CONCAVE HYDROCARBON CYCLOPHANE
π-PRISMANDS

Tanja Lahtinen
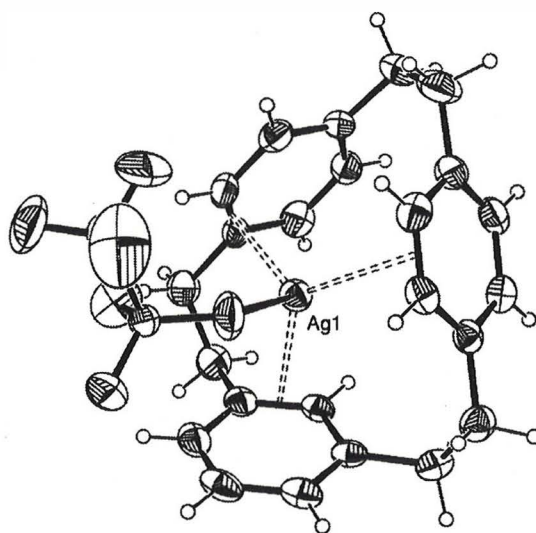
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By

TANJA LAHTINEN

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To Jarmo

LIST OF ORIGINAL PUBLICATIONS

This is based on the following original publications, which are referred to in the text by their Roman numerals.

I   T. Seppälä, E. Wegelius and K. Rissanen, [2.2.2]*m,p,p*- and [2.2.2]*m,m,p*-Cyclophane-Ag-triflate: New π-Prismand Complexes, *New J. Chem.*, **22** (1998) 789.
https://doi.org/10.1039/A803490G

II   T. Lahtinen, E. Wegelius, K. Airola, E. Kolehmainen and K. Rissanen, Concave π-Prismand Hydrocarbon [2.2.2]Cyclophanes and their Crystalline Ag-triflate Complexes, *J. Prakt. Chem.*, **3** (1999) 237.
https://doi.org/10.1002/(SICI)1521-3897(199904)341:3<237::AID-PRAC237>3.0.CO;2-F

III   T. Lahtinen, E. Wegelius and K. Rissanen, Synthesis and X-ray Structures of New Concave π-Prismand Hydrocarbon [2.2.1]*m,p,p*- and [2.2.1]*p,p,p*-Cyclophanes, *New J. Chem.*, **25** (2001) 905.
https://doi.org/10.1039/B102725P

IV   T. Lahtinen, E. Wegelius, J. Linnanto and K. Rissanen, Small Hydrocarbon Cyclophanes: Synthesis, X-ray Analysis and Molecular Modelling, *Eur. J. Org. Chem.*, (2002) 2935.
https://doi.org/10.1002/1099-0690(200209)2002:17<2935::AID-EJOC2935>3.0.CO;2-Y

V   J. Bobacka, T. Lahtinen, J. Nordman, S. Häggström, K. Rissanen, A. Lewenstam and A. Ivaska, All-Solid-State Ag+-ISE Based on [2.2.2]*p,p,p*-Cyclo*p*hane, Electroanalysis, 13 (2001) 723.
https://doi.org/10.1002/1521-4109(200105)13:8/9<723::AID-ELAN723>3.0.CO;2-R

VI   J. Bobacka, T. Lahtinen, H. Koskinen, K. Rissanen, A. Lewenstam and A. Ivaska, Silver Ion-Selective Electrodes Based On π-Coordinatong Ionophores Without Heteroatoms, *Electroanalysis*, **14** (2002) 1353.
https://doi.org/10.1002/1521-4109(200211)14:19/20<1353::AID-ELAN1353>3.0.CO;2-O

PREFACE

This work was carried out at the Department of Chemistry, University of Jyväskylä from autumn 1997 to 2002.

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Jyväskylä, May 2003

Tanja Lahtinen

ABSTRACT

Small hydrocarbon cyclophanes, *viz.* [2.2.2]-, [2.2.1] and [2.2.0]cyclophanes, were designed and synthesised as possible hosts for silver cation complexation in order to study how small and strained hydrocarbon cyclophane can be and still act as π-prismand. In the present study sulphone pyrolysis was selected as a synthetic route and thiols and dibromides were chosen as starting materials for the high dilution synthesis. Four new π-prismands were found.

X-ray crystallography was used to verify and to study the cyclophane structures. Some of the structures are the precursors of the synthesised π-prismands, so it was possible to follow the conformational changes in those structures along the synthesis route.

ISE measurements were used to study the utilization of cyclophanes as selective binding receptors. All-solid-state ion-selective electrodes (ISEs) were constructed by using cyclophanes as π-coordinating ionophores in solvent polymeric membranes. Four structurally similar cyclophanes, *i.e.* [2.2.2]*p,p,p*-cyclophane (**2**), [2.2.2]*m,p,p*-cyclophane (**47**), [2.2.1]*p,p,p*-cyclophane (**49**) and [2.2.1]*m,p,p*-cyclophane (**48**) were studied as ionophores for Ag^+. The selectivity pattern of the solid-contact ISEs was found to depend strongly on the structure of the cyclophane. The *p,p,p*-cyclophanes are more selective to Ag^+ than the corresponding *m,p,p*-cyclophanes where one phenyl ring is coupled in the *meta* position.

As an introduction a short review of the literature on the cyclophanes, and especially π-prismand cyclophanes, are presented from a supramolecular point of view and their behaviour as cation receptors is discussed.

CONTENTS

ABBREVIATIONS

	Decacyclo[13.13.2 $^{1.15}$.2 $^{8.22}$.2 $^{3.27}$.1 $^{6.10}$.1 $^{13.17}$.1 $^{20.24}$]-Hexatriaconta-1,3(57),6,8,12,14,16(58),19,21,23(59), 26,28,30(60),33,-35,39,43,45,49,53,55-heneicosaene
ISE	ion-selective electrode
IR	infrared
KOH	potassium hydroxide
m	meta
M	molar
NMR	nuclear magnetic resonance
p	para
PVC	polyvinyl chloride
Å	Ångström, 10^{-10} m
KTpClPB	potassium tetrakis(4-chlorophenyl)borate
o-NPOE	2-nitrophenyl octyl ether

1 REVIEW OF THE LITERATURE

Cyclophanes, bridged aromatic compounds, exhibit many interesting physical and chemical properties.[1,2] They possess unusual structures, unique synthetic challenges and undergo interesting conformational processes.[3] Cyclophanes have been known since 1899 when Pellegren synthesised the first cyclophane [2.2]*meta*cyclophane (1) by the Wurtz coupling reaction, but the actual emerge of cyclophanes dates from the 1950s.[3,4]

Cyclophanes represent the central class of synthetic receptors (hosts) in molecular recognition. All types of substrates (guests), from inorganic and organic cations and anions to neutral molecules, have been complexed by tailor-made cyclophanes. In these complexation processes, all known modes of intermolecular binding interactions have been used. A majority of the crown ethers[5-8] and cryptands[9-11] and all of the spherands[12,13] and cavitands[14-18] for cation complexation are cyclophanes. For example dibenzo-18-crown-6 is also known as hexaoxa[7.7]orthocyclophane and calixarenes[19-27] as metacyclophanes.[28]

Hydrocarbon cyclophanes play a significant role in supramolecular chemistry which is the fastest developing area in chemistry today.[29] Several definitions of supramolecular chemistry exist including "the chemistry of noncovalent bond" or "nonmolecular chemistry" but a more colloquial definition would be chemistry beyond the molecule".[30-32] Supramolecular chemistry is based on weak interactions, the electrostatic forces other than those of full covalent bonds that holds together supramolecular complexes.[32-33] Those forces are considered as hydrogen bonding, ion pairing, metal-to-ligand attractions, π-acid to π-base interaction and van der Waals

attractions.[34,35] These are the same interactions which control recognition in biological processes.[36,37]

In general supramolecular chemistry studies the binding of one molecule to an another, that is, host-guest chemistry.[38-40] Commonly the host is a large molecule or aggregate such as an enzyme or synthetic cyclic compound possessing a sizeable, central hole or cavity. The guest may be a monoatomic cation, a simple inorganic anion, or a more sophistigated molecule such as a hormone, pheromone or neurotransmitter.[32]

1.1 CYCLOPHANE π-PRISMAND HOSTS

In biological systems enzymes are typical host molecules and substrates are perfect guests and their selectivities go far beyond the present capacity of artificial molecules.[41] These complexes are somewhat different from those formed between simple molecules or ions. The whole or at least a considerable part of the substrate molecule is accomodated within the enzyme cavity, so that a large area of the substrate surface is in contact with the enzyme through the multiple binding sites that are appropriately located and oriented. As a result, the substrate is strongly bound and fixed tightly in the active site in enzyme. Such a complex is possible only if the complexing molecules possess multiple and convergent binding sites that are well located and oriented in a well-defined structure.[39,42]

The basic idea behind synthesising host molecules like cyclophanes was to create artificial molecules that could imitate biological systems, such as enzymes, antibodies or receptors, which could then be used to advantage in pharmaceutical chemistry.[43-45]

Like enzymes cyclophanes can bind other molecules or metals by using non-covalent interactions like hydrogen bonds or the cation-π interaction.[46-51]

The majority of synthesised cyclophane hosts can be divided into two basic classes: hydrocarbon cyclophanes[29,52-55] ,and cyclophanes that contain heteroatoms.[56-63]

1.1.1 Hydrocarbon cyclophane π-prismands

Hydrocarbon cyclophanes are cyclic bridged aromatic compounds which are built up solely from carbon and hydrogen.

Most π-prismands are hydrocarbon cyclophanes. The name π-prismand was first introduced by Pierre *et al.*[64] for the silver complex of [2.2.2]*p,p,p*-cyclophane (**3**) (figure 1). π-Prismands are molecules that possess an eccentric structure, such as spatial shape and cryptation, involving π-sites where the aromatic subunit serves as a π donor.
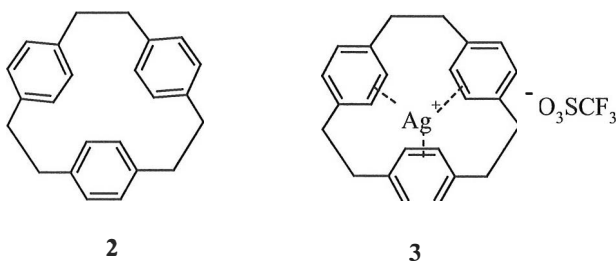

2   **3**

Figure 1 [2.2.2]*p,p,p*-Cyclophane (**2**) and [2.2.2]*p,p,p*-cyclophane-Ag$^+$-complex (**3**).[64]

Another interesting π-prismand was synthesised by Boekelheide *et al.*[65] They studied gas-phase dimerisation[66] of benzocyclobutenes in a stream of nitrogen and found that increasing the concentration of benzo[1,2:4,5]dicyclobutene in the hot zone of the

pyrolysis tube produced [2₆](1,2,4,5)cyclophane (**4**) (deltaphane) (figure 2). The structure and geometry of deltaphane (**4**) was determined by single crystal X-ray analysis and it showed the molecule framework to be rigid and highly symmetrical. The carbon atoms in **4** lie essentially in three planes mutually inclined at 120°. The rigid geometry of deltaphane with its internal cavity circumscribed by three benzene rings seemed ideal for metal ion complexation of the π-prismand type. Although deltaphane (**4**) is essentially insoluble in tetrahydrofuran, it rapidly dissolves in tetrahydrofuran containing silver triflate forming silver triflate complex (**5**) .[65]
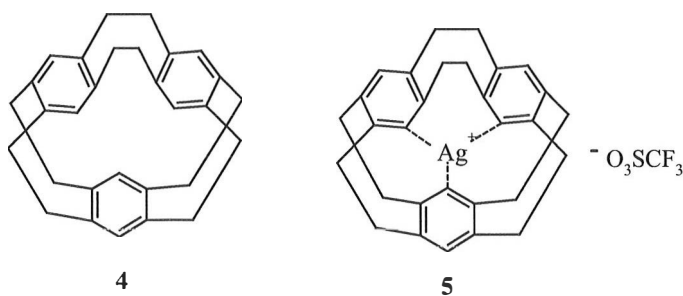

4   **5**

Figure 2 Deltaphane (**4**) and deltaphane-Ag⁺-complex (**5**).[65]

There are a number of methods of synthesising hydrocarbon cyclophanes[29], but it is evident that symmetrical hydrocarbon cyclophanes are more commonly synthesised than unsymmetrical ones, presumably due to the greater convenience of synthetic methods such as Wurtz coupling.[4] Sulphone pyrolysis counts the most important reaction for the synthesis of unsymmetrical hydrocarbon cyclophanes.

1.1.1.1 Wurtz coupling

Wurtz coupling has often been applied to obtain small cyclophane rings.[4,67,68] Basically it is the interaction of two alkyl or benzylic halides and sodium metal to give a symmetrical product (Figure 3).[4,69] However, the original Wurtz coupling of two benzylic halides is no longer considered practical due its low yield and number of side reactions and is thus seldomly used nowadays.
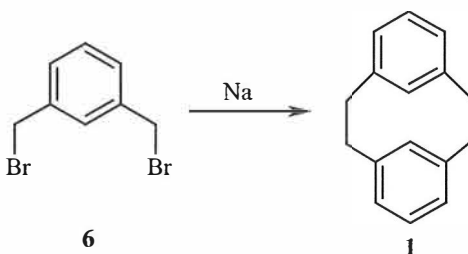

Figure 3 Example of Wurtz coupling reaction.[29]

The original Wurtz reaction method has been improved many times.[29] In 1957 Müller and Röscheisen[70] improved the Wurtz reaction since the side reactions, i.e. elimination and rearrangement and very low yields, were so common in original Wurtz coupling reaction. The low yields obtained from the original Wurtz reactions are mainly explained by fact that the reaction proceeds partly in the heterogeneous phase. Müller and Röscheisen modified the procedure by adding tetraphenylethylene to permit a homogenous reaction. On addition of tetraphenylethylene, the sodium is dissolved in the form of a dark-red disodium compound and the reaction can now take place in the homogeneous phase. When a vibration mixer is used, catalytic quantities of

tetraphenylethylene are sufficient.[71] As a result the convenient and reliable method of synthesising cyclophanes with better yields was achieved.[72-75]

The first π-prismand, [2.2.2]*p,p,p*-cyclophane (**2**), was synthesised by using a modified Wurtz reaction from 1,4-bis(bromomethyl)benzene (**7**) (Figure 4).[64,76]
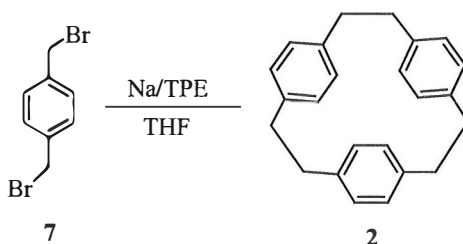

Figure 4 Example of modified Wurtz reaction.[64]
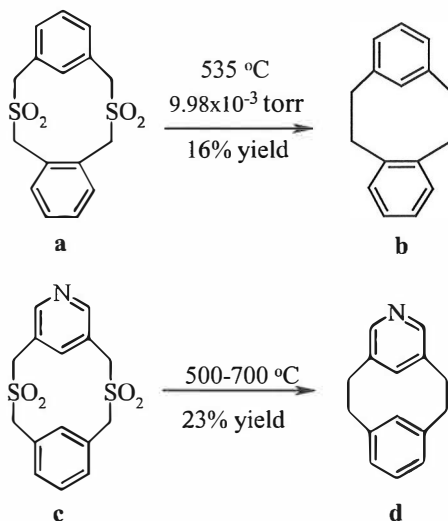
1.1.1.2 Sulphone pyrolysis

As an alternative to the Wurtz coupling-type direct cyclization, cyclization can be generated by first synthesising a large sulphur-containing ring. This sulphide precursor can be oxidized to sulphone and the sulphone groups can be eliminated by pyrolysis. This procedure counts among the most important reactions in cyclophane chemistry.[77-79]

It offers access to a large diversity of macrocycles, highly strained macrocycles as well as macrocycles containing labile moieties or functional groups. Several bonds can be created simultaneously and yields are comparably high (figure 5).[80-86]

In the process of sulphone pyrolysis sublimation of the starting material is important for elimination to take place in the gas phase. Therefore conditions have to be chosen so that complete sublimation takes place at first and the reaction time in the hot region of

the oven remains short. The temperature for sublimation is much lower than the temperature for pyrolysis.[77]

Figure 5 Example of pyrolysed molecules hydrocarbon (**b**) and heterophane (**d**).[77]

In the study of the sulphone pyrolysis mechanism Vögtle and Rossa[87] note two possible radical mechanisms for thermal cyclization of disulphone (figure 6). Both of the SO_2 molecules can be eliminated in a single step (one-step mechanism) or the process can occur stepwise (two-step mechanism). In the stepwise process one SO_2 molecule is eliminated and after that two $R^•$ radicals recombine to form a C-C bond before the second SO_2 molecule is eliminated. However the intermediate, which contains only one SO_2 molecule, cannot be isolated.[88,89]
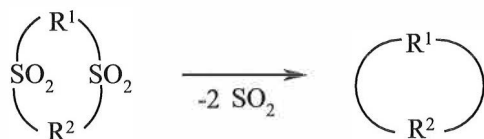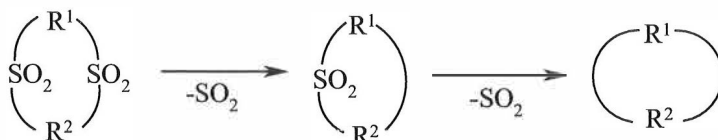
one-step mechanism:

two-step mechanism:

Figure 6 Pyrolysis of a disulphone.[87]

Staab *et al.*[90] studied the influence of the temperature on the yield of the reaction. They varied the temperature of pyrolysis in 20°C steps over the range 500-580°C. Yield varied between 28% and 86%, which is surprising in view of the small variation in temperature. The optimum yield was achieved at 560°C.

1.1.2 Heteraphane π-prismand

The cyclophane nomenclature system is independent of the complicated IUPAC rules. It was introduced by Cram[91] and subsequently systematized by Schubert[92], later further systematized and extended by Smith[29,93] and thereafter by Vögtle and Neumann.[94,95] According to the cyclophane nomenclature system phanes can be subdivided into cyclophanes (more precisely, benzenophanes), heterophanes[96-100] and heteraphanes.[100-103] Heterophanes contain hetero atoms in the aromatic ring, while in heteraphanes these are in the bridge (figure 7).[29]
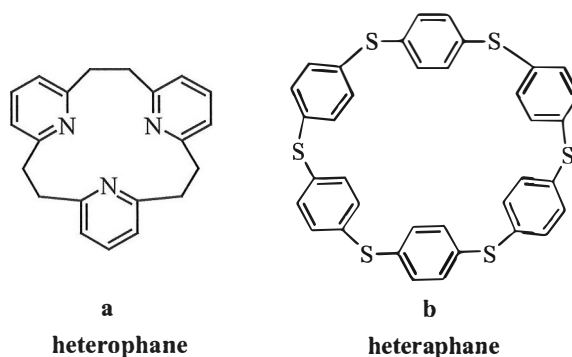
a
heterophane

b
heteraphane

Figure 7 Example of heterophane (**a**) and heteraphane (**b**).[29]

Gleiter *et al.*[104-108] have synthesised a number of bicyclic compounds with nitrogen at both bridgehead positions, in which triple bonds are incorporated in the middle of the alkane chains (figure 8).
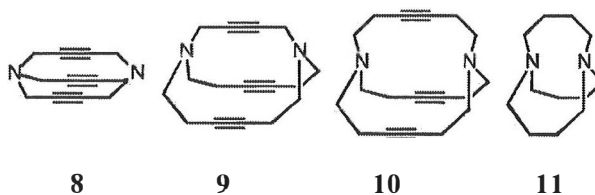

8   **9**   **10**   **11**

Figure 8 Molecules **8**, **9**,**10** and **11**.[108]

The triple bonds have two functions: They expand the cage of the corresponding diazabicycloalkane along the N⋯N axis and they act as additional soft donors, forming a "π-belt" around the cavity. In case of **10** the intrabridgehead distance allows not only double *in, in*-protonation but also strong complexation of copper(I) and silver(I) in the center of the molecule.[107]

In addition to alkyne units they also took into consideration 1,4-substituted benzene rings as linear and rigid spacer groups and compared those to the triyne **10**. The introduction of benzene rings causes a further elongation of the cage while the soft coordination sites are maintained. The synthesis of the bicyclophanes **12-14** were prepared by one-pot synthesis *viz.* three-component condensation of the appropriate terminal diamines and dibromides (figure 9).[108]
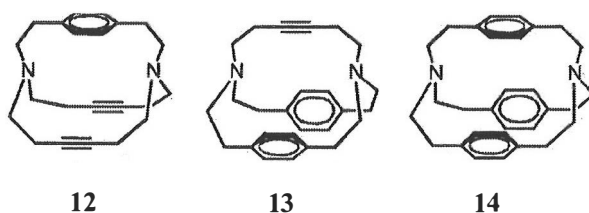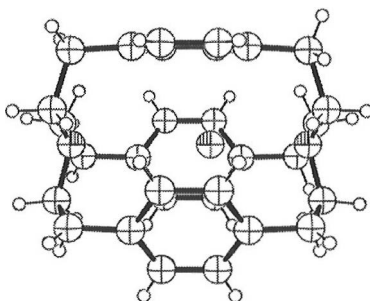

Figure 9 Molecules **12**, **13** and **14**.[108]

To test the ability to complex a soft metal ion they produced a 1:1 complex of **14** with silver triflate which was the first nitrogen-capped π-prismand complex (**15**) (figure 10).[108]

15

Figure 10 Nitrogen-capped π-prismand **15** (triflate anion excluded and only one site of the disordered Ag$^+$ ion is shown).[108]

The spatial arrangement of the benzene rings in bicyclophane **14** is closely related to the [2.2.2]*p,p,p*-cyclophane (**2**) and deltaphane (**4**). Both compounds **2** and **4** form silver complexes in which the metal ion lies exterior to the cyclophane moiety and undergoes rapid exchange in solution. In the case of **15**, X-ray single crystal analysis showed that the two nitrogen bridgeheads cap the cavity and force the silver ion to stay near the center of the cage disordered over two equivalent positions.[108]

1.1.3 Complexation in hydrocarbon cyclophane π-prismand

Cyclophanes are characterized by their aromatic ring or rings, which may in principle act as rigid structural units, as hydrophobic and/or van der Waals binding sites and as π-donors or acceptors. These aromatic rings confer on the inclusion cavities well-defined structure and sufficient depth.[109]

Hydrocarbon cyclophanes have one main binding site which consists of an aromatic ring or rings. Another factor that greatly influences complexation is the steric fit, which can be specified as the size of the ring or size of the cavity.

1.1.3.1 Steric fit

As a result of ligand preorganization, most macrocyclic ligands exhibit significant selectivity toward certain metal ions based on the size. When the radius of the metal ion matches the radius of the ligand cavity, the complex is usually more stable than the complexes of other metal ions of equal charge. One obvious reason for size-matching selectivity is that when the size of the ligand cavity and the size of the metal ion match, the metal ion can be positioned in the center of the ligand cavity and in the ligand plane with optimal metal ion-donor atom distances. This environment should allow optimal ligand-metal ion interaction and will result in maximal complex stability.[110]

However, a macrocyclic ligand may adopt a completely different conformation after complexation. Different conformations may have different cavity sizes. Therefore, predicting selectivity on the basis of the size of the cavity before complexation may be misleading. It is important to remember that the dimensions of the cavity of a macrocyclic ligand are not always well defined or easily estimated, especially when the ligand is rather flexible. A flexible ligand may have a large number of possible conformations during the complexation and may adopt a very different conformations than in the free state. A flexible ligand may also compress or expand its cavity dimensions to accommodate different metal ions. A flexible ligand usually displays less size selectivity toward metal ions. However, when the macrocyclic ligand is rather rigid,

size selectivity and size-matching effects are more dominat. For example, cryptands, that are more rigid than their corresponding monocyclic macrocycles, display a much greater size selectivity (figure 11).[29,110]
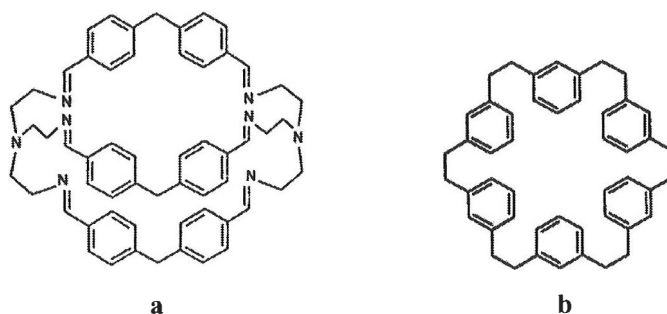

a   b

Figure 11 Example of cryptand (**a**) and monocyclic cyclophane (**b**).[10,29]

In cyclophanes aromatic structural units ensure the necessary rigidity of the molecular structure and thereby improve the preorganization of coordination sites for cooperative binding of the guest.[64,65]

1.1.3.2 π-Cation interaction between silver(I) and aromatic ring

The existence of donor-acceptor complexes between aromatic moieties and silver(I)cation has been known since beginning of the 20th century. In 1938 Winsten and Lucas[111] defined the bond between Ag^+ and the aromatic ring to be a resonance of three forms, *viz.* a hybrid structure (figure 12).
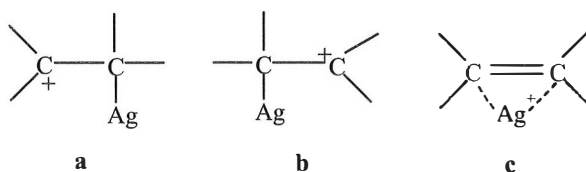
Figure 12 The three resonance forms (**a**, **b** and **c**) of a hybrid structure.[111]

Andreews and Keefer[112] studied the solubilities of several aromatic hydrocarbon in aqueous silver nitrate solutions. The solubility of the several hydrocarbons in aqueous solutions increased along with the increase in silver ion concentration to a greater degree than was consistent with the supposition that only a 1:1, $AgAr^+$, was formed. Both Andreews and Keefer[112], and Winsten and Lucas[111] ended up the same conclusion for the complex structure formed by benzene and a silver ion. The silver ion is located above the plane of the ring at a position equidistant from the six ring carbon atoms. Therefore the silver ion would be in a position to utilize the π-electrons of the ring to form covalent bonds with any of the six ring carbons.[111,112]

A few years later Mulliken[113] and Dewar[114] presented their interpretations of the structure of complex. The main idea in both theories was that Ag^+ is located on one side from the benzene ring toward the region between but somewhat above two carbon atoms of the ring. This was further systematized by Taylor *et al.*[115] and Amma *et al.*[116], who come to the conclusion that if the silver ion behaves as an electron acceptor from the aromatic, utilizing a 5s, 5p or some hybrid orbital thereof, the best position for the metal ion is in the π-cloud above one of the carbon atoms of the ring. On the other hand not only the electron transfer from the π-system to the metal is important but also the metal to aromatic back-donation is important, then the best overlap between the filled

metal d orbitals and the antibonding π^* molecular orbital of the π-system is achieved with the metal located in the π-cloud equidistant between two carbon atoms of the ring.[113-116] In most cases a compromise is reached in the complexation.

Cyclic aromatic hydrocarbons can complex with small metal cations to form π-complexes. Complexation of this type is especially effective for molecules that possess suitably sized π-electron-rich cavities, such as π-prismands [2.2.2]p,p,p-cyclophane (**2**) and [2_6](1,2,4,5)cyclophane (**4**) (deltaphane) and related structures.[64,65,117] The single crystal X-ray structure analysis showed that in the [2.2.2]p,p,p-cyclophane-Ag$^+$ triflate complex (**3**) the silver ion is not located inside the cyclophane cavity (formed by the three benzene rings) but lies at an average distance of 2.59 Å from the six nearest aromatic carbon atoms and about 2.49 Å from the centres of the nearest ring double bonds. The silver atom is external by 0.23 Å from the mean plane of these bonds. In the deltaphane-Ag$^+$ triflate complex (**5**) the single crystal X-ray structure analysis showed that the silver atom lies an avarage distance of 2.43 Å from the three nearest carbon atoms, and 0.23 Å from the plane of these atoms on the external side away from the center of the cyclophane moiety. The silver triflate complexes **3** and **5**, have the common structural feature that the silver ion is external to the cyclophane moiety and is not present in the π-prismand cavity (figure 13).[65]
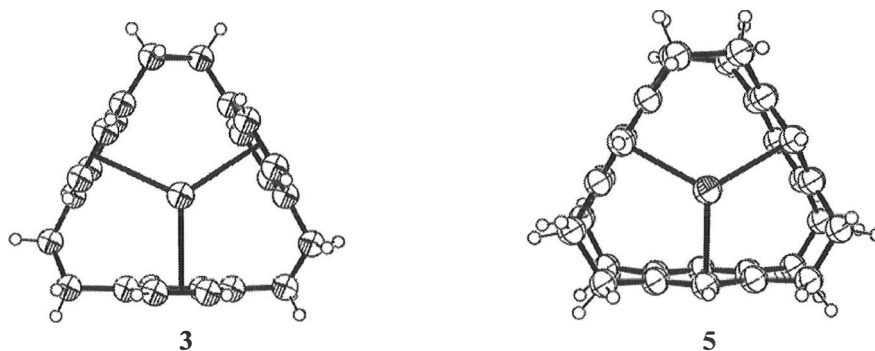
3   **5**

Figure 13 The X- ray structures of [2.2.2]*p,p,p*-cyclophane-Ag$^+$-(**3**) and deltaphane-Ag$^+$-complex (**5**) (anions excluded).[65,118]

In the endohedral complexes of [2.2.2]*p,p,p*-cyclophane (**2**), the exact location of metal atom in relation to the π-prismand cavity depends on its coordination number and the size of the cation, for example silver(I) coordinates $3\times\eta^2$ and is symmetrically bound 0.23-0.24 Å outside of cavity, while the gallium(I), tin(II) and germanium(II) complex in the $3\times\eta^6$ mode, well within the cavity.[64,65,117-122]

[2.2.2]*p,p,p*-Cyclophane (**2**) not only forms endohedral complexes with soft metals, but can also form exohedral complexes of varying metal-ligand stoichiometry with chromium(0), arsenic(III), antimony(III) and bismuth(III).[117,121,123]

2 EXPERIMENTAL

2.1 AIM OF THE STUDY

Cyclophanes play a significant role in supramolecular chemistry and the research for new cyclophane ligands continues intensively. The concept of the cyclophane is broad and many other macromolecules like calixarenes,[19-27] cavitands[14-18] and benzo crown ethers[5-8] can be included in this category. In supramolecular chemistry the binding in complexes is based on weak interactions *e.g.* hydrogen bonding, van der Waals forces, π-π stacking, cation-π interaction, hydrofobic effects *etc.*[33-35] It is therefore very important to know how these interactive forces function and what kind of effect they have on each other.

The aim of this study was to prepare small and strained hydrocarbon cyclophanes and to study how small and strained molecule can be and still act as π-prismand. Pyrolysis was used to synthesise the hydrocarbon cyclophanes and X-ray crystallography to study the structure and complexation. ISE measurements were performed to study whether the hydrocarbon cyclophane molecules could be used as selective materials (*e.g.* electrodes, extracting agents, *etc.*).

2.2 SYNTHESIS [I-IV]

Sulphone pyrolysis was selected as the synthetic route. It is a very convenient method for synthesising unsymmetrical cyclophanes and yields are relatively high.

2.2.1 Disulphides [I-IV]

High dilution cyclization is generally used in cyclophane chemistry. The preparation of cyclic sulphides is one of the most commonly studied cyclization reactions and the most commonly used reaction is between a bromide electrophile and sulphur nucleophile (thiol, thiourea, sodiumsulphide or thioacetamide) (Scheme 1).[77,78]
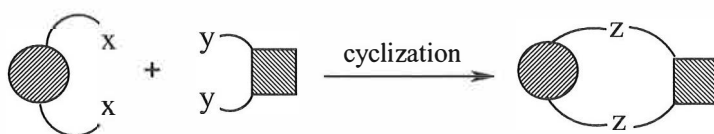
Scheme 1 Schematic picture of cyclization.[77]

It is known both theoretically and experimentally that low concentrations favour the formation of cyclic products and one of the breakthroughs in high dilution technique was that it is not necessary to use a large amount of solvent if the rate of addition is kept low.[78,124-127] In theory, the purely statistical Monte Carlo method states that the amount of cyclic products increase with the increase of dilution and best result is achieved by using equivalent amounts of reagents.[78,128-130]

Special apparatus has been developed to achieve low concentrations and low rates of addition in high dilution synthesis (scheme 2). The cooler has special dilution components in which the reagents are first diluted by continuously refluxing solvent before entering to the reaction flask.
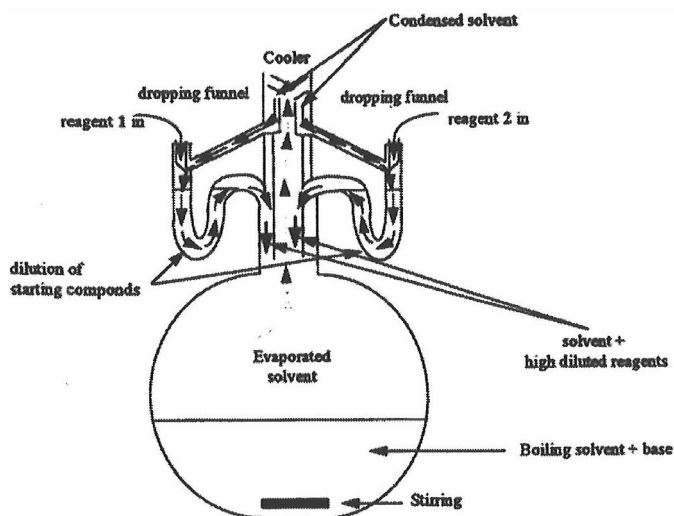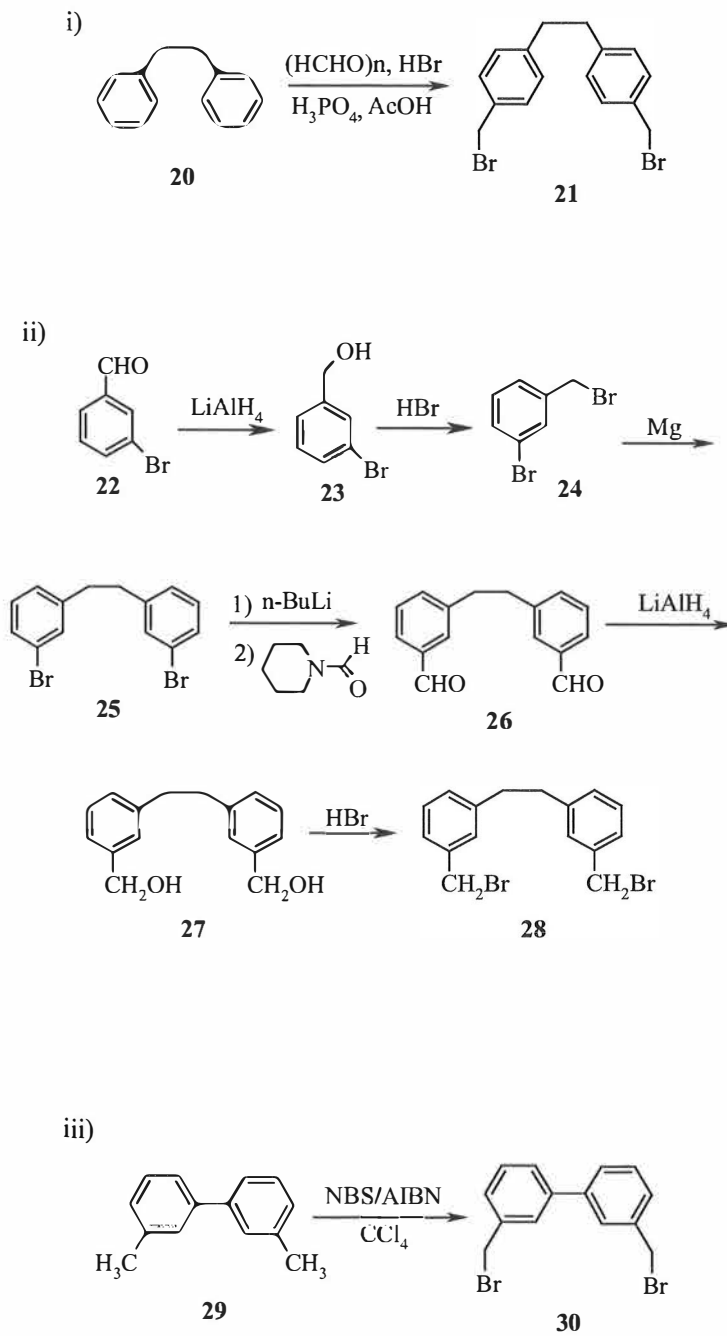
Scheme 2 Schematic picture of high dilution apparatus.[124]

In this study the macrocycles were synthesised using high dilution method. The starting materials for cyclization were synthesisied by well-known synthetic methods (Scheme 3a and 3b).[131,132]

Thiols:[131]
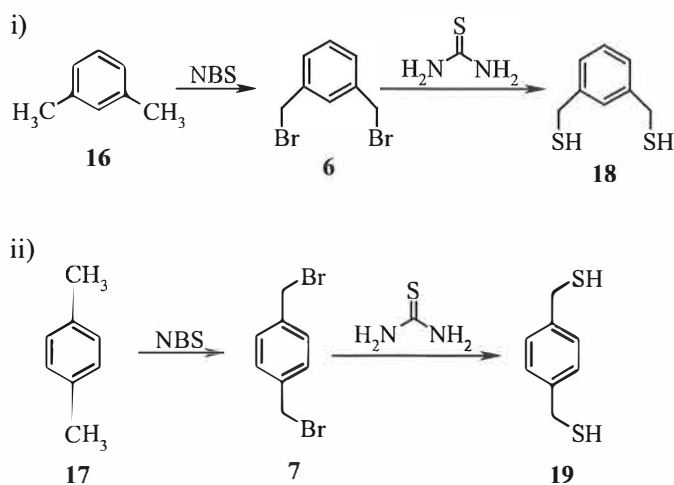
*Scheme 3a* Scheme for synthesis of starting materials.[131]

Dibromides:[131,132]

i)

20 → (HCHO)n, HBr / H₃PO₄, AcOH → **21**

ii)

22 → LiAlH₄ → **23** → HBr → **24** → Mg →

25 → 1) n-BuLi 2) → **26** → LiAlH₄ →

27 → HBr → **28**

iii)

29 → NBS/AIBN / CCl₄ → **30**

Scheme 3b Scheme for synthesis of starting materials.[131,132]

In this study[I-IV] cyclization takes place in toluene in the presence of a base (potassium hydroxide), which is dissolved in abs. ethanol and thiols are used as nucleophiles. Usually in the high dilution method the starting materials are added simultaneously from separate dropping funnels into the boiling solvent which contains the base. In this way adjustment of the dropping rate is difficult.

In this study standard cyclization method was modified. Both starting materials were dissolved in toluene and placed in the same dropping funnel. The base (KOH dissolved in abs. ethanol) was placed in the other dropping funnel. The starting materials and base were simultaneously added to the boiling solvent (toluene). In this way equivalent amounts of starting materials in each drop were ensured. After adding all the reagents, the resulting reaction mixtures were refluxed for 1 to 3 hours (Scheme 4a, 4b and 4c).
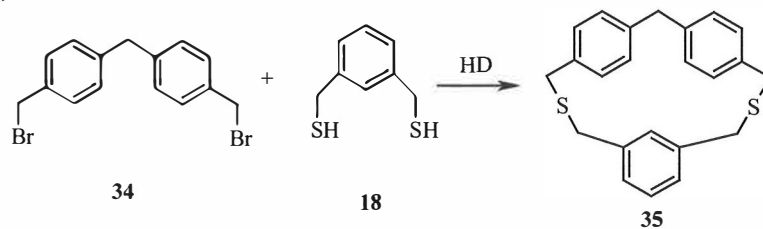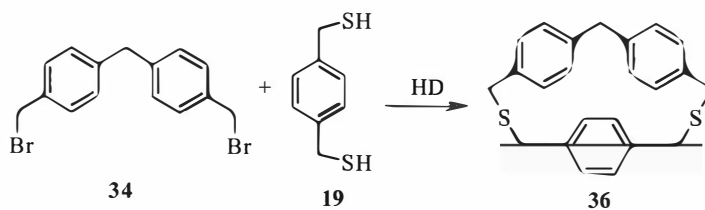
1,10-Dithia[3.3.2]cyclophanes: [I-II]

i)

28 + **18** —HD→ **31**

ii)

28 + **19** —HD→ **32**

iii)

21 + **18** —HD→ **33**
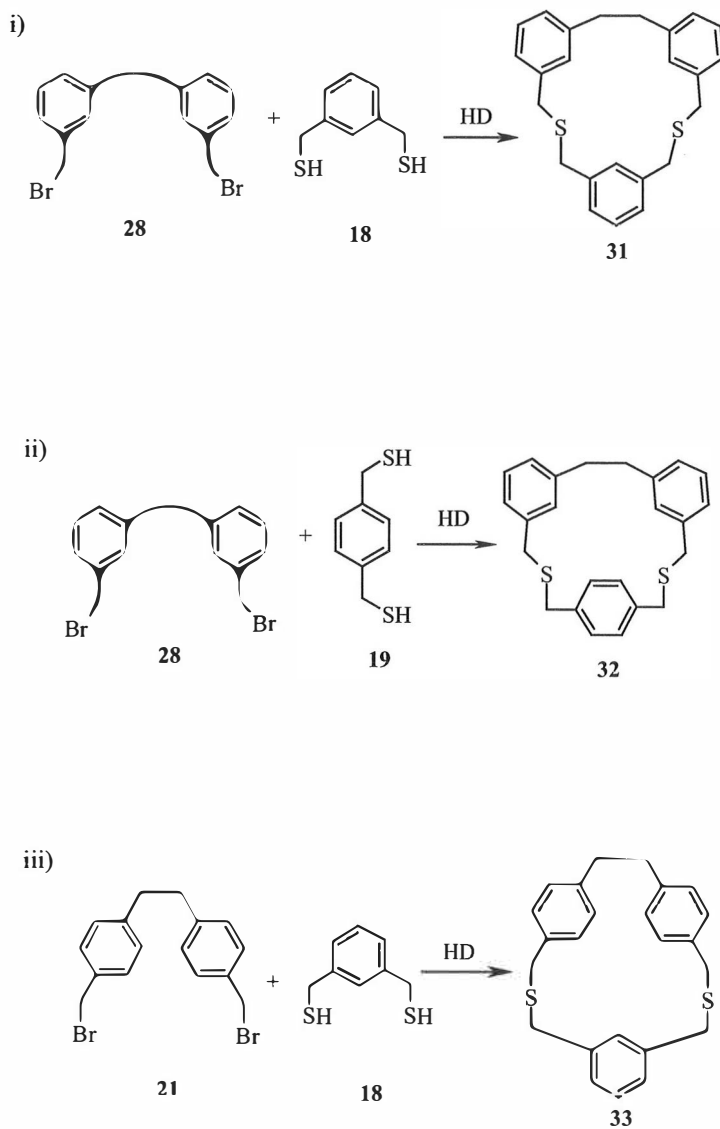
Scheme 4a Scheme for synthesis of disulphides.[I-II]

1,10-Dithia[3.3.1]cyclophanes: [III]

i)

34   **18**   **35**

ii)

34   **19**   **36**

Scheme 4b Scheme for synthesis of disulphides.[III]

1,10-Dithia[3.3.0]cyclophanes: [IV,133,134]

i)

3   **1**   **37**

ii)

30   **19**   **38**
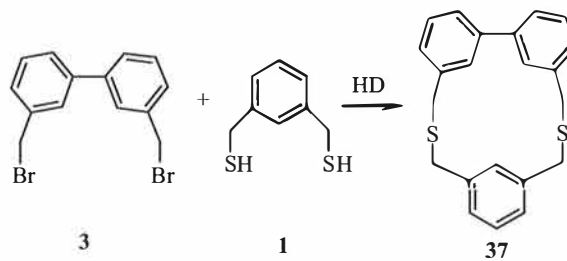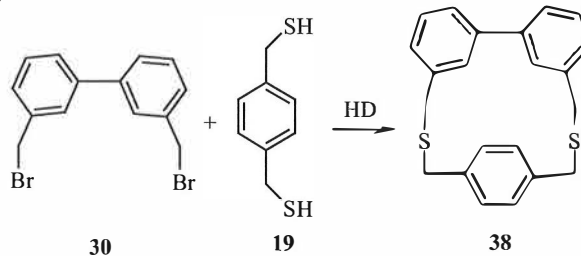
Scheme 4c Scheme for synthesis of disulphides.[IV,133,134]

In high dilution synthesis the product always contains a small amount of polymer. In the present study it was removed by filtration through silicagel using chloroform as a solvent. After evaporation the compounds were purified by recrystallisation.
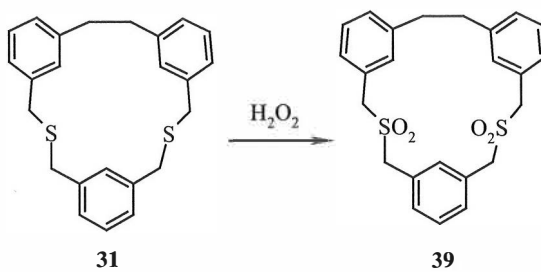
2.2.2 Disulphones [I-IV]

There are two possible ways to convert the sulphur-containing ring into the desired hydrocarbon cyclophane, *viz.* direct extraction of sulphur by photolysis or the two-step reaction in which sulphides are first oxidized to the sulphones after which the sulphone groups are eliminated by pyrolysis.[77,135]

In the present study[I-IV] two-step reaction was used. Disulphides were oxidized to disulphones by hydrogen peroxide in acidic conditions using toluene as a solvent (scheme 5a, 5b and 5c). All the synthesised disulphones were insoluble to organic solvents and the melting points were over 300 $^{\circ}$C. IR spectrocopy was used to characterize the sulphones (the SO_2 groups give strong absorption bands between 1300-1100 cm^{-1}).

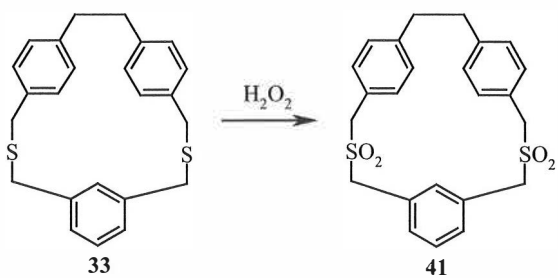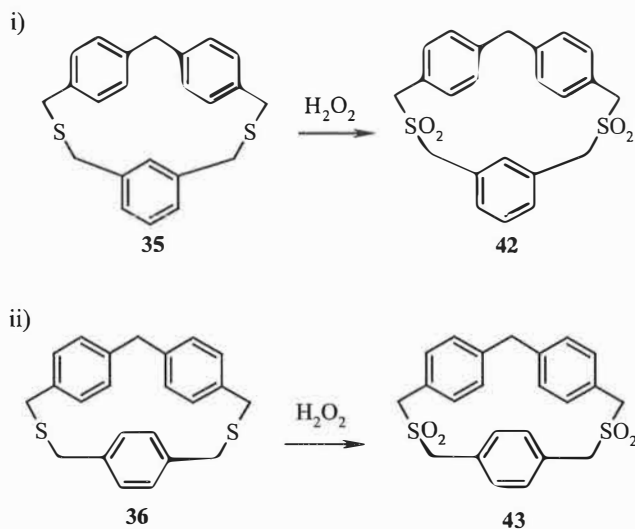1,10-Dithiatetroxide[3.3.2]cyclophanes: [I-II]

i)

31   39

ii)

32   40

iii)

33   41
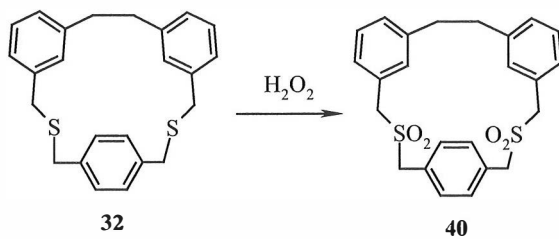
Scheme 5a Scheme for synthesis of disulphones.[I-II]

1,10-Dithiatetroxide[3.3.1]cyclophanes: [III]

i)

**35**   H$_2$O$_2$ **42**

ii)

36   H$_2$O$_2$ **43**

Scheme 5b Scheme for synthesis of disulphones.[III]

1,10-Dithiatetroxide[3.3.0]cyclophanes: [IV, 133,134]

i)

37   H$_2$O$_2$ **44**

ii)

38   H$_2$O$_2$ **45**
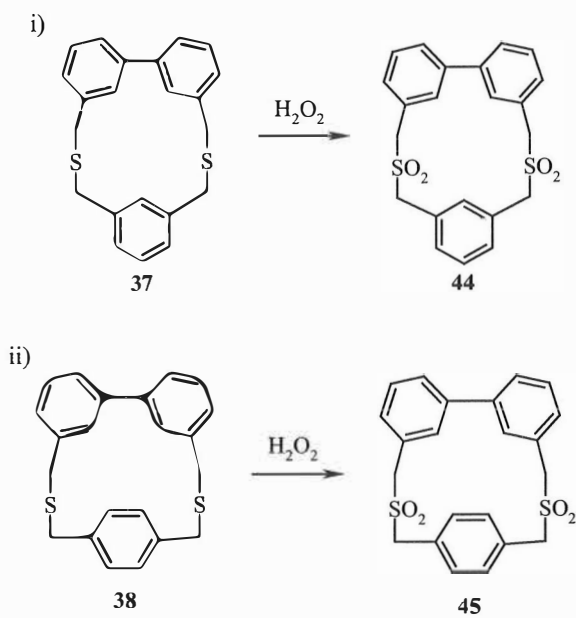
Scheme 5c Scheme for synthesis of disulphones.[IV,133,134]

2.2.3 Hydrocarbons [I-IV]

The hydrocarbon cyclophanes were synthesised from disulphones by pyrolysis. The pyrolysis mechanism was described in the review of the literature, chapter 1.1.1.2 (page 14). For the pyrolysis of disulphones, ring oven pyrolysis apparatus was used. The apparatus was built at the mechanical workshop of the Kekulé-Institut für Organische Chemie und Biochemie in the University of Bonn in accordance with the instructions given by Prof. Vögtle. The pyrolysis apparatus is constructed from four movable and separately adjustable ring ovens. Inside of the ovens is a removable quartz tube (length 40 cm, diameter 0.8 cm), which is connected to a vacuum system capable of producing 8×10^{-6} torr vacuum (figure 14 and scheme 6).
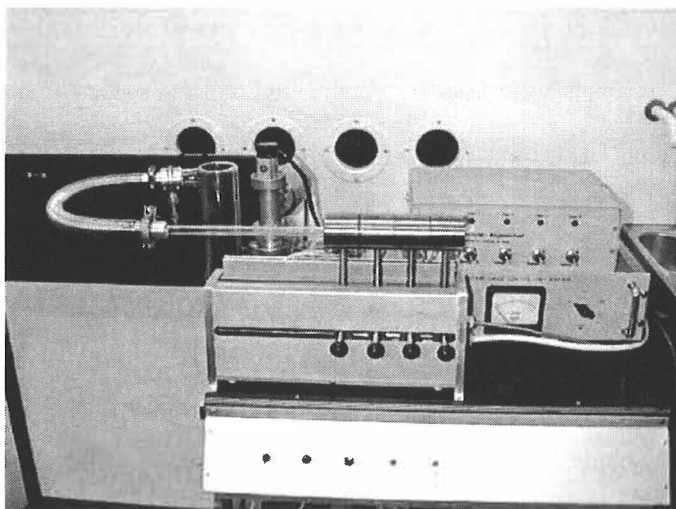

Figure 14 Pyrolysis apparatus.
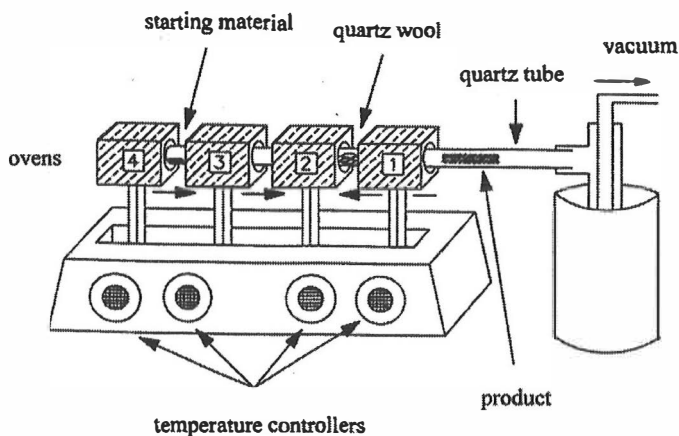
*Scheme 6* Schematic picture of pyrolysis apparatus.[132]

The starting material is placed in the end of the quartz tube. In this study the amount of the starting material (disulphone) varied between 50 and 60 mg. The first two ovens of the pyrolysis apparatus were used for sublimation and the second two ovens for the pyrolysis reaction. The sublimation temperature varied between 150 and 250°C and the temperature in the pyrolysis zone varied between 600 and 620°C. The vacuum used was always the highest possible and varied between 2×10^{-4} and 8×10^{-6} torr (scheme 7a, 7b and 7c).

As a result of the pyrolysis a very pure product was obtained. No chromatographic separation was needed because after pyrolysis the main product and by-products were separated in two adjacent layers in the quarz tube with the white (main product) layer first and the yellow (by-products) layer behind it as observed from the open end of the quarz tube. Therefore it was possible to separate the main product from the by-products mechanically.

[2.2.2]Cyclophanes: [I-II]

i)

40 → pyrolysis → **46**

ii)

41 → pyrolysis → **47**
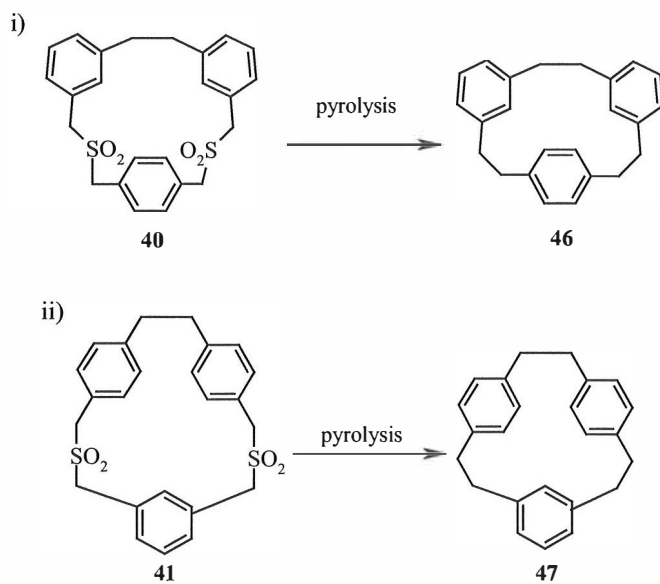
Scheme 7a Scheme for synthesis of hydrocarbons.[I-II]

[2.2.1]Cyclophanes: [III]

i)

42 → pyrolysis → **48**

ii)

43 → pyrolysis → **49**
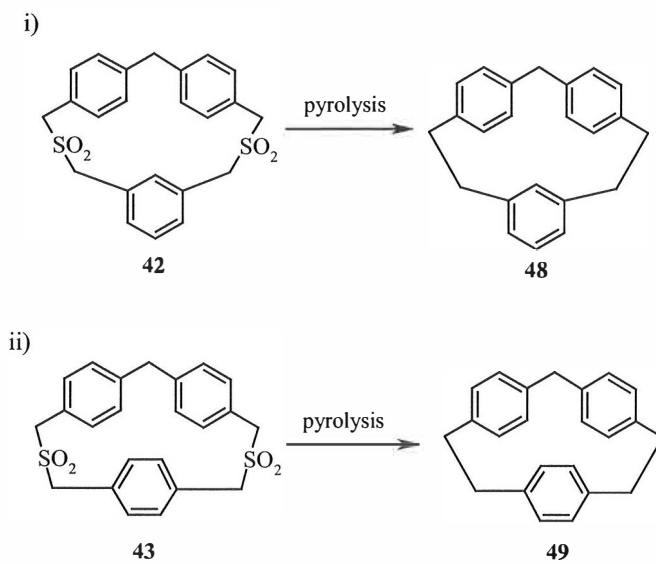
Scheme 7b Scheme for synthesis of hydrocarbons.[III]

[2.2.0]Cyclophanes: [IV, 133,134]

i)

44 → 50

ii)

45 → 51
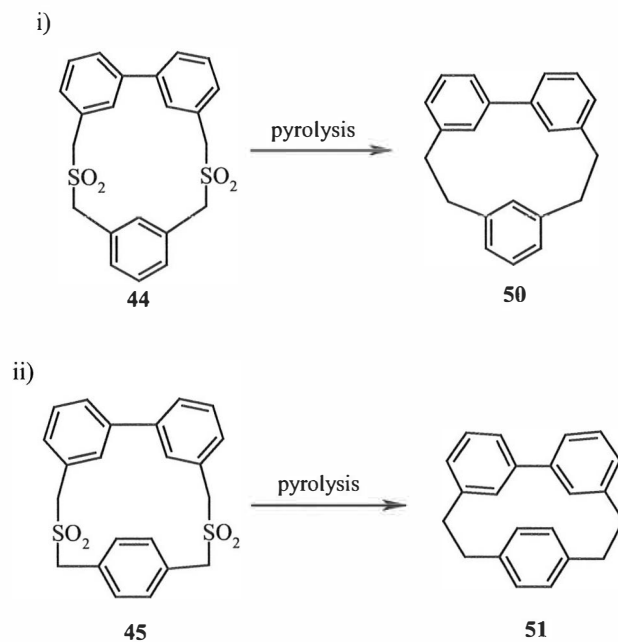
Scheme 7c Scheme for synthesis of hydrocarbons.[IV,133,134]

2.2.4 Silver complexes [I-IV]

The main focus of the present studies was how small and strained hydrocarbon cyclophane can be and still act as a π-prismand. The complexation abilities of the hydrocarbon cyclophanes were surveyed by the same procedure used by Pierre *et al.*[64] for the preparation of the silver triflate complex of [2.2.2]*p,p,p*-cyclophane (**3**). The complexation was done by mixing equimolar amounts of free ligand in dichloromethane and silver triflate in tetrahydrofuran. The mixture was stirred and allowed to evaporate very slowly to dryness in darkness at room temperature (Scheme 8a and 8b). The

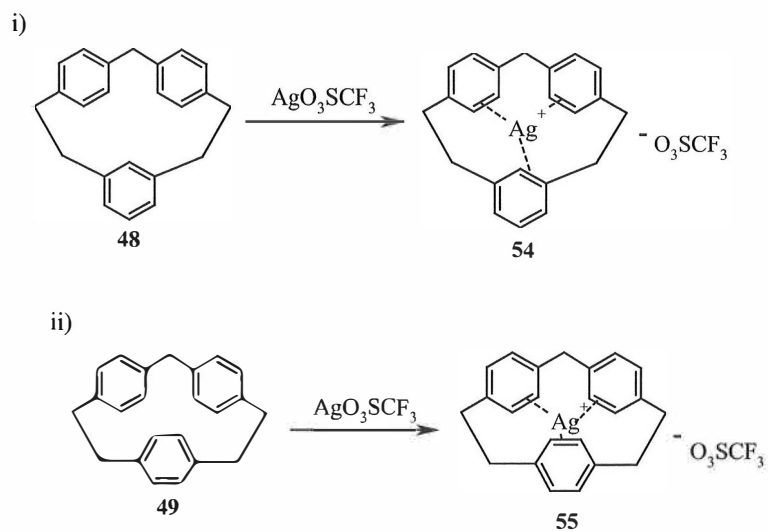complexation was proved by NMR spectroscopy and verified by single crystal X-ray structure analysis.

[2.2.2]Cyclophane-Ag$^+$-complexes: [I-II]

i)

ii)
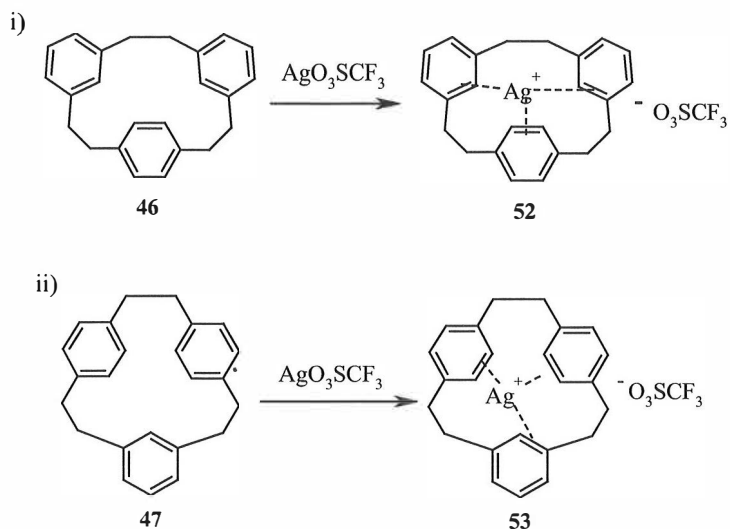
Scheme 8a Scheme for synthesis of silver complexes.[I-II]

[2.2.1]Cyclophane-Ag$^+$-complexes: [III]

i)

ii)

Scheme 8b Scheme for synthesis of silver complexes.[III]

2.3 STRUCTURAL STUDIES AND APPLICATIONS

2.3.1 Molecular structures [I-IV]

Molecular structures were studied by single crystal X-ray structure analysis and in some cases molecular modeling was used to obtain more information about the structures.[136,137, IV] Structural isomers of [2.2.2]cyclophanes[I-II], [2.2.1]cyclophanes[III] and [2.2.0]cyclophanes[IV] were compared to each other. Single X-ray crystallography gives direct information about the conformation and complexation in molecular systems. After extensive trials to grow crystals for all the compounds synthesised in the present study, it proved possible to analyse 15 different structures by X-ray crystallography.

In the [2.2.2]cyclophanes[I-II,IV] disulphide **33** crystallised in monoclinic space group (P2$_1$/n) with one molecule in the asymmetric unit. The bond distances and angles do not show any abnormal values. The two –CH$_2$-S-CH$_2$- bridges cause **33** to have a conformation in which the *meta*-substituted benzene ring is forced to enter (self-include) the cleft created by two *para*-substituted benzene rings. The screw-like conformation of the benzene rings makes **33** helically chiral (figure 15).
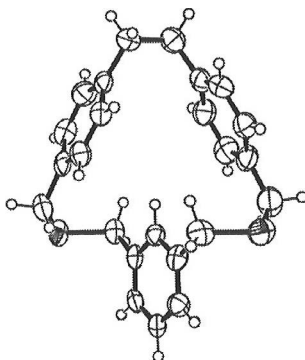
33

Figure 15 X-ray structure of 1,10-dithia[3.3.2]*m,p,p*-cyclophane (**33**).[II]

Hydrocarbon **46** crystallised in an acentric monoclinic space group (*P2₁*) with two different molecules in the asymmetric unit. The uncomplexed hydrocarbon **47** crystallised in an acentric orthorhombic space group (*Pca2₁*) with two conformationally different molecules in the asymmetric unit (figure 16).
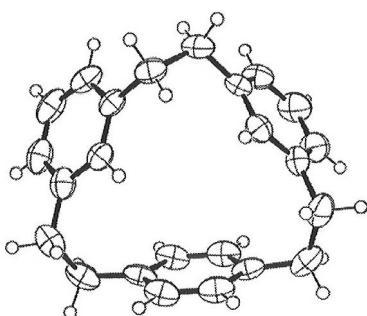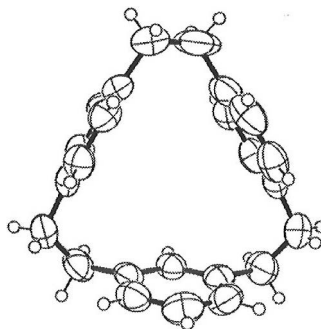
46   **47**

Figure 16 X-ray structures of [2.2.2]cyclophane hydrocarbons **46** and **47**.[II,IV]

The complexation abilities of cyclophanes **46** and **47** were tested by the same procedure used by Pierre *et al.*[64] for the preparation of the Ag-triflate complex of [2.2.2]*p,p,p*-cyclophane (**3**). The molecular structures of **52** and **53** were compared with the [2.2.2]*p,p,p*-cyclophane-Ag-triflate (**3**). The structures of the complexes are remarkably similar, keeping in mind that the [2.2.2]*p,p,p*-cyclophane (**2**) has an 18-membered ring the [2.2.2]*m,p,p*-cyclophane (**47**) a 17-membered and the [2.2.2]*m,m,p*-cyclophane (**46**) only a 16-membered ring. The reduction in ring size is caused by the change in the spatial connections inside the isomeric $C_{24}H_{24}$ skeleton. Although the formal ring size is reduced from the *p,p,p*- to the *m,m,p*-isomer, the cavities or clefts in all three isomers are nearly equal size. In all of the [2.2.2]cyclophane Ag^+-complexes the silver ion is located in the cleft or pocket created by the three phenyl rings. The interaction (bonding) between the silver ion and the cyclophane is accomplished by π-bonding (figure 17).

52   **53**
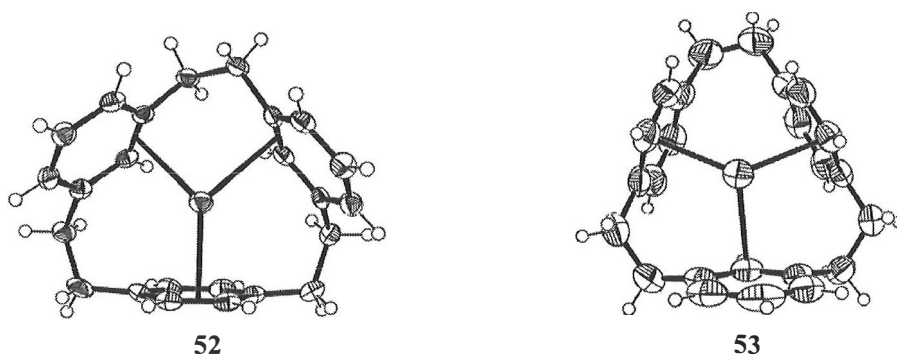
Figure 17 X-ray structures of [2.2.2]cyclophane Ag^+-complexes **52** and **53** (triflate anions excluded).[I,II]

In the [2.2.1]cyclophanes[III] disulphide **35** crystallised in an orthorhombic space group (*Pnca*) and disulphide **36** in a monoclinic space group (*P2₁/n*). In both cases, the bond

distances and angles do not show any abnormal values. The two –CH$_2$-S-CH$_2$- bridges cause **35** to have a conformation in which the *meta*-substituted benzene ring is forced to enter (self-include) the cleft created by two the *para*-substituted benzene rings. The screw-like conformation of the benzene rings makes **35** helically chiral similary as **33**. In compound **36**, all the aromatic rings are 1,4-substituted, which leads to a slightly more strained conformation than in the case of **35** (figure 18).

35   **36**
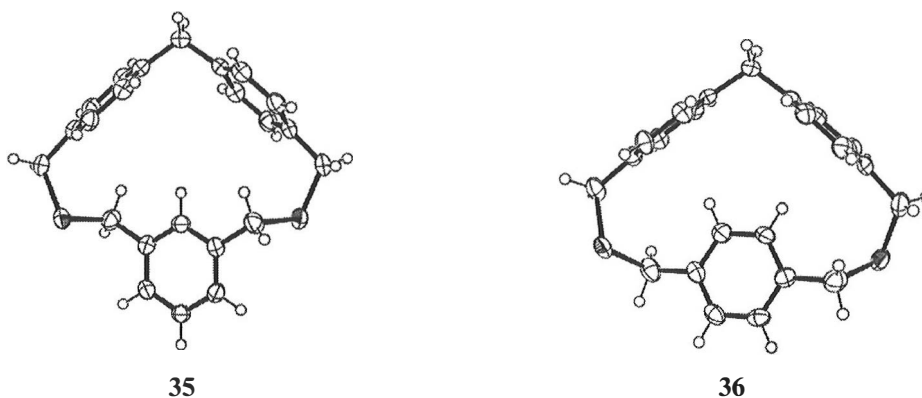
Figure 18 X-ray structures of 1,10-dithia[3.3.1]cyclophanes **35** and **36**.[III]

Hydrocarbon cyclophane **48** crystallised in an orthorhombic space group (*P2$_1$nb*) and **49** in a tetragonal space group (*P4$_1$*). Hydrocarbon **49** is rigid and highly symmetrical in the same way as deltaphane (**4**).[65] The distances between the centroids of the benzene rings in **49** are 4.19(1), 4.20(1) and 4.20(1) Å, the corresponding distances in deltaphane (**4**) are 4.06(1), 4.06(1) and 4.11(1) Å (figure 19).

48 **49**
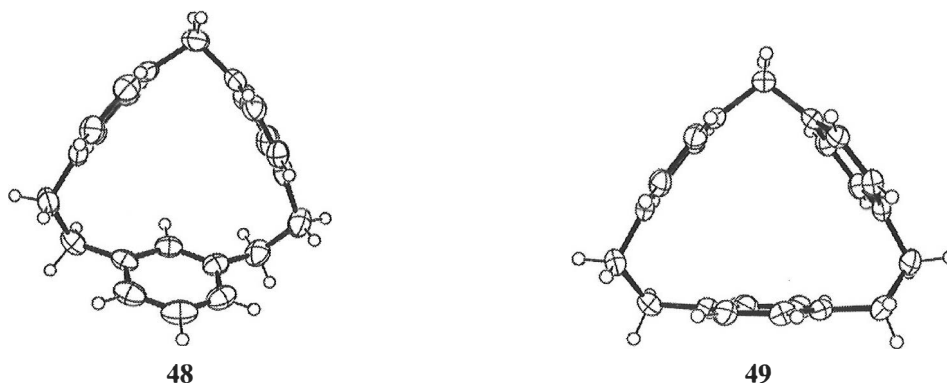
Figure 19 X-ray structures of [2.2.1]cyclophane hydrocarbons **48** and **49**.[III]

The structures of the hydrocarbons and the corresponding silver triflate complexes of [2.2.1]cyclophanes are remarkably similar in both cases (**48** → **54** and **49** → **55**). The silver triflate complex of **54** crystallised in an orthorhombic space group ($P2_12_12_1$) and **55** in monoclinic space group (*Cc*). In case of **54** the interaction between Ag^+ and the cyclophane is accomplished by π-bonding with one of the double bonds in each of the two *para*-substituted phenyl rings and with one carbon atom in the *meta*-substituted phenyl ring (as in the case of the deltaphane-Ag^+ complex (**6**))[65] (figure 20).

54 **55**
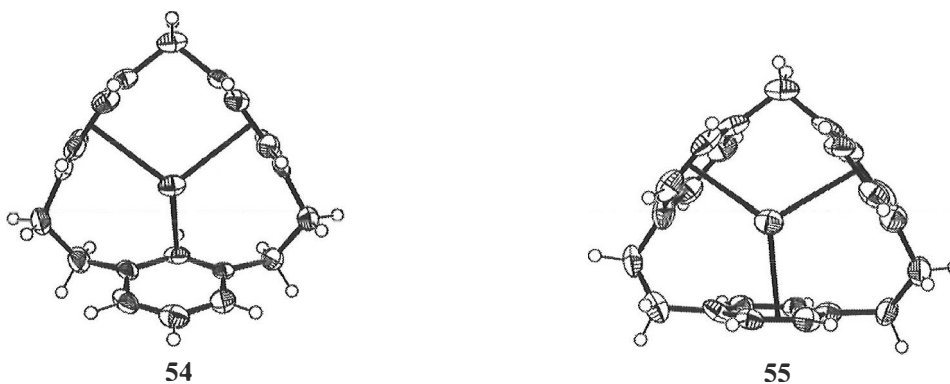
Figure 20 X-ray structures of [2.2.1]cyclophane Ag^+-complexes (triflate anions excluded).[III]

In the [2.2.0]cyclophanes[IV], disulphides **37** and **38** crystallised in a monoclinic space group (*P2₁/n*). The structures are strained and forced near to planar form due to very strained diphenyl parts of the molecules (figure 21).

37   **38**

Figure 21 X-ray structures of 1,10-dithia[3.3.0]cyclophanes **37** and **38**.[IV]

Disulphones in the present study are highly insoluble which makes it very difficult to obtain crystal structure from them. However the in case of **44** small amount of disulphone was present in the NMR tube of hydrocarbon **50** as an impurity and crystalled out. Disulfone **44** crystallised in a monoclinic space group (*P2₁/c*) (figure 22).

44

Figure 22 X-ray structure of 1,10-dithiatetroxide[3.3.0]*m,m,m*-cyclophane **44**.[IV]

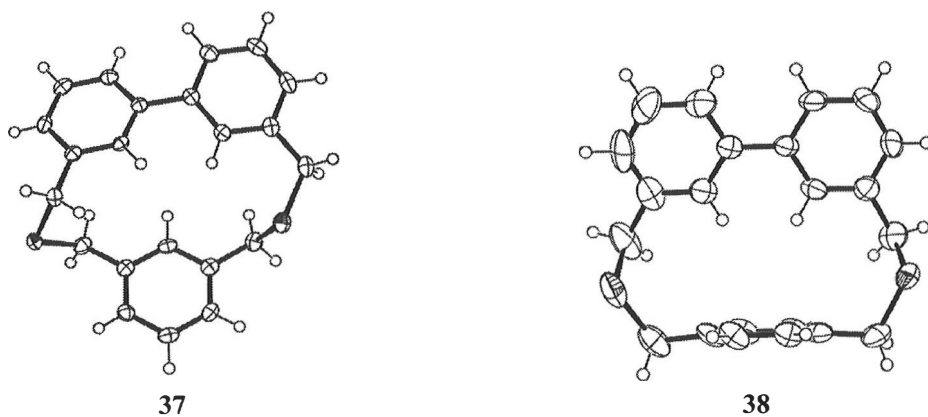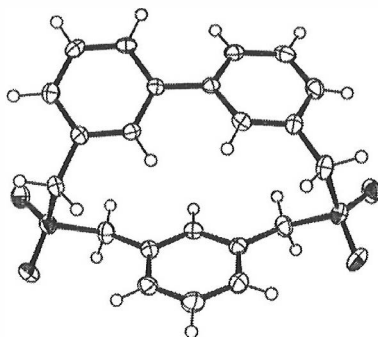Hydrocarbon **51** crystallised in a triclinic space group (*P-1*). The structure of hydrocarbon **51** is highly strained due to the biphenyl component of the molecule. The angles in [2.2.0]*p,m,m*-cyclophane (**51**) in the best least-squares planes through the aromatic rings are 161.6(1)°, 50,8(1)° and 53.1(1)°. The same angles in [2.2.2]*p,p,p*-cyclophane (**2**) are 61.2(1)°, 61.5(1)° and 60.4(1)°, which is almost an ideal π-prismand and shape as an triangle. In [2.2.0]*p,m,m*-cyclophane (**51**) the typical π-prismand face-to-face structure is converted close to planarity and the flexibility between the aromatic rings that makes the adoption of various conformations possible is partially lost (figure 23). The X-ray structure of **51** and molecular orbital calculations of **50** indicate that the cavities of [2.2.0]cyclophanes are too small for the purpose of complexing metal atoms or small molecules (figure 23 and 24).[IV]
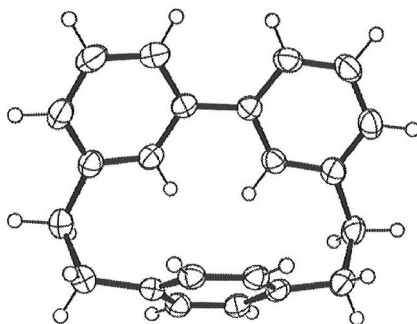
51

Figure 23 X-ray structure of [2.2.0]*m,m,p*-cyclophane (**51**).[IV]
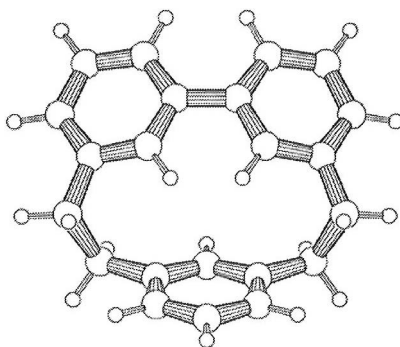
Figure 24 The calculated structure of [2.2.0]*m,m,m*-cyclophane (**50**).[IV]

The well-known [2.2.2]*p,p,p*-cyclophane (**2**) has an 18-membered ring structure, its isomeric cyclophanes [2.2.2]*m,m,p*- (**46**) and *m,p,p*-cyclophane (**47**) have 16 and 17 membered rings, respectively, while deltaphane (**4**) has only 14 members, all of which are known as π-prismands. The smaller π-prismands [2.2.1]*m,p,p*- (**48**) and [2.2.1]*p,p,p*-cyclophane (**49**) have a different number of carbons in the bridges between the benzene rings. Reduction of an ethylene to a methylene bridge between two benzene rings reduces the flexibility of the cyclophane hydrocarbons and makes them more strained;

however, the ring size is comparable to the [2.2.2]cyclophane π-prismands, the number of carbons in the macrocycle structures being 16 in **48** and 17 in **49**. In the structures of [2.2.0]cyclophanes the two aromatic rings are bonded together without an ethane bridge, giving a partially inflexible structure and decreasing to size of the ring. As an result the cavities of [2.2.0]cyclophanes are too small to complex metal atoms or small molecules and differ in this way from [2.2.2]- and [2.2.1]cyclophanes.

2.3.2 ISE measurements [V-VI]

There is a growing need to monitor some aspects of our environment in real time. Various sensors are used for this purpose. Sensors can be divided into two general categories: physicals and chemicals. Physical sensors are sensitive to such physical responses as temperature, pressure, magnetic field and force, and these do not have a chemical interference. Chemical sensors which rely on a particular chemical reaction for their response.[138,139] A chemical sensor is a device which responds to a particular analyte in a selective way through a chemical reaction and can be used for the qualitative or quantitative determination of the analyte. Ion-selective electrodes (ISE´s) are chemical sensors, more precisely electrochemical sensors. Since some selective chemistry takes place at the surface of the electrode producing an interfacial potential, ion-selective electrodes are also classified as potentiometric chemical sensors.

Utilization of cyclophanes as selective binding receptors has been studied.[140] Vögtle *et al.*[141] have studied the complexation of silver metal cation and spheriphanes by liquid-liquid extraction experiments and compared them with the well-known π-prismand [2.2.2]*p,p,p*-cyclophane (**2**). The [2.2.2]*p,p,p*-cyclophane (**2**) allowed efficient

extraction over a wide range of concentrations. However, the most efficient silver-ion extraction was accomplished by $C_{60}H_{60}$, which compared to [2.2.2]*p,p,p*-cyclophane (**2**), extracted more than twice as much Ag^+ at low concentrations (up to 1 x 10^{-3} M). At higher concentrations the $C_{60}H_{60}$ complex precipitated. Concave hydrocarbons utilization as ionophores was also studied and the PVC/[2.2.2]*p,p,p*-cyclophane membrane showed a remarkable selectivity towards silver against alkali-metal, alkaline-earth-metal, and thallium ions.[141]

In the present study[V-VI] all-solid-state ion-selective electrodes (ISEs) were constructed by using cyclophanes as π-coordinating ionophores in solvent polymeric membranes. Four structurally similar cyclophanes, *i.e.* [2.2.2]*p,p,p*-cyclophane (**2**), [2.2.2]*m,p,p*-cyclophane (**47**), [2.2.1]*p,p,p*-cyclophane (**49**) and [2.2.1]*m,p,p*-cyclophane (**48**) were studied as ionophores for Ag^+. The ion-selective membranes were composed of the corresponding ionophore (1%), potassium tetrakis(4-chlorophenyl)borate (0.5%), 2-nitrophenyl octyl ether (65-66%), and PVC (32-33%). The ion-selective membrane was placed on top of a layer of the conducting polymer, poly(3,4-ethylenedioxythiophene) (PEDOT), working as ion-selective transducer. The selectivity pattern of the solid-contact ISEs was found to depend strongly on the structure of the cyclophane. The *p,p,p*-cyclophanes are more selective to Ag^+ than the corresponding *m,p,p*-cyclophanes where one phenyl ring is coupled in the *meta* position. The effect of *para/meta* coupling of the phenyl rings is more pronounced for the [2.2.2]cyclophanes with their larger ring size. These results shows that both the symmetry and the ring size of the cyclophanes influence selectivity. Apparently a symmetrical arrangement of the phenyl groups in the ionophore is a favourable for cation-π interaction (table 1 and figure 24).

Table 1. Composition of ISE membranes, % (w/w)

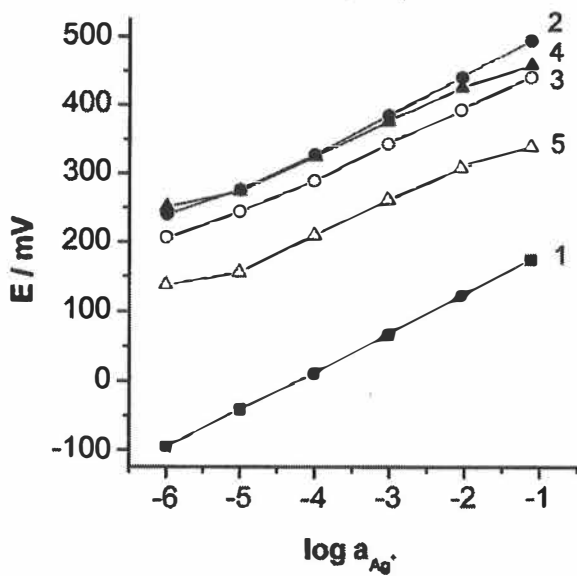| ISE	Ionophore(concentration)	KTpClPB	o-NPOE	PVC
1	No ionophore	1.5%	65.2%	33.3%
2	[2.2.2]p,p,p-cyclophane (1%)	0.5%	65.1%	33.4%
3	[2.2.2]m,p,p-cyclophane (1%)	0.5%	65.1%	32.9%
4	[2.2.1]p,p,p-cyclophane (1%)	0.5%	66.0%	32.4%
5	[2.2.1]m,p,p-cyclophane (1%)	0.5%	65.9%	32.6%

Figure 24 Calibration plot for Ag$^+$-ISEs with membrane compositions 1-5 (table 1) without 0.1 M KNO$_3$ background electrolyte .[VI]

3 SUMMARY AND CONCLUSIONS

In the present study sulphone pyrolysis was selected as a synthetic route due its convenience as a method of synthesising unsymmetrical hydrocarbon cyclophanes. Thiols and dibromides were chosen as starting materials for the high dilution synthesis.

The complexation abilities of the hydrocarbon cyclophanes were tested by the same procedure as that used by Pierre *et al.*[64] for the preparation of the Ag-triflate complex of [2.2.2]*p,p,p*-cyclophane (**3**). Four new π-prismands were found and the structures of the Ag$^+$-complexes verified by single crystal X-ray analysis. The X-ray structures of the known [2.2.2]*p,p,p*-cyclophane-Ag$^+$-complex (**3**) and deltaphane-Ag$^+$-complex (**5**) were compared to the X-ray structures of the π-prismands synthesised in the present study. After extensive trials to grow crystals from each of synthesised compounds suitable crystals for X-ray structural analysis were obtained from 15 molecules. In this way conformational changes within the molecules along the synthesis route could be followed.

Ion-selective electrodes (ISEs) were constructed by using cyclophanes as π-coordinating ionophores in solvent polymeric membranes. Four structurally similar cyclophanes, *viz.* [2.2.2]*p,p,p*-cyclophane (**2**), [2.2.2]*m,p,p*-cyclophane (**47**), [2.2.1]*p,p,p*-cyclophane (**49**) and [2.2.1]*m,p,p*-cyclophane (**48**) were studied as ionophores for Ag$^+$. The selectivity pattern of the solid-contact ISEs was found to depend strongly on the structure of the cyclophane. The *p,p,p*-cyclophanes showed significantly higher Ag$^+$-selectivity than the corresponding *m,p,p*-cyclophanes and the structure of the [2.2.2]*p,p,p*-cyclophane ionophore seems to be particularly favourable

for Ag^+-π interaction, resulting in ISEs with the best Ag^+-selectivity among the cyclophanes studied.

In the present study shape modification where the size of the ring is reduced by shrinking one bridge from the cyclophane molecule seems to have a tremendous impact on the flexibility of the cyclophane molecules and their ability to adopt various comformations when complexing silver ion.

Receptors with multiple binding sites are among the most worthwhile targets for molecular recognition studies because the multiple binding sites lead to increased binding affinity.[28,142] In case of the multiple binding receptors synthetic systems should allow to explore how binding information can be transferred selectively from one binding site to a second binding site over large distances in a molecule.

The more binding sites cyclophanes or other host molecules have the more possibilities they have to bind guest molecules. Unfortunately synthetic receptors with multiple binding sites in a well defined spatial orientation are rare, and it is poorly understood how the binding of a guest at one complexation site influences binding affinity at the second, adjacent site. For this reason it is very important to know precisely how one or two binding sites and modification of the size of the molecule affect in host-guest chemistry and what the limitations are. As in the case of the small hydrocarbon cyclophanes and their silver cation complexes studied here.

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