undertaken in collaborration with Dr. Hardy, using a crystal enclosed in a Lindemann capillary.

In contrast, the thiol (40) when recrystallised from/

from cyclohexane gave unsolvated material with normal ν (S-H) at 2546 cm^{-1} (figure 22b) and melting point 137-8°. The crystals or orthorhombic, space group $P2_12_12_1$ with $Z = 4$, showing that spontaneous resolution occurs. This space group has been found for phenol (35), and the similarity of unit cell dimensions suggests the possibility of SH ··· O hydrogen bonds.



(a) Figure 22 (b)

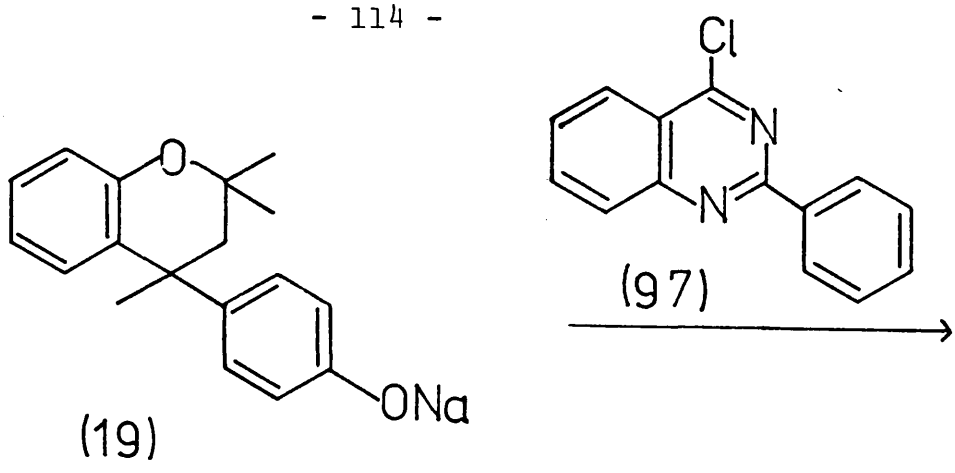
ν (S-H) for thiol (40); (a) carbon tetrachloride clathrate; (b) unsolvated host (2600 - 2400cm^{-1}).

Other solvents forming 3 host : 1 guest adducts with (40) are bromotrichloromethane and 1,1,1-trichloroethane, with melting points 50 - 80° and 45 - 80° respectively. Their infra-red spectra display ν(S-H) 2506cm^{-1} with $\Delta\nu^{a}_{\frac{1}{2}}$ even larger at 100cm^{-1}. However unsolvated material is obtained when very pure thiol is used, but deliberate addition of Dianin's compound (2%) ensures that solvated/

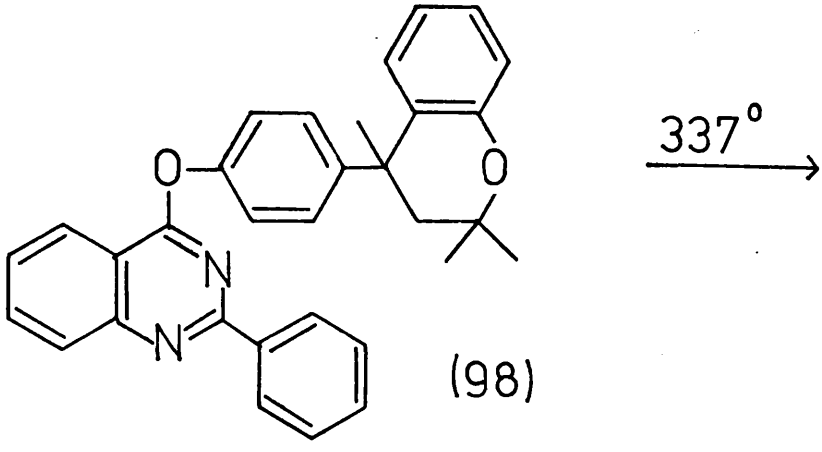
solvated crystals are produced. Somewhat similarly, tri-o-thymotide, when recrystallised from pure methanol does not form a clathrate, but does if seeded with crystals of the acetone clathrate. [179] Poorly formed crystals were formed with t-butanol and t-butylamine, with some inclusion of the guest. Benzene, ether, ethanol, acetone, [89] dioxan, fluorotrichloromethane, t-butylbromide, t-butylchloride or t-butylacetylene did not form inclusion compounds but not all these recrystallisation were performed using (40) containing Dianin's compound.

The p-amino analogue of Dianin's compound (100) has also been prepared. This compound is isolectronic and similar in shape to Dianin's compound. To form isomorphous inclusion compounds NH ••• N hydrogen-bonded hexamers would have to replace OH ••• O hexamers. In general NH ... N hydrogen bonding is slightly weaker than in corresponding OH ••• O systems, but there is an extra hydrogen on each nitrogen atom to be accommodated. The synthetic route [280] to (100) chosen is shown in scheme 2. The first step involves the condensation of the sodium salt of Dianin's compound on 4 - chloro - 2 - phenylquinazoline (97) (named Am-ex-01 by Aldrich) in dry diglyme. This reaction proceeds reproducibly to give (98) in 80% yield, but in some runs a little unreacted Dianin's compound was present in the product

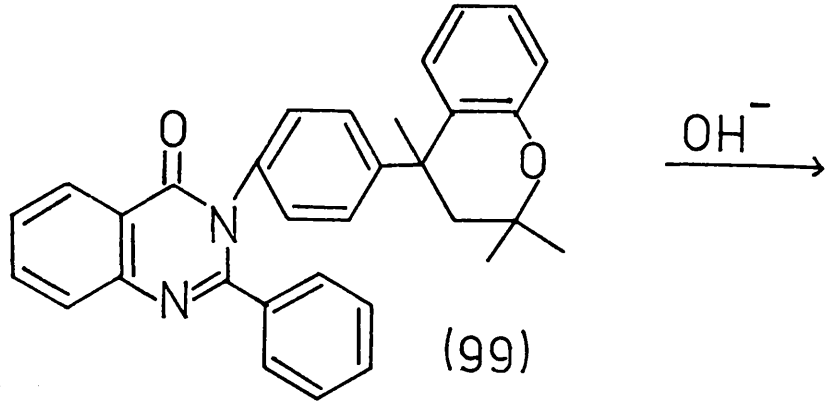
but/



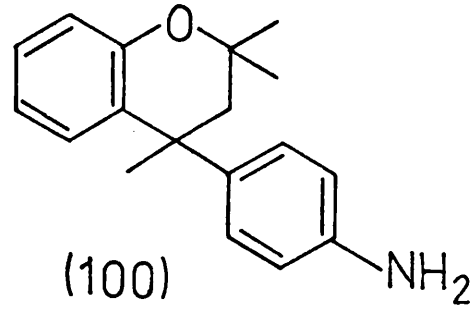
(19)



(98)



(99)



(100)

Scheme 2.

but this was readily removable by KOH extraction from a toluene solution of crude (98). The dried amyl alcohol recrystallised product undergoes a Chapman rearrangement quantitatively on heating at 337° in a Wood's metal bath to give (99). Temperatures higher than 350° result in the formation of 2,2,4-trimethylchromene (29) readily identifiable by its sharp characteristic odour. The crude red glassy product could be hydrolysed without purification by KOH in ethylene glycol to give the amine (100), which with standard ether extraction was obtained in 93% yield in greater than 95% purity as judged by n.m.r. This corresponds to an overall conversion of Dianin's compound to the corresponding amine of 72%. Completely unexpectedly, both the quinazolines intermediates required for this synthesis have been found to form inclusion compounds and these are discussed later.

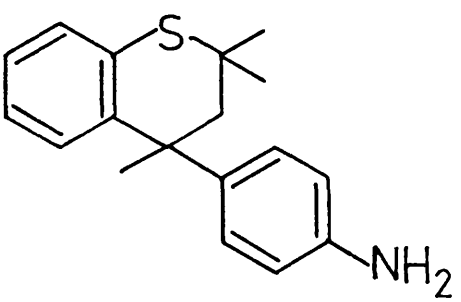
The amine was subjected to a series of inclusion experiments but no clathrates were formed with nitromethane, cyclohexane, benzene, ethanol, toluene, carbon tetrachloride or 1,1,1-trichloroethane. It was found that spontaneous resolution occurs when the amine is recrystallised from ethanol, the crystals having space group $P2_12_12_1$ and Z = 4, isomorphous with the thiol. A tentative explanation for this is that competitive/

competitive hetero atom to amine hydrogen bonding is present instead of NH ··· N hydrogen bonding. An ethanol solution of the amine was seeded with two single crystals of Dianin's compound in an attempt to nucleate clathrate formation but no solvent inclusion occurred. A large transparent crystal of the amine weighing 31.35mg. was found to have an $[\alpha]_{578}^{25}$ of - 9.76° (-9.65° at half concentration), but it was not established that this crystal was single. An attempt to prepare optically resolved (19) by diazotisation of this amine was undertaken, however before this could be completed, Brienne and Jacques [79] achieved this resolution and found that resolved (19) did not form inclusion compounds.

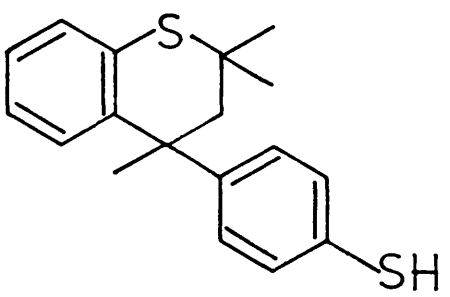
On the premise that NH ···O hydrogen bonding occurs in amine (100) it was hoped that in the corresponding thiachromanyl amine (101) also prepared via scheme 2, NH ··· S hydrogen bonding would be less competitive over NH ··· N hydrogen bonding. It should be appreciated however that while this partly served as motivation for the experiment, it can in no way be considered definitive since many other factors such as size, shape and polarity may be involved. Not too unexpectedly carbon-tetrachloride, t-butanol, cyclohexane, acetone and 1,1,1-trichloroethane were not included, the last experiment using (101) containing 2% Dianin's compound.

Very/

Very disappointingly, the thiol (102) prepared via scheme 1 did not include cyclohexane, dioxan, t-butanol, carbon tetrachloride or 1,1,1-trichloroethane, the last two experiments employing (102) doped with 2% Dianin's compound highlighting the sensitivity of known hosts to even minor modifications.



(101)



(102)

2. Quinazoline inclusion compounds.

Totally unexpectedly, compounds (98) and (99), prepared merely as synthetic intermediates on the way to the amine (100) have both been found to be novel inclusion compounds.

Unsolvated (98), when recrystallised from toluene or amyl alcohol was found to melt at 172-3°. However, when recrystallised from benzene or dioxan, 1:1 crystalline adducts were formed. Both complexes exhibited unusual melting point behaviour. At about 90°, the crystals appeared to dampen, probably as a result of escaped solvent vapour dissolving the external faces of the crystals. Small bubbles of gas were observed to escape from the crystals at about 95° and the crystals were almost totally melted at 99°. At 100°, recrystallisation set in and the new crystals melted at 172-3°. Almost certainly the crystals are changing modification at about 100°. Both guests are retained very tightly, there being no loss after eight hours heating at 45° and 0.5mm. Thiophene, pyrrole, furan, pyridine, fluorobenzene, chlorobenzene, tetrahydrofuran, heptane and acetonitrile do not form inclusion compounds.

By/

By comparison, compound (99) is remarkable in that it forms inclusion compounds with a wide range of solvents of diverse functionality and size.[281] The guest species, the host : guest ratio and the melting points of all thirty adducts are tabulated in Table (XI). Compounds not included are methanol, ethanol, sec-butanol, n-butanol, n-pentane, acetone, ethyl acetate, toluene, diethyl ether, di-isopropyl ether, iodobenzene, iodocyclohexane, chlorobenzene, diglyme and ethylene glycol. Nitromethane is quixotic in that the crystals of (99) may be obtained solvated or unsolvated. The host is so soluble in a few other solvents that no crystals could be obtained e.g. from cyclo-octatetraene or cyclo-octa-1,5-diene.

TABLE (XI)

Inclusion compounds formed by (99).

Guest	Mole ratio of[a] host : guest	Melting point.
cyclopropane	1 : 1	104 - 120°
cyclobutane	2 : 1	110 - 126°
cyclopentane	2 : 1	120 - 136°
cyclohexane	2 : 1	120 - 136°
cycloheptane	2 : 1	110 - 134°
cyclooctane/		

Guest	Mole ratio of host : guest [a]	Melting point
cyclooctane	2 : 1	108 - 117°
cyclodecane	2 : 1	107 - 114°
methylcyclohexane	2 : 1	115 - 120°
fluorocyclohexane	2 : 1	119 - 135°
chlorocyclohexane	2 : 1	107 - 127°
bromocyclohexane	2 : 1	119 - 127°
cyclopentanone	1 : 1	109 - 116°
cyclohexanone	2 : 1	111 - 127°
benzene	1 : 1	122 - 134°
o-xylene	2 : 1	126 - 133°
p-xylene	2 : 1	110 - 120°
fluorobenzene	2 : 1	114 - 118°
anisole	2 : 1	105 - 112°
iso-butanol	2 : 1	120 - 122°
t-butanol	1 : 1	90 - 100°
t-butylamine	2 : 1	114 - 135°
tetrahydrofuran	1 : 1	123 - 137°
tetrahydropyran	1 : 1	105 - 134°
1,4-dioxan	1 : 1	107 - 130°
tetrahydrothiophene	2 : 1	110 - 131°
acetic acid	1 : 1	118 - 138°
carbon tetrachloride	1 : 1	105 - 112°
1,2-dibromoethane	2 : 1	103 - 120°
1,2-dibromotetrafluoroethane	2 : 1	121 - 128°
nitromethane	1 : 1	100 - 109°

a. Determined by multiple integration of the ^{1}H n.m.r. spectrum ($CDCl_3$ solution), and/or microanalysis for halogen, and given to the nearest integral ratio.

The adducts were prepared by recrystallisation of the unsolvated host (obtained from methanol) from the appropriate pure dry solvent using standard techniques except for a few cases detailed below. The collected crystals were then dried under vacuum in a heated drying pistol.

The cyclopropane clathrate was prepared in a sealed tube equipped with a "rotaflo" stopper and sidearm for attachment to a vacuum line. The sealed tube containing host and guest was immersed in a stirred oil bath behind a safety screen and heated till dissolution occurred (about 100°) and then left to cool and crystallise in a draught-free environment.

It was necessary to synthesise cyclobutane. This was achieved by Wurtz coupling [282, 283] of 1,4-dibromobutane mediated by lithium amalgam. The preparation of lithium amalgam is extremely hazardous but this is not indicated in the literature description.[284] Full details are given in the experimental section. The yield of cyclobutane obtained was 70%, exactly the same as the literature yield. It has been reported [285] that the cyclobutane prepared in this way is 90% pure with 4% n-butane produced. After washing with water to remove the dioxan used as solvent, only a small signal corresponding/

corresponding to the methyl groups of n-butane was observed in the n.m.r. spectrum. Cyclohexyl iodide which was not included was prepared by a literature route by hydroiodination of cyclohexene.[286]

In the case of non-volatile guests, the crystals were washed with n-pentane to remove surface liquid and then dried. The host : guest stoichiometry was determined by ^{1}H n.m.r. integration but occasionally by microanalysis for halogen.

Unlike Dianin's compound and similar systems, in this new host there is no hydrogen bonding function so normal van der Waals attractive forces must play a key rôle in holding the host structure together, just as previously described for tri-o-thymotide. It was found that any of these clathrates could be heated at 45° below 0.5mm. for prolonged periods without detectable loss of guest. Even the cyclopropane inclusion compound survived this treatment despite the fact that the pure guest boils at -38°. However it was discovered that after 1½ years standing at room temperature and pressure, the cyclopropane had leaked out presumably by slow diffusion through the crystal lattice or defects. The melting point behaviour of the inclusion compounds is typical of those in which

van/

van der Waals forces bind the host lattice. The melting points and their ranges vary significantly from guest to guest. In some cases, after the adducts are totally melted, recrystallisation occurs in the melt with these crystals melting at about 177°, the temperature at which the unsolvated host melts.

As a generalisation, cycloalkanes, their derivatives and substituted aromatic compounds are included in a 2 : 1 ratio; cyclic ethers and small polar guests are included in a 1 : 1 ratio. In an effort to establish more about the nature of these inclusion compounds, the cycloalkane complexes were examined by thermogravimetric/thermal volatilisation analysis. The information obtained from these experiments is displayed in table (XII) * About 25mg. samples of the appropriate cycloalkane inclusion compound was heated at 3°/minute at 10^{-5}mm. Hg and the weight loss recorded electronically. Any volatiles emitted from the samples pass through a series of successively colder traps (0°, -45°, -78°, - 120°, -196°), the pressure being measured before each trap on Piranni gauges and recorded electronically on the same chart as weight loss measurements. As can be seen, no weight loss occurs below 95° for cyclopropane rising to 129° for cyclohexane then falling for cycloheptane. The melting points/

* We thank Dr. I.C. McNeill of this department for these measurements.

Table (XII)

Thermal analysis data for some clathrates of (99).

Guest molecule	weight loss %	T_{TH} (escape) ^{o}C[a]	T max ^{o}C[b]	Melting point ^{o}C
cyclopropane	7.0 (8.2)[c]	95	125	104 - 120
cyclobutane	6.0 (5.6)[d]	116	130	110 - 126
cyclopentane	6.0 (6.9)[d]	122	140	120 - 136
cyclohexane	8.0 (8.2)[d]	129	141	120 - 136
cycloheptane	9.5 (9.4)[d]	104	128	110 - 134

a. Approximate onset of weight loss for heating rate of 3^{o}/min.

b. Temperature of maximum solvent loss as indicated by thermal volatilsation analysis.

c. Calculated for a host : guest ratio of 1 : 1.

d. Calculated for a host : guest ratio of 2 : 1.

points as observed on the hot stage apparatus mirrors this behaviour. The temperatures of maximum solvent loss show the same trend. Intuitively, for a set of closely related inclusion compounds, it would be expected that the guest which has the best fit for the cavity would form the most stable adduct and possess a higher melting point, i.e. cyclohexane in this case. Significantly, the cyclopropane complex with its 1 : 1 ratio exhibits only one weight loss peak which possibly indicates that all the guest molecules are included in identical cavities and not that the two molecules in are in different voids. Since no solvent is lost until the crystals have been heated to or near their melting points, this suggests that total dismantling of the crystal lattice is required for liberation of the guest, consistent with complete three-dimensional enclosure of the guests in clathrate-type cages.

It is interesting that fluoro-, chloro- and bromocyclohexane are included by (99) but the larger iodocyclohexane is not. Benzene is included in a 1 : 1 ratio but p-xylene in a 2 : 1 ratio. It was somewhat surprising that toluene did not form an inclusion compound, even when seeded with crystals of the benzene or p-xylene adducts. Possibly the toluene is too large to sustain a 1 : 1 adduct and insufficient host to guest van der Waals contacts are made to give a 2 : 1 adduct. The bulkier methylcyclohexane does form a 2 : 1 clathrate/

clathrate however. o - and p -xylene are both included but m-xylene is not further illustrating the host's sensitivity to size and shape factors.

X-ray studies.

Several crystals of (99) obtained from different solvents have been examined crystallographically and the results are summarised in table (XIII). As can be seen there are two unsolvated forms, one from methanol and one from ethanol. From visual examination of unsolvated crystals obtained from other solvents, only the methanol type of diamond-shaped crystals are obtained. Cyclohexane, methylcyclohexane and 1,2-dibromo-tetrafluoroethane crystals are isomorphous being triclinic, but t-butanol crystals are monoclinic. To obtain detailed information about the crystal packing and the nature of the cavity a full X-ray structural analysis of a single crystal of the methylcyclohexane complex has been undertaken in collaboration with Dr. Hardy. The crystals are triclinic, space group $P\bar{1}$ with unit cell parameters: a = 18.649, b = 19.443, c = 9.390A^{o}; α = 78.88, β = 98.97, γ = 118.16^{o}. The crystal structure, with 79 non-hydrogen atoms in the asymmetric unit was solved by use of quartets (a novel developement of direct methods) as pioneered/

Table (XIII)

Crystal data for (99) obtained from various solvents.

Recrystallised from	Host : guest ratio	Space Group	Crystal system.
methanol	0	$P2_{1/c}$	monoclinic
ethanol	0	$P\bar{1}$	triclinic
cyclohexane	2 : 1	$P\bar{1}$	triclinic
methylcyclohexane	2 : 1	$P\bar{1}$	triclinic
1, 2-dibromo-tetrafluoroethane	2 : 1	$P\bar{1}$	triclinic
t-butanol	1 : 1	$P2_{1/c}$	monoclinic

pioneered by Dr. C.J. Gilmore of this department. The final R factor is 0.098. The asymmetric unit, is displayed in figure 23, showing two host molecules and a single guest molecule. Figure 24 is a projection on the b,c - plane. The molecules represented by light thin lines comprise the bottom of the cavity and the heavy dark lines, closer to the viewer represent the four molecules forming the sides. Two guest molecules related by a centre of symmetry occupy the single cavity. The top of the cavity is not drawn for clarity. By drawing appropriate sections of the unit cell, it has been shown that the cavity is three dimensionally enclosed so this inclusion compound is therefore of the clathrate type (figure 25).

Thiachromanyl analogues of (98) and (99)

The thiachromanyl analogues of (98) and (99), compounds (103) and (104) respectively were prepared according to scheme 2 as before to test for inclusion ability. Compound (103) unlike (98) did not form adducts with benzene and dioxan or cyclohexane and amyl alcohol. Compound (104) however like (99) formed inclusion compounds with many of the solvents tried. Details of these adducts are presented in table (XIV). Their stoichiometry/

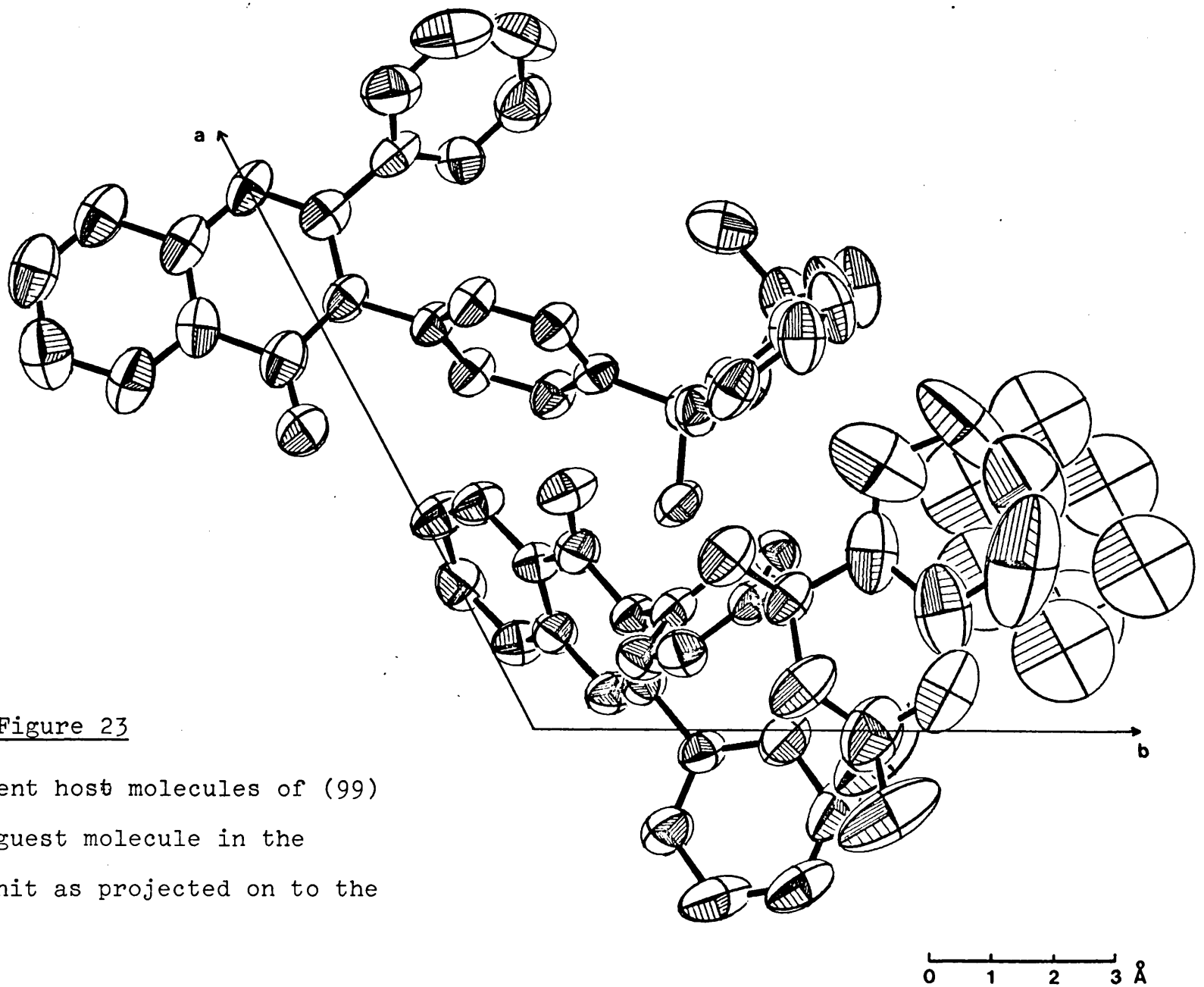


Figure 23

Two independent host molecules of (99) and the one guest molecule in the asymmetric unit as projected on to the ab-plane.

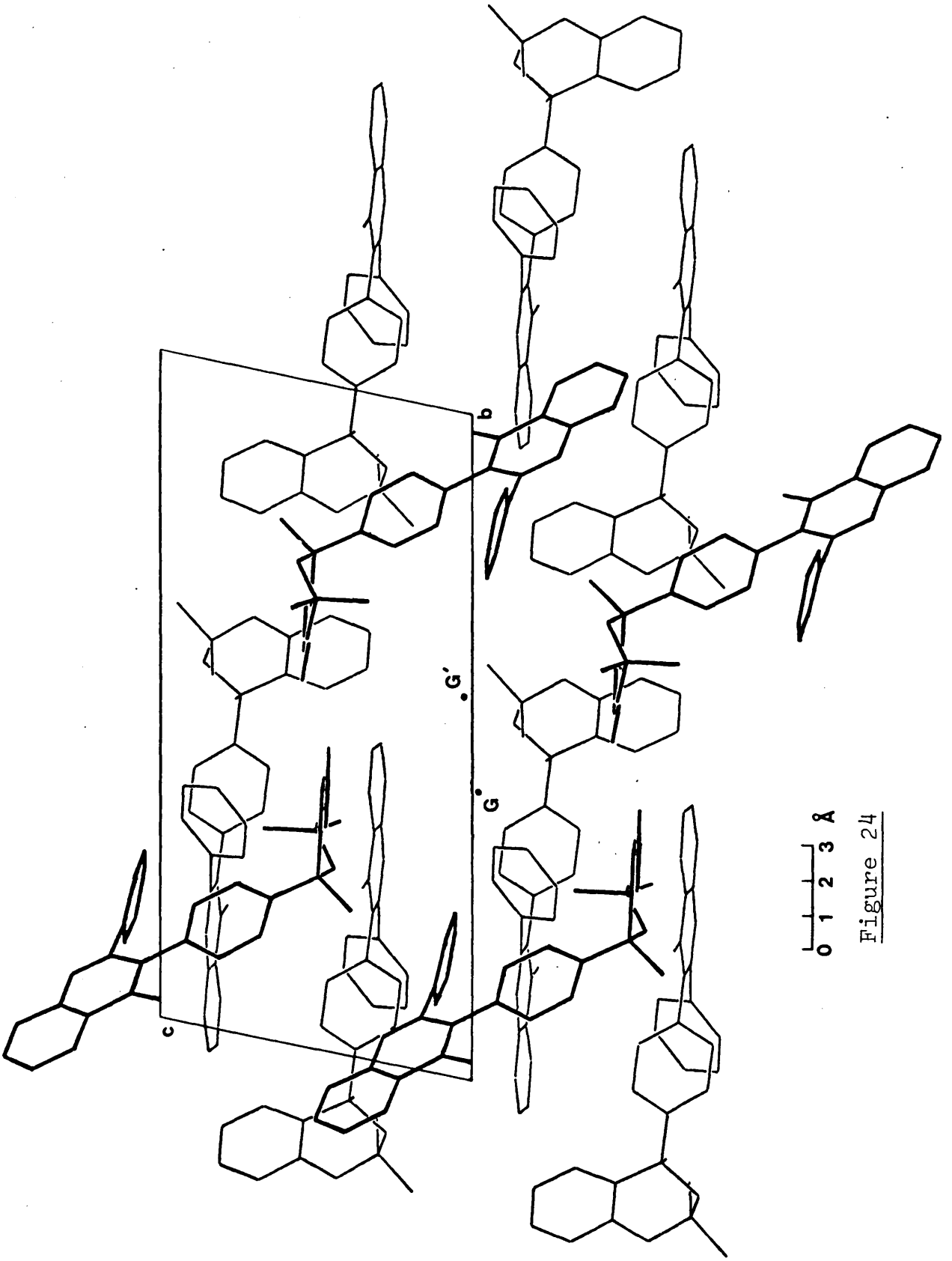
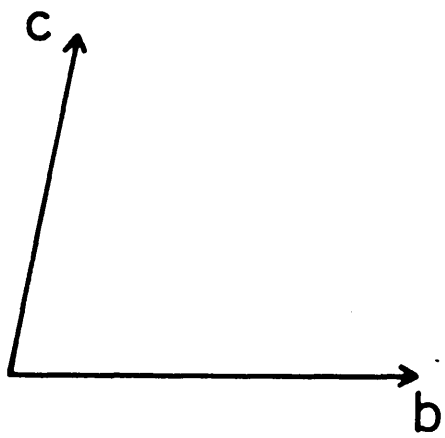
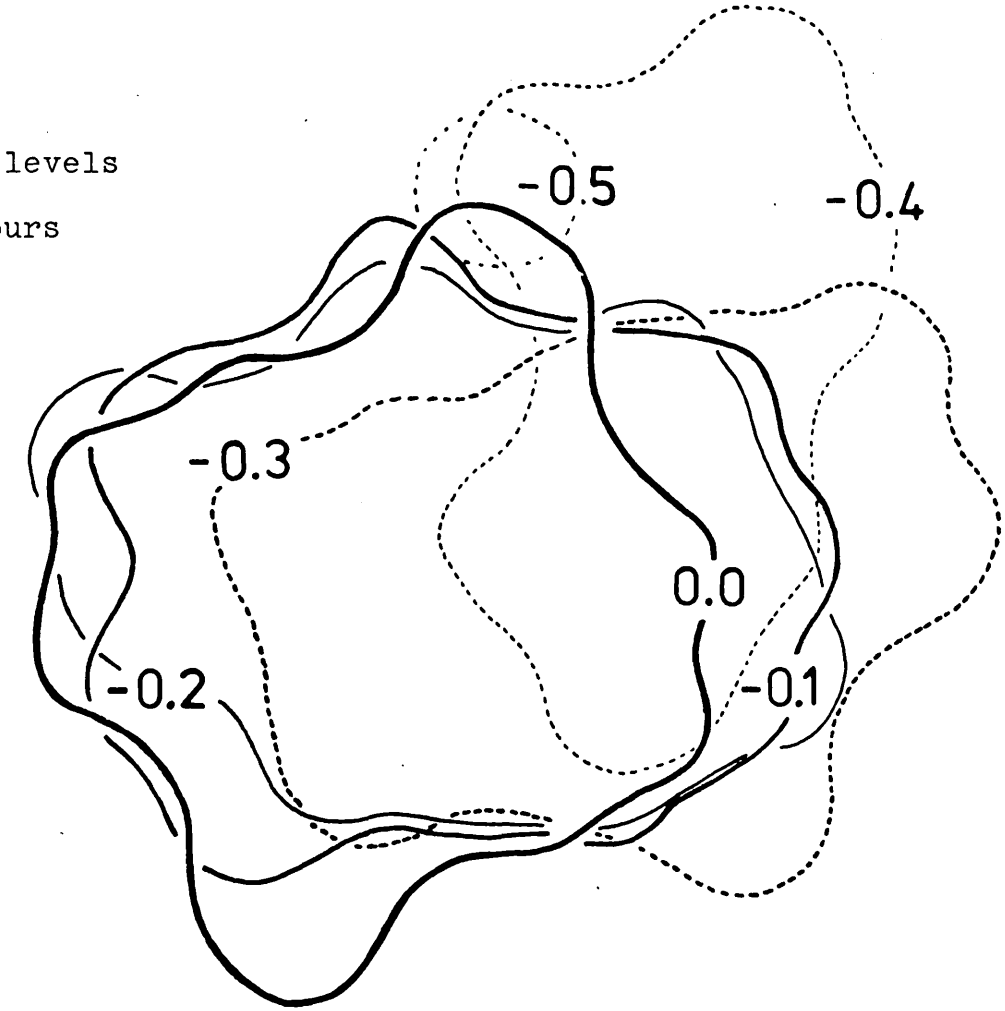


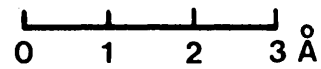
Figure 24

Figure 25

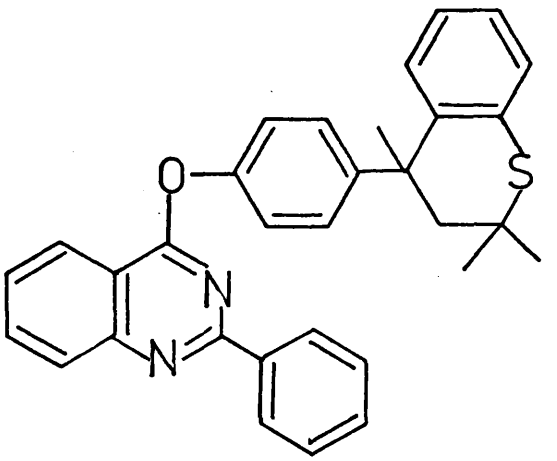
The space available in the cage in cross-section at various fractional levels parallel to the bc-plane. The contours shown represent only half of the centrosymmetric cage.



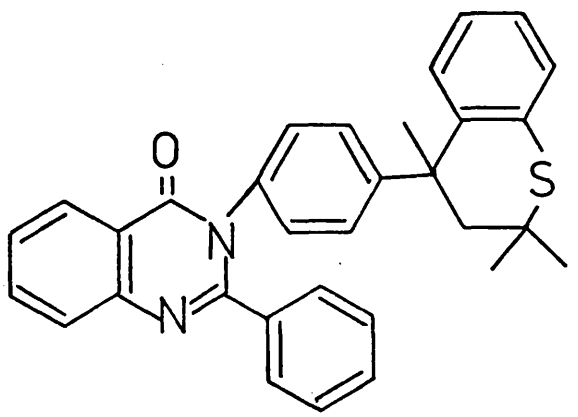




stoichiometry, melting points and stability are similar to those found for (99) suggesting that similar crystal packing may occur, although no X-ray studies have been carried out.



(103)



(104)

Table (XIV)

Inclusion compounds formed by (104)

Guest	Mole ratio of[a] host : guest	Melting point
cyclopentane	2 : 1	128 - 138°
cyclohexane	2 : 1	130 - 139°
cycloheptane	2 : 1	129 - 140°
tetrahydrofuran	1 : 1	97 - 123°
1, 4-dioxan	2 : 3	129 - 147°
toluene	2 : 1	145 - 149°
t-butylamine	1 : 1	116 - 121°
carbon tetrachloride	1 : 1	112 - 115°
1,1, 1-trichloroethane	3 : 2	105 - 109°
chloroform[b]	1 : 1	70 - 90°

a. Determined by multiple integration of the ^1H n.m.r. spectrum ($CDCl_3$ solution), and/or microanalysis for halogen and given as nearest integral ratio.

b. Scavanged from a mixture of ca 5% (V/V) $CHCl_3$ in hexamethyldisilane, the latter being included to only a slight extent (6%).

Selectivity experiments for the quinazolinone hosts (99) and (104).

Both (99) and (104) exhibit significant selective inclusion behaviour towards mixtures of hydrocarbon solvents. Thus on a single recrystallisation of (99) from an equimolar mixture of cyclopentane, cyclohexane and cycloheptane, the relative percentages included were found by ^{1}H n.m.r. to be 38%, 39% and 23% respectively. The corresponding results for (102) employing the same mixture are 18%, 47% and 35%. Recrystallisation of (99) from pure n-pentane gives unsolvated material, however, when recrystallised from an equimolar mixture of n-pentane and cyclopentane inclusion in the ratio of 1 : 7 is observed. The inclusion of n-pentane in these circumstances may be attributed to the auxiliary guest effect.[287] (99) shows duality of behaviour on recrystallisation from an equimolar mixture of o - and p-xylene : in one experiment, unsolvated material was obtained whereas in a second run these solvents were included in a 1 : 5 ratio with overall host : guest ratio of 2 : 1. A single recrystallisation of (102) from the above xylene mixture showed preferential inclusion of the o-isomer in this case (5 : 1). Recrystallisation of (104) from a 50/50 mixture of o - to m - xylene gave a guest ratio of 4 : 1 respectively.

"Since it is impossible to predict molecular crystalline structure a priori, the discovery of a new clathrate has been and still is a matter of chance".

L.C. Fetterley in "Non-Stoichiometric Compounds", Academic Press, 1964, ed. L. Mandelcorn, p. 497.

3. The hexa-hosts.

An intrinsic factor involved in the molecular packing of the clathrates formed by Dianin's compound (19) and related systems and also those formed by hydroquinone (18) and phenol is the linking of the OH groups of six host molecules by a network of hydrogen bonds, such that the oxygen atoms form a hexagonal arrangement (A) shown in figure 26. Struck by the parallel between the temporary unit which is subject to collapse as the groups R are varied and the permanent consolidated structure of benzene (B), a number of hexa-substituted benzenes have been prepared, [288] compounds (105) - (126),(Table (XV)) in order to ascertain if these latter compounds might possess an increased tendency to crystallise forming non-close-packed structures with possible inclusion properties. It may be noted that unit (A) corresponds to (B) both in terms of overall geometric aspect and hexamer dimensions (c.f. distances d and d' in the figure where Z denotes a general atom or group attached directly to the central benzene ring). A literature search revealed that a few of these compounds had been previously been prepared and encouragingly a number of these materials had been found to retain certain solvents, though at the time of publication, the nature of/

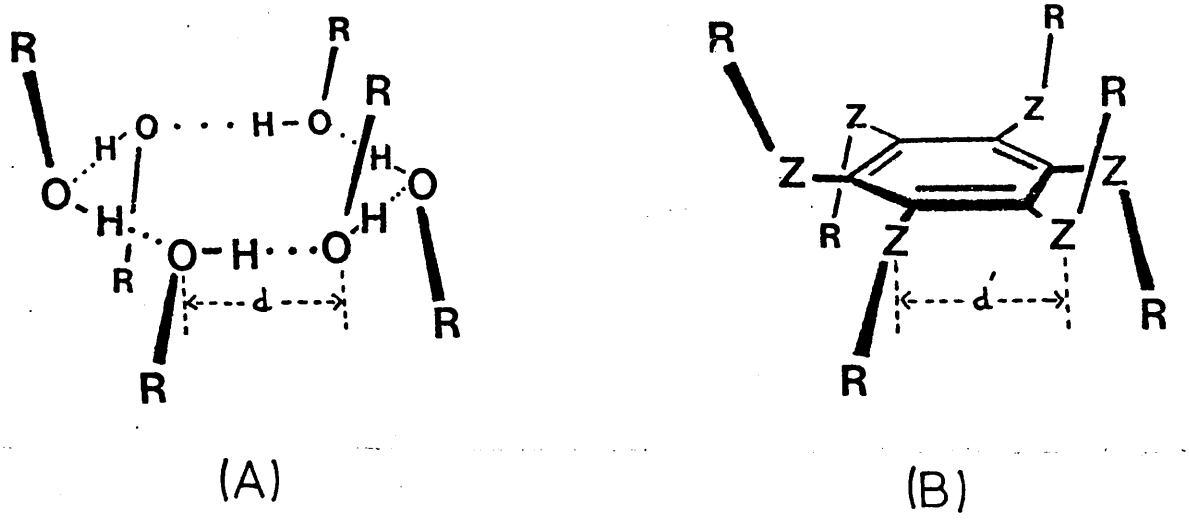
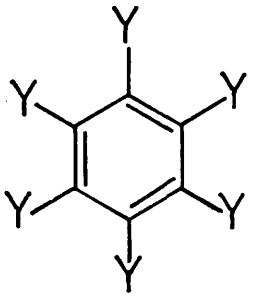


Figure 26

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

TABLE (XV)

Hexa-substituted benzenes.



Y	Compound	Y	Compound
SPh	(105) *	$CH_2SeC_6H_4Bu^t$-p	(116)
$SC_6H_6CH_3$-p	(106)	$CH_2OC_6H_4Ad$-p	(117)
CH_2OPh	(107) *	$CH_2SC_6H_4Ad$-p	(118)
CH_2SPh	(108) *	CH_2S Naphthyl-β	(119)
CH_2SePh	(109)	$CH_2OC_6H_4OCH_3$-p	(120)
CH_2NHPh	(110)	CH_2 S C_6H_4OH-p	(121)
CH_2OCH_2Ph	(111)	CH_2 S $C_6H_4NH_2$-p	(122)
CH_2SCH_2Ph	(112) *	CH_2 S Cyclohexyl	(123)
$CH_2OC_6H_4Pr^i$-p	(113)	CH_2 O Cyclohexyl	(124)
$CH_2OC_6H_4Bu^t$-p	(114)	CH_2 O Cyclopentyl	(125)
$CH_2SC_6H_4Bu^t$-p	(115) *	CH_2 S Hexyl^n	(126) *

* Previously reported : see experimental section for references.

of inclusion compounds was less well understood. While the present work was in progress, a number of "Octopus" molecules based on a hexa-substituted benzene nucleus, have been shown to be capable of binding metal cations in solution. [289]

Compounds (105) and (106) were prepared by reaction of hexachlorobenzene with the appropriate cuprous thiophenolates. An attempt to prepare hexa-p-methoxyphenylthiobenzene the same way was not successful, and similarly reaction of C_6Cl_6 with p-t-butylphenylthio-cuprate led to the production of mainly penta-substituted benzene. All other compounds were prepared by the action of the appropriate phenol, thiol, selenol, amine or alcohol on hexakis(bromomethyl)benzene, $C_6(CH_2Br)_6$ in the presence of base. p-t-butylbenzene selenol was prepared by a literature route by addition of selenium to p-t-butylphenyl magnesium bromide and subsequent hydrolysis. p-(1-adamantyl) thiophenol was prepared from p-(1-adamantyl)phenol via the dimethylthiocarbamates [276] as used for preparing (40) and (102). The synthesis of benzyl selenol was achieved but unfortunately, no hexakis (benzylselenomethyl) benzene was obtained. Rather disproportionation occurred with dibenzylselenide and sodium selenide being formed even at 78° in ethanol. Full details and relevant references are given in the experimental/

experimental section.

On recrystallisation from suitable solvents, a wide range of inclusion behaviour was found for the following compounds:-

(105), $C_6(SPh)_6$; (107), $C_6(CH_2OPh)_6$;
(108), $C_6(CH_2SPh)_6$; (112), $C_6(CH_2SCH_2Ph)_6$;
(115), $C_6(CH_2SC_6H_4Bu^t\text{-}\underline{p})_6$; (116), $C_6(CH_2SeC_6H_4Bu^t\text{-}p)_6$;
(118), $C_6(CH_2SC_6H_4Ad\text{-}p)_6$; (119), $C_6(CH_2S\ Naphthyl\text{-}\beta)_6$;
(121), $C_6(CH_2SC_6H_4OH\text{-}\underline{p})_6$; (122), $C_6(CH_2SC_6H_4NH_2\text{-}\underline{p})_6$;
(123), $C_6(CH_2S\ Cyclohexyl)_6$; (125), $C_6(CH_2O\ Cyclopentyl)_6$.

The details are presented in the following tables.

Standard recrystallisation techniques were employed except for the cases in which the host is very insoluble in the guest even at the boiling point so sealed tubes were used instead. The inclusion compounds possess the usual properties of van der Waals bound hosts. The guest escape temperatures are different in all cases. In virtually every case, on the hot stage the crystals were observed to darken and split then become completely opaque but with the external morphology being retained. Close to the melting point of the unsolvated material, the/

TABLE (XVI)

Inclusion behaviour for (105), $C_6(SPh)_6$.

Guest molecule	Mole ratio of host : guest	Guest escape temperature °C.
CCl_4	1 : 2[a]	90
CCl_3CH_3	1 : 2[b]	70 - 80
CCl_3Br	1 : 1[a]	90 - 100
CCl_3SCl	1 : 2[a]	70 - 85
CCl_3NO_2	1 : 1[a]	50 - 60

a. Determined by microanalysis for halogen.

b. Determined by n.m.r. integration.

The following solvents are not included:

CCl_3CN, CCl_3F, $CHCl_3$, CH_2Cl_2, CCl_3CCl_2H, CH_3I, CH_3OH,[c] C_6H_6, n-decane,[c] cyclohexane,[c] t-butanol,[c] di-(trimethylsilyl)-acetylene.[c]

c. Recrystallisation performed in sealed tube.

TABLE (XVII)

Inclusion behaviour for (107), C_6 $(CH_2OPh)_6$.

Guest molecule	Mole ratio of host : guest[a]	Guest escape temperature °C.
toluene	1 : 2	90
1,4-dioxan	1 : 3	40
tetrahydrothiophene	1 : 1	95

a. Determined by ^1H n.m.r. integration and given to nearest integer.

The following solvents are not included:

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

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included[b]		Overall host : guest ratio[c]
50/50 o-xylene/p-xylene	85	15[d]	1 : 2
50/50 o-xylene/m-xylene	50	50	1 : 2
50/50 mesitylene/pseudo-cumene	65	35	1 : 2
50/50 o-xylene/p-xylene	90	10[e]	2 : 1

b. Measured by multiple ^1H n.m.r. integration and given to nearest 5%.

c. Given to nearest integral ratio.

d. Average for two experiments.

e. Sorption experiment in which 200mg. (107) was stirred at room temperature for 24 hours in 8ml. solvent.

TABLE (XVIII)

Inclusion behaviour for (108), C_6 $(CH_2$ S Ph$)_6$.

Guest molecule	Mole ratio of host : guest[a]	Guest escape temperature °C.
toluene	1 : 1	70
dioxan	1 : 2	55-75

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

The following solvents are not included:

cyclohexane, cyclopentane, tetrahydrofuran, tetrahydropyran and tetrahydrothiophene.

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included[b]		Overall host : guest ratio[c]
50/50 o-xylene/p-xylene	90	10	1 : 2
50/50 o-xylene/m-xylene	45	55	1 : 1

b. Measured by multiple ^{1}H n.m.r. integration and given to nearest 5%.

c. Given to nearest integral ratio.

TABLE (XIX)

Inclusion behaviour for (112), $C_6(CH_2SCH_2Ph)_6$.

Guest molecule	Mole ratio of host : guest[a]	Guest escape temperature °C.
cyclohexane	1 : 1	-
toluene	1 : 1	-
dioxan	1 : 1	-
acetone	1 : 2	ambient
1,1,1-trichloroethane	1 : 1	120
ethyl acetate	1 : 1	61
acetyl chloride	2 : 1	ambient

a. Determined by ^1H n.m.r. integration and given to nearest integer.

The following solvents are not included: cycloheptane, cyclooctane, n-decane, ethanol.

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included[b]	Overall host : guest ratio[c]
50/50 o-xylene/p-xylene	25 75	1 : 1
50/50 o-xylene/m-xylene	0	0
50/50 o-xylene/p-xylene	0[d]	0
50/50 mesitylene/pseudo-cumene	0	0
33/33/33 cyclo-pentane/-hexane/ -heptane	30 40 30	1 : 1

b. Measured by multiple ^1H n.m.r. integration and given to nearest 5%.

c. Given to nearest ratio.

d. Sorption experiment in which (112) was stirred at room temperature for 24 hours in the solvent.

TABLE (XX)

Inclusion behaviour for (115), C_6 $(CH_2SC_6H_4Bu^t\text{-}\underline{p})_6$.

Guest molecule	Mole ratio of host : guest [a]
cyclohexane	1 : 2
cycloheptane	1 : 2
cyclooctane	1 : 2
toluene	1 : 2
iodobenzene	1 : 2
phenylacetylene	1 : 2
1-methylnaphthalene	1 : 2
2-methylnaphthalene	1 : 2
bromoform	1 : 2
1,1,1-trichloroethane	1 : 2
squalene	2 : 1
hexamethyldisilane	2 : 1

a. Determined by ^1H n.m.r. integration or microanalysis for halogen and quoted to nearest integer.

The following solvents are not included:

mesitylene, 1,5-diidopentane, citral, hexamethyldistannane, di(trimethylsilyl)-acetylene, ethanol, t-butanol, n-heptane, n-decane.

Selectivity experiments for (115).

Recrystallisation solvent mixture	Respective % of guest included[b]			Overall host : guest ratio[c]
50/50 o-xylene/p-xylene	95	5[d,e]		1 : 2
50/50 o-xylene/m-xylene	85	15		2 : 3
50/50 mesitylene/pseudo-cumene	10	90		1 : 2
50/50 1-/2-methylnaphthalene	50	50		1 : 2
33/33/33 cyclo-pentane/-hexane/ -heptane	20	45	35	1 : 2

b. Measured by multiple ^{1}H n.m.r. integration and given to nearest 5%.

c. Given to nearest integral ratio.

d. Average for solvated material formed in two experiments.

e. Shows duality of crystallisation behaviour : on one occasion, unsolvated material was deposited.

TABLE (XXI)

Inclusion behaviour for (116), C_6 $(CH_2SeC_6H_4Bu^t\text{-}\underline{p})_6$.

Guest molecule	Mole ratio of host : guest[a]
cyclooctane	2 : 3
toluene	1 : 2
dioxan	2 : 3

a. Determined by ^1H n.m.r. integration and quoted to nearest integer.

Squalene is not included and (116) was too soluble in bromoform.

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included[b]			Overall host : guest ratio[c]
50/50 o-xylene/p-xylene	90	10[d]		1 : 1
50/50 o-xylene/m-xylene	80	20[d]		1 : 2
50/50 1-/2-methylnaphthalene	0			0
33/33/33 cyclo-pentane/-hexane/ -heptane	20	45	35	1 : 2

b. Measured by multiple ^1H n.m.r. integration and given to nearest 5%.

c. Given to nearest integral ratio.

d. Shows duality of crystallisation behaviour ; on one occasion, unsolvated material was deposited.

TABLE (XXII)

Inclusion behaviour for (118), C_6 $(CH_2SC_6H_4Ad\text{-}\underline{p})_6$.

Guest molecule	Mole ratio of host : guest[a]
toluene	1 : 1[b]
dioxan	1 : 1
o-xylene	1 : 2

a. Determined by ^1H n.m.r. integration and quoted to nearest integer.

b. Unsolvated material is sometimes obtained.

Cyclooctane is not included and no crystals could be obtained from bromoform.

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included[c]		Overall host guest ratio[d]
50/50 o-xylene/m-xylene	70	30[e]	1 : 2
50/50 o-xylene/p-xylene	0		0

c. Measured by multiple ^1H n.m.r. integration and given to nearest 5%.

d. Given to nearest integral ratio.

e. On one occasion, unsolvated material was obtained.

TABLE (XXIII)

Inclusion behaviour for (119), $C_6(CH_2SNaphthyl\text{-}\beta)_6$.

Guest molecule	Mole ratio of host : guest[a]
toluene	1 : 1[b]
o-xylene	2 : 1

a. Determined by ^1H n.m.r. integration and quoted to nearest integer.

b. On one occasion, unsolvated material was obtained.

Cyclohexane, cyclooctane and dioxan are not included.

(119) was too soluble in bromoform to crystallise.

Selectivity experiments

Recrystallisation solvent mixture	Respective % of guest included.[c]		Overall host : guest ratio[d]
50/50 o-xylene/p-xylene	20	80[e]	1 : 1
50/50 o-xylene/m-xylene	0		0

c. Measured by multiple ^1H n.m.r. integration and given to nearest 5%.

d. Given to nearest integral ratio.

e. On one occasion, unsolvated material was obtained.

TABLE (XXIV)

Inclusion behaviour for (121), $C_6(CH_2SC_6H_4OH\text{-}\underline{p})_6$.

Guest molecule	Mole ratio of host : guest[a]	Guest escape temperature °C.
acetone	1 : 3	65 - 90
methanol	1 : 4	75
dioxan	2 : 7	90 - 100

a. Determined by ^1H n.m.r. integration and given to nearest integer.

Ethanol, t-butanol and methyl acetate are not included.

TABLE (XXV)

Inclusion behaviour for (122), $C_6(CH_2SC_6H_4NH_2\text{-}\underline{p})_6$.

1,4-dioxan forms an inclusion compound with a host : guest ratio of 3 : 1, from which guests escapes over the range 25° - 70°. However, it requires 16 hours at 0.5mm. and room temperature to reduce this ratio by half. Acetone, tetrahydrofuran and tetrahydropyran do not form inclusion compounds.

TABLE (XXVI)

Inclusion behaviour for (123), C_6 (CH_2 S Cyclohexyl)$_6$.

Guest molecule	Mole ratio of host : guest [a]	Guest escape temperature °C.
benzene	2 : 3	105 - 125
toluene	2 : 3	75 - 95
methyl acetate	2 : 3	60 - 70
1,1,1-trichlorethane	2 : 3	125 - 140
dioxan	2 : 3	100 - 120
1,4-dimethylcyclohexane [b]	2 : 3	100 - 115
nitrobenzene/nitrosobenzene	1 : 2[c]	95 - 125

a. Determined by ^{1}H n.m.r. integration and given to nearest integral ratio.

b. Mixture of isomers.

c. Mainly nitrobenzene included but crystals were light green.

Nitromethane is the only solvent tried not to be included.

Selectivity experiments.

Recrystallisation solvent mixture	Respective % of guest included.[d]		Overall host : guest ratio[e]
50/50 o-xylene/p-xylene	80	20	2 : 3
50/50 o-xylene/m-xylene	80	20	2 : 3

d. Measured by ^{1}H n.m.r. integration and quoted to nearest 5%.

e. Given to nearest integral ratio.

TABLE (XXVII)

Inclusion behaviour for (125), C_6 (CH_2O Cyclopentyl)$_6$.

Guest molecule	Mole ratio of host : guest [a]	Guest escape temperature °C.
chloroform	1 : 1	-
1,1,1-trichloroethane	1 : 1	65 - 90
cyclohexane	2 : 5	60 - 80

a. Determined by weight loss.

Benzene is not included.

Table (XXVIII)

Selectivity experiments for various hexa-hosts using the quaternary mixture, 1 : 1 : 1 : 1, o-, m-, p-xylene, ethylbenzene. The ratios of m - and p-xylene are combined.

Host	Xylenes % o, m-/p-, EtPh			Overall host to guest : ratio[a]
(107), $C_6(CH_2OPh)_6$	50	50	-	1 : 2
(107), $C_6(CH_2OPh)_6$	55	45	-[b]	5 : 1
(108), $C_6(CH_2SPh)_6$	25	35	40	1 : 1
(108), $C_6(CH_2SPh)_6$	0		[b]	0
(115), $C_6(CH_2SC_6H_4Bu^t\text{-}p)_6$	75	25	-[c]	1 : 2
(115), $C_6(CH_2SC_6H_4Bu^t\text{-}p)_6$	35	65	-	1 : 2
(115), $C_6(CH_2SC_6H_4Bu^t\text{-}p)_6$	45	55	-[b]	4 : 1

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

b. Sorption experiment in which the appropriate host is stirred at room temperature for 24 hours with the solvent mixture.

c. Performed under identical conditions simultaneously.

the crystals appear to clear and then melt normally. Almost certainly, a change in crystal modification is occurring thereby allowing guest escape. As can be seen from the tables, many of these new hosts also exhibit substantial selectivity towards hydrocarbon mixtures. Most of these experiments were performed using 100mg. of the appropriate host. Reproducible results were obtained on a 20g. scale for (107), C_6 $(CH_2$ $OPh)_6$ but not for (115), C_6 $(CH_2SC_6H_4Bu^t$-p$)_6$ which is more soluble and precipitates as tiny crystallites, hence rendering it difficult to wash off surface liquid. In nearly all the binary xylene experiments, preference was found for the p-isomer over the m and p-isomers. Compounds (112), C_6 $(CH_2SBz)_6$ and (118), C_6 $(CH_2$ SC_6 H_4 Ad - p$)_6$, however preferentially included p-xylene from equimolar o - and p -xylene mixtures. Disappointingly, the selectivities towards tertiary and quaternary mixtures were much less significant except that sometimes very little ethylbenzene was included from equimolar mixtures of the three xylenes and ethylbenzene.

As has been observed before for other systems the slight modification of some of these hexa-hosts results in the total eradication of inclusion ability. For example, both/

both (107), C_6 $(CH_2OPh)_6$ and (108), C_6 $(CH_2SPh)_6$ form adducts but (109), the analogous selenide and (110), C_6 $(CH_2NHPh)_6$ do not. Similarly (112), C_6 $(CH_2SBz)_6$ forms many complexes but the corresponding ether (111) does not.

It is very likely that not all the hexa-hosts adopt the conformation shown in figure 26B in their solid state structures. Examination of space-filling models shows that other conformations are possible. An attempt was made to effectively tie up the three aromatic residues on the same side of the central aromatic ring by introducing a hydrogen bonding moiety in the p-position so that three groups on one side of the molecule would mutually hydrogen bond or would bond to three similar groups of another molecule thus creating a closed cage in either case. Accordingly, compounds (121), C_6 $(CH_2SC_6H_4OH\text{-}p)_6$ and (122), the corresponding p-amino analogue were synthesised and both have been found to form inclusion compounds but the nature of the hydrogen bonding and the cavity will not be determined without an X-ray structural analysis.

The CCl_4 adduct of (105), C_6 $(SPh)_6$ has been X-ray crystallographically examined in collaboration with Dr. Hardy, the single yellow crystal being sealed in

a/

a Lindemann capillary to arrest the escape of guest. It has been shown that the crystals are trigonal with space group $R\bar{3}$ and Z = 3, with unit cell dimensions referred to hexagonal axes $\underline{a} = \underline{b} = 14.263A^{\circ}$ and $\underline{c} = 20.717A^{\circ}$, $\alpha = \beta = 90^{\circ}$, $\gamma = 120^{\circ}$. The analysis, now nearing completion has revealed that two molecules of CCl_4 are included in each cavity. The cavity is long (~ $12A^{\circ}$) and appears to have a slight constriction in the middle. Alternate aromatic residues point up and down from the central aromatic ring just as in Dianin's compound, phenol and water. A crystal packing diagram showing a projection on to the ac-plane is shown in figure 27. It has not yet been established whether the cavities are completely closed. This structure is very similar to the clathrate form of phenol (see figure 7). A single crystal of the unsolvated form of this host was obtained by recrystallisation from pentachloroethane. The crystal is triclinic, space group $P\bar{1}$, Z = 1. A X-ray structural analysis is also underway on a single crystal of the dioxan inclusion compound of (112), $C_6(CH_2SBz)_6$. The crystals are monoclinic, space group $P2_{1/c}$, Z = 2.

There is strong evidence that the cavities in some of these compounds are open channels.

(i) Sorption experiments in which unsolvated host e.g. (105), $C_6(CH_2OPh)_6$ includes guest when stirred at room temperature in/

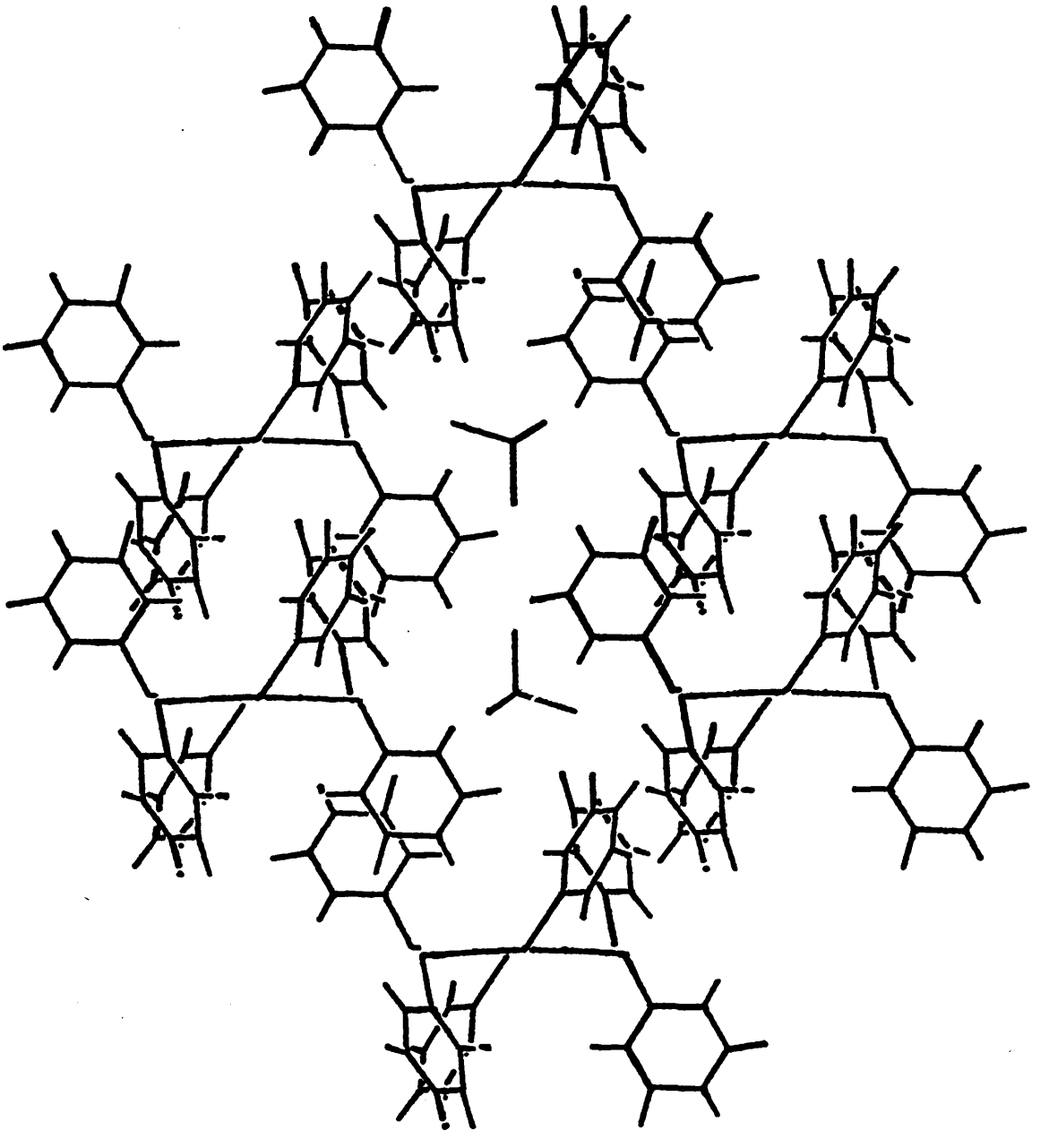


Figure 27

Crystal packing diagram of the CCl_4 adduct of (105) as projected on the ac-plane. Four molecules, immediately above and below the guest molecules have been removed for clarity. The scale is 0.212" = 1A°.

in the solvent. However, an alternative explanation is that some unsolvated material dissolves then is precipitated as a less soluble adduct.

(ii) The inclusion of the long linear molecule squalene in (115), C_6 $(CH_2SC_6H_4Bu^t\text{-}\underline{p})_6$.

(iii) The ready loss of toluene from (116), C_6 $(CH_2SeC_6H_4Bu^t\text{-}\underline{p})_6$ for example.

(iv) A very interesting observation was the anisotropic loss of acetyl chloride from (112), C_6 $(CH_2SBz)_6$. The single transparent crystal became opaque in seven minutes, as a result of solvent loss, on the vertical faces only, the horizontal faces remaining clear for five minutes, after which cracks appeared across the whole crystal.

An attempt was made to include the extremely pyrophoric white phosphorous in compound (105), C_6 $(SPh)_6$ since the P_4 tetrahedron is of similar dimension to CCl_4, already known to form an adduct. It was hoped that the guest would be stabilised as a result of protection from air in the clathrate cavities. Thus (105) was recrystallised from a mixture of white P in AnalaR CS_2 (approximately 2 : 1) giving beautifully formed crystals of (105) which did not include any guest, as/

as determined from melting point evidence. A similar attempt using the quinazolinone (99) as the prospective host also led to deposition of unsolvated material.

Helium has been included in faujasite, an alumino-silicate zeolite, but there has never been any attempt reported to include the smallest possible molecule, namely hydrogen since all known hosts have too large escape routes from their cavities. Until recently, the accepted value for the van der Waals radius of hydrogen was 1.2A°, but of late, a value of 1.0A° has been proposed. Assuming the latter value to be correct, it was hoped to include hydrogen gas in hexakis (bromomethyl) benzene, C_6 $(CH_2Br)_6$ which crystallises in the trigonal system with space group $R\bar{3}$ and c-axis dimension of 5.38A° referred to a hexagonal unit cell. [290] From this dimension must be subtracted 3.35A° for the thickness of a benzene ring leaving a cavity, 2.03A° thick with sides blocked off by six interlocking bromine atoms, just large enough for the prospective guest (figure 28).

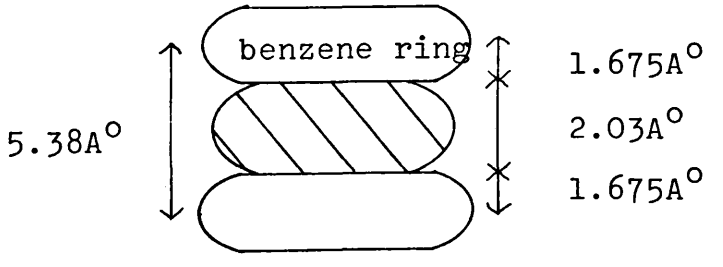


Figure 28 Schematic diagram of C_6 $(CH_2Br)_6$ (bromines not shown) showing the 2.03A° cavity.

The hexabromide (10g) in 1,2-dibromoethane (100ml) was heated to 185° in 285 atmospheres of hydrogen with rocking and allowed to cool slowly overnight.* The crystals obtained however did not contain any hydrogen.

Finally an attempt was made to use two of the hexa-hosts as n.m.r. shift reagents. It was hoped that the conformation showed in figure 26B would be retained in solution and that a suitable substrate would be included in the cavity formed by the three substituents on the same side of the central benzene ring. If a preferred orientation of the guest was favoured because of steric factors, shifts in a suitable guest molecule's n.m.r. signals may be expected. Compound (121) was dissolved in 6N KOD (prepared by adding KOH pellets to D_2O) and a few microdrops of p-cymene added. No splitting of the aromatic protons was observed unlike that previously observed for α-C.D. [230] A similar experiment using neat (126) (m.p. 12°) and p-cymene did not produce the desired effect.

It is hoped that in the not too distant future, that in the light of crystallographic studies it may be possible to tailor-make systems for specific inclusion or separation purposes.

* We are grateful to Dr. G. Knox of Strathclyde University for his assistance in this experiment.

EXPERIMENTAL

^{1}H n.m.r. spectra were recorded on Varian T-60, HA-100 and XL-100 instruments with $CDCl_3$ as solvent and TMS as internal standard except where indicated otherwise. ^{13}C n.m.r. spectra were recorded on the XL-100 machine. Ultra-violet spectra were measured on a Unicam SP8000 spectrometer. Mass spectra were recorded using A.E.I.-G.E.C. MS12 and MS902 instruments. Optical rotations were measured on a Perkin-Elmer 141 polarimeter. Infra red spectra were recorded on Perkin-Elmer 225 and Unicam SP1000 instruments. Melting points were determined on a Kofler hot-stage apparatus (except for samples in sealed tubes for which a Gallenkamp instrument was used) and are uncorrected. T.L.C. was carried out using Kieselgel G (Merck) for analytical purposes. Mallinckrodt silicic acid was used for columns. Solvents were removed on a rotary evaporator at reduced pressure. "Under nitrogen" means conducted in an atmosphere of commercial oxygen-free nitrogen straight from the cylinder; "dry nitrogen" is bottled nitrogen passed through silica gel and conc. sulphuric acid, and "pure nitrogen" is obtained by passage through alkaline pyrogallol, silica gel and conc. sulphuric acid.

Abbreviations

s	singlet
d	doublet
t	triplet
q	quartet

4-p-hydroxyphenyl-2,2,4-trimethylchroman, (19).

Dianin's compound was prepared [51] by the HCl gas catalysed condensation of phenol and mesityl oxide and isolated as the methanol clathrate, (host : guest = 3 : 1 and not 2 : 1 as stated throughout the literature), m.p. 155-6°, in 47% yield.

O-(p-4-(2,2,4-trimethylchromanyl) phenyl) dimethylthiocarbamate, (95).

This was prepared by condensation of the sodium salt of Dianin's compound (19) and dimethylthiocarbamoyl chloride using the method of Newman and Karnes [276] as described in reference 89, except that washing crude (95) in benzene/ hexane mixture with 10% KOH solution was necessary to remove unreacted Dianin's compound.

The yield was 90% m.p. 143-5°.

S-(p-4-(2,2,4-trimethylchromanyl) phenyl) dimethylthiocarbamate, (96).

Pure dry (95), (10.5g, 0.03 mol) was heated [89, 276] in an evacuated pyrolysis tube at 270° in a Wood's metal bath for 1.5 hours. The resultant gummy glass was pure by n.m.r. but a little was recrystallised from ethanol-benzene giving clusters of glassy needles m.p. 128-9°. (Found C, 71.10; H, 7.25; N, 3.65; S, 8.84%. $C_{21}H_{25}NO_2S$ requires C, 70.98; H, 7.05; N, 3.94; S 9.02%; M355).

m/e/

m/e 355; ν max (KBr) 1665cm^{-1} (C = O); τ ($CDCl_3$) 9.06, 8.28, 8.65 (each 3H, s), 7.76 (2H, AB_q, δ_{AB} = 0.31 p.p.m., J_{AB} = 14Hz), 6.95 (6H, s), 2.5 - 3.3 (8H, aromatic ^{1}H).

4-p-mercaptophenyl - 2,2,4-trimethylchroman, (40).

This was prepared [276] according to reference 89 but the hydrolysis was carried out under pure nitrogen and the reaction time doubled to 20 hours. The yield of white material, pure by n.m.r. was 100%. The cyclohexane recrystallised material had m.p. 137-8° (some sublimation at 107°); ν max (KBr) 2546cm^{-1} (S-H). Clathrates with a 3 : 1 host : guest ratio are formed with:

(i) CCl_4 (Found Cl, 14.98%. $3C_{18}H_{20}OS \cdot CCl_4$ requires Cl 15.67%); m.p. 45-90°; ν max (nujol) 2506cm^{-1}, $\Delta\nu^a_{\frac{1}{2}}$ 71cm^{-1}.

(ii) CCl_3Br (Found halogen, 18.85%. $C_{18}H_{20}OS \cdot CCl_3Br$ requires halogen 18.85%); m.p. 50-80°; ν max (nujol) 2506cm^{-1}, $\Delta\nu^a_{\frac{1}{2}}$ 100cm^{-1}.

(iii) CCl_3CH_3 (ratio by n.m.r. integration); m.p. 45-80°; ν max (nujol) 2506cm^{-1}, $\Delta\nu^a_{\frac{1}{2}}$ 100cm^{-1}.

4-p-aminophenyl -2,2,4-trimethylchroman, (100).

(99) (4.5g, 0.0095mol) was heated [280] at 150° for 22 hours in 100ml. of ethylene glycol with KOH pellets (6.5g) under pure nitrogen with magnetic stirring. After ether/

ether extraction (3 x 100ml), washing with brine and removing the solvent, the amine (100), (2.37g, 93%) was recrystallised from ethanol or CCl_4 giving prisms m.p. 136-7° (sealed tube). (Found C, 80.59; H, 7.62; N, 5.51%. $C_{18}H_{21}NO$ requires C, 80.86; H, 7.92; N, 5.24%; M 267.162306); m/e 267.16204; ν max (KBr) 3463, 3368cm^{-1} (N-H); τ ($CDCl_3$) 9.03, 8.63, 8.32 (each 3H,s), 7.81 (2H, AB_q δ_{AB} = 0.288 p.p.m., J_{AB} = 14Hz), 6.2 - 6.7 (2H, broad NH_2), 2.6 - 3.6 (aromatic ^1H).

4-p-aminophenyl-2,2,4-trimethylthiachroman, (101).

This was prepared [280] analogously to (100) from (104), (6.7g, 0.0137mol) which on hydrolysis yielded the crude amine (3.6g, 92.5%), which was greater than 95% pure by n.m.r. Recrystallisation from ethanol after decolourising with powdered animal charcoal gave colourless needles, m.p. 137-8°. (Found C, 76.14; H, 7.46; N, 4.65; S, 11.67%. $C_{18}H_{21}NS$ requires C, 76.30; H, 7.47; N, 4.94; S, 11.31%; M.283); m/e 283; ν max (KBr) 3435, 3347cm^{-1} (N-H); τ ($CDCl_3$) 8.9, 8.61, 8.27 (each 3H,s) 7.73 (2H, AB_q, δ_{AB} = 0.32p.p.m., J_{AB} = 14Hz), 6.49 (2H, broad NH_2), 2.7-3.4 (8H, aromatic ^1H).

O-(p-4-(2,2,4-trimethylthiachromanyl) phenyl)-dimethylthiocarbamate.

This compound was prepared [89, 276] analogously to (95)/

(95), but using 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman (31), (9.8g, 0.033mol). After work up and recrystallisation from methanol (450ml.), 9.69g (80%) of glistening white needles were obtained, m.p. 140 - 1°. (Found C, 67.93; H, 6.83; N, 3.68; S, 17.60%. $C_{21}H_{25}NOS_2$ requires C, 67.85; H, 6.78; N, 3.77; S, 17.26%, M 371); m/e 371; ν max (KBr) 1538, 1498, 1206, 1168, 1119cm^{-1}; τ ($CDCl_3$) 8.88, 8.57, 8.17 (each 3H,s) 7.68 (2H, AB_q, δ_{AB} = 0.32 p.p.m., J_{AB} = 14Hz), 6.67, 6.54 (each 3H, s, NCH_3), 2.65 - 3.15 (8H aromatic ^1H).

S-(p-4-(2,2,4-trimethylthiachromanyl) phenyl) dimethylthiocarbamate.

O-(p-4-(2,2,4-trimethylthiachromanyl) phenyl) dimethylthiocarbamate (7.5g, 0.02 mol) was heated for 1.5 hours at 270° in a Wood's metal bath [89, 276] to give a quantitative yield of the title compound, greater than 95% pure by n.m.r. A little material was recrystallised for analysis with difficulty from n-pentane-ethanol-benzene mixture, m.p. 105.5 - 107.5°. (Found C, 68.18; H, 6.75; N, 3.73, S, 17.70%. $C_{21}H_{25}NOS_2$ requires C, 67.85; H, 6.78; N, 3.77; S, 17.26%; M 371) m/e 371; ν max (KBr) 1666cm^{-1} (C = O); τ ($CDCl_3$) 8.88, 8.57, 8.19 (each 3H, s), 7.69 (2H, AB_q, δ_{AB} = 0.33 p.p.m. J_{AB} = 14Hz), 6.93 (6H, s, NCH_3), 2.5 - 3.1 (8H, aromatic ^1H).

4-p-mercaptophenyl-2,2,4-trimethylthiachroman, (102).

The above S-thiocarbamate crude from rearrangement (6.5g, 0.0175 mol) was dissolved in methanol (100ml) and

10%/

10% NaOH added (40ml, 5X excess) and the mixture stirred magnetically under reflux for 20 hours under nitrogen.[89, 276] On cooling water (50ml) was added and the mixture acidified with H_2SO_4 till pH4 with cooling. After standard extractions with benzene (750ml), there was obtained after solvent removal, a white powder, pure by n.m.r, 4.9g (93%). On recrystallisation from cyclohexane - ethanol, fine white needles were obtained m.p. 137-8°. (Found C, 72.07; H, 6.79; S, 21.02%. $C_{18}H_{20}S_2$ requires C, 71.96; H, 6.71; S, 21.34%; M 300); $^{m}/_{e}$ 300; ν max (KBr) 2542cm^{-1} (S-H); τ ($CDCl_3$) 8.90, 8.60, 8.25 (each 3H,s), 7.74 (2H, AB_q, δ_{AB} = 0.32 p.p.m. J_{AB} = 14 Hz), 6.64 (1H, S<u>H</u>), 2.6 - 3.2 (8H, aromatic ^{1}H).

4-<u>p</u>-(2,2,4-trimethylchroman - 4 - yl) - phenyloxy - 2 - phenylquinazoline. (98).

Dianin's compound (19) (13.95g, 0.05mol) as the methanol adduct was added to a magnetically stirred suspension of 60% NaH (2.4g, 0.06mol) in dry diglyme (30ml.) under nitrogen. After heating until all the phenol had dissolved, 4-chloro-2-phenylquinazoline (97) (12g, 0.05 mol) was added [280] and the mixture stirred at 145° for 40 mins. then poured on to crushed ice (500g). In order to remove traces of the extremely insoluble Dianin's compound (19), the crude product in toluene (750ml)/

(750ml) was extracted with aqueous KOH (5N, 4 x 100ml). After evaporating the solvent, the dense granular product was recrystallised from amyl alcohol giving unsolvated crystals m.p. 172-3°, 15.1g (80%). (Found C, 81.15; H, 6.06; N, 6.06%. $C_{32}H_{28}N_2O_2$ requires C, 81.33; H, 5.97; N, 5.93%; M472). $^m/_e$ 472; ν max (KBr) 1572, 1484, 1201, 710cm^{-1}; τ ($CDCl_3$) 8.94, 8.58, 8.22 (each 3H, s), 7.68 (2H, AB_q, δ_{AB} = 0.32 p.p.m. J_{AB} = 14Hz) 1.6 - 3.2 (17H, aromatic ^{1}H).

Recrystallisation of unsolvated (98) from benzene gives a 1 : 1 adduct with this solvent; melting starts 89 - 93°, rearrangement of microcrystallites at 95°, and finally melting at 171-2°. (Found C, 82.97; H, 6.37%. $C_{38}H_{34}N_2O_2$ requires C, 82.88; H, 6.22%), ν max (KBr) 683cm^{-1}. Dioxan also forms a 1 : 1 adduct as shown by ^{1}H n.m.r.

3-p-(2,2,4-trimethylchroman-4-yl) - phenyl - 2-phenyl-4 (3H) - quinazolinone. (99)

(98) (4.72g, 0.01mol) was heated in an evacuated sealed tube in a Wood's metal bath at 337° for 5½ hours.[280] The resultant red glass was recrystallised from methanol (or nitromethane), giving unsolvated (99), m.p. 176.5° - 178°, 3.8g (80%). (Found C, 81.56; H, 6.24; N, 6.01%. $C_{32}H_{28}N_2O_2$ requires C, 81.33; H, 5.97; N, 5.93%; M 472); $^m/_e$ 472; ν max (KBr) 1688cm^{-1} (C = O); τ $CDCl_3$) 9.28/

9.28, 8.63, 8.31 (each 3H,s), 7.79 (2H, AB_q, δ_{AB} = 0.27 p.p.m. J_{AB} = 14Hz), 1.5 - 3.3 (17H, aromatic ^1H). Unsolvated (99) when recrystallised from many solvents, formed stable adducts (Table (XI)).

4-p-(2,2,4-trimethylthiachroman-4-yl)-phenyloxy - 2 -phenylquinazoline. (103)

This compound was prepared analogously to (98) using 4-p-hydroxyphenyl-2,2,4-trimethylthiachroman.[280] The crude solid was collected on a sinter and washed with aqueous NaOH (5N, 2 x 100ml.) and brine giving a white solid (80%) which was pure by ^1H n.m.r. Unsolvated crystals were obtained on recrystallisation from amyl alcohol, mpt. 188-9°. (Found C, 78.6; H, 5.91; N, 5.45; S, 6.80%. $C_{32}H_{28}N_2$ OS requires C, 78.65; H, 5.77; N, 5.74; S, 6.56%; M488); m/e 488; νmax (KBr) 1484, 1380, 1347, 1209, 703cm^{-1}; τ ($CDCl_3$) 8.78, 8.52, 8.13 (each 3H, s), 7.59 (2H, AB_q δ_{AB} = 0.34 p.p.m. J_{AB} = 14Hz), 1.4 - 2.9 (17H, aromatic ^1H).

3-p-(2,2,4-trimethylthiachroman-4-yl)1phenyl - 2-phenyl-4 (3H) - quinazolinone (104).

This was prepared by pyrolysis of (103) using the same conditions described above for (99). Recrystallisation from ethanol gave unsolvated material (80%), melting initially at ca. 146.5 - 149°, followed by crystallisation and finally melting at 173.4° - 175°. (Found C, 78.91; H, 6.10, N, 5.46; S, 6.34%. $C_{32}H_{28}N_2$ OS requires

C,/

C, 78.65; H, 5.77; N, 5.74; S, 6.56%; M488); $^{m}/_{e}$ 488, ν max (KBr) 1686cm^{-1} (C = O); τ ($CDCl_3$) 9.09, 8.61 8.26 (each 3H, s), 7.73 (2H, AB_q δ_{AB} = 0.28 p.p.m., J_{AB} = 14Hz), 1.6 - 3.2 (17H, aromatic ^{1}H). Several solvents gave stable crystalline adducts with (104); (Table (XIV)).

Lithium amalgam.

This preparation is extremely hazardous. p-cymene was thoroughly dried by refluxing with sodium for 24 hours and then distilling from sodium (b.p. 80°/10mm). Redistilled Hg (1kg) and p-cymene (180ml) were heated in a 1 l. 3 necked r.b. flask equipped with a wide air condenser in an oil bath at 180 - 190°. A large enamel tray was positioned beneath the entire apparatus in case of breakage. Lithium metal (5g) was added in very small pieces and pushed beneath the mercury with a glass rod having an inverted cup at the end. [284] The resultant reaction is very violent with mercury and p-cymene rising more than a foot up the condenser. The amalgamation was completed in 1.5 hours.

Cyclobutane.

The p-cymene was decanted and replaced with dry dioxan (300ml), and the condenser replaced with a mercury-sealed stirrer. The second neck was equipped with a pressure/

pressure equalising dropping funnel, containing 1,4-dibromobutane (43.2g, 0.2mol) in 20ml. dry dioxan. The third neck bore a Liebig, through which water was pumped at 50° (55° in the last hour of the reaction) by a combined thermostat/peristaltic pump.* This condenser was fitted with dry ice chilled traps, protected from moisture with drying tubes, to collect the volatile product. The dibromide was added dropwise over 3 hours and the product collected in the traps. The yield after washing with water to remove dioxan was 6.9g, 70% (lit. [282] 70%); τ ($CDCl_3$) 8.04.

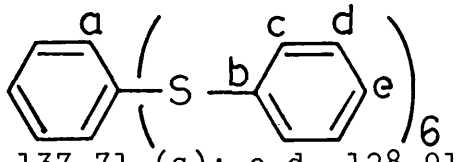
Hexaphenylthiobenzene (105).

Ph SCu was prepared by the reaction of freshly prepared Cu_2O and thiophenol in refluxing ethanol for 24 hours with efficient mechanical stirring. The yield of pink-yellow material is 90% m.p. 285° (decomp). (105) was synthesised by a literature route[291] by reaction of PhSCu and hexachlorobenzene in quinoline/pyridine at 210° in a Wood's metal bath for 24 hours. The crude mixture was poured on to conc. HCl in ice and the black rubbery solid thus isolated extracted with $CHCl_3$ (soxhlet) for 48 hours. After removing the solvent, a brown oil remained which crystallised well from carbon tetrachloride.

Further crystallisation from CCl_4 resulted in the formation/

* A Griffin and George Circostat was kindly lent by Dr. A.G. Cairns-Smith.

formation of magnificent trigonal yellow crystals, yield 30%, which were of the CCl_4 inclusion compound, m.p. 186 - 186.5°, after the loss of guest at 90°. (Found C, 51.74; H, 3.23; S, 17.98; Cl, 25.1%. $C_{42}H_{30}S_6 \cdot 2CCl_4$ requires C, 51.07; H, 2.92; S, 18.59; Cl, 27.41%. $C_{42}H_{30}S_6$ requires M726); m/e 726; ν max. (KBr) 1577, 1476, 1438, 1024, 744, 738, 704, 689cm^{-1}; τ ($CDCl_3$) 2.4 - 3.4; ^{13}C (δ $CDCl_3$)



a, 148.08 (s); b, 137.71 (s); c,d, 128.91, 128.17 (d); e, 126.14 (d); U.V. (CCl_4) λ 323nm, ϵ 107.6.

Inclusion compounds are also formed with:

(ii) CCl_3CH_3, host : guest = 1 : 2 guest escape 70 - 80°.

(iii) CCl_3Br (Found halogen, 22.4%, $C_{42}H_{30}S_6 \cdot CCl_3Br$ requires halogen, 20.13%), guest escape 90 - 100°.

(iv) CCl_3SCl (Found Cl, 24.8%, $C_{42}H_{30}S_6 \cdot 2CCl_3SCl$ requires halogen, 25.81%), guest escape 70 - 85°.

(v) CCl_3NO_2 (Found Cl, 13.8% $C_{42}H_{30}S_6 \cdot CCl_3NO_2$ requires Cl, 11.93%), guest escape 50 - 60°.

p-tolythiocuprate.

Redistilled p-thiocresol (b.p. 74°/10mm), (41.3g, 0.33 mol), freshly prepared Cu_2O (18.6g, 0.13 mol) and 95% ethanol (400ml) were stirred under reflux in a pure nitrogen/

nitrogen atmosphere for 40 hours. The filtered product was washed with ethanol to give a grey-pink powder (44g, 93%) m.p. 260° (decomp). (Found C, 44.8; H, 3.74; S, 17.30%. $C_7 H_7 S Cu$ requires C, 45.04; H, 3.78; S, 17.17%); ν max (KBr) 1488, 1185, 1087, 804, 799, 493 cm^{-1}.

Hexa-p-tolylthiobenzene, (106).

p-tolylthiocuprate (42g, 0.225 mol), hexachlorobenzene (9.5g, 0.033 mol), redistilled quinoline (b.p. 100°/10mm.) (150ml.) and pyridine (15ml.) were heated in a 500ml. flask under pure nitrogen in a Wood's metal bath for 25.5 hours, at 210°. After cooling, the mixture was poured into conc. HCl (140ml.) in crushed ice with stirring. The black rubbery solid was collected next day and soxhlet extracted with chloroform (350ml.) for 2 days. T.L.C. indicated the presence of 4 compounds so the entire extracted material was purified by silicic acid column chromatography, with $CHCl_3$ as eluant. The first yellow band contained the desired material, but large amounts of polymeric material was strongly absorbed on to the silica. Recrystallisation of the first yellow material from ethanol-benzene gave the product as fine yellow needles, m.p. 197 - 200°, in less than 1% yield. (Found C, 70.80; H, 5.37; S, 23.66%. $C_{48} H_{42} S_6$ requires C, 71.08; H, 5.22; S, 23.71%; M810); $^{m}/_{e}$ 810; ν max (KBr) 1487/

1487, 1177, 1016, 810, 492cm^{-1}; τ ($CDCl_3$) 7.7 (18H, s), 2.8 - 3.3 (24H aromatic ^1H); U.V. (CCl_4) λ 325, ϵ 143.3. No inclusion compound were formed with CCl_4 or CCl_3 CH_3.

p-methoxyphenylthiocuprate.

p-methoxybenzene thiol (Aldrich) (10g, 0.0714 mol), freshly prepared Cu_2O (4.7g, 0.033 mol) and 95% ethanol (80ml.) were stirred mechanically under nitrogen for 44 hours in a pure nitrogen atmosphere. It was necessary to add 30ml. more EtOH during the reaction. The filtered yellow product weighed 10.5g. (72.5%), m.p. 255° (decomp.). (Found C, 41.21; H, 3.39; S, 12.24; 12.60%. C_7 H_7CuOS requires C, 41.50; H, 3.482; S, 15.82%); ν max (KBr) 1595, 1490, 1288, 1246, 1173, 1035, 822, 814cm^{-1}.

Attempted preparation of hexa-p-methoxyphenylthiobenzene.

The method used was the same as that described for (106). The product was mainly polymer and none of the desired product was obtained by purifying the extracts by column chromatography.

p-t-butylphenylthiocuprate.

The method was the same as that described for p-methoxyphenylthiocuprate. The grey solid (50% yield) melted with decomposition at 252°, but a satisfactory analysis was not obtained.

Attempted/

Attempted preparation of hexa-p-t-butylphenylthiobenzene.

The method described for (105) was employed but hexa-substituted material was not obtained. The fine yellow needles had m.p. 207-9°; Cl, 3.76%.

Hexakis (bromomethyl) benzene.

To a boiling solution of hexamethylbenzene (65g, 0.4 mol) in 1,2-dibromoethane (1.5l) was added [292] slowly over 2 hours. AnalaR bromine (175ml , 40% excess) and refluxing continued for 30 hours. On cooling, the product (250g, 98%) was collected by filtration and recrystallised from 1,2-bibromoethane, m.p. 309-10°, (301° with decomposition in sealed tube). (Found C, 22.78; H, 1.98; Br, 74.99%. $C_{12}H_{12}Br_6$ requires C, 22.67; H, 1.904; Br, 75.37%; M635); $^{m}/_{e}$ centred on 635, with 1 : 6 : 15 : 20 : 15 : 6 : 1 isotope pattern; ν max (KBr) 3037, 1489, 1447, 1221, 1194, 800, 725, 654, 603, 524cm^{-1}.

Hexakis (phenoxymethyl) benzene, (107).

Sodium phenoxide in phenol was reacted with hexakis (bromomethyl) benzene (6.355g, 0.01mol) as described in the literature [293], but under a nitrogen atmosphere and heating at 110° for 24 hours, and after suitable work up, the yield of (107) was 70%. Purification was readily achieved by recrystallisation from toluene giving the di-toluene adduct m.p. 227-8° (guest escape 90°). (Found C, 80.67/

C, 80.79; H, 6.05%. $C_{48}H_{42}O_6$ requires C, 80.67; H, 5.92%; M714); m/e 714; ν max (KBr) 1597, 1496, 1223, 1168, 752cm^{-1}; τ ($CDCl_3$) 4.8 (12H, broad CH_2), 2.5 - 3.4 (30H aromatic ^1H). Reproducible yields were also achieved on a 0.1 molar scale. The inclusion behaviour of this compound is shown in Table (XVII).

Hexakis (phenylthiomethyl) benzene, (108).

Sodium (2.3g, 0.1 mol) was dissolved in amyl alcohol (100ml.) then thiophenol (9g, 0.09mol) and $C_6(CH_2Br)_6$ (6.355g, 0.01mol) added and stirred under reflux for 9 hours, under nitrogen. [294] When cold, the mixture was added to iced water (400ml) and the white solid collected by filtration and dried yielding (7.55g, 92%). This was recrystallised from toluene giving a 1 : 1 adduct. Solvent free material was obtained by crystallising from cyclohexane, m.p. 192-3°. (Found C, 71.13; H, 5.41; S, 23.48%. $C_{48}H_{42}S_6$ requires C, 70.81; H, 5.21; S, 23.65%; M810); m/e 810; ν max (KBr) 1581, 1479, 1437, 1025, 752, 732, 689cm^{-1}; τ ($CDCl_3$) 4.66 (12H broad CH_2) 2.6 - 3.0 (30H, aromatic ^1H). An inclusion compound is also formed with dioxan (host : guest = 1 : 2); see Table (XVIII).

Hexakis (phenylselenomethyl) benzene, (109).

The procedure adopted is analogous to the preparation of $C_6(CH_2SPh)_6$ but using PhSeH and pure nitrogen. The yield/

yield was 86% for a 0.01 molar preparation. Glassy needles were obtained when recrystallised from toluene, m.p. 161-2°. (Found C, 52.90; H, 4.16%. $C_{48}H_{42}Se_6$ requires C, 52.80; H, 3.90%; M1092) $\frac{m}{e}$ (max 703; ν max (KBr) 1572, 1475, 1434, 1069, 1019, 1000, 736, 725, 686cm^{-1}; τ($CDCl_3$) 5.74 (12H, broad CH_2), 2.4 - 2.9 (30H, aromatic ^1H). Dioxan and toluene do not form inclusion compounds.

Hexakis (phenylaminomethyl) benzene, (110).

In a pure nitrogen atmosphere, $C_6(CH_2Br)_6$ (6.355g, 0.01mol) and redistilled aniline (b.p. 93-4°/10mm, 100ml) were stirred for 27 hours at 150°, then the aniline removed at the water pump to leave a crude red solid which was digested with toluene and decolourised with animal charcoal. White needles crystallised out, 3.4g (47%), mpt. 214.5 - 215.5°. (Found C, 81.46; H, 7.0; N, 11.66%, $C_{48}H_{48}N_6$ requires C, 81.32; H, 6.82; N, 11.85%; M696) $\frac{m}{e}$ 696; ν max (KBr) 3392, 3293cm^{-1} (N-H); τ($CDCl_3$, 220MHz) 5.94 (6H, broad NH), 6.54 (12H, broad CH_2), 3.45 (12H, d, meta aromatic ^1H), 3.36 (6H, t, para aromatic ^1H), 2.88 (12H, t, ortho aromatic ^1H).

Toluene, dioxan, CCl_4 and $CHCl_3$ do not form inclusion compounds.

Hexakis (benzyloxymethyl) benzene, (111).

The procedure was similar to that used for (107) and/

and the scale was the same (0.01 molar). Heating at 165° was maintained for 30 hours as the sodium salt of benzyl alcohol precipitated out. Excess benzyl alcohol was removed by distillation (b.p. 102-4°/10mm) and the residual oil recrystallised from toluene, giving white needles, (37.5%) m.p. 121.5 - 123.5°. (Found C, 81.17; H, 6.81%. $C_{54}H_{54}O_6$ requires C, 80.90; H, 6.89%; M798); $\underline{m}/\underline{e}$ 798; ν max (KBr) 1512, 1451, 1354, 1347, 1057, 702cm^{-1}; τ ($CDCl_3$) 5.69 (12H, s, $C\underline{H}_2$), 5.50 (12H, s, $C\underline{H}_2$), 2.5 - 2.85 (30H, aromatic ^{1}H). Toluene, cyclohexane, t-butanol, nitromethane, dioxan, tetrahydrofuran and tetrahydropyran are not included.

Hexakis (benzylthiomethyl) benzene, (112).

This was prepared [294] similarly to (108) on a 0.01 molar scale but using benzyl thiol. The yield of (112) was quantitative. Purification was readily achieved by recrystallisation from toluene giving a 1 : 1 adduct, which was desolvated by heating overnight at 60° and 0.5mm, m.p. 150-2°. (Found C, 72.43; H, 6.19; S, 21.55%. $C_{54}H_{54}S_6$ requires C, 72.44; H, 6.08; S, 21.48%; M894); $\underline{m}/\underline{e}$ 894; ν max (KBr) 1599, 1492, 1447, 1229, 716, 706, 696cm^{-1}; τ ($CDCl_3$) 6.48 (12H, s, $C\underline{H}_2$), 6.64 (12H, s, $C\underline{H}_2$) 2.4 - 2.9 (30H, aromatic ^{1}H). Details of the inclusion compounds are given in Table (XIX).

Benzyl/

Benzyl selenol.

A literature preparation [295] was followed. All solvents were degassed at the water pump and pure nitrogen used throughout. Grey selenium (24g, 0.304mol), $NaBH_4$ (12g) and dry ice chilled dry ethanol (600ml) were placed in a 2l. 3-necked flask immersed in ice and stirred magnetically. As the flask warms up, very vigorous hydrogen evolution occurs. The ice bath was then removed and redistilled benzyl chloride (b.p. 72°/10mm) (35.3ml, 0.304mol) added dropwise and left stirring for five hours. Water (800ml.) was then added and then dilute HCl till pH was 4-5 (substantial H_2Se evolution) and nitrogen bubbled through the mixture to remove H_2Se (trapped with 5% aqueous lead acetate). A rapid extraction with $CHCl_3$, (3 x 400ml.) was then performed, the extracts being run into a nitrogen filled conical flask containing blue silica gel. The solvent was then removed and the grey residue distilled giving an almost colourless free-flowing liquid b.p. 95-99°/10mm, (25.6g, 50%, lit. 51%), with spectroscopic properties as reported; e.g. ν max (neat liquid) 2280cm^{-1} (SeH); τ ($CDCl_3$) 10.09 (1H, t, $J_{C\underline{H}_2\text{-}Se\underline{H}}$ = 6.5Hz, Se$\underline{H}$).

Dibenzylselenide.

The distillation residues of the previous compound were further distilled and the title compound obtained in low/

low yield, [295] b.p. 125-30°/0.05mm, which melted at 45-45.5° after recrystallisation from n-pentane. m/e 261, M^+; ν (max (CCl_4) 3022, 1595, 1489, 1448, 1026, 695cm^{-1}; τ($CDCl_3$) 6.2 - 6.4 (4H, CH_2), 2.6 - 2.9 (10H, aromatic ^1H).

Dibenzyldiselenide.

After using the freshly prepared benzyl selenol, the flasks etc. were washed with ethanol and the ethanol solution of selenol left open to the air overnight. Next day, the light yellow crystalline diselenide [295] was collected by filtration, m.p. 92 - 93.5°. m/e 340, M^+; ν max (KBr) 1600, 1596, 1457, 1178, 764, 755, 703, 697, 600cm^{-1}; τ($CDCl_3$) 6.06 - 6.28 (4H, CH_2), 2.5 - 2.9 (10H, aromatic ^1H).

Attempted preparation of hexakis (benzylselenomethyl) benzene.

The same method as described for (108) but using benzyl selenol was tried, but no hexa-substituted product was obtained, probably as a result of overheating, since red Se was produced. This was repeated using ethyl alcohol as solvent instead of amyl alcohol but the $C_6(CH_2Br)_6$ was isolated unchanged along with dibenzylselenide indicating that disproportionation had occurred.

Hexakis (p-isopropylphenoxymethyl) benzene (113).

Sodium (2.3g, 0.10mol), redistilled p-isopropylphenol (b.p. 104 - 6°/10mm), (13.62g, 0.10 mol) and 110ml. of dry/

dry redistilled diglyme (b.p. 53°/8mm) were heated under nitrogen and when all dissolved $C_6(CH_2Br)_6$ (6.355g, 0.01mol) was added and the mixture stirred under reflux for 22 hours. When cool, water was added, the crude product collected by filtration and washed with base yielding 8.9g (90%) of product. This was recrystallised from toluene giving the product as fine white needles, m.p. 212.5° - 214°. (Found C, 82.05; H, 8.29%. $C_{66}H_{78}O_6$ requires C, 81.94; H, 8.127%; M966); m/e 966; ν max (KBr) 2956, 1610, 1411, 1232, 1178, 1012, 826cm^{-1}; τ ($CDCl_3$) 8.81 (36H, d, CH_3, J = 13Hz), 7.17 (6H, d, $C(CH_3)_2H$, J = 13Hz), 4.84 (12H, broad CH_2), 2.8 - 3.3 (24H, AA'BB' aromatic ^1H).

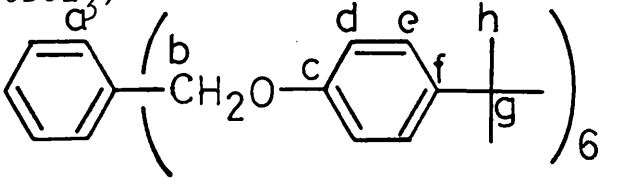
Dioxan, tetrahydrofuran and tetrahydrothiophene do not form inclusion compounds.

Hexakis (p-t-butylphenoxymethyl) benzene, (114).

The procedure described for (113) was followed but using p-t-butylphenol (15g, 0.1 mol) and $C_6(CH_2Br)_6$ (6.355g, 0.01mol) to yield crude (114), 8.31g, (80%). Fine white needles were obtained from toluene, m.p. 253-7°. (Found C, 82.25; H, 8.647%. $C_{72}H_{90}O_6$ requires C, 82.35; H, 8.648%; M1050); m/e 1050; ν max (KBr) 2960, 1512, 1233, 1182, 1011, 829cm^{-1}; τ ($CDCl_3$) 9.72 (54H, s, t-butyl), 4.87 (12H, broad CH_2), 2.74 - 3.3 (24H, AA'BB' aromatic ^1H).

^{13}C n.m.r. (δ, $CDCl_3$)

a,/

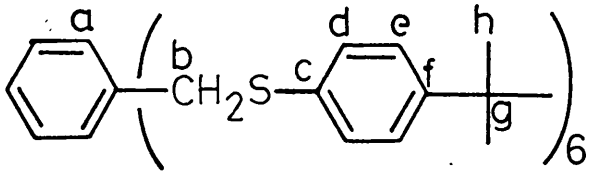


a, 137.97(s); b, 63.62 (t); C, 156.35 (s); d, 114.28 (d); e, 126.20 (d); f, 143.87(s); g, 34.04(s); h, 31.48 (q).

Inclusion compounds were not formed with cyclohexane, cyclooctane, squalene, p-xylene or dioxan.

Hexakis (p-t-butylphenylthiomethyl) benzene (115).

The procedure described for (108) was adopted [294] but using p-t-butylthiophenol (13g, 0.08mol) and $C_6(CH_2Br)_6$ (6.355g, 0.01mol). The crude white product amounted to 10.5g, (91.5%) Glassy needles were obtained on recrystallisation from toluene, which were desolvated for analysis, m.p. 182-3°. (Found C, 75.30; H, 7.85; S, 16.80%. $C_{72}H_{90}S_6$ requires C, 75.34; H, 7.91; S, 16.76%); ν max (KBr) 2954, 1496, 1119, 1012, 814, 543cm^{-1}; τ($CDCl_3$) 8.70 (54H, S, t-butyl ^{1}H), 5.94 (12H broad CH_2), 2.7 - 2.98 (24H, aromatic ^{1}H). ^{13}C n.m.r. (δ, $CDCl_3$)



a, 126.28(s); b, 33.34 (t); C, 135.75(s); d, e, 126.03, 130.62 (d); f, 150.70 (s); g, 34.46(s); h, 31.25(q).

Details of the inclusion behaviour of this host are given in Table (XX). Reproducible yields were obtained on a 0.1 molar scale.

t-butylbenzene/

t-butylbenzene.

This was prepared by a literature route [296] using $AlCl_3$ (333.4g, 2.5mol) in benzene (2228ml, 25 mol) and t-butanol (475ml, 5 mol) yielding t-butylbenzene (420g, 70%, lit. 70%), b.p. 169°. ν max (neat liquid) 2944, 1493, 760, 696, 544cm^{-1}; τ ($CDCl_3$) 8.69 (9H, s, t-butyl ^1H), 2.6 - 3.0 (5H, aromatic ^1H).

p-bromo-t-butylbenzene.

t-butylbenzene (67g, 0.5 mol) and bromine (80g, 0.5 mol) were stirred [297] in a 500 cc. r.b. flask with a reflux condenser and a drying tube at 0° and the flask illuminated with a 150W tungsten bulb. The reaction started after 15 mins. and illumination at ambient temperature was continued for 5 days. $Na_2S_2O_5$ solution was added, the solution made slightly basic and then extracted with n-pentane (3 x 150ml) and the extracts washed with brine and water and then the solvent removed. The remainder was distilled at atmospheric pressure using a bunsen burner. A little t-butylbenzene came over first. The product has a remarkably high vapour pressure, distilling over at 200° although the boiling point is 230°, m.p. 16°. The yield was 90g (84%, lit. 60%). (Found C, 56.12; H, 5.88; Br, 37.9%. $C_{10}H_{13}Br$ requires C, 56.35; H, 6.15; Br, 27.5%; M213); m/e 213; ν max (neat liquid) 2944, 1490, 1107, 1006, 820, 726, 340cm^{-1}. τ ($CDCl_3$) 8.74 (9H, s, t-butyl ^1H), 2.60 - 2.94 (4H AA' BB', aromatic/

aromatic ^{1}H).

Attempted preparation of p-t-butylbenzene selenol.

All reagents were carefully dried and pure nitrogen used throughout. [298] In a 500ml. 3-necked conical flask was placed magnesium (8g, 0.33 mol) and 30ml. of an ether solution of p-bromo-t-butylbenzene (71g, 0.33 mol in 166ml. ether) which were stirred magnetically. [299] After the reaction started (15 mins.) the remainder of the solution was added dropwise over 45 minutes and stirring continued for ¼ hour. The dropping funnel was replaced with an addition flask containing black Se (21.33g, 0.27 mol) and the solid added over 30 mins. with vigorous stirring continued for 1 hour. The mixture was thrown into ice (200g in a 1 l. beaker) and AnalaR HCl was added (25ml.) (caution, H_2Se evolved) and then extracted with ether (2 x 400ml). The extracts were washed with brine, dried and the solvent removed leaving a black oily residue. Distillation at the water pump afforded only a little t-butylbenzene. Oil pump distillation gave 2 fractions.

(i) 140°/0.1mm; a yellowish liquid which solidified on standing. This was recrystallised from ethanol and the white needles obtained (2.5g) melted at 128-9°, lit 128-9° for the Grignard coupling product, 4, 4'-di-t-butyldiphenyl.

(Found C, 90.34; H, 10.08%. $C_{20}H_{26}$ requires C,/

C, 90.15; H, 9.84%; M266); $^{m}/_{e}$ 266; ν max (KBr) 2954, 1492, 822, 555cm^{-1}; τ($CDCl_3$) 8.66 (18H, s, t-butyl ^{1}H), 2.46 - 2.74 (8H, aromatic ^{1}H).

(ii) 180°/0.07mm : a red liquid solidifying to a yellow solid. This was dissolved in ethanol, a few drops of benzene added and the solution allowed to cool slowly with continuous magnetic stirring. An amorphous yellow powder (17g) was obtained and this was recrystallised from ethanol to give yellow needles of a compound (m.p. 73.5 - 74.5°, lit. [299] 75° for p-t-butylbenzenediselenide. (Found C, 56.70; H, 6.47%. $C_{20}H_{26}Se_2$ requires C, 56.61; H, 6.18% M 424); $^{m}/_{e}$ 424; ν max (KBr) 2953, 1492, 1390, 1109, 1006, 816, 541cm^{-1}; τ($CDCl_3$) 8.71 (18H, s, t-butyl ^{1}H), 2.4 - 2.86 (8H, AA' BB' aromatic ^{1}H).

p-t-butylbenzene selenol.

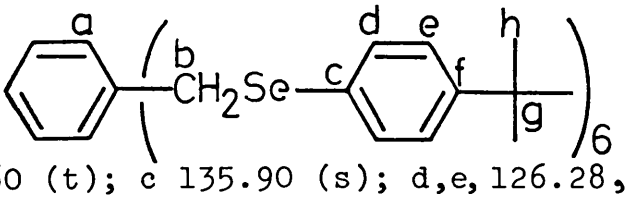
The procedure described above was repeated [299] but at the extraction stage rapid working was essential and 400ml. of ether was used in total. The extracts were dried by passage through a sinter full of anhydrous Na_2SO_4 (30 sec.) The residue was distilled at the water pump. A fair amount of t-butylbenzene was obtained but at 112 - 114°/8mm, the selenol containing a very little t-butylbenzene was obtained as an almost colourless liquid/

liquid, 4.1g, 5.8%. This material was used at once in the next synthesis. (Found $^{m}/_{e}$ 214.02588. $C_{10}H_{14}{}^{80}Se$ requires 214.02605; $^{m}/_{e}$ 212.02667. $C_{10}H_{14}{}^{78}Se$ requires 212.026850); ν max (neat liquid) 2960, 2317 (Se-H), 1503, 1398, 1365, 1268, 1113, 1008, 817cm^{-1}; τ ($CDCl_3$) 8.73 (9H, s, t-butyl ^{1}H), 8.59 (1H, SeH), 2.56 - 3.0 (4H, AA'BB', aromatic ^{1}H).

Hexakis (p-t-butylphenylselenomethyl) benzene, (116).

The selenol (4g) was added to a solution of sodium (1g) in n-pentanol (50ml) and then $C_6(CH_2Br)_6$ (1g) added and the mixture stirred for 3.5 hours at 140° under pure nitrogen. NaBr precipitated the instant the hexabromide was added. When cool, ice was added, the mixture filtered and the solid washed with NaOH, brine and water giving fairly pure (116), 2.044g, 91%. This material was recrystallised from toluene giving white needles of the adduct which was desolvated for analysis, m.p. 179.5 - 181.5°. (Found C, 60.63; H, 6.41%. $C_{72}H_{90}Se_6$ requires C, 60.50; H, 6.35%); ν max (KBr) 2940, 1386, 1108, 1006, 998, 815, 547 cm^{-1}; τ($CDCl_3$) 8.69 (54H, s, t-butyl ^{1}H), 5.82 (12H, broad CH_2), 2.6 - 2.9 (24H, aromatic ^{1}H).

^{13}C n.m.r. (δ, $CDCl_3$)



a, 126.40 (s); b, 26.60 (t); c 135.90 (s); d,e, 126.28, 133.67 (d); f, 150.07 (s); g, 34.54 (s); h, 31.3 (q).

Details of the inclusion behaviour of this compound are given in Table (XXI).

1-adamantylbromide.

This was prepared by a simplified modification of the literature method.[300] Adamantane (100g, 0.735mol) was refluxed with Br_2 (150ml, 2.925 mol) for 5.5 hours. On cooling, aqueous $Na_2 S_2 O_5$ was added and when colourless, aqueous $Na_2 CO_3$ was added. After stirring overnight, the slurry was filtered in a large sintered glass funnel and washed with carbonate till slightly basic and then brine till neutral. The crude material (80%) was recrystallised twice from methanol, giving a 71% yield of pure material, m.p. 118-9°. (Found C, 55.90; H, 7.09; Br, 36.95%. $C_{10}H_{15}Br$ requires C, 55.84; H, 7.03, Br, 37.15%; M215); $^{m}/_{e}$ 215; ν max (KBr) 2905, 2852, 1455, 1342, 1276, 1025, 805, 765, 674cm^{-1}; τ ($CDCl_3$) 8.22 (6H),7.88 (3H), 7.60 (6H).

p-1-adamantylphenol.

Adamantyl bromide (69g, 0.321 mol) and phenol (345g, 10 x excess) were heated with stirring at 100 - 110° for 30 hours.[301] On cooling, water was added with vigorous stirring to form a slurry. This slurry in a large sinter, was washed with boiling water (8 x 1 l) to remove the phenol leaving the product (64g, 87.5%) which was recrystallised from methanol giving very fine white needles/

needles, m.p. 181.5 - 182.5°. (Found C, 83.95; H, 8.99%. $C_{16}H_{20}O$ requires C, 84.16; H, 8.83%; M288) m/e 288; ν max (KBr) 3000 - 3500 (O-H), 2904, 2823, 1513, 1446, 1246, 833, 806, 538cm^{-1}; τ ($CDCl_3$) 7.8 - 8.5 (15H, adamantyl ^{1}H), 5.32 (1H, s, OH), 2.7 - 3.4 (4H aromatic ^{1}H.)

Hexakis (p-1-adamantylphenoxymethyl) benzene, (117).

To adamantylphenol (1.35g, 0.0047 mol) in dry diglyme (12ml) was added sodium (0.14g, 0.00609 mol) and the mixture heated till dissolved. $C_6(CH_2Br)_6$ (0.4192g, 0.00066 mol) was then added and the mixture refluxed for 21 hours under dry nitrogen. When cool, water was added giving a milky non-filterable solution. This was transferred to a separating funnel with ether and washed with water to remove the diglyme. Some organic material floated on top of the water layer. The solid and dried ether extracts were combined and digested with $CHCl_3$ and transferred to another flask. There remained a residue which was unreacted hexabromide. The chloroform was removed, the residue washed with ether and recrystallised from toluene to give the product in about 60% yield, m.p. > 350°. It is very insoluble and tends to creep up the sides of vessels. (Found C, 84.22, H, 8.42%. $C_{108}H_{126}O_6$ requires C, 85.32; H, 8.35% (unsatisfactory)); ν max (KBr) 2894, 2840, 1510, 1234, 1008, 832, 807, 544 cm^{-1}; τ($CDCl_3$) 7.7 - 8.6 (90H, adamantyl ^{1}H), 4.88 (12H/

(12H, broad CH_2), 2.78 - 3.54 (24H, AABB aromatic ^1H). Toluene and dioxan do not form inclusion compounds with (117).

O-(4-adamantylphenyl)-dimethylthiocarbamate.

This compound was prepared [276] on a 0.05 molar scale as described for (95) in pure nitrogen. To sodium (1.15g) in dry ethanol (60ml) was added adamantylphenol (11.416g), then the ethanol removed under vacuum (0.005mm/2 hours) and dimethylthiocarbamoyl chloride (10.5g, 0.085 mol) in dry redistilled dimethylformamide (60ml) added and the mixture stirred for 2 hours at 60°. After extraction with benzene/hexane (4 : 1) (4 x 2ooml) and washing with KOH (5%) then brine, 14.2g (88%) of the product was obtained. This was recrystallised from methanol (21) giving fine white needles, m.p. 201.5 - 203°. (Found C, 72.32; H, 7.89; N, 4.59; S, 10.36%. $C_{19}H_{25}NOS$ requires C, 72.33; H, 7.99; N, 4.44; S, 10.16%; M315); $^m/_e$ 315; max (KBr) 2900, 2843, 1503, 1392, 1287, 1207, 1171, 1135cm^{-1}; ($CDCl_3$) 7.8 - 8.6 (15H, adamantyl ^1H), 6.58, 6.71 (each 3H, s, NCH_3) 2.6 - 3.14 (4H, AA'BB' aromatic ^1H).

S-(4-adamantylphenyl)-dimethylthiocarbamate.

The corresponding O-carbamate (5.1g, 0.0162 mol) was heated [276] in an evacuated sealed tube at 270° for 70 mins. The/

The yield of product was quantitative, being pure enough for direct hydrolysis. A little was recrystallised from benzene to give large glassy needles, m.p. 137-8°. (Found C, 72.37; H, 7.98; N, 4.68; S, 10.24%. $C_{19}H_{25}NOS$ requires C, 72.33; H, 7.99; N, 4.44; S, 10.16%; M315); $^{m}/_{e}$ 315; νmax (KBr) 2890, 1656 (C = O), 1353, 1086, 1009, 803, 686, 554cm^{-1}; τ($CDCl_3$) 7.8 - 8.3 (15H, adamantyl ^{1}H), 6.97 (6H, s, NCH_3) 2.5 - 2.86 (4H, aromatic ^{1}H).

4,4'-(1-adamantylphenyl) disulphide.

An initial attempt to prepare the previous compound by the same method but heating a 275° for 1.5 hours resulted in the formation of the title disulphide as well as the S-carbamate. The disulphide was isolated by fractional crystallisation from benzene-ethanol as fine white needles, m.p. 186-7°. (Found C, 79.10; H, 8.02; S, 12.94%. $C_{32}H_{38}S_2$ requires C, 78.96; H, 7.87; S, 13.17%; M486) $^{m}/_{e}$ 486; νmax (KBr) 2892, 2835, 1487, 1003, 799, 531cm^{-1}; τ($CDCl_3$) 7.8 - 8.6 (30H, adamantyl ^{1}H), 2.5 - 3.0 (8H, aromatic ^{1}H).

p-1-adamantylthiophenol.

The S-carbamate (5g, 0.0159 mol) crude from rearrangement in methanol (100ml), NaOH pellets (3.18g, 0.079 mol) in water (30ml) were heated under reflux in pure nitrogen for 22 hours. On cooling, dilute HCl was added/

added with stirring to pH5 and the mixture extracted with benzene (4 x 200ml) and washed with brine. The solvent was evaporated to give the crude thiol (4g, 100%) which was pure enough for further reaction. The thiol was recrystallised from cyclohexane, m.p. 106 - 106.5°. Satisfactory analysis was not obtained possibly because of sublimation and "creeping". (Found C, 78.83; H, 8.43; S, 11.89%. $C_{16}H_{20}S$ requires C, 78.60; H, 8.02; S, 13.1%; M244.12857); M 244.12838; νmax (KBr) 2890, 2840, 2546 (S-H), 1493, 799, 531 cm^{-1}; τ($CDCl_3$) 7.8 - 8.6 (15H, adamantyl ^1H), 6.66 (1H, s, S$\underline{H}$) 2.6 - 3.06 (4H, aromatic ^1H). This thiol is unstable in solution with respect to oxidation, with 4,4'-(1-adamantyl-phenyl) disulphide being precipitated on prolonged standing but appears to be perfectly stable in the solid state.

Hexakis (p-1-adamntylphenylthiomethyl) benzene, (118).

Adamantylthiophenol (3.7g, 0.0152 mol) was added to a solution of sodium (0.35g, 0.0152 mol) in amyl alcohol (25ml) in pure nitrogen with stirring and then $C_6(CH_2Br)_6$ (1.0708g, 0.00168 mol) added and the mixture heated under reflux for 15 hours, with 25ml. further degassed amyl alcohol being added half-way through to wash sublimed thiol back into the reaction flask. On cooling, iced water was added, the solid filtered, washed with base and thenbrine to give the product (2.513g, 92%). This/

This was recrystallised from toluene to give very fine needles, m.p. 308 - 308.5° (slight decomp). (Found C, 79.99; H, 7.89; S, 12.27%. $C_{108}H_{126}S_6$ requires C, 80.23; H, 7.85; S, 11.9%; ν max (KBr) 2894, 2840, 1492, 1445, 1010, 802 cm^{-1}; τ ($CDCl_3$) 7.6 - 8.6 (90H, adamantyl ^1H), 5.88 (12H, broad $C\underline{H}_2S$), 2.5 - 3.0 (24H, aromatic ^1H). The results of inclusion experiments are shown in Table (XXII).

Hexakis (2-napthylthiomethyl) benzene, (119).

This was prepared similarly to (108) on a 0.01 molar scale but using naphthalene-2-thiol (14.4g, 0.09 mol) and a pure nitrogen atmosphere. The yield of crude yellowish material was 8.6g, (77.5%). When recrystallised from CCl_4 - $CHCl_3$ the melting point was 209 - 11°. (Found C, 77.67; H, 4.82; S, 17.31%. $C_{72}H_{54}S_6$ requires C, 77.83; H, 4.86; S, 17.33%); ν max (KBr) 3047, 1627, 1586, 1501, 1132, 944, 857, 812, 743, 473cm^{-1}; τ ($CDCl_3$) 5.54 (12H, broad $C\underline{H}_2$), 2.2 - 3.0 (42H, aromatic ^1H). The results of inclusion experiments are shown in Table (XXIII).

Hexakis (p-methoxyphenoxymethyl) benzene, (120).

p-methoxyphenol was redistilled under reduced pressure giving white material (b.p. 152-4°/10mm, m.p.53°). The procedure was the same as that described for (113), being carried/

carried out on a 0.01 molar scale but using p-methoxyphenol (11.16g, 0.09 mol) and refluxing was continued for 27 hours. The usual work-up afforded brown-white material (7.74g, 87%) which was recrystallised from toluene to give very fine needles, m.p. 225-7°. (Found C, 72.57; H, 6.11%. $C_{54}H_{54}O_6$ requires C, 72.49; H, 6.04%; M894); m/e 894; νmax (KBr) 1506, 1220, 1038, 822cm^{-1}; τ($CDCl_3$) 6.26 (18H, s, OCH_3), 4.87 (12H broad CH_2), 3 - 3.4 (24H, aromatic ^1H). No inclusion compounds were formed with toluene, cyclohexane, or xylene mixtures.

Hexakis (p-hydroxyphenylthiomethyl) benzene, (121).

Under pure nitrogen, to a solution of sodium (1.533g, 0.066 mol) in absolute alcohol (75ml) was added p-mercaptophenol (8.416g, 0.0667 mol) and then $C_6(CH_2Br)_6$ (4.237g, 0.00666 mol) and the mixture stirred for 20 hours under reflux. On cooling, still under nitrogen, dilute HCl was added to pH5 then H_2O (60ml). The solvent was removed but the white powder remaining, which was soluble in water was shown to be the hexasodium salt by i.r. and n.m.r. The solid was redissolved in ethanol and the pH decreased to 2, then the solvent removed leaving a white solid (4.35g, 72%) which was recrystallised from anisole, m.p. 228-30°. (Found C, 63.36; H, 4.92; S, 20.92%. $C_{48}H_{42}O_6S_6$ requires C, 63.54; H, 6.47; S, 21.19%; M906); m/e (max) 567; νmax (KBr) 3650 - 3060 (O-H)/

(O-H) 1602, 1538, 1496, 1236, 831cm^{-1}; τ (acetone -D_6) 5.80 (12H, broad C$\underline{H}_2$), 2.6 - 3.3 (24H, aromatic ^{1}H), 1.34 (6H, s, O$\underline{H}$). The results of inclusion experiments are shown in Table (XXIV).

Hexakis (p-aminophenylthiomethyl) benzene, (122).

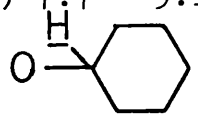
To a solution of sodium (2.3g, 0.1 mol) in absolute alcohol (90ml) under pure nitrogen was added 4-aminothiophenol (11.268g, 0.09 mol) and then C_6 $(CH_2Br)_6$ (6.355g, 0.01 mol) and the mixture stirred under reflux for 17 hours. When cool, ice was added, the solid filtered, washed with base, brine and then water yielding a white powder (8.692g, 97%). This was recrystallised from anisole to give fine needles m.p. 210 - 12°. (Found C, 64.10; H, 5.44; N, 9.49; S, 21.80%. $C_{48}H_{48}N_6S_6$ requires C, 63.90; H, 5.37; N, 9.32; S, 21.33%; M900); $\underline{m}/\underline{e}$ (max) 531; ν max (KBr) 3510, 3427 (N-H), 1623, 1600, 1497, 1286, 1177, 826, 511cm^{-1}; τ (acetone-D_6) 5.80 (12H, broad C$\underline{H}_2$), 5.17 (12H, broad N$\underline{H}_2$), 2.7 - 3.5 (24H, AA'BB' aromatic ^{1}H). Results of inclusion experiments are given in Table (XXV).

Hexakis (cyclohexylthiomethyl) benzene, (123).

This was prepared similarly to (108) on a 0.01 molar scale but using cyclohexylthiol (10.44, 0.09 mol). The crude white solid (7.38g, 86%) was recrystallised from toluene/

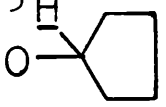
toluene and desolvated for analysis, m.p. 248 - 250.5°. (Found C, 68.10; H, 9.41; S, 22.52%. $C_{48}H_{78}S_6$ requires C, 68.05; H, 9.28; S, 22.70%; M846); $\frac{m}{e}$ 846; ν max (KBr) 2922, 2824, 1447, 1197, 999cm^{-1}. τ($CDCl_3$) 7 - 9.2 (66H, cyclohexyl ^{1}H), 6.03 (12H, broad $C\underline{H}_2S$). Results of inclusion experiments are presented in Table (XXVI).

Hexakis (cyclohexyloxymethyl) benzene, (124).

Cyclohexanol was redistilled, (b.p. 159 - 61°). Sodium (2.3g, 0.1 mol) was added to cyclohexanol (110ml) under nitrogen with magnetic stirring and $C_6(CH_2Br)_6$ (6.355g, 0.01 mol) added and the mixture maintained at 140° for 22 hours. When cool, the solvent was removed leaving a brown oil. The addition of water and ethanol caused the precipitation of a yellow-brown powder (4g, 53%). This was purified by silicic acid column chromatography, with $CHCl_3$ as eluant, and recrystallised from toluene as white crystals, m.p. 169 - 72°. (Found C, 76.59; H, 10.13%. $C_{48}H_{78}O_6$ requires C, 76.76; H, 10.46%; M750); $\frac{m}{e}$ (max) 651 (M^+-cyclohexyloxy); ν max (KBr) 2928, 2853, 1445, 1356, 1079, 949cm^{-1}; τ($CDCl_3$) 7.7 - 9.1 (60H, cyclohexyl ^{1}H), 6.33 - 6.8 (6H, ) 5.36 (12H, broad $C\underline{H}_2O$). The inclusion behaviour of this compound has not been investigated.

Hexakis/

Hexakis (cyclopentyloxymethyl) benzene, (125).

This was prepared similarly to (124) on a 0.01 molar scale but using cyclopentanol. The yield of yellow solid was 2.4g, 36%. After column chromatography, and recrystallisation from benzene, the melting point of the white crystals was 167 - 9°. (Found C, 75.45; H, 9.95% $C_{42}H_{60}O_6$ requires C, 75.63; H, 9.97%; M666); m/e (max) 580; ν max (KBr) 2943, 2864, 1338, 1176, 1076, 1046cm^{-1}; τ ($CDCl_3$) 7.94 - 9.0 (48H, cyclopentyl ^1H) 5.83 - 6.16 (6H, ) 5.5 (12H, broad CH_2O). Results of inclusion experiments are given in Table (XXVII).

Hexakis (n-hexylthiomethyl) benzene, (126).

This was prepared according to the methol of H.J. Backer [294] on a 0.01 molar scale using n-hexylthiol, in 95% yield. The oily product was purified by recrystallisation from chilled ethanol, m.p. 11.5 - 12°. τ($CDCl_3$) 7.98 - 9.4 (66H), 7.15 - 7.66 (12H), 6.0 (12H, broad CH_2).

Hexamethyldisilane.

An attempt was made to prepare this compound by reacting methylmagnesium iodide with a mixture of chloromethylsilanes but no pure product was obtained. Instead/

Instead a literature route [302] was followed by reacting chlorotrimethylsilane (100ml, 0.78 mol) with sodium-potassium sand (3.6g Na, 25g K) in xylene (200ml). It proved very difficult to separate the product from xylene but eventually this was achieved with low recovery by spinning band disillation with a final yield of about 20%, b.p. 113°, m.p. 12°.

REFERENCES

Several excellent general review articles on inclusion compounds have been published and are listed as references 1 - 17.

1. G. Zilberstein, Bull. Soc. Chim. France, 1951, 18, D.33.
2. W. Schlenk, Fortschr. Chem. Forsch, 1951, 2, 92.
3. F. Cramer, Angew. Chem, 1952, 64, 437.
4. F. Cramer, "Einschlussverbindungen", Springer-Verlag, 1954.
5. H.M. Powell, J. Chem. Soc., 1954, 2658.
6. G. Montel, Bull. Soc. Chim. France, 1955, 1013.
7. F.D. Cramer, Rev. Pure Appl. Chem., 1955, 5, 143.
8. H.M. Powell, Rec. Trav. Chim.,1956, 75,885.
9. F. Cramer, Angew Chem.,1956, 68,115.
10. L. Mandelcorn, Chem. Rev.,1959, 59, 827.
11. J.F. Brown, Sci. Amer., 1962, 207,82.
12. M. Hagan, "Clathrate Inclusion Compounds", Reinhold, 1962.

13/

13. L. Mandelcorn, ed, "Non-Stoichiometric Compounds", Academic Press, 1964.

14. C. Asselineau and J. Asselineau, Ann. Chem., 1964, 9, 461.

15. V.M. Bhatnagar, "Clathrate Compounds", Chemical Publishing Co., 1970.

16. C. Solacolu and I. Solacolu, Stud. Cert. Chem., 1973, 21,1307.

17. S.G. Frank, J. Pharm. Sci., 1975, 64, 1585.

18. V.M. Bhatnagar, J. Struct. Chem., 1967, 8, 513.

19. W. Schlenk, Ann. Chem., 1973, 1145.

20. H. van Bekkum, J.D. Remijnse and B.M. Wepster, Chem. Comm, 1969, 67.

21. D. French, Adv. Carbohydrate Chem, 1957, 12, 189.

22. J.A. Thoma and L. Stewart, in "Starch; Chemistry and Technology", R.L. Whistler and E.F. Paschall, eds, Vol. 1, Academic Press, 1965.

23. D.W. Griffiths and M.L. Bender, Adv. Catalysis, 1973, 23, 209.

24. F.R. Senti and S.R. Erlander, in "Non-Stoichiometric Compounds, ed L. Mandelcorn, Academic Press, 1964.

25/

25. K.H. Froemming and J. Opperman, Arch. Pharm, 1974, 681; Chem. Abs. 1974, 81, 169205.

26. L.F. Fieser and M.Fieser, "Steroids", Reinhold, 1967.

27. W.C. Herndon, J. Chem. Ed, 1967, 44, 724.

28. J.N. van Niekerk, Acta Cryst, 1948, 1, 44.

29. M. Gomberg and C.S. Schoepfle, J. Amer Chem. Soc., 1915, 37, 2569.

30. H. Hartley and N.G. Thomas, J. Chem. Soc., 1906, 89, 1013.

31. G.B. Barlow and A.C. Clamp, J. Chem. Soc., 1961, 393.

32. J. Milgrom, J. Phys. Chem., 1959, 63,1843.

33. H.R. Allcock, "Phosphorus - Nitrogen Compounds", Academic Press, 1972.

34. H.R. Allcock, Chem. Rev., 1972, 72, 715.

35. D.J. Williams and D. Lawton, Tetrahedron Letters, 1975, 111.

36. V.M. Bhatnagar, Chem. Age India, 1963, 14, 688.

37. J.L. Flippen, J. Karle and I.L. Karle, J. Amer. Chem. Soc., 1970, 92, 3749.

38/

38. G.A. Jeffrey and R.K. McMullan, Prog. Inorg. Chem, 1967, 8, 43.

39. V.M. Bhatnagar, J. Chem. Ed., 1963, 40, 646.

40. R.K. McMullan, W. Saenger, J. Fayos and D. Mootz, Carbohydrate Res., 1973, 31, 37.

41. V.M. Bhatnagar, J. Struct. Chem., 1965, 6, 760.

42. A. Bhattacharjei and A. Bhaumik, J. Chromatogr, 1975, 115, 250.

43. C. Brabant, B. Blanck, and A.L. Beauchamp, J. Organometallic Chem., 1974, 82, 231.

44. R.F. Hunter, R.A. Morton and A.T. Carpenter, J. Chem. Soc.,1950, 441.

45. D. Belitskus, G.A. Jeffrey, R.K. McMullan and N.C. Stephenson, Inorg. Chem.,1963, 2, 873.

46. M.F. Pilbrow, J.C.S. Dalton, 1975, 2432.

47. A.P. Dianin, J. Russe. Phys. Chem. Soc., 1914, 46, 1310.

48. W. Baker and J.F.W. McOmie, Chem. and Ind., 1955, 256.

49. H.M. Powell, J. Chem. Soc., 1948, 61.

50. H.M. Powell and B.D.P. Wetters, Chem. and Ind., 1955, 256.

51./

51. W. Baker, A.J. Floyd, J.F.W. McOmie, G. Pope, A.S. Weaving and J.H. Wild, J. Chem. Soc.,1956, 2010.

52. W. Baker, J.F.W. McOmie and A.S. Weaving, J. Chem. Soc., 1956, 2018.

53. G.G. Kondrateva, Metody. Polsich. Khim. Reaktivov Prep.,1969, 20, 199; Chem. Abs.,1972, 76, 113017.

54. D.B.G. Jaquiss, Ger. Offen. 2335854, 1974; Chem. Abs., 1974, 81,26162.

55. L. Mandelcorn, N.N. Goldberg and R.E. Hoff, J. Amer. Chem. Soc., 1960,82,3297.

56. L. Mandelcorn, R.W. Auxier and C.W. Lewis, U.S. 2949424, 1960, Chem. Abs., 1961, 55, 11364.

57. J.E. Mock, J.E. Myers and E.A. Trabant, Ind. Eng. Chem., 1961, 53, 1007.

58. W.R. Lawton, Belg. 632833, 1963; Chem. Abs., 1964, 61, 3851.

59. C.K. Johnson, Fr. 1530511, 1968; Chem. Abs.,1969, 71,13717.

60. M.G. Allen and G.W. Beèle, U.S. 3632843, 1972; Chem. Abs., 1971, 74, 43074.

61./

61. H.L. Hoffman, G.R. Breeden and R.W. Liggett, J. Org. Chem., 1964, 29, 3440.

62. M. Davies and W.C. Child, Spect. Acta, 1965, 21, 1195.

63. M. Davies and K. Williams, Trans. Far. Soc., 1968, 64, 529.

64. J.S. Cook, R.G. Heydon and H.K. Welsh, J.C.S. Faraday II, 1974, 1591.

65. J.L. Flippen, J. Karle and I.L. Karle, J. Amer. Chem. Soc., 1970, 92, 3749.

66. D.E. Palin and H.M. Powell, J. Chem. Soc., 1948, 815.

67. J.L. Flippen and J. Karle, J. Phys. Chem., 1971, 75, 3566.

68. F.B. Wilson, Ph.D. Thesis, University of Glasgow, 1971.

69. D.H. Desty, A. Goldup and D.G. Barnard-Smith, Brit 973306, 1964; Chem. Abs., 1965, 62,2655.

70. A. Goldup and G.W. Smith, Separ. Sci., 1971, 6, 791.

71. A.A. McConnell, D.D. MacNicol and A.L. Porte, J. Chem. Soc. A, 1971, 3516.

72./

72. P. Gregoire and J. Meinnel, Compte Rend. Acad. Sci. C., 1971, 272, 347.

73. L.D. Kispert and J. Pearson, J. Phys. Chem.,1972, 76, 133.

74. A.P. Kuleshov, V.I. Trofimov and I.I. Chkeidze, Khim. Vys. Energ.,1973, 7, 82; Chem. Abs, 1973, 79, 25604.

75. A.P. Kuleshov and V.I. Trofimov, Khim. Vys. Energ., 1973, 7, 143; Chem. Abs., 1973, 78, 146926.

76. E.W. Aslaksen Phys. Lett. A, 1972, 40, 47.

77. P. Gregoire, Y. Marqueton, J. Gallier and J. Meinnel, Bull. Soc. Sci. Bretagne, 1973, 48, 91; Chem. Abs., 1973, 79, 108930.

78. S.H. Wilen, Topics in Stereochemistry, 1971, 6, 128.

79. B.J. Brienne and J. Jacques, Tetrahedron Letters, 1975, 2347.

80. R.M. Barrer and V.H. Shanson, J.C.S. Chem. Comm., 1976, 333.

81. D.D. MacNicol, Chem. Comm., 1969, 836.

82. D.D. MacNicol,H.H. Mills and F.B. Wilson, Chem. Comm., 1969, 1332.

83./

83. D.D. MacNicol and F.B. Wilson, Chem. Comm., 1971, 786.

84. D.D. MacNicol, J.C.S. Chem. Comm., 1973, 621.

85. R.J. Cross, J.J. McKendrick and D.D. MacNicol, Nature, 1973, 245, 146.

86. D.D. MacNicol and J.D. White, unpublished results.

87. D.D. MacNicol, unpublished results.

88. A.D.U. Hardy, J.J. McKendrick and D.D. MacNicol, J.C.S. Chem. Comm., 1974, 972.

89. J.J. McKendrick, Ph.D. Thesis, University of Glasgow, 1974.

90. D.D. MacNicol, A.D.U. Hardy and J.J. McKendrick, Nature, 1975, 256, 343.

91. A.D.U. Hardy, J.J. McKendrick and D.D. MacNicol, J.C.S. Chem. Comm., 1976, 355.

92. K. Fries and G. Fickewirth, Ber,1908, 41, 371; Ann, 1908, 362, 42.

93. W. Baker, R.F. Curtis and J.F.W. McOmie, J. Chem. Soc., 1951, 76.

94. J.B. Niederl,R.A. Smith and M.E. McGreal, J. Amer. Chem. Soc., 1931, 53, 3390.

95./

95. W. Baker and D.M. Besly, J. Chem. Soc., 1939, 195.

96. W. Baker and D.M. Besly, J. Chem. Soc., 1940, 1103.

97. W. Baker, R.F. Curtis and M.G. Edwards, J. Chem. Soc., 1951, 83.

98. W. Baker, R.F. Curtis and J.F.W. McOmie, J. Chem. Soc., 1952, 1774.

99. W. Baker, D.F. Downing, A.E. Hewilt-Symonds and J.F.W. McOmie, J. Chem. Soc., 1952, 3796.

100. M.P.V. Boarland, J.F.W. McOmie and R.N. Timms, J. Chem. Soc., 1952, 4691.

101. W. Baker, J.F.W. McOmie and J.H. Wild, J.Chem.Soc., 1957, 3060.

102. T. Ohta and S. Togano, Japan Kokai 75131533; Chem. Abs., 1976, 84, 114208.

103. K. Yamada and N. Sugiyama, Bull. Chem. Soc. Japan, 1965, 38, 2057, 2061.

104. F. Cramer, "Einschlussverbindungen", Springer-Verlag, 1954, p.46.

105. F. Cramer and G.H. Elschnig, Chem. Ber., 1956, 89, 1.

106. F. Cramer and H. Windel, Chem. Ber., 1956, 89, 354.

107./

107. M. Gomberg and C.J. West, J. Amer. Chem. Soc., 1912, 34, 1529.

108. A. Schonberg and A. Mustafa, J. Chem. Soc., 1947, 997.

109. E. Bergmann, O. Blum-Bergmann and A.F.v. Christiani, Ann, 1930, 483, 80.

110. E.M. Gieser, U.S. 2851500, 1958; Chem. Abs., 1959, 53, 6055.

111. E. Terres and W. Vollmer, Petroleum Z., 1935, 31 No. 19, 1; Chem. Abs., 1935, 29, 8302.

112. B.A. Nikitin, Compt. Rend. Acad. Sci. U.R.S.S., 1939, 24, 562; Chem. Abs., 1940, 34, 1894.

113. ibid. p.565; Chem. Abs., 1940, 34, 1895.

114. ibid. 1940, 29, 571; Chem. Abs., 1941, 35, 3510.

115. L.I. Kashtanov and L.N. Sokolova, J. Gen. Chem. U.S.S.R. 1951, 21, 1619; Chem. Abs., 1952, 46 8043.

116. B.A. Nikitin, M.P. Koval'skaya and M.F. Pushlenkov Izvest. Akad. Nauk. S.S.S.R. Odtel. Khim. Nauk., 1951, 661; Chem. Abs., 1952, 46, 5944.

117. B.A. Nikitin and M.P. Koval'skaya, ibid. 1952, 24; Chem. Abs., 1952, 46, 6919.

118./

118. O.J. Wehrhahn and M.v. Stackelberg, Naturwissensch, 1954, 41, 358.

119. M.v. Stackelberg, Rec. Trav. chim., 1956, 75, 902.

120. M. v. Stackelberg, A. Hoverath and C. Scheringer, Z. Elektrochem, 1958, 62, 123.

121. P.H. Lahr and H.L. Williams, J. Phys. Chem., 1959, 63, 1432.

122. S.A. Allison and R.M. Barrer, Trans. Far Soc., 1968, 64, 547.

123. ibid., p.557.

124. R.E. Cover, U.S. 3314884, 1967; Chem. Abs., 1967, 67, 13598.

125. Y.N. Kazankin, F.I. Kazankina, A.A. Palladiev and A.M. Trofimov, Dokl. Akad. Nauk, S.S.S.R, 1972, 205, 1128; Chem. Abs., 1972, 77, 172102.

126. Y.N. Kazankin, F.I. Kazankina, A.A. Palladiev and A.M. Trofimov J. Gen. Chem. U.S.S.R., 1973, 43, 2650.

127. M.F. Pushlenkov and V.A. Ignatov, J. Gen. Chem. U.S.S.R., 1974, 44, 2347.

128./

128. Y.N. Kazankin, F.I. Kazankina, A.A. Palladiev and A.M. Trofimov, U.S.S.R. 411062, 1974; Chem. Abs., 1974, 80,119701.

129. Y.N. Kazankin, A.A. Palladiev and A.M. Trofimov, J. Gen. Chem. U.S.S.R., 1973, 43, 2648.

130. ibid., 42, 2363.

131. B.A. Nikitin and E.M. Ioffe, Dokl. Akad. Nauk. S.S.S.R., 1952, 85, 809; Chem. Abs., 1953, 47, 394.

132. A.M. Trofimov and Y.N. Kazankin, Radiokhimiya, 1965, 7, 288; Chem. Abs., 1966, 64, 2999.

133. ibid., 1966, 8, 720; Chem. Abs., 1967, 66, 61399.

134. ibid., 1968, 10, 445; Chem. Abs., 1968, 69, 92527.

135. E. Terres and K. Thewalt, Brennstoff Chem., 1957, 38, 257; Chem. Abs., 1958, 52, 1948.

136. L.I. Kashtanov and N.V. Kazanskays, Trudy Moskov Inzhenemo - Ekonom. Inst., 1954, No. 1, 139; Chem. Abs., 1956, 50, 11270.

137. M. Gomberg and L.H. Cone, Ann, 1910, 376, 236.

138. D.E. Palin and H.M. Powell, J. Chem. Soc., 1947, 208.

139. F. Wohler, Ann, 1849, 69, 297.

140./

140. A. Clemm, Ann., 1859, 110, 357.

141. F. Mylius, Ber.,1886, 19, 1007.

142. J. Schmidlin and R. Lang, Ber., 1910, 43, 2818.

143. D.E. Palin and H.M. Powell, J. Chem. Soc., 1948, 571.

144. D.E. Palin and H.M. Powell, J. Chem. Soc., 1948, 815.

145. H.M. Powell and M. Guter, Nature, 1949, 164, 240.

146. H.M. Powell, J. Chem. Soc., 1950, 300.

147. ibid., p.468.

148. D.F. Evans and R.E. Richards, J. Chem. Soc., 1952, 3295.

149. G. Peyronel and G. Barbieri, J. Inorg. Nucl. Chem., 1958, 8, 582.

150. H. Meyer and T.A. Scott, J. Phys. Chem. Solids, 1959, 11, 215.

151. D.F. Ball and D.C. McKean, Spect. Acta, 1962, 18, 933.

152. B.E. Bryant, U.S. 3076742, 1963; Chem. Abs., 1963, 59, 5079.

153. G. Gnauck Z. Chem., 1964, 4, 186; Chem. Abs., 1964, 61, 6482.

154./

154. E. Hunt and H. Meyer, J. Chem. Phys., 1964, 41, 353.

155. A. B. Harris, E. Hunt and H. Meyer, J. Chem. Phys., 1965, 42, 2851.

156. T.R. Kutty, J. Ind. Inst. Sci., 1971, 53, 154; Chem. Abs., 1971, 75, 118079.

157. X. Gerbaux, C. Berthel, A. Hadni and M. Mohan, Spect. Acta, 1973, 29A, 1695.

158. J.W. Anthonsen, J. Molec. Struct., 1974, 23, 468.

159. J.E.D. Davies and W.J. Wood, J.C.S. Dalton, 1975, 674.

160. S.C. Wallwork and H.M. Powell, J. Chem. Soc., 1956, 4855.

161. J.H. van der Waals, Trans. Far. Soc., 1956, 52, 184.

162. N.G. Parsonage and L.A.K. Staveley, Mol. Phys., 1959, 2, 212.

163. ibid., 1960, 3, 59.

164. D.F. Evans and R.E. Richards, Nature, 1952, 170, 246.

165. Y.N. Kazankin, A.A. Palladiev and A.M. Trofimov, J. Gen. Chem. U.S.S.R., 1972, 42, 2604.

166./

166. H.G. McAdie, Can. J. Chem., 1966, 44, 1373.

167. H. Ohigashi and Y. Kurita, J. Mag. Res., 1969, 1, 464.

168. Y. Hazoni, P. Hillman, M. Pasternak and S. Ruby, Physics Letters, 1962, 2, 337.

169. G.J. Perlow, C.E. Johnson and M.R. Perlow in "Noble Gas Compounds", H.H. Hyman, ed, University of Chicago Press, 1963, p.279.

170. J. Gallier and P. Gregoire, Compt. Rend. Acad. Sci, 1972, 275, 1343.

171. K. Fukushima, J. Mol. Struct., 1973, 18, 277.

172. K.D. Cleaver, J.E.D. Davies and W.J. Wood, J. Mol. Struct., 1975, 25, 224.

173. H.M. Powell, Brit. 678312-3, 1952; Chem. Abs., 1953, 47, 3532.

174. D.J. Chleck and C.A. Ziegler, Nucleonics, 1959, 17, 130.

175. C.O. Hommel, F.J. Brousaides and R.L. Bersin, Anal Chem., 1962, 34, 1608.

176. D.J. Chleck and C.A. Ziegler, U.S. 3084062, 1963; Chem. Abs., 1963, 59, 4659.

177. H. Shimojima, Y. Nakayama K. Matsumoto and H. Hyodo, Proc. Intern. Conf. Peaceful Uses at. Energy/

Energy, (3rd), Geneva, 1964, 14, 313; Chem. Abs., 1966, 65, 5209.

178. R. Spallino and G. Provenzal, Gazz. Chim. Ital., 1909, 39, 325.

179. W. Baker, B. Gilbert and W.D. Ollis, J. Chem. Soc., 1952, 1443.

180. A.C.D. Newman and H.M. Powell, J. Chem. Soc., 1952, 3747.

181. D. Lawton and H.M. Powell, J. Chem. Soc., 1958, 2339.

182. S. Brunie, A. Navaza and G. Tsoucaris, Acta Cryst., 1975, 31A, 5127.

183. W.D. Ollis and I.O. Sutherland, Chem. Comm., 1966, 402.

184. A.P. Downing, W.D. Ollis, I.O. Sutherland, J. Mason and S.F. Mason, Chem. Comm., 1968, 329.

185. A.P. Downing, W.D. Ollis and I.O. Sutherland, J. Chem. Soc. B, 1970, 24.

186. S. Brunie and G. Tsoucaris, Cryst. Struct. Commun. 1974, 3, 481; Chem. Abs., 1974, 81, 83171.

187. H.M. Powell, Nature, 1952, 170, 155.

188. M.K. Hargreaves and B. Modarai, Chem. Comm., 1969, 16.

189./

189. A. Bavely and E.W. Robb, U.S. 3047432, 1962; Chem. Abs., 1962, 57, 17092.

190. K.A. McLauchlan, Nucl. Magn. Res. Chem. Proc. Symp., Cagliari, Italy, 1964,313; Chem. Abs., 1967, 66, 6910.

191. A. Goldup and A.B. Morrison, Brit. 1070775, 1967; Chem. Abs., 1967, 67, 63923.

192. N.M. Wu, D.W. Barrett and W.S. Koski, Mol. Phys., 1973, 25, 437.

193. G. Ciranni, A. Guarino, E. Pizzella and E. Passagno, J. Labelled Compounds, 1965, 1, 1; Chem. Abs., 1965, 63,5555.

194. G. Ciranni, A. Guarino, R. Pizzella, E. Passagno, B. Rabe and G. Rabe, AEC Accession No. 1938, Rept. No. EUR 2452e, 1965; Chem. Abs., 1966, 65, 13112.

195. R. Anschutz, Ber., 1892, 25, 3506; Ann., 1893, 273, 94.

196. R. Anschutz, Ber., 1892, 25, 3512; Ann., 1893, 273, 73.

197. W. Baker, W.D. Ollis and T.S. Zealley, J. Chem. Soc., 1951, 201.

198. W. Baker, B. Gilbert, W.D. Ollis and T.S. Zealley, Chem. and Ind., 1950, 333.

199./

199. W. Baker, B. Gilbert, W.D. Ollis and T.S. Zealley, J. Chem. Soc., 1951, 209.

200. W. Baker, J.B. Harborne, A.J. Price and A. Rutt, J. Chem. Soc., 1954, 2043.

201. A.P. Downing, W.D. Ollis and I.O. Sutherland, Chem. Comm., 1967, 171.

202. W. Baker, A.S. El-Nawawy and W.D. Ollis, J. Chem. Soc., 1952, 3163.

203. G. Schroeter and O. Eisleb, Ann., 1909, 367, 101.

204. W.D. Ollis, J.F. Stoddart and I.O. Sutherland, Tetrahedron, 1974, 30, 1903.

205. W.D. Ollis J.A. Price, J.S. Stephanatou and J.F. Stoddart, Angew. Chem. Int. Ed., 1975, 14, 169.

206. W.D. Ollis, J.S. Stephanatou, J.F. Stoddart and A.G. Fenige, Angew. Chem. Int. Ed., 1976, 15, 223.

207. D.J. Brickwood, W.D. Ollis and J.F. Stoddart, J.C.S. Chem. Comm., 1973, 638

208. W.D. Ollis, J.F. Stoddart and M. Nógrádi, Angew. Chem. Int. Ed., 1975, 14, 168.

209. L. Párkányi, A. Kálmáin and M. Nógrádi, Acta Cryst., 1975, B31, 2716.

210./

210. H. Stetter and E.-E. Roos, Chem. Ber., 1955, 88, 1390.

211. W. Lautsch and D. Gunther, Naturwissensch., 1957, 44, 492.

212. R. Herschfield and M.L. Bender, J. Amer. Chem. Soc., 1972, 94,1376.

213. Y. Murakami, J. Sunamoto and K. Kano, Bull. Chem. Soc. Japan, 1974, 47, 1238.

214. R.L. Whistler in "Starch : Chemistry and Technology", eds R.L. Whistler and E.F. Paschall, Academic Press, 1965, Vol. 1, Chapter 14, p.331.

215. F. Cramer and H. Hettler, Naturwissensch., 1967, 54, 625.

216. P.C. Manor and W. Saenger, Nature, 1972, 237, 392.

217. F. Cramer and F.M. Henglein, Chem. Ber., 1957, 90, 2561.

218. K. Kainuma, A. Nogami and C. Mercier, J. Chromatog., 1976, 121, 361.

219. W.S. McClenahan, E.B. Tilden and C.S. Hudson, J. Amer. Chem. Soc., 1942, 64, 2139.

220. B. Casu, M. Reggiani, G.G. Gallo and A. Vigevani, Carbohydrate Res., 1970, 12, 157.

221./

221. F. Cramer, G. Mackensen and K. Sensse, Chem. Ber., 1969, 102, 494.

222. R.K. McMullan, W. Saenger, J. Fayos and D. Mootz, Carbohydr. Res., 1973, 31, 211.

223. W. Saenger and M. Notlemeyer, Chem. Ber., 1976, 109, 503.

224. W. Saenger, K. Beyer and P.C. Manor, Acta Cryst., 1976, B32, 120.

225. M. Notlemeyer and W. Saenger, Nature, 1976, 259, 629.

226. K. Takeo and T. Kuge, Agr. Biol. Chem., 1970, 34, 568.

227. J.A. Hamilton, L.K. Steinrauf and R.L. Van Etten, Acta Cryst., 1968, B24, 1560.

228. F. Cramer, W. Saenger and H-C. Spatz, J. Amer. Chem. Soc., 1967, 89, 14.

229. F. Cramer, Chem. Ber., 1951, 84, 851; ibid., 1953, 86, 1576.

230. D.D. MacNicol, Tetrahedron Letters, 1975, 3325.

231. F. Cramer and W. Dietsche, Chem. Ber., 1959, 92, 378.

232. M. Miklojczyk and J. Drabowicz, Tetrahedron Letters, 1972, 2379.

233./

233. F. Cramer and W. Dietsche, Chem. Ber., 1959, 92, 1739.

234. F. Cramer and W. Kampe, J. Amer. Chem. Soc., 1965, 87, 1115.

235. T.S. Straub abd M.L. Bender, J. Amer. Chem. Soc., 1972, 94, 8875.

236. N. Hennrich and F. Cramer, J. Amer. Chem. Soc., 1965, 87, 1121.

237. R.L. Van Etten, J.F. Sebastian, G.A. Clowes and M.L. Bender, J. Amer. Chem. Soc., 1967, 89, 3242, 3253.

238. D.E. Tutt and M.A. Schwartz, J.C.S. Chem. Comm., 1970, 113; J. Amer. Chem. Soc., 1971, 93, 767.

239. K. Flohr, R.M. Paton and E.T. Kaiser, J.C.S. Chem. Comm., 1971, 1621.

240. R.M. Paton and E.T. Kaiser, J. Amer. Chem. Soc., 1970, 92, 4723.

241. K. Flohr, R.M. Paton and E.T. Kaiser, J. Amer. Chem. Soc., 1975, 97, 1209.

242. C. v. Hooidonk and J.C.A.E. Breebaart-Hansen, Rec. Trav. Chim., 1970, 89, 289.

243. H.J. Brass and M.L. Bender, J. Amer. Chem. Soc., 1973, 95, 5391.

244./

244. W.I. Congdon and M.L. Bender, Bioorganic Chem., 1971, 1, 424.

245. Y. Matsui, K. Mochida, O. Fukumoto and Y. Date, Bull Chem. Soc. Japan, 1975, 48, 3645.

246. T.S. Straub abd M.L. Bender, J. Amer. Chem. Soc., 1972, 94, 8881.

247. D.W. Griffiths and M.L. Bender, J. Amer. Chem. Soc., 1973, 95, 1679.

248. D.L. Van der Jagt, F.L. Killian and M.L. Bender, J. Amer. Chem. Soc., 1970, 92, 1016.

249. R. Breslow and P. Campbell, Bioorganic Chem., 1971, 1, 140.

250. M. Mitani, T. Tsuchida and K. Koyama, J.C.S. Chem. Comm., 1974, 869.

251. F. Cramer and G. Mackensen, Angew Chem. Int. Ed., 1966, 5, 601 ; Chem. Ber., 1970, 103, 2138.

252. R. Breslow and L.E. Overman, J. Amer. Chem. Soc., 1970, 92, 1075.

253. W.B. Gruhn and M.L. Bender, Bioorganic Chem., 1974, 3, 324.

254. Y. Kitaura and M.L. Bender, Bioorganic Chem., 1975, 4, 237.

255. J. Emert and R. Breslow, J. Amer. Chem. Soc., 1975, 97, 650.

256./

256. Y. Iwakura, K. Uno, F. Toda, S. Onozuka, K. Hattori and M.L. Bender, J. Amer. Chem. Soc., 1975, 97, 4432.

257. R. Breslow, H. Kohn and B. Siegel, Tetrahedron Letters, 1976, 1645.

258. D.M. Sand and H. Schlenk, Anal. Chem., 1961, 33, 1624.

259. H. Schlenk, J.L. Gellerman, J.A. Tillotson and H.K. Mangold, J. Amer. Oil Chem. Soc., 1957, 34, 377.

260. Y. Suzuki, T. Maki and K. Mineta, Japan Kokai 7596530; Chem. Abs., 1975, 83, 205898.

261. E. Akito, Y. Nakajima and M. Horika, Japan Kokai 75129520; Chem. Abs., 1976, 84, 58617.

262. Y. Suzuki, H. Iwasaki and F. Kamimoto, Japan Kokai 7589306; Chem. Abs., 1976, 84, 16737.

263. A. Mifune, Y. Katsuda and T. Yoneda, Ger. Offen 2357826, 1974; Chem. Abs., 1975, 82, 39586.

264. H. Schlenk, D.M. Sand and J.A. Tillotson, U.S. 2827452, 1958; Chem. Abs., 1958, 52, 12901.

265. S.M. Parmertier and E.E. Allen, U.S. 3553191, 1971; Chem Abs., 1971, 74, 88879.

266. Y. Matsui, H. Naruse, K. Mochida and Y. Date, Bull. Chem. Soc. Japan, 1970, 43, 1909, 1910.

267./

267. T. Oguma, Y. Saito and T. Kobayashi, Japan Kokai 75142790; Chem. Abs., 1976, 84, 117800.

268. J. Szejtli and E. Banky-Elod, Staerke, 1975, 27, 386; Chem. Abs., 1976, 84, 32918.

269. T. Nagai and Y. Murata, Japan Kokai 7375526; Chem. Abs., 1974, 80, 71050.

270. T. Nagai, Japan Kokai 75116617; Chem. Abs., 1976, 84, 111654.

271. H. Trommsdorff, Fr. Demande 2209582, 1974; Chem. Abs., 1975, 82, 144957.

272. M. Hayashi and I. Takatsuki, Ger. Offen. 2128674, 1971; Chem. Abs., 1972, 76, 59978.

273. S. Ohno, Japan Kokai 75160416; Chem. Abs., 1976, 84, 126774.

274. S. Umezawa and K. Tatsuta, Bull. Chem. Soc. Japan, 1968, 41, 464.

275. H. Kurita, M. Kawazu and K. Takashima, Japan Kokai 75140476; Chem. Abs., 1976, 84, 136002.

276. M.S. Newman and H.A. Karnes, J. Org. Chem., 1966, 31, 3980.

277. A.D.U. Hardy, D.D. MacNicol, J.J. McKendrick and D.R. Wilson, Tetrahedron Letters, 1975, 4711.

278. M.R. Crampton in "The Chemistry of the Thiol Group", ed. S. Patai, 1974, part 1, ch.8.

279./

279. L.C. Fetterley in "Non-Stoichiometric Compounds ed. L. Mandelcorn, Academic Press, 1964, p.503.

280. R.A. Scherrer and H.R. Beatty, J. Org. Chem., 1972, 37, 1681.

281. A.D.U. Hardy, D.D. MacNicol and D.R. Wilson, J.C.S. Chem. Comm., 1974, 783.

282. D.S. Connor and E.R. Wilson, Tetrahedron Letters, 1967, 4925.

283. K.B. Wiberg and D.S. Connor, J. Amer. Chem. Soc., 1966, 88, 4437.

284. J. Alexander and G.S.K. Rao, J. Chem. Ed., 1970, 47, 277.

285. J.A. Barnard, A.J. Cocks and R. K-Y. Lee, J.C.S. Faraday I, 1974, 1782.

286. H. Stone and H. Shechter, Org. Synth., 1963, 4, 543.

287. S. Brøozowski, Rocz. Chem., 1973, 47, 831.

288. D.D. MacNicol and D.R. Wilson, J.C.S. Chem. Comm., 1976, 494.

289. F. Vögtle and E. Weber, Angew. Chem. Int. Ed., 1974, 13, 814.

290. P. Marsau, Acta Cryst., 1965, 18, 851.

291./

291. R. Adams, W. Reifschneider and M.D. Mair Croatica Chem. Acta, 1957, 29, 277; R. Adams and A. Ferretti, J. Amer. Chem. Soc., 1959, 81, 4297.

292. H.J. Backer, Rec. Trav. chim., 1935, 54, 745.

293. ibid., p.837.

294. ibid., p.905.

295. D.L. Klayman and T.S. Griffin, J. Amer. Chem. Soc., 1973, 95, 197.

296. R.C. Huston, W.B. Fox and M.N. Binder, J. Org. Chem., 1938, 3, 251.

297. C.S. Marvel, M.B. Mueller, C.M. Himil and J.F. Kaplan, J. Amer. Chem. Soc., 1939, 61, 2773.

298. c.f. D.G. Foster, Org. Syn., 1955, 3, 771.

299. H.J. Backer and J.B.G. Hurenkamp, Rec. Trav. chim., 1942, 61, 802.

300. H. Stetter, M. Schwarz and A. Hirschhorn, Chem. Ber., 1959, 92, 1629.

301. K. Okamoto, K. Matsubara and T. Kinoshita, Bull. Chem. Soc. Japan, 1972, 45, 1191.

302. G.R. Wilson and A.G. Smith, J. Org. Chem., 1961, 26, 557.

"On from room to room I stray
Yet mine Host can ne'er espy
And I know not to this day
Whether guest or captive I."

Sir William Watson (1856 - 1936)

World - Strangeness