SYNTHESIS AND PROPERTIES OF CALIX [4] NAPHTHALENES

TOTAL OF 10 PAGES ONLY MAY BE XEROXED

(Without Author's Permission)

ZHAOPENG LI

by

Zhaopeng Li (B.Sc., M.Sc.)

Hebei, China

A thesis submitted to

the School of Graduate Studies

in fulfilment for the requirements

for the degree of Doctor of Philosophy

Department of Chemistry
Memorial University of Newfoundland
St. John's, Newfoundland, Canada
January 1996
©
The author has granted an irrevocable non-exclusive licence allowing the National Library of Canada to reproduce, loan, distribute or sell copies of his/her thesis by any means and in any form or format, making this thesis available to interested persons.

The author retains ownership of the copyright in his/her thesis. Neither the thesis nor substantial extracts from it may be printed or otherwise reproduced without his/her permission.

---

ISBN 0-612-17612-6
Absract

This work describes the synthesis and some properties of a new class of cyclic formaldehyde-naphthol tetrarnerers which are analogous to the better-known calixarenes and resorcinarenes. These new compounds are of interest for their potential supramolecular properties. The "calixnapthalenes", their derivatives and homologues, which are the subjects of this thesis, offer some potential advantages over the calixarenes and resorcinarenes. For example, the presence of the fused second aromatic ring in each naphthalene group (the "upper" rim) can allow for the formation of many functionalized calixnapthalenes which could enhance potential receptor abilities. Furthermore, fixed conformations of most calixnapthalenes are dissymmetric and have potential applications as chiral hosts, or chiral ligands.

The prototype calixnapthalenes 8, 10 and 11 were synthesized by the direct condensation of 1-naphthol and formaldehyde under basic conditions. A limited mechanistic study indicates that formation of these compounds occurs via a "pseudocalixnapthalene" pathway. VT \(^1\)H NMR analyses show that 8, 10 and 11 are conformationally flexible at temperatures above -60 °C. However, the corresponding tetrabenzoates 8a, 10a and 11a, and tetraacetates 8b, 10b and 11b exist preferentially in the "partial cone" and "1,3-alternate" conformations at -50 °C. The coalescence temperatures of these esters are in the temperature range -10 to 0 °C. Simple molecular modeling calculations indicate that these same
two conformations are also the two lowest-energy conformations.

A water-soluble calix[4]naphthale (20) was synthesized from 1,8-naphthalene sultone (6) under basic conditions. Under acidic conditions, 6 formed only oxy-calix[4]naphthale (30) and linear oligomeric compounds 28 and 29.

Synthesis of calixnaphthale 35 was effected by a self-condensation reaction of 2-hydroxy-3-hydroxymethyl naphthale (36) under TFA catalysis. Calixnaphthale 35 is promising as a supramolecular building block as it shows a coalescence temperature of -20 °C, and exists in a "cone" conformation.

Dihomocalix[4]naphthale 46 was synthesized from 3-hydroxy-2-naphthoic acid (7a) via a convergent synthetic procedure. V T 1H NMR studies suggest that in CDCl3 solution the preferred conformation of 46 at -60 °C is "1,2-alternate". X-ray diffraction of 46 shows that it exists as a "1,2-alternate" or centrosymmetric conformation in the solid state.

The calix[4]naphthale 62 and dihomocalixnaphthale 70 were both synthesized from the precursor 2,3-dihydroxynaphthale (7b) by convergent syntheses. Both 62 and 70 have rigid conformations at ambient temperature.

Finally, a novel naphthale-tethered calixspherand 95 which possesses a "cone" conformation was synthesized. Attempted synthesis of other calixnaphthalenes from 1,5- and 1,3-dihydroxynaphthale and synthesis of a functionalized calixresorcinarene were not successful.
Acknowledgements

I wish to thank my supervisor, Dr. P. Georghiou for his direction, encouragement, and patience. I wish to thank Dr. C. Jablonski and Dr. H. Anderson for their guidance and proofreading of this manuscript.

Sincere thanks go to Dr. D. J. Burnell for his advice and allowing me to use some of his research facilities; and to Dr. G. Bodwell for his valuable suggestions.

I wish to thank Dr. C. Jablonski, Ms. N. Brunet, Mr. D. Miller, and E. Vessey for NMR spectra; Dr. B. Gregory and Miss M. Baggs for EI mass spectra; Dr. J. Banoub and Mr. E. Gentil for ES mass spectra; and Dr. J. Bridson and Mr. D. Miller for X-ray crystallography.

I wish to thank to Mr. D. Murphy for his help in formatting this thesis.

The financial support from the Department of Chemistry, the School of Graduate Studies, Memorial University of Newfoundland, Dr. C. Decicco, and Dr. P. Georghiou were greatly appreciated.

I wish to thank Mr. Yi Ren and the entire Georghiou group, Burnell group, and Bodwell group for their help and friendship over the past four years.

Finally, I am indebted to my wife, Yulan and my son, Yanling for their full understanding and support.
# Table of Contents

Abstract .................................................................................................................. i  
Acknowledgements .................................................................................................. iii  
Table of Contents ....................................................................................................... iv  
List of Figures ........................................................................................................... vii  
List of Tables ............................................................................................................ ix  
List of Symbols, Abbreviations, and Acronyms ......................................................... x  
Dedication .................................................................................................................. xii  

## Chapter 1. Introduction

1.1. Introduction ......................................................................................................... 1  
1.2. Synthesis of Calixarenes .................................................................................. 3  
1.3. Chemical Modifications of Calixarenes ......................................................... 12  
1.4. Conformational Properties of Calixarenes .................................................... 12  
1.5. Complexation Properties of Calixarenes ....................................................... 17  
1.6. Industrial Applications of Calixarenes .......................................................... 19  
1.7. Calix[n]naphthalenes ...................................................................................... 20  

## Chapter 2. Calix[4]naphthalenes Derived from 1-Naphthol

2.1. Introduction ......................................................................................................... 23  
2.5. Summary .................................................................................................................................. 55
2.6. Experimental ................................................................. 56

Chapter 3. Calix[4]naphthalenes Derived from 1,8-Naphthalene Sultone

3.1. Introduction .................................................................................. 65
3.3. Complexation Studies ............................................................... 78
3.4. Summary .......................................................................................... 80
3.5. Experimental .............................................................................. 81


4.1. Introduction .................................................................................. 92
4.2. Synthesis of Calixnaphthalenes ................................................. 93
4.3. Synthesis of Dihomocalixnaphthalenes ...................................... 99
4.4. Summary .......................................................................................... 108
4.5. Experimental .............................................................................. 109

Chapter 5. Calix[4]naphthalenes Derived from 2,3-Dihydroxynaphthalene

5.1. Introduction .................................................................................. 127
5.2. Synthesis of Calixnaphthalenes ................................................. 128
5.3. Synthesis of Dihomocalixnaphthalenes ...................................... 142
5.4. Dilithation of 2,3-Dimethoxynaphthalene .................................. 146
5.5. Attempted Synthesis of Allhomocalixnaphthalenes 150
5.6. Summary 152
5.7. Experimental 153

Chapter 6. Other Calixnaphthalenes, Functionalized Calixresorcinarennes and Calixspherands

6.1. Attempted Synthesis of Other Calixnaphthalenes 192
6.2. Attempted Synthesis of Functionalized Calixresorcinarennes 195
6.3. Calixspherands 196
6.4. Summary 204
6.5. Experimental 205

References 212

Appendix I. Data of X-ray Crystallography of Compound 46 222

Appendix II. 'H NMR Spectra of Compounds 227
List of Figures

Fig. 1.1. Four Conformations of p-tert-Butylcalix[4]arenes .......... 13
Fig. 1.2. Four Stereoisomers of Calix[4]resorcinarenes .......... 16
Fig. 2.1. 'H NMR Spectrum of the Crude Product from the Condensation of 1-Naphthol with Formaldehyde. ......................... 25
Fig. 2.2. 'H NMR Spectrum of Calix[4]naphthalene 8 ............. 28
Fig. 2.3. 'H NMR Spectrum of Calix[4]naphthalene 10 .......... 30
Fig. 2.4. 'H NMR Spectrum of Calix[4]naphthalene 11 .......... 32
Fig. 2.5. VT 'H NMR Spectra of 8a ......................... 44
Fig. 2.6. HH COSY Spectrum of Methylene Protons in 8a at -50°C ...... 46
Fig. 2.7. VT 'H NMR Spectra of 10a .......... 48
Fig. 2.8. HH COSY Spectrum of Methylene Protons in 10b at -50 °C ... 49
Fig. 2.9. VT 'H NMR Spectra of 11a ................. 50
Fig. 2.10. VT 'H NMR Spectra of 8b ....................... 52
Fig. 2.11. VT 'H NMR Spectra of 10b ..................... 53
Fig. 2.12. VT 'H NMR Spectra of 11b ..................... 54
Fig. 3.1. 'H NMR Spectrum of 20 .......... 69
Fig. 3.2. ESMS Spectrum of 20 ......................... 71
Fig. 4.1. VT 'H NMR Spectra of 35 ......................... 97
<table>
<thead>
<tr>
<th>Fig.</th>
<th>Description</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2</td>
<td>VT $^1$H NMR Spectra of 51</td>
<td>104</td>
</tr>
<tr>
<td>4.3</td>
<td>VT $^1$H NMR Spectra of 46</td>
<td>106</td>
</tr>
<tr>
<td>4.4</td>
<td>ORTEP Diagram of the Molecular Structure of 46</td>
<td>107</td>
</tr>
<tr>
<td>6.1</td>
<td>HH COSY Spectrum of 95</td>
<td>200</td>
</tr>
<tr>
<td>6.2</td>
<td>NOED Spectra of 95</td>
<td>201</td>
</tr>
</tbody>
</table>
List of Tables

Table 2.1. Effect of Reaction Temperature and Time on Formation of 8, 10, and 11 ................................................................. 35
Table 2.2. Effect of Base on Formation of 8, 10, and 11 .................... 36
Table 2.3. Characteristics of $^1$H NMR Signals of Conformers of 8, 10, and 11 ........................................................................... 42
Table 2.4. Potential Energy (kcal/mol) of 8, and 10 Calculated by Alchemy III® ................................................................. 47
Table 3.1. Intensity of Fluorescence Emission (at $\lambda=340$ nm) of Aqueous Naphthalene Solution in the Presence of 20 .................. 79
Table 6.1. Assignments of the $^1$H NMR Spectrum of 95 ................... 203
### List of Symbols, Abbreviations, and Acronyms

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Abbreviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ac</td>
<td>Acetyl</td>
</tr>
<tr>
<td>APT</td>
<td>Attached proton test</td>
</tr>
<tr>
<td>bp</td>
<td>Boiling point</td>
</tr>
<tr>
<td>CC</td>
<td>Column chromatography</td>
</tr>
<tr>
<td>COSY</td>
<td>Correlated spectroscopy</td>
</tr>
<tr>
<td>disy</td>
<td>Dissymmetric</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>DMSO</td>
<td>Dimethyl sulfoxide</td>
</tr>
<tr>
<td>EI</td>
<td>Electron impact</td>
</tr>
<tr>
<td>ESMS</td>
<td>Electrospray mass spectrometry</td>
</tr>
<tr>
<td>FAB</td>
<td>Fast atom bombardment mass spectrometry</td>
</tr>
<tr>
<td>Hetcor</td>
<td>Hetero atom correlation</td>
</tr>
<tr>
<td>hv</td>
<td>Irradiation, photoreaction</td>
</tr>
<tr>
<td>IR</td>
<td>Infrared spectoscopy</td>
</tr>
<tr>
<td>J</td>
<td>Coupling constant</td>
</tr>
<tr>
<td>mp</td>
<td>Melting point</td>
</tr>
<tr>
<td>MS</td>
<td>Mass spectrometry</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
<td>-------------</td>
</tr>
<tr>
<td>NOED</td>
<td>Nuclear Overhauser effect Difference spectroscopy</td>
</tr>
<tr>
<td>NOBA</td>
<td>p-Nitrobenzyl alcohol</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>p</td>
<td>para</td>
</tr>
<tr>
<td>PCC</td>
<td>Pyridinium chlorochromate</td>
</tr>
<tr>
<td>PLC</td>
<td>Preparative thin layer chromatography</td>
</tr>
<tr>
<td>r.t.</td>
<td>Room temperature</td>
</tr>
<tr>
<td>sy</td>
<td>Symmetric</td>
</tr>
<tr>
<td>tert</td>
<td>tertiary</td>
</tr>
<tr>
<td>THF</td>
<td>Tetrahydrofuran</td>
</tr>
<tr>
<td>TFA</td>
<td>Trifluoroacetic acid</td>
</tr>
<tr>
<td>TLC</td>
<td>Thin-layer chromatography</td>
</tr>
<tr>
<td>TMEDA</td>
<td>N,N,N',N':Tetramethylethylenediamine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethylsilyl</td>
</tr>
<tr>
<td>TPE</td>
<td>1,1,2,2-Tetraphenylethene</td>
</tr>
<tr>
<td>VT</td>
<td>Variable temperature</td>
</tr>
</tbody>
</table>
To my wife, Yulan and son, Yanling.
Chapter 1.

Introduction

1.1. Introduction.

For over 150 years, organic chemists have been predominantly concerned with the nature of the covalent bond in organic molecules. However, it has long been known that non-covalent bonding is extremely important, especially in biological systems. The fascinating properties of enzymes, antibodies, membranes and their receptors, carriers, and channels, depend upon the controlled and efficient use of weak intermolecular interactions. Selective recognition and material transport, high catalytic activity, fast conductance of electrical impulses from the brain to nerve terminals, and replication processes all rely on the reversible formation of complexes and assemblies held together by noncovalent bonding.¹

Many organic chemists have been inspired by studying biochemical phenomena. Much effort is devoted to the design and synthesis of chemical systems capable of performing specific functions such as enzyme mimics. For example, Breslow's group² has shown that cyclodextrin derivatives can catalyze the hydrolysis of certain esters. Sanders³ has found that macrocyclic porphyrins can enhance the rate and stereoselectivity of some Diels-Alder
reactions. As a final example, Cram has designed a partial transacylase mimic from spherand compounds.4

Organic chemists also try to create novel organic compounds, which will have wide applications in industry. Typical examples include: (1) efficient homogenous solution catalysts; (2) receptors and molecular sensors having unprecedented sensitivities; (3) separation techniques; (4) electronic devices for information and energy storage and transfer; (5) polymers and mesophases with unusual electro-optical properties; and (6) tools for the mapping of the human genome and for investigating the origin of protein folding.1 The understanding, exploration and utilization of phenomena involving non-covalent bond interactions constitute a new area of chemistry known as supramolecular chemistry.

The cornerstones of supramolecular chemistry are the discovery of crown ethers by Peterson,6 and their elaboration to spherands by Cram,6 and to cryptands by Lehn.7 Other supramolecular compounds involving clefts, cyclophanes, and cyclodextrins are being currently investigated by many research groups.8-11

In the 1970s, Gutsche12 reinvestigated the condensation of para-substituted phenols with formaldehyde. He obtained cyclical- tetra-, hexa-, and octamers, which were named “calix[n]arenes” as typified by structure 1. In the term calix[n]arene, “calix” describes the cup-like shape or conformation of this
macrocyclic array, "arene" indicates the presence of aryl components, and the numeral "n" indicates the number of aromatic units.

Another class of cyclic tetramers made from resorcinol and acetaldehyde have been developed by Högberg\textsuperscript{13} and Cram.\textsuperscript{14} These cyclic tetramers as depicted by structure 2, are named as calix[4]resorcinarenes, although they do not have the same shape with calixarene 1.

1.2. Synthesis of Calixarenes and homocalixarenes.

1.2.1. Synthesis of Calixarenes.

The origin of the reaction which forms calixarenes can be traced back to von Baeyer's discovery of phenol-formaldehyde condensation. In 1872, Baeyer published a paper\textsuperscript{15} describing this condensation reaction. In 1902, Leo Baekeland filed for a patent\textsuperscript{16} describing the preparation, based on Baeyer's discovery, of a material he called "Bakelite". The structure of Bakelite remained
essentially unknown until the 1940s when Zinke realized that in the Bakelite process, phenol reacts at both of the ortho- and para- positions to form highly cross-linked polymers in which each phenolic residue is attached to three other phenolic residues. Zinke therefore carried out a reaction of a para-substituted phenol with formaldehyde under base conditions and obtained a more tractable product to which he assigned a cyclic tetrameric structure, 1.

The significance of Zinke's compound was not realized until Gutsche proposed to use it as a biomimic. In order to obtain synthetically useful methods, Gutsche modified the original reaction procedures. Depending on the amount of base catalyst, reaction time and temperature, the cyclic tetra-, hexa- or octamer can be obtained through the direct condensation of \( p \)-**tert**-butylphenol with formaldehyde in a one-pot syntheses. Calix[\( n \)]arennes with an odd number of \( p \)-**tert**-butylphenol units (\( n=5 \) or 7) have also been prepared but the yields are distinctly lower. The higher members of the family, where \( n=9-16 \), have been isolated by high performance liquid chromatography (HPLC).

Scheme 1.1.

\[
\begin{align*}
&\text{R} \\
&\text{OH} \\
&\text{O} \\
&\text{HCHO} \\
&\text{NaOH} \\
&\text{Xylenes} \\
\end{align*}
\]

1

\[
\begin{align*}
\text{R} &= \text{**tert**-butyl} \\
n &= 4-16
\end{align*}
\]
Calixarenes bearing different substituents in the para-positions cannot be obtained by one-pot procedures. The first such compounds were prepared in a stepwise convergent manner, as depicted in Scheme 1.2. Starting with an 

Scheme 1.2.

2-bromo-4-alkylphenol, a sequence of alternating hydroxymethylation and condensation steps led to a linear oligomer with a hydroxymethyl group at one end. After dehalogenation (deprotection of the 2-position at the other end), cyclization could be achieved under high dilution conditions.

The fragment condensation procedure (Scheme 1.3.) is simple and more flexible with respect to the possible substituents on the aromatic rings.
Such a procedure was successful in the synthesis of various calix[4]arenes, where the yields in the cyclization step may reach 30-35\%\textsuperscript{16b}.

Bridged calix[4]arenes in which two opposite phenolic units are linked by an aliphatic chain have analogously been synthesized by reaction of bisbromomethylated phenols with suitable diphenols such as $\alpha,\omega$-(4)-hydroxyphenylalkanes (Scheme 1.4).

\textbf{Scheme 1.3.}

\textbf{Scheme 1.4.}
In addition to acid- or base-induced condensation of phenol compounds with formaldehyde, Chasar has found that some phenols react with paraformaldehyde upon heating for 12 h at 175 °C to form cyclic tetramers (Scheme 1.5).\textsuperscript{19}

Scheme 1.5.

\[
\text{R} = \text{tert-butyl}
\]

Resorcinols are more reactive than \( p \)-alkyl phenols. Acid-catalysed condensation at temperatures ranging from ambient to that of boiling ethanol with aldehydes other than formaldehyde which, due to its high reactivity, probably also substitutes in the C-2 position leads to cyclic tetramers known as calix[4]resorcinarenes in good to excellent yields.\textsuperscript{12} In contrast to phenol-derived calix[4]arenes, larger cyclic oligomers are rarely observed (Scheme 1.6).
1.2.2. Synthesis of homocalixarenes.

To alter the cavity size and the conformations of the macrocycle, the methylene bridge can be replaced with longer carbon chains. Several routes as shown below lead to ethylene-bridged macrocyclic aromatic compounds, also known as [2,2]cyclophanes.

1.2.2.a. Hofmann Elimination Procedure.

The [2,2]paracyclophane can be obtained through a 1,6-Hofmann elimination procedure. A quaternary ammonium hydroxide is cleaved through Scheme 1.7.
pyrolysis to produce a polyene intermediate, which cyclizes to give [2,2]paracyclopahanes via an apparent [6+6] process.²⁰

1.2.2.b. Müller-Röscheisen Cyclization Procedure.

Using a modified Wurtz reaction, or Müller-Röscheisen cyclization procedure, Jenny et al.²¹ were able to obtain higher oligomeric [2ₙ]cyclophanes from 1,3-bis(bromomethyl)benzene with sodium tetraphenylethene (TPE) in THF at -80 °C, as depicted in Scheme 1.8.

**Scheme 1.8.**

![Scheme 1.8](image)

1.2.2.c. Wittig Reaction Procedure.

A one-pot Wittig reaction procedure (Scheme 1.9) was reported to produce a cyclic tetramer with a double bond bridge, which was hydrogenated to give an alicyclic alixarene.²²

1.2.2.d. Dithia-Intermediated Cyclization Procedure.

A general synthetic route to [2,2]cyclophanes uses dithia[3,3]cyclophanes as key intermediates. Such intermediates can be subjected directly to photochemical sulphur extrusion,²³ or be oxidised to sulphone compounds.
which are pyrolyzed to the same [2.2]cyclophane.\textsuperscript{24} From the dithia-[3.3]-cyclophane intermediate, a second choice involves carrying out a Wittig rearrangement followed by Raney-Ni reduction.\textsuperscript{25} A third choice involves a Stevens rearrangement followed by Raney Ni reduction.\textsuperscript{26} Scheme 1.10 outlines these procedures.

Scheme 1.9.
1.2.2.e. Samarium(II) Iodide-Mediated Reaction Procedure.

Self-coupling reaction of 1,3-bis(bromomethyl)benzene in the presence of five equivalents of SmI$_2$ in THF gave [2,3]metacyclophane in 10% yield.$^{27}$

Scheme 1.11.

For longer carbon chain-bridged cyclophanes, the coupling reaction of a dianion with a dihalide is a common approach. This method however suffers from low yields. For example, a meta cyclophane was obtained in only 1% yield by the reaction of the dianion of 2,6-dimethylanisole with the $\alpha,\omega$-dibromide.$^{28}$

Scheme 1.12.
1.3. Chemical Modifications of Calixarenes.

It should be pointed out that simple calixarenes have had only a few applications in supramolecular chemistry to date. However, a major advantage of these calixarenes is that they are easily amenable to chemical modification. Chemical modification can occur at either the lower rim, which contains the phenolic hydroxyl groups or the upper rim, which is the aromatic nucleus.

The lower rim is easily derivatized to ethers or esters. Reinhoudt modified the lower rim by a polyethylene oxide bridge to form 1,2- and 1,3-calix[4]-bis-crowns, double calix[4]arenes and double calixcrown. Reinhoudt joined the hydroxy group by another aromatic tether to form calixspherands. Shinkai used a lower rim functionalization approach to introduce chirality by treating p-sulphonatocalix[6]arenes with (S)-1-bromo-2-methylbutane.

The upper rim can be modified by electrophilic substitution. Shinkai introduced a sulphonic acid group at the upper rim to afford water-soluble calixarenes. Böhmer produced bridged calixarenes by introducing an aliphatic tether at the upper rim. Cram modified both the lower and upper rim of calixresorcinarenes to produce cavitands, carcerands and hemi-carcerands.


The conformationally mobile nature of calixarenes and the ability of chemists to capture and "freeze", or conformationally lock the system into one or
another of them, are particularly fascinating aspects of calixarene chemistry. Shaping the basket plays a potentially vital role in the design of calixarenes as enzyme mimics, for host-guest interactions depend on complementarity in shape as well as functionality.

X-ray crystallography has shown that \textit{p-tert}-butylcalix[4]arene exists in the "calix" or "cone" conformation in the crystalline state as Gutsche predicted.\textsuperscript{35} In solution, three other conformations exist besides the cone conformation. These are named "partial cone", "1,2-alternate" and "1,3-alternate" and are shown in Figure 1.1.

\textbf{Fig.1.1. Four Possible Conformations of \textit{p-tert}-Butylcalix[4]arenes.}
The four conformers are interconvertible at ambient temperature. Evidence for the dependence of the rate of the interconversion among the four possible stereoisomers on the nature of the solvent has been found. Gutsche showed that in nonpolar solvents such as toluene, chloroform and carbon disulphide, the barrier for interconversion is higher than that in polar solvents. For example, the inversion barriers of \( p\text{-}\text{tert-butyl} \text{calix}[4]\text{arene} \) is 14.7 kcal/mol in chloroform, while it is 11.8 kcal/mol in pyridine. Pochini found that a calixarene derivative stays in the "cone" conformation at room temperature in chloroform but it is conformationally flexible in methanol-\( d_4 \). The solvent dependence of interconversion barriers is attributed to the disruption of the intramolecular hydrogen bonding that is a major force for maintaining the calixarene in the "cone" conformation.

Since the pathway for conformational inversion in calixarenes involves the rotation of the aryl groups in a direction that brings the hydroxy groups through the annulus of the macrocyclic ring, replacing the hydroxy groups with larger moieties could fix the conformation. The most convenient way to curtail the conformational interconversion is to convert calixarenes to their ethers or esters. Rizzoli found the tetraacetate of \( p\text{-}\text{tert-butyl} \text{calix}[4]\text{arene} \) is fixed in the "partial cone" conformation while McKervey found that most of the ether derivatives of \( p\text{-}\text{tert-butyl} \text{calixarene} \) are fixed in cone conformations. Shinkai found that the metal cation present in the base strongly affects the conformational distribution.
obtained in batch reactions in yields higher than 50% with acetaldehyde.

Fortunately, in many cases, the ccc isomer is the predominant one and has been

cis-trans-trans (clt); (g) trans-cis-trans (ict); (r) trans-trans-trans (mtr)

(2) Four different diastereomers are possible, which are (1) cis-cis-cis (ccc); (6)

Due to the dissymmetric bridging-CH2-groups in calix[4]resorcinarenes

\[
\text{compound 3b, c, d, e, f, g, h, i, j, k, l, m, n, o, p, q, r, s, t, u, v, w, x, y, z}
\]

adopts the "1,3-alternate" conformation is the tert-N,N-dimethylimidocarboxamoyl

by using Cs2CO3 in DME. The only example of an unbranched calix[4]arene that

calix[4]arenes 3a fixed in the "1,5-alternate" conformation in 77% isolated yield

such as Cs in acetone. Reinscheidt, 41 synthesized terd-alkylated

alternate" conformers result when the base contains non-tertiary metal cations

calix[4]arenes such as Li, Na, and K in DME whereas "partial cone" and "1,3-

cone" conformer predominates when the base contains small sized metal

in the terd-alkylation of p-tert-butylicarboxyl[4]arene by ethyl bromoacetate. The
dodecylaldehyde, benzaldehyde, thiophenecarboxaldehyde or ferrocenecarboxaldehyde. In some cases, especially after short reaction times, the ctt or cct isomer has been isolated (while the tct and ttt isomers have been observed only in small amounts). One driving force for the formation of the cyclic tetramer and of the ccc isomer is the possibility of intramolecular hydrogen bonding between the resorcinol units. Therefore, the synthesis also works with 2-alkylresorcinols, but not with hydrogen-bond acceptors such as COOR or NO₂ in the C-2 position.

Fig.1.2. Four Possible Stereoisomers of Calix[4]resorcinarenes (2).
1.5. Complexation Properties of Calixarenes.

Undoubtedly the most interesting property of calixarenes is their ability to function as molecular baskets and bind ionic and neutral guests in supramolecular arrays. Like crown ethers, calixarenes are excellent receptors and carriers for metal cations. Calixarenes possessing ether or amide functions have as high as 10,000 to 1 selectivity for Na\(^+\) over K\(^+\).\(^{44}\) A dicarboxylic acid calixcrown synthesized by Ungaro\(^{45}\) shows selectivity of complexation with divalent cations such as calcium. These selectivities in complexation abilities have practical applications (see Section 1.6).

Derivatized calixarenes are also anion receptors. An upper rim functionalised calixarene with a transition metal designed by Beer\(^{46}\) can bind halide, nitrate, hydrosulphate and dicarboxylate anion species.

Calixarenes can also form complexes with neutral molecules. The inclusion and expression of a neutral guest in the molecular cavity of the \(p\)-tert-butyl tetramer, were foreseen by Gutsche.\(^{12c}\) Similar inclusion complexes have been found with benzene, xylene, anisole and pyridine.\(^{18c}\) By X-ray diffraction, Atwood\(^{47}\) has demonstrated an example of inclusion complexation of water by a \(p\)-sulphonatocalix[4]arene. A water molecule occupies the distorted conical cavity with its two hydrogen atoms directed toward the two nearest juxtaposed benzene rings. Structures of this type may provide important clues about how water molecules interact with aromatic moieties in biological systems. The \(p\)-tert-
butyl hexamer forms complexes with methanol and chloroform, and although the 
$p$-tert-butyl octamer also forms a crystalline complex with chloroform, it is much 
less stable than the complex that is formed with the hexamer. One example of 
an inclusion complex with complete $C_{nv}$ symmetry is the 1:1 clathrate of a 
calix[4]arene tetracarbonate and acetonitrile. The inclusion of neutral organic 
guests in $p$-tert-butylcalixarene in solution in the form of 1:1 complexes is found 
with water as solvent. Shinkai$^{49}$ has interpreted electronic spectral changes in 
Phenol Blue in water containing a $p$-sulphonatocalix[6]arene in terms of specific 
complex formation within the cavity of the latter with the hydroxy groups 
stabilizing the charge-separated excited state of the guest. Cram$^{49}$ found 
derivatized calixresorcinarene can “imprison” molecules. The prisoner can be 
chemically modified by using light waves and small reagents which are capable 
of passing through the holes in the cage when it remains within the walls of its 
highly secure molecular “prison”. More importantly, once the “prisoner” was 
secured, it could be transformed within the inner phase into some compounds 
previously unobtainable because of their high reactivity. Since the transformed 
prisoner had no cell mates and few visitors were allowed in or out, it could exist 
in solitary confinement having nothing to react with, and therefore be completely 
stable. Cram was thus able to produce underivatized cyclobutadiene, to oxidize 
hydroquinone to quinone and reduce quinone to hydroquinone, and to 
selectively alkylate phenol derivatives.
1.6. **Industrial Applications of Calixarenes.**

Due to their unusual geometries, their high melting points, their high thermal and chemical stabilities, their low solubilities in many solvents and their low toxicity, calixarenes are capable of many actual and potential industrial applications. Most of the applications of calixarenes are related to their complexational properties with ionic and neutral molecules. Izatt\(^{50}\) utilized calixarenes to recover cesium ion from an aqueous solution of a mixture of ions found in a solution of nuclear waste materials. Shinkai has at least six patents to describe the extraction of $\text{UO}_2^{2+}$ from seawater.\(^{12d,16d}\) Calixarenes can form kinetically stable complexes for diagnostic or other medical applications.\(^{51}\) Ion-sensitive electrodes and ion-sensitive field-effect transistors for $\text{Na}^+$, $\text{K}^+$, and $\text{Cs}^+$ have been described, and the incorporation of soft donor groups (containing S and/or N functions) has led also to sensors for heavy- and transition metals ($\text{Ag}^+$, $\text{Cu}^{2+}$, $\text{Cd}^{2+}$, $\text{Hg}^{2+}$, $\text{Pb}^{2+}$).\(^{52}\) The ability of calixarenes to form complexes with neutral molecules has been used by Perrin and Vicens\(^{53}\) to separate isomeric xylenes by using $p$-tert-butylcalix[8]arene as a stationary phase in gas-solid chromatography. Calixarenes can also remove chloroform from drinking water.\(^{16c}\) Water-soluble calixarenes have been used by Gutsche\(^{54}\) in solid-liquid extractions of aromatic guests. Most recently Atwood\(^{55}\) and Shinkai\(^{56}\) independently reported that calix[8]arene could separate $\text{C}_{60}^-$ and $\text{C}_{70}^-$fullerenes.

Calixarenes have many potential applications for optical, electronic and
magnetic sensors. Resorcinol-based calixarenes show strong and specific interactions via hydrogen bonding with certain sugars. These interactions may lead to specific sensors.\textsuperscript{57} Calixarenes may open possibilities to various chromogenic,\textsuperscript{58} fluorogenic\textsuperscript{59} and "light-switchable" ionophores.\textsuperscript{60} New liquid crystalline materials have been obtained from tungsten-capped calix[4]arenes.\textsuperscript{61} The p-nitro derivatives of calixarene ethers show nonlinear optical properties useful for frequency doubling of laser light.\textsuperscript{62} They may be ordered within polymer material by strong electric fields or by the Langmuir-Blodgett method.\textsuperscript{63} The latter technique has also been used to produce "perforated" monolayers leading to membranes with permeabilities defined at the molecular level.\textsuperscript{64} Calixarene derivatives are also potential enzyme mimics. Gutsche has designed an aldolase and a heme mimic\textsuperscript{129} from calixarenes. Shinkai\textsuperscript{65} found that the p-alkylicalixarene salt 4 could catalyze the base hydrolysis of p-nitrophenyl dodecanoate (Scheme 1.13).

1.7. Calix[n]naphthalenes.

Most calixarenes prior to the commencement of the work described in this thesis were confined to benzene rings only. In 1939, Poh\textsuperscript{66} reported a cyclic tetramer formed by condensation of formaldehyde with 4,5-dihydroxy-2,7-
naphthalene disulphonic acid (chromotropic acid). The evidence which they used to support their assignment however is ambiguous. In an earlier report, Georghiou\textsuperscript{67} concluded instead from similar evidence that linear oligomers and/or polymers were formed.

The properties and applications of calixarenes are determined by the size of their cavities and the number of hydroxy groups. The width of a benzene ring is 6.8 Å, but that of a naphthalene ring is 8.4 Å. It is expected that the cavity of analogues of the calixarenes bearing naphthalene rings would therefore be deeper. Naphthalene rings can bear several hydroxy groups or other functional groups, which would also enhance the receptor ability of the cavity. In addition,
the B ring in naphthol has four free positions available to be functionalised. As stated before, one of the main reasons for the ever increasing interest in calixarenes is their ability to act as enzyme mimics. A main feature of enzymes is their chirality. Unsubstituted or para-substituted calixarenes are achiral. However, due to the inherent dissymmetry of naphthols such as 1-naphthol (5), 1,8-naphthalene sultone (6), and 3-hydroxy-2-naphthoic acid (7a), the corresponding calixnaphthalenes would be chiral.

This thesis describes the research undertaken toward the synthesis of the calix[4]naphthalenes and homocalix[4]naphthalenes from 1-naphthol (5), 1,8-naphthalene sultone (6), 3-hydroxy-2-naphthoic acid (7a), and 2,3-dihydroxy-naphthalene (7b). This thesis also describes the results of investigations of their conformational properties through variable temperature (VT) $^1$H NMR experiments and simple molecular mechanics calculations. Preliminary results of some complexation studies will also be presented.
2.1. Introduction.

1-Naphthol is similar to phenol in its chemical properties, but shows greater reactivity. For example, it is convertible into ethers merely by heating with an alcohol and sulphuric acid, and undergoes the Bucherer transformation into a naphthylamine on heating with ammonia and bisulphite. Thus, it more closely resembles resorcinol rather than phenol in many reactions. This great reactivity is connected with the special properties of the 1,2-bond of the naphthalene nucleus, which is shorter than any other bond in benzene.

The complexity of the reaction of 1-naphthol with formaldehyde is well-known. It has been assumed that cross-linked polymers are formed since reaction can occur at both C-2 and C-4, the positions that are respectively ortho and para to the hydroxy group. In 1907, Breslauer and Pictet reported obtaining an amorphous product having empirical formula C_{23}H_{16}O_{3} from the reaction of 1-naphthol with formaldehyde in the presence of potassium carbonate. Abel reported obtaining a “brown, brittle, alkali-soluble resin” on heating 1-naphthol with formaldehyde in 50% acetic acid containing a small quantity of hydrochloric acid.
It was rationalized that due to its great reactivity, the condensation of 1-naphthol with formaldehyde under acidic conditions is so fast that it forms a polymer. Under basic conditions, the condensation is not so fast. However, 1-naphthol is sensitive to oxygen especially in aqueous basic media leading to products that are quinone-like.

When we reinvestigated the base-induced reaction of 1-naphthol with formaldehyde in DMF, we isolated and identified three isomeric tetrameric compounds which were termed "calix[4]naphthalenes" by analogy with the calix[4]arenes and calix[4]resorcinarenes. However, unlike the calix[4]arenes derived from \(p\)-substituted phenols and resorcinol respectively, several different structural isomers can theoretically exist for the calix[4]naphthalenes. Additionally, the conformations that are possible for some of these isomers are more complicated due to the dissymmetry of the naphthalene rings.


When a solution containing purified 1-naphthol, formaldehyde and potassium carbonate was heated in DMF under reflux for 35 h, a crude product was obtained which thin-layer chromatography (TLC) indicated to be a complex mixture. The \(^1\)H NMR spectrum of this crude product however had surprisingly clearly-defined features (Figure 2.1). In particular, the signals in the \(\delta\) 4.0-4.8
Fig. 2.1. $^1$H NMR Spectrum of the Crude Product from the Condensation of 1-Naphthol with Formaldehyde in CD$_3$COCD$_3$. 
ppm region resemble those usually seen for the methylene-bridge protons of the various isomers of calixarene derivatives.

The limited solubility of the crude product in the usual organic solvents prohibited purification by chromatographic techniques. However, fractional crystallization of the crude reaction mixture afforded three crystalline products. Mass spectra indicated that these products were isomeric tetrarers, each having a molecular ion peak at \( m/z = 624 \).

If only the A ring of 1-naphthol is considered, four isomers for cyclic tetramers which can be formed from the condensation of 1-naphthol with formaldehyde are possible, assuming a conformationally flexible structure. These are depicted as 8-11. Using symmetry considerations alone, 8 would be expected to have eleven, 9 would have twelve and 10 would have twenty-three \(^{13}\text{C}\) NMR resonance signals. Isomer 11, the least symmetrical of the isomers, could be expected to show forty-four carbon signals.

The initial substance to precipitate from the crude reaction mixture consists of at least two compounds as ascertained by TLC. Crystallization from acetone yielded a homogeneous product whose \(^{13}\text{C}\) NMR (DMSO-\(d_6\)) spectrum shows eleven signals consisting of five quaternary aromatic carbon signals, five methine aromatic carbon signals, and a single aliphatic methylene carbon signal.
The $^1$H NMR spectrum of 8 (Figure 2.2) includes a relatively high-field aromatic signal which is a four-proton singlet at $\delta$ 6.62 ppm due to the four intra-annular naphthalene protons (H-41, H-42, H-43 and H-44). The methylene protons (on C-10, C-20, C-30 and C-40) appear as an eight-proton singlet at $\delta$ 4.29 ppm. This data together with the HETCOR, NOED spectra and MS data is
Fig. 2.2. $^1$H NMR Spectrum of Calix[4]naphthalene 8 in DMSO-$d_6$. \\

![NMR Spectrum](image)
consistent for structure 8 which possesses C₄ symmetry. The relatively higher-field aromatic signal in this and the other isomers can be accounted for by examination of molecular models which reveal that the intra-annular protons can be situated in the shielding region of the naphthalene ring. That the methylene protons appear as a singlet at ambient temperature indicates that the compound has a flexible structure and that the positions of these methylene protons are rapidly interchanging.

The second compound obtained from the crude reaction product was crystallized from ethyl acetate. This compound was the same substance that initially co-crystallized with 8. The ¹³C NMR (DMSO-d₆) spectrum of this pure product reveals only twenty-one clearly defined signals of the expected twenty-three. However, the APT-¹³C NMR spectrum shows that there are ten quaternary aromatic carbon signals, ten methine aromatic carbon signals and three aliphatic methylene carbon signals. A pair of quaternary carbon signals and a pair of aromatic methine signals clearly overlap. In addition, the height of one of the aliphatic methylene carbon signals is double that of each of the other two.

The ¹H NMR spectrum of 10 (Figure 2.3) shows the higher-field aromatic signals as two (two-proton) singlets of equal intensity at δ 6.83 and 6.72 ppm for the intra-annular protons. The methylene protons appear as three singlets, at δ 4.40, 4.29 and 4.08 ppm with relative intensities in the ratio of 1:2:1. In addition to this data, the HETCOR, NOED spectra and MS data are consistent for
structure 10 which has a plane of symmetry through the C-20 and C-40 methylene groups which are perpendicular to the macrocyclic ring. This isomer is also conformationally flexible at ambient temperature.

The third isomer was recrystallized from diethyl ether. Its $^{13}$C NMR (DMSO-$d_6$) spectrum shows forty-two clearly resolved signals of the expected forty four, with some obvious overlapping in the group of signals centered at $\delta$ 124.5 ppm. The APT-$^{13}$C NMR spectrum clearly indicates twenty quaternary aromatic carbon signals, twenty methine aromatic carbon signals, of which the same group of signals centered at $\delta$ 124.5 ppm was not clearly resolved, and four aliphatic methylene carbon signals.

The $^1$H NMR spectrum of 11 (Figure 2.4) shows four relatively high-field aromatic (one-proton) singlets of equal intensities, at $\delta$ 6.80, 6.70, 6.66 and 6.64 ppm for the four intra-annular protons. The methylene protons appear as four two-proton singlets of equal intensities, at $\delta$ 4.45, 4.32, 4.21 and 4.09 ppm. This data together with the HETCOR, NOED spectra and MS data were also consistent for structure 11 which does not possess any symmetry. This isomer is also conformationally flexible at ambient temperature. When the $^1$H NMR spectra of these three isomers are superimposed, they are obviously the major components of the crude reaction product which has methylene bridges. The ratio of the three isomers 8:10:11 in the crude reaction product estimated from integration of the intra-annular aromatic signals in the range $\delta$ 6.5-6.9 ppm.
Fig. 2.4. $^1$H NMR Spectrum of Calix[4]naphthalene 11 in DMSO-$d_6$. 

$\text{ppm}$
is approximately 1.0:2.2:3.0. The total isolated yield of the three isomers was only 25%, with the ratios of the isolated isomers being 1.0:1.6:0.5. We have been unable to isolate, nor is there any evidence from the $^1$H NMR spectra for any significant amount of the fourth potential isomer, 9.

The yield of calix[4]naphthalenes is low (ca. 25-30%). The dark brown residue which presumably consists of different sized linear oligomers and oxidation products was not separated and characterized.

In basic solution open to the air and at high temperature, 1-naphthol undergoes many changes due to oxidation by molecular oxygen to form quinone-like products and biphenols. Scheme 2.1 shows some possible oxidations of 1-naphthol by molecular oxygen under basic conditions.

Attempts have made to optimize the formation of calix[4]naphthalenes by changing temperature, reaction time, base catalysts and solvents.

2.2.1. Effect of Reaction Temperature and Time.

The effects of reaction temperature and time on the product yields are summarized in Table 2.1. When the reaction was carried out 20.5 °C in DMF in the presence of potassium carbonate, the starting material remains unchanged. At 60-70 °C, the starting material disappeared after stirring for 100 h, but only a small amount of products was seen by TLC. When refluxed, the starting
Scheme 2.1.
material disappeared in 20 h and a small amount of products was detected by TLC. When refluxed for 30 h, a total isolated yield of 25% for the three products was obtained. Longer reaction times did not improve the yields markedly.

**Table 2.1. Effect of Temperature and Time on Formation of 8, 10 and 11.**

<table>
<thead>
<tr>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.5</td>
<td>100</td>
<td>No reaction (TLC).</td>
</tr>
<tr>
<td>60-70</td>
<td>100</td>
<td>Starting material disappeared, and a small amount of products formed (TLC).</td>
</tr>
<tr>
<td>90-100</td>
<td>20</td>
<td>Starting material disappeared, and a small amount of products formed (TLC).</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>Yield 25% (isolated)</td>
</tr>
<tr>
<td></td>
<td>35</td>
<td>Yield 31% (isolated)</td>
</tr>
<tr>
<td></td>
<td>40</td>
<td>Yield 27% (isolated)</td>
</tr>
</tbody>
</table>

### 2.2.2. Effect of Base.

The effect of bases on the formation of calix[4]naphthalenes was investigated. Table 2.2 shows the results when the reactions were carried out under N₂ in refluxing DMF for 30 h using various bases under identical conditions. It seems that the larger alkaline cation (Cs⁺>K⁺>Na⁺) appears to give better yields. It was also found that a soft counteranion favours the formation of calix[4]naphthalenes (CO₃²⁻>OH⁻). A possible reason could be the higher
solubility of Cs₂CO₃ over other bases, in DMF.

Table 2.2. Effect of Base on Formation of 8, 10, and 11.

<table>
<thead>
<tr>
<th>Base</th>
<th>NaOH</th>
<th>Na₂CO₃</th>
<th>KOH</th>
<th>K₂CO₃</th>
<th>Cs₂CO₃</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield (%)</td>
<td>trace</td>
<td>5</td>
<td>10</td>
<td>25</td>
<td>35</td>
</tr>
</tbody>
</table>

2.2.3. Effect of Reaction Media.

The condensation of 1-naphthol with formaldehyde in DMF gave calix[4]-naphthalenes 8, 10 and 11. However, if this condensation was carried out in aqueous, or 1:1 DMF/H₂O, very dark brown resinous products were obtained. This result shows that the aqueous solvent facilitates the oxidation of 1-naphthol by molecular oxygen (see Scheme 2.1).

2.2.4. Effect of Inert Atmosphere.

Two parallel experiments were conducted. In one, N₂ was bubbled into the reaction solution, and in the other, no N₂ was bubbled. It was found that the yield of the desired products under the former conditions is 10% higher than under the latter conditions. This supports the hypothesis suggested that the oxidation of 1-naphthol or its derivatives is a major side reaction (see Scheme 2.1).


Gutsche¹² has proposed two mechanisms for the formation of calixarenes. One is the "pseudocalixarene" pathway, in which a linear tetramer is the
precursor of calixarenes. The other is the "hemicalixarene" pathway, in which calixarenes are formed from the coupling of two dimers.

A mechanism for the formation of calix[4]naphthalenes 8, 10, and 11 as shown in Scheme 2.2 has been proposed. In this mechanism, the first step is initiated by the formation of a naphthoxide ion which effects a nucleophilic addition to the highly reactive carbonyl group of formaldehyde. The alkylation can occur at either the ortho or para position to the hydroxy group. Since the 4-position has a peri-relationship with the 5-position of B ring in 1-naphthalol, it is sterically hindered. Furthermore, hydrogen bonding could exist between the naphthalene hydroxy and the hydroxymethyl group which would stabilize the transition state leading to the ortho product 12. The reaction proceeds further to form an ortho-naphthoquinone methide 13, which reacts with another phenolate ion in a Michael-like process to form dinaphthylmethy compounds or longer linear oligomers. The condensation of ortho-quinone methide intermediate 13 can occur at either the ortho or para position of a second 1-naphthol to give 14 or 15, respectively. It is likely that if 14 is indeed formed during the reaction it would be labile to oxidation under the reaction conditions which were employed. The dimer 15 could in turn condense with a third 1-naphthol to give 16 or 16a. The trinaphthyl adduct 16 can couple with another methide, 13, at either of the two reactive sites to give 17 and 18, respectively. Intermediate
Scheme 2.2.
17 is the penultimate precursor of 11 and intermediate 18 is the penultimate precursor of 8. The trimer intermediate 16a, could react with methide 13 to produce 19, the penultimate precursor of 10. None of the steps envisioned in Scheme 2.1 would lead to the formation of the C₈₄ symmetrical tetramer 9, which is consistent with the observed results. From the experimental data above, we concluded that the ortho-quinone methide 13 is a key intermediate. Chaulk obtained a spiro compound derived from a 4-bromo derivative of 13 under similar conditions, which supports our conclusion. Product analysis suggests that the formation of calixnaphthalenes follows the "pseudocalixnaphthalene" pathway, rather than the "hemicalixnaphthalene" pathway.


All three calix[4]naphthalenes are conformationally flexible at ambient temperatures, as evidenced by the sharp signals for all of the methylene bridge and intra-annular protons (Fig. 2.2, Fig. 2.3, and Fig. 2.4). Conformational rigidity of 8, 10 and 11 was not seen even at -50 °C.

A pathway for the conformational inversion in calixnaphthalenes should involve the rotation of the naphthyl groups in a direction that brings the hydroxy groups sequentially through the annulus of the macrocyclic ring. Therefore, replacing these groups with larger moieties should serve to fix the conformation.
One of the most convenient methods is to convert calixnaphthalenes to their corresponding esters. In addition, since the solubilities of 8, 10 and 11 in common organic solvents is very low, it was expected that these esters would have greater solubilities. The tetrabenzyolations of 8, 10 and 11 were carried out with benzoyl chloride and sodium hydride in anhydrous THF to give 8a, 10a and 11a. Stirring at room temperature for 10 h was required for completion of reaction. This reaction time is longer than that usually required for benzoylations of phenols or naphthols. Acetylations of 8, 10 and 11 were carried out in acetic anhydride under refluxing conditions which are more vigourous than those usually required for acetylations of phenols or naphthols. The resulting tetrabenoates and tetraacetates of the calixnaphthalenes were readily soluble in dichloromethane and chloroform, which facilitated the study of their conformational properties.

Dynamic NMR spectroscopy has become an immensely important tool for the study of conformational properties of organic compounds in solution. This technique can provide information relating to the type of conformation, the nature and relative ratio of different conformers, and the energetics of transformations between the conformers. In this study, coalescence temperature can be used to indicate the rigidity of a conformer.76

By analogy with the calix[4]arennes, calix[4]naphthalenes can adopt four major types of conformations: "cone", "partial cone", "1,2-alternate" and "1,3-
alternate" (see Fig. 1.1, p13). The anticipated characteristics of the $^1$H NMR signals of these conformers are shown in Table 2.3.

Referring to the generic structure 1 (Fig. 1.1, p13), if 8 is conformationally flexible, the intra-annular protons and methylene bridge protons would both appear as singlets. If 8 is fixed in a "cone" conformation, the four intra-annular protons have the same chemical environments and would appear as a singlet. Although the four methylene bridges are identical, each pair of geminal protons are diastereotopic, forming an AB quartet. In the "partial cone" conformation, four intra-annular protons are non-equivalent, consequently they would appear as four singlets. The geminal methylene bridge protons also appear as four AB quartets. In the "1,2-alternate" conformation, there are two types of intra-annular protons and they would therefore appear as two singlets. There are two types of methylene bridges and they would appear as two AB quartets. Finally, in the "1,3-alternate" conformation, four intra-annular protons are identical and they would appear as a singlet. The four methylene bridges also are identical and they would appear as a singlet.

If 10 is conformationally flexible, the intra-annular protons would appear as two singlets, whereas the methylene bridge proton would appear as three singlets having an integration ratio 1:2:1. In the "cone" conformation, the intra-annular proton would remain as two singlets, but the methylene bridge protons would appear as three AB quartets due to the coupling of the geminal protons.
Table 2.3. Characteristics of $^1$H NMR of Conformers of 8, 10, and 11.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Intra-annular Protons</th>
<th>Methylene Protons</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>flexible</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cone</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>partial cone(sy)</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>partial cone(dissy)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1,3-alternate</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>1,2-alternate(sy)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>1,2-alternate(dissy)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

There are two kinds of "partial cone" conformations, a "symmetric" one in which two adjacent hydroxyl groups are on the same side, and a "dissymmetric" one in which two adjacent hydroxyl groups are on different sides. In both of them, the four intra-annular protons become different and they would appear as four singlets. The four methylene bridges also become different and the methylene bridge protons would appear as four AB quartets. Although the two "partial cone" conformers have the same $^1$H NMR characteristics, they have different potential energies, which will be discussed later. Similarly, there are two kinds of "1,3-alternate" conformations, a "symmetric" and a "dissymmetric".
The former has two types of intra-annular protons which would appear as two singlets. The methylene bridge protons would appear as two singlets and two AB quartets. Finally, the dissymmetric “1,2-alternate” conformation has four different intra-annular protons, which would appear as four singlets. It also has three different types of methylene bridges, which would appear as three AB quartets.

If 11 is conformationally flexible, the intra-annular protons would appear as four distinct singlets, whereas the methylene bridge protons would appear as four distinct singlets. In any of the fixed conformations, “cone”, “partial cone”, “1, 3 -alternate”, or “1,2-alternate”, the intra-annular protons would appear as four singlets, and the methylene bridge protons would appear as four distinct AB quartets.

Figure 2.5 shows the $^1$H NMR (CD$_2$Cl$_2$) spectra of tetrabenzoate 8a taken at: (a) 20 °C; (b) 0 °C; (c) -20 °C; and (d) -50 °C. The signals of methylene bridge protons are very broad, and those of the intra-annular protons are so broad that they can be hardly seen at room temperature (Fig.2.5a). This indicates that 8a undergoes fast interconversion at room temperature, but that the rate of its conformational inversion is much slower than that of the corresponding calix[4]naphthalene 8, which is conformationally flexible at -50 °C.

The low temperature $^1$H NMR spectra shown in Fig. 2.5 reveal much
Fig. 2.5. VT 'H NMR Spectra of 8a in CD₂Cl₂.
information about the conformations of 8a. As the temperature is decreased to 0 °C, the \(^1\)H NMR signals become flatter. Below 0 °C, complex sharper signals appear. Therefore, 0 °C was assigned as the coalescence temperature of 8a.\(^7\) At -50 °C, conformational freezing is indicated by the presence of well-defined signals in the δ 4.0-5.0 ppm and δ 5.8-8.4 ppm ranges. In order to interpret the spectrum at -50 °C, a COSY experiment was conducted. The COSY spectrum shown in Fig.2.6 of 8a confirmed that the singlets at δ 7.14, 7.08, 5.86 and 5.83 ppm (see Fig.2.2) are due to the intra-annular protons on C-41 to C-44. A conformer which would result in the intra-annular protons being observed as four singlets is a "partial cone" conformer. This is analogous to "partial cone" conformers observed in the calix[4]arenes.\(^1\)\(^2\)-\(^1\)\(^8\) This is confirmed by the COSY spectrum shown in Fig.2.6, which shows four AB systems due to the methylene geminal protons. However, at least one other conformer is present as evidenced by the large unresolved signal centred at δ 4.26 ppm and the corresponding aromatic intra-annular proton signal which appears as a singlet at δ 6.45 ppm.

According to the expected \(^1\)H NMR characteristics of conformers of 8 and hence of 8a, shown in Table 2.3, the other conformer which demonstrates a singlet signal at δ 4.26 ppm, and a singlet at δ 6.45 ppm could be "cone", or "1,3-alternate". Molecular modelling calculations reveal that the "1, 3-alternate" conformer has lower potential energy than the "cone" conformer (see Table 2.4). It suggested that it is the "1,3-alternate" that coexists with the "partial cone"
Fig. 2.6. HH COSY Spectrum of Methylene in 8a at -50°C in CD$_2$Cl$_2$. 
conformer.

Figure 2.7 shows the $^1$H NMR (chloroform-$d$) spectra of 10a taken at: (a) 50 °C; (b) 20 °C; (c) 0 °C; (d) -20 °C; and (e) -50 °C. The signals of the intra-annular protons and methylene bridge protons in the $^1$H NMR spectrum of tetrabenzoates 10a at +20 °C are broad. As the temperature rises to +50 °C, the signals become sharper. When the temperature was decreased, the signals became more complex, and reveal a coalescence temperature at about 0 °C. At -50 °C, conformational freezing is apparent by the presence of well-defined signals in the δ 4.0-5.0 ppm and δ 5.8-8.4 ppm ranges. The COSY spectrum of 10a at -50 °C (Fig.2.8) is considerably more complex than that of 8a. At least eighteen pairs of doublets and up to four singlets can be discerned in the

<table>
<thead>
<tr>
<th></th>
<th>8a</th>
<th>10a</th>
</tr>
</thead>
<tbody>
<tr>
<td>cone</td>
<td>32.22</td>
<td>32.25</td>
</tr>
<tr>
<td>partial cone (sy)</td>
<td>27.44</td>
<td></td>
</tr>
<tr>
<td>partial cone (dissy)</td>
<td>22.92</td>
<td>35.20</td>
</tr>
<tr>
<td>1,3-alternate</td>
<td></td>
<td>33.89</td>
</tr>
<tr>
<td>1,2-alternate (sy)</td>
<td>28.28</td>
<td>37.99</td>
</tr>
<tr>
<td>1,2-alternate (dissy)</td>
<td></td>
<td>39.57</td>
</tr>
</tbody>
</table>
Fig. 2.7. VT 'H NMR Spectra of 10a in CDCl₃.
Fig. 2.8. HH COSY Spectrum of Methylene in 10a at -50 °C in CDCl₃.
methylene proton region. At least six signals (singlets) due to the intra-annular protons can also be discerned, albeit with difficulty. As with 8a, the "partial cone" conformer could account for eight pairs of doublets; a "1,2-alternate" (dissymmetric) conformer could account for an additional six pairs of doublets; and a "1,2-alternate" (symmetric) conformer could account for an additional four pairs of doublets and two singlets. Low temperature $^1$H NMR reveals that 10a populates several conformers, although the molecular modelling calculations suggest that the "cone" and the "1,3-alternate" are the two lower-energy conformers.

The VT $^1$H NMR spectra of 11a are shown in Fig. 2.9. Since each conformer of 11a has four AB systems, the spectra were too complex to be meaningfully assigned.

The VT $^1$H NMR spectra of tetraacetates 8b, 10b and 11b are shown in Fig. 2.10, Fig. 2.11 and Fig. 2.12 respectively. They have the same features with regard to the intra-annular protons and methylene protons and are a little simpler due to the absence of the benzoate aromatic signals. Compared with the spectra of the corresponding tetrabenzoates 8a, 10a and 11a, tetraacetates 8b, 10b and 11b have sharper signals at the same temperature, and have lower coalescence temperatures (-10 °C).
Fig. 2.10. VT $^1$H NMR Spectra of 8b in CDCl$_3$. 
Fig. 2.11. VT $^1$H NMR Spectra of 10b in CDCl$_3$. 
Fig. 2.12. VT $^1$H NMR Spectra of 11b in CDCl$_3$. 
2.5. Summary.

Three cyclic tetramers 8, 10 and 11 were successfully synthesized from the condensation of 1-naphthol with formaldehyde in DMF under basic conditions. These are a new class of macrocyclic naphthalene compounds, which are potential supramolecular building blocks. By analogy with the calix[n]arenes and calix[n]resorcinarenes, these cyclic tetramers were named "calix[4]naphthalenes". A limited mechanistic interpretation based on product analysis suggests that the formation of calix[4]naphthalenes 8, 10 and 11 follows the "pseudocalixnaphthalene" pathway, rather than the "hemicalixnaphthalene" pathway. The well-resolved $^1$H NMR signals observed for both the naphthalene protons and the methylene bridge protons of the three calix[4]naphthalenes 8, 10 and 11 indicate that there is rapid conformational interconversion in these molecules at ambient temperatures. However, their corresponding tetrabenzoates 8a, 10a and 11a and tetraacetates 8b, 10b and 11b are frozen preferentially in the "partial cone" and "1,3-alternate" conformations at -50 °C. The coalescence temperatures of these acetates and benzoates are in the range of -10 °C to 0 °C. Molecular modelling calculations suggest that the "partial cone" and "1,3-alternate" are the two lowest-energy conformations, which is consistent with the results obtained from VT $^1$H NMR experiments.
2.6. Experimental.

General Methods. All reaction were performed under \( \text{N}_2 \) unless otherwise indicated. Organic solutions were concentrated using a rotary evaporator. Flash column chromatography was performed according to the procedure of Still\(^{77a} \) using MERCK silica gel 230-400 mesh. Preparative thin layer chromatography (PLC) plates were made from Aldrich silica gel (TLC standard grade, 2-25 µ) with 14% calcium sulphate. Thin-layer chromatography was performed on precoated silica gel 60 \( F \) plates (Merck, Darmstadt, FRG).

Materials. Chemical reagents and solvents whose synthesis are not described were purchased from Aldrich or Fluka and were used as received with the following exceptions. Dry dichloromethane was obtained by distillation of ACS grade dichloromethane from calcium hydride. Dry chloroform was obtained from ACS grade chloroform by washing with concentrated sulphuric acid (95%) and water sequentially, drying over anhydrous calcium chloride for 24 h and distilling. Dry \( N,N \)-dimethylformamide (DMF) was obtained from by drying ACS grade DMF over calcium sulphate over 72 h and fractional distillation under reduced pressure. Dry diethyl ether, tetrahydrofuran (THF), and \( p \)-dioxane were obtained from the ACS grade solvents by drying with KOH for 48 h and distilling from purple sodium benzophenone ketyl under \( \text{N}_2 \).

Instrumentation. Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (IR) spectra were recorded on a
Mattson Polaris FT instrument. Data are presented as follows: frequency of absorption (cm⁻¹), intensity (s=strong, m=medium, w=weak, br=broad), and assignment (when appropriate). Low resolution and high resolution (HRMS) mass spectral (MS) data were obtained using a V.G. Micromass 7070HS instrument. MS data are presented as follows: m/z, intensity, and assignment (when appropriate). Fast atom bombardment (FAB) MS were obtained with a Kratos MS50TC spectrometer at the Dept. of Chemistry, U. N. B., Fredericton, N.B. using the following operating conditions: Vacc = 4,000 volts; FAB gun set at 7.0-7.5 Kv, using Xenon as the FAB gas; resolution = 1500; accelerating voltage = 6 Kv. ¹H NMR spectra were recorded with a GE GN-300NB spectrometer at 300.117 MHz and chemical shifts are relative to internal TMS. Data are presented as follows: chemical shift, multiplicity (s=singlet, d=doublet, dd=double doublet, t=triplet, q=quartet, m=multiplet), coupling constant (J, Hz), integration, and assignment (H#). The assignments are based on HH COSY, CH Hetcor, and NOED. ¹³C NMR spectra were recorded at 75 MHz and were obtained from zero-filled 16K data tables to which a 1-2 Hz exponential line-broadening function had been applied. Chemical shifts for ¹³C NMR spectra are relative to the respective solvents (δ 77.0 for CDCl₃; δ 53.8 for CD₂Cl₂). The assignments are based on CH Hetcor and APT. Proton nuclear Overhauser effect differences (NOED) spectra were obtained from zero-filled 32K data tables to which a 1-2 Hz exponential line-broadening function had been applied. A set of
four "dummy" scans was employed to equilibrate the spins prior to data acquisition. No relaxation delay was applied between successive scans of a given frequency. Data collection for the X-ray structure was made on a Rigaku AFC6S diffractometer at 298K. Additional details were given in Appendix I.

Calix[4]naphthalenes (8), (10) and (11).

To a solution of 1-naphthol (distilled under reduced pressure or recrystallized from hexane, 1.44 g, 10 mmol) in DMF (10 mL) were added aqueous formalin solution (37% formaldehyde, 0.70 mL, 8.6 mmol) and aqueous potassium carbonate (10%, 1.0 mL, 0.72 mmol). The blue solution was refluxed under N₂ for 35 h and then cooled to room temperature. When the reaction mixture was poured into a mixture of ice (50 g) and 5% hydrochloric acid (10 mL), a brown precipitate formed. The precipitate was filtered and washed with deionized water until the washings were neutral to pH paper and then dried.
under vacuum. The dried crude product was crystallized from acetone. The first precipitate obtained from the solution is compound 8 (0.15 g, 10%) as a colourless powder. The mother liquor from the filtration was evaporated and the residue was dissolved in hot ethyl acetate. When the solution was cooled to room temperature, compound 10 precipitated as a colourless powder (0.25 g, 16%). The mother liquor from the ethyl acetate recrystallization was evaporated to dryness. The residue was recrystallized from diethyl ether to give 11 as a light yellow powder (79 mg, 5%). Compound 8: mp >300 °C (with decomposition); IR (KBr, cm⁻¹): 3404 (s, br, OH), 1680 (s), 1665 (w), 1600 (s), 1502 (m), 1400 (s); ¹H NMR (DMSO-d₆): δ 4.29 (s, 8H, H-10, H-20, H-30, H-40), 6.62 (s, 4H, H-41, H-42, H-43, H-44), 7.53 (m, 8H, H-5, H-6, H-15, H-16, H-25, H-26, H-35, H-36), 8.02 (m, 4H, H-4, H-14, H-24, H-34), 8.19 (m, 4H, H-7, H-17, H-27, H-37); ¹³C NMR (DMSO-d₆): δ 31.9 (t, C-10, C-20, C-30, C-40), 119.9 (s, C-1, C-11, C-21, C-31), 122.6 (d, C-4, C-14, C-24, C-34), 123.8 (d, C-7, C-17, C-27, C-37), 124.5 (C-5, C-15, C-25, C-35), 125.2 (C-6, C-16, C-26, C-36), 125.8 (C-3, C-13, C-23, C-33), 128.0 (C-8, C-18, C-28, C-38), 128.6 (C-41, C-42, C-43, C-44), 131.5 (C-9, C-19, C-29, C-39), 147.9 (C-2, C-12, C-22, C-32); MS (m/z): Intensity (%): 624 (M⁺, 52), 622 (56), 620 (32), 468 (13), 467 (22), 466 (17), 465 (18), 464 (13), 449 (28), 448 (22), 447 (18), 435 (4), 312 (100), 311 (70), 310 (88), 297 (66), 281 (38), 268 (12), 265 (20), 253 (12), 252 (23), 239 (20), 158 (73), 144 (100).

Compound 10: mp >300 °C (with decomposition), IR (KBr, cm⁻¹): 3404 (s, br,
The 'H NMR signal of the protons indicated in boldface type was irradiated.
17), 7.98 (d, 1H, H-27), 8.08 (d, 1H, H-7), 8.18-8.22 (m, 4H, H-4, H-14, H-24, H-36); NOED (%): H-30 / H-44 (0.60), H-30 / H-43 (1.0), H-30 / H-33 (1.83), H-30 / H-27 (0.61), H-10 / H-41 (0.85), H-10 / H-7 (4.12), H-20 / H-43 (0.90), H-20 / H-42 (0.85), H-20 / H-17 (0.84), H-40 / H-41 (0.67); $^{13}$C NMR (DMSO-$d_6$): δ 30.0 (t, C-30), 31.6 (t, C-10), 31.7 (t, C-20), 33.2 (t, C-40), 120.2, 120.4 (s, C-1, C-39), 120.6, 120.9 (s, C-11, C-21), 122.3, 122.4, 122.5, 122.8 (d, C-4, C-14, C-24, C-36), 123.5 (d, C-27), 123.6 (d, C-17), 123.8 (d, C-7), 124.0 (d, C-33), 124.3, 124.4, 124.5(x3), 125.1, 125.2, 125.4 (d, C-5, C-6, C-15, C-16, C-25, C-26, C-34, C-35), 125.5, 125.6, 125.7, 125.8 (s, C-3, C-13, C-23, C-37), 127.5, 127.7, 127.9, 128.2 (s, C-8, C-18, C-28, C-38), 128.1 (d, C-44), 128.7 (d, C-42), 129.1 (d, C-43), 129.4 (d, C-41), 131.1, 131.3, 131.4, 131.5 (s, C-9, C-19, C-29, C-39), 147.6, 147.7, 147.9, 148.0 (s, C-2, C-12, C-22, C-38); MS (m/z), Intensity (%): 625 (M$^+$+1, 19), 624 (M$^+$, 39), 623 (8), 622 (12), 606 (13), 480 (10), 468 (14), 313 (12), 312 (32), 311 (19), 310 (17), 297 (23), 295 (11), 282 (10), 281 (20), 268 (4), 265 (9), 252 (10), 171 (10), 160 (15), 144 (100).

Tetra-O-benzoylcalix[4]naphthalenes (8a), (10a) and (11a).

To a solution of 8 (0.312 g, 0.5 mmol) in THF (50 mL) containing DMF (5 mL) was added NaH (50% oil dispersion, 0.29 g, 6.2 mmol). The solution was stirred under N$_2$ for 30 min at room temperature. Benzoyl chloride (0.42 g, 3.0 mmol) was added dropwise to the stirred solution. The reaction mixture was
stirred for an additional 6 h at room temperature. The reaction mixture was poured into a mixture of ice (100 g) and 5% hydrochloric acid (50 mL). A yellow precipitate formed. The precipitate was filtered and washed with water until the washings were neutral to pH paper. After vacuum drying, the crude product was recrystallised twice from dichloromethane/hexane to afford 8a (0.21 g, 44%) as a light yellow powder. Calix[4]naphthalenes 10 and 11 were converted to the corresponding tetrabenzoates 10a and 11a with 40% and 36% yields respectively by using the same procedure. Tetrabenzoate 8a: mp 300-310 °C (with decomposition); IR (nujol, cm⁻¹): 1729 (s, carbonyl), 1650 (w), 1504 (s), 1402 (s); ¹H NMR (CDCl₃) at 50 °C: δ 4.29 (s, br, 8H, methylene), 6.63 (s, br, 4H, intra-annular), 6.96-8.11 (m, 36H, other aromatic); ¹³C NMR (CDCl₃) at 50 °C: 33.0 (methylene), 107.9-134.2 (aromatic), 165.4 (carbonyl); MS (FAB+, NOBA as a matrix, m/z), intensity (%): 1041 (M⁺+Na⁺, 5.5), 1040 (M⁺, 1.3), 936 (1.4), 935 (1.7), 919 (0.3), 831 (0.5), 482 (0.5), 460 (1.7). Tetrabenzoate 10a: mp 324-334 °C (with decomposition); IR (nujol, cm⁻¹): 1737 (s, carbonyl), 1600 (w), 1500 (s), 1404 (m); ¹H NMR (CDCl₃) at 50 °C: δ 4.10, 4.35, 4.63 (s, br, 8H, methylene), 6.60, 6.85 (sx2, br, 4H, intra-annular), 7.21-8.19 (m, 36H, other aromatic); ¹³C NMR (CDCl₃) at 50 °C: 34.7-30.40 (methylene), 121.3-143.4 (aromatic), 164.6, 164.9 (carbonyl); MS, (FAB+, NOBA as a matrix, m/z), Intensity (%): 1062 [(M⁺+Na⁺), 5.5], 1040 (M⁺, 10.0), 936 (3.6), 935 (6.5), 918 (1.5), 830 (2.1), 459 (1.2). Tetrabenzoate 11a: mp 215-225 °C (with
decomposition), IR (nujol, cm\(^{-1}\)): 1737 (s, carbonyl), 1680 (w), 1604 (w), 1502 (s), 1400 (s); \(^1\)H NMR (CDCl\(_3\)) at 50 °C: 3.99, 4.30, 4.40, 4.63 (sx4, br, 8H, methylene), 6.53, 6.60, 6.78, 6.93 (sx4, br, 4H, intra-annular), 7.47, 7.97 (mx2, 36H, other aromatic); \(^{13}\)C NMR (CDCl\(_3\)) at 50 °C: 29.6, 30.8, -13.1, 35.0 (methylene), 121.5-144.9 (aromatic), 164.5, 164.6, 164.8, 164.9 (carbonyl); MS (FAB+, NOBA as a matrix, m/z). Intensity (%): 1060 ((M+Na)*, 5), 1038 (M*-2, 14), 957 (5), 949 (1), 935 (12), 934 (17), 917 (2), 829 (6), 813 (2), 724 (2), 707 (2).

_Tetra-O-acetylcalix[4]naphthalenes (8b, (10b) and (11b)._}

Into acetic anhydride (8 mL) containing acetic acid (2 mL) and concentrated sulphuric acid (0.5 mL) was added 8 (100 mg, 0.17 mmol). The suspension was refluxed for 10 h. After cooling to room temperature, the solution was poured into a mixture of ice (20 g) and 5% hydrochloric acid (20 mL). After 30 min, a white precipitate formed. After filtration, the precipitate was washed with water until the washings were neutral to pH paper. The crude product was dried under vacuum and then purified by flash chromatography using dichloromethane as eluent. Compound 8b was obtained as a white powder (63.5 mg, 50%). Calix[4]naphthalene 10, and 11 were converted to the corresponding tetraacetates 10b and 11b in 52% and 48% yields respectively by using the same procedure as the above. Tetraacetate 8b: mp 310-320 °C; IR
(nujol, cm⁻¹): 1749 (s, carbonyl), 1700 (w), 1502 (s), 1404 (s); ¹H NMR (CDCl₃) at 50 °C: δ 2.40 (s, 12H, COCH₃), 4.24 (s, br, 8H, methylene), 6.45 (s, br, 4H, intra-annular), 7.26-7.92 (m, 16H, other aromatic); ¹³C NMR (CDCl₃): 20.6 (COCH₃), 32.6 (methylene), 121.8-143.6 (aromatic), 169.5 (carbonyl); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 815 ((M+Na)+, 1), 792 (M⁺, 1), 749 (1), 707 (1), 665 (1), 481 (1), 459 (2). Tetraacetate 10b: mp 324-334 °C; IR (nujol, cm⁻¹): 1762 (s, carbonyl), 1600 (w), 1550 (w), 1502 (s), 1400 (s); ¹H NMR (CDCl₃) at 50 °C: 2.45, 2.38 (s x 2, br, 12H, COCH₃), 3.88, 4.61, 4.25 (s x 3, br, 8H, methylene), 6.52 (s, br), 6.66 (d, br, 4H, intra-annular), 7.33-7.80 (m, 16H, aromatic); ¹³C NMR (CDCl₃) at 50 °C: 20.7 (COCH₃), 34.7, 32.8, 30.7 (methylene), 121.5-143.6 (aromatic); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 815 ((M+Na)+, 2), 813 (8), 792 (M⁺, 9), 771 (2), 765 (2), 749 (19), 732 (1), 723 (2), 708 (11), 690 (1), 665 (8), 648 (2). Tetraacetate 11b: mp 290-300 °C; IR (nujol, cm⁻¹): 1756 (s, carbonyl), 1600 (m), 1550 (m), 1500 (s), 1404 (s); ¹H NMR (CDCl₃) at 50 °C: 2.22, 2.32, 2.40, 2.42 (s x 4, br, 12H, COCH₃), 3.85, 4.18, 4.26, 4.63 (s x 4, br, 8H, methylene), 6.37, 6.42, 6.60, 6.69 (s x 4, br, 4H, intra-annular), 7.36-7.88 (m, 16H, other aromatic); ¹³C NMR (CDCl₃) at 50 °C: 20.7, 20.5 (COCH₃), 34.7, 32.8, 30.7 (methylene), 121.5-143.8 (aromatic), 169.9, 169.2 (carbonyl); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 815 ((M+Na)+, 2), 793 (M⁺+1, 3), 750 (5), 707 (3), 665 (3), 622 (1).
Chapter 3.

Calix[4]naphthalenes Derived from 1,8-Naphthalene Sultone

3.1. Introduction.

One of Gutsche's original motivations for studying calixarene chemistry was to try to develop enzyme mimics. The design and synthesis of hosts for suitable enzyme mimics are strong driving forces for the further development of calixarene chemistry. Most biological processes take place in an aqueous medium. However, the simple calixarenes are insoluble in water and therefore, they cannot be used to mimic the binding of substrates by enzymes, antibodies, and receptors, nor to mimic the transport of ions across biological membranes mediated by ionophores as natural carriers. Much effort has been spent to enhance the water-solubilities of calixarenes. The first water-soluble calixarene was prepared by Ungaro by treating p-tert-butylcalix[4]arene with NaH and tert-butyl-α-bromoacetate in THF, to give a tetraester. Saponification followed by acidification of the tetraester produces the corresponding tetraacid whose solubility in water is ca. 10^{-3} M. Shinkai has synthesized some calixarenes which are much more water-soluble by first removing the tert-butyl group of the p-tert-butylcalixarenes with AlCl₃ via a retro Friedel-Crafts reaction and then carrying out sulphonation with an excess of concentrated sulphuric acid. The
corresponding *para*-substituted sulphonatocalix[4]arene was formed. This water-soluble calixarene can form solution state complexes with metal cations, organic cations and neutral molecules.

Calixnaphthalenes, like calixarenes, are insoluble in water. Their poor water-solubilities limit their potential applications. When each of calix[4]naphthalenes 8, 10, and 11 was treated with concentrated sulphuric acid, a very dark tar was obtained from which no desired product could be detected. This presumably is due to the easy oxidation of calix[4]naphthalenes under these conditions, although the reaction was not investigated any further. Instead, the commercially available sulphonyl group-containing hydroxynaphthalene, 1,8-naphthalene sultone (6) was used as a starting compound.

![Chemical Structures](image)

Sultone 6 is an internal ester of the corresponding hydroxy sulphonic acid. Since the five-membered sultone ring is fused at the *peri* positions of the naphthalene ring, it is strained and, as a result, 6 has some unique chemical properties.
In contrast to the behaviour of aliphatic sulphonyl esters which result in carbon-sulphur bond fission products on nucleophilic substitution, the reaction of nucleophiles with 1,8-naphthalene sultone involves nucleophilic attack at the sulphur atom with the sulphur-oxygen bond fission. 1,8-Naphthalene sultone readily undergoes electrophilic substitution reactions. The substitution usually occurs at the 4-position (the para position with respect to the sultone ring oxygen atom). Scheme 3.1 illustrates some nucleophilic and electrophilic reactions of 1,8-naphthalene sultone.

Scheme 3.1.

3.2. Synthesis of peri-Sulphonatocalixnaphthalenes.

3.2.1. Synthesis of peri-Sulphonatocalixnaphthalenes under Basic Conditions.

Commercially available 1,8-naphthalene sultone (6) is a 50:50 aqueous dark brown paste. Attempts to remove the water by drying under vacuum at
116 °C (refluxing toluene) resulted in sublimation to give pure 6 as colourless fine crystals. The commercial product was therefore purified by sublimation to afford pure 6 prior to use.

When 6 was treated with potassium carbonate, the corresponding sulphonate dianion 6b, was presumably formed in situ. Condensation of 6b with formaldehyde gave, after acidification, the cyclic tetrameric product 20 in 15% yield as shown in Scheme 3.2.

Scheme 3.2.

The \(^1\text{H} \text{NMR} \) spectrum (Fig. 3.1) of 20 shows two sharp singlets at \( \delta 4.44 \) and \( 4.00 \) ppm which correspond to the two nonequivalent methylene bridges. The sharpness of these and all the other signals in the \(^1\text{H} \text{NMR} \) spectrum indicates that there is conformational flexibility at ambient temperature. Its \(^{13}\text{C} \) NMR spectrum reveals only twelve signals, which is consistent with the \( C_{2v} \) symmetry of structure 20.
Fig. 3.1. \(^1\)H NMR Spectrum of 20 in DMSO-\(d_6\).
Further characterization of 20 was carried by using electrospray mass spectrometry (ESMS). In the positive ion mode, an aqueous solution of 20 did not electro spray. In the negative ion mode the mass spectrum shown in Fig. 3.2 was obtained.

Peaks corresponding to the ions due to the deprotonated molecule \([M-2H]^2-\), \([M-3H]^3-\) and \([M-4H]^4-\) at \(m/z=471.5\), 313.7 and 235.3 respectively, were obtained. The peaks at 537.3, 358.0, and 321.0 correspond to the pseudo molecular ions \([M+6Na-8H]^2-\), \([M+6Na-9H]^3-\), and \([M+Na-4H]^3-\) respectively. The strong peak at \(m/z=287.4\) is due to the ion \([M-3H-SO_3H]^2-\) which corresponds to the loss of a sulphonate group from the \([M-3H]^3-\) ion. This assignment can be confirmed as derived from the parent ion at \(m/z=313.7\) by low-energy MS/MS. The MS/MS spectrum (Fig. 3.2) of the parent ion at \(m/z=313.7\) also shows fragments at \(m/z=235.3\) and 229.7. The former fragment corresponds to the \([M-4H]^4-\) ion which is formed from the \(m/z=313.86\) ion by loss of a proton. The fragment at 229.7 corresponds to the \([M-4H-H_2O]^4-\).

Like the calixnaphthalenes derived from 1-naphthol, there are three theoretically possible isomeric peri-sulphonatocalix[4]naphthalenes besides 20, namely, 21, 22 and 23. However, only 20 was obtained. A proposed mechanism of formation of 20 is shown in Scheme 3.3.
In the sulphonate dianion (6b), the 4-position is much more electron-rich than the 2-position. The condensation of 6b with formaldehyde occurs at the 4-position with great preference to give the α,γ-dienone 24. This intermediate 24 can react with another molecule of sulphonate dianion 6b to form a para-para dimer 25. Following the hemicalixnaphthalene pathway, dimer 25 will lead only to 20, the observed C₄ᵥ compound.

### 3.2.2. Attempted Synthesis of Derivatized *peri*-Sulphonato-calixnaphthalenes under Basic Conditions.

The isolated yield of 20 is low, because of the difficulty of separation due to its great polarity. It was hypothesized that conversion of 6 to a sulphone by a Grignard reaction could avoid this problem.

When 6 was treated with ethylmagnesium bromide, however an unexpected product was obtained. The structure was elucidated by ¹H and ¹³C NMR.
as 26. This indicates that the methylene group attached to the sulphonyl group is acidic enough to form a carbanion which can couple with another molecule of 6 (Scheme 3.4).

By using a literature procedure, phenyl (1-hydroxy-8-naphthyl)sulphone (27) was obtained when 6 was treated with phenylmagnesium bromide. However, when the condensation of 26, or 27, with formaldehyde under basic conditions was attempted, no defined product was observed in the $^1$H NMR spectra of the crude products. Presumably, the bulky sulphonate ester group prevents 26 or 27 from cyclizing to form calixnaphthalenes.
3.2.3. Synthesis of *peri*-Sulphonatocalixnaphthalene under Acidic Conditions.

When 6 was refluxed with formaldehyde in the presence of 3% sulphuric acid in glacial acetic acid for 2 h, a dimer 28, and a trimer 29 were formed. When the reaction time was prolonged to six days, an oxy-*peri*-sulphonatocalixnaphthalene, 30, was obtained (Scheme 3.5).

In the $^1$H NMR spectrum of 30, two singlets appear at $\delta$ 3.90 and 5.24 ppm respectively. The former was assigned to the methylene protons (H-13 and H-33), which is confirmed by HETCOR ($\delta$ 30.46 ppm for C-13 and C-33 in its $^{13}$C NMR spectrum). The latter was assigned to the oxymethylene protons (H-3, H-23), which was confirmed by HETCOR ($\delta$ 57.19 ppm in its $^{13}$C NMR spectrum). Its FAB MS did not show a molecular ion ($M^+$), but a weak $M^+^2$ peak (1%) was
evident. Under strong acidic conditions the dimer 28 can hydrolyse to 28a, which undergoes O-alkylation to give 25a. Self-condensation of 25a produced 30 (Scheme 3.6).

Scheme 3.5.

Scheme 3.6.
3.2.4. Convergent Stepwise Synthesis of peri-Sulphonato-calixnaphthalene (20).

As described in the previous section, the dimer 28 could be obtained easily. Functionalization at the 2- and 2'-positions could be potentially effected by bromomethylation or formylation to form 31 or 32 respectively. The coupling reaction of 31 with 28 would give a cyclic tetramer 20 as outlined in Scheme 3.7.

Scheme 3.7.
When the sultone 6, sultone dimer 28 or sultone trimer 29 were treated with paraformaldehyde in the presence of HBr, only 4-bromomethyl-1,8-naphthalene sultone (34) was obtained in each case (Scheme 3.8). Thus, for 6, substitution of a naphthalene ring by a bromomethyl cation only occurred at the 4-position. For 28 and 29, retro-Friedel-Crafts reactions must have occurred. Attempts to functionalise the 2- and 2'-positions of 28 by treatment with α,α-dichloromethyl methyl ether in the presence of TiCl₄ resulted in no reaction, and only the starting material was recovered.

Scheme 3.8.
At this stage, attempts were made to hydrolyse the sultone dimer 28 to its corresponding free hydroxy sulphonic acid, 25b. It was anticipated that the electron-donating ability of the free hydroxy group would enhance the reactivity of the 2-position in the condensation reaction with formaldehyde. When the dimeric sulphonic acid 25 was treated with paraformaldehyde in the presence of HBr and ZnBr₂ in acetic acid, a dark brown crude product was obtained (Scheme 3.9). The ¹H NMR spectrum of this crude product showed that it was a mixture of many oligomers or polymers. Reverse-phase preparative thin layer chromatography (PLC) separation was conducted, but we were unable to obtain any desired product as revealed by ¹H NMR.

**Scheme 3.9.**

![Scheme 3.9](image)

3.3. **Complexation studies.**

Water-soluble calixarene hosts can form complexes with neutral aromatic
guests in aqueous solution. Shinkai has investigated the complexation properties of the \( p \)-sulphonatocalix[6]arene with a variety of guest molecules. The formation of complexes was evidenced by the enhancement of solubilities of aromatic guests in water. Quantification of the aromatic guests was achieved by employing fluorescence spectrometry.

We examined the effect of \( peri \)-sulphonatocalix[4]naphthalene (20) on the solubility of naphthalene in water by measuring the fluorescence emission intensities of aqueous naphthalene solutions. The results as summarized in Table 3.1 show that the solubility of naphthalene guests in water was not enhanced, but was dramatically decreased in the presence of 20. Thus, the complexation of 20 with a naphthalene guest does not appear to be formed, whereas a possible "salting out" effect occurred.

Table 3.1. Intensity of Fluorescence Emission (at \( \lambda = 340 \) nm) of Aqueous Naphthalene Solution in the Presence of 20.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>( C_{\text{host}} \times 10^{-3} M )</td>
<td>2.0402</td>
<td>1.0201</td>
<td>0.5101</td>
<td>0.2267</td>
<td>0.0000</td>
</tr>
<tr>
<td>Intensity</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>200</td>
</tr>
</tbody>
</table>

In order to form a complex with neutral guests, the macromolecular host should be conformationally rigid, and have defined hydrophilic and hydrophobic parts. The failure of 20 to act a host can be ascribed to the fact that 20 is
conformationally flexible and, in addition, its hydrophilic parts, namely the hydroxy and sulphonic acid groups, are separated by the hydrophobic naphthalene rings.

3.4. Summary.

The condensation reaction of 1,8-naphthalene sultone (6) with formaldehyde under basic conditions gave peri-sulphonatocalix[4]naphthalene (20). A limited mechanistic analysis shows that the formation of peri-sulphonatocalix[4]naphthalene (20) follows the "hemicalixnaphthalene" pathway, but does not follow the "pseudocalixnaphthalene" pathway. Under acidic conditions, the condensation reaction of 1,8-naphthalene sultone (6) with formaldehyde gave oxy-peri-sulphonatocalix[4]naphthalene (30), linear dimer 28 and trimer 29 in good yields.

When 1,8-naphthalene sultone (6) was treated with two equivalents of ethylmagnesium chloride, the sulphone-bridged dimer 26 was obtained.

Complexation studies showed that the peri-sulphonatocalix[4]-naphthalene (20) did not enhance the solubility of naphthalene in water, and therefore did not act as an anticipated "host".
Scanning the first quadrupole while selecting a given m/z value with the third
and 60 eV were used in MS-MS experiments. Precursor ion scans were obtained by
resulting fragments were analyzed by the third quadrupole. Collision energies of
pressure of 2x10⁻⁶ mBar for collisional activation of the sample ions. The
collision gas was added in the enclosed chamber of the hexapole to give a
were produced by collision with argon in the second (RF only) hexapole. Argon
conducted on the same instrument. Fragment ion spectra of mass-selected ions
mode using a Horse heart Myoglobin solution. MS/MS experiments were
were averaged over 4-5 scans. The mass scale was calibrated in the negative ion
without Channel Analyzer mode (MCA) with a scan dwell time of 1. Spectra were
at 0.50 KV throughout the operation. ESMS were obtained by scanning in the
mode. The operating voltage of the ES capillary was 3.00 KV and the HV Ion was
processsing. The temperature of the ES ionization source was maintained at 70
Spectrometry Data System software was used for data acquisition and

486. 66 MHz personal computer equipped with a Fisons MassLynx mass
electrospray ionization source, capable of analyzing ions up to m/z 4000. A
on a Fisons VG-Quattro triple quadrupole mass spectrometer equipped with an
Electrospray mass spectra (ESMS) in the negative mode were recorded

Chapter 2.

For general experimental conditions and instrumentation employed, see

3.5. Experimental.
To a solution of freshly sublimed 1,8-naphthalene sultone (6) (2.06 g, 10 mmol) in DMF (10 mL) under N₂ were added formalin (aqueous 37% formaldehyde solution, 0.70 mL, 8.6 mmol) and Cs₂CO₃ (2.0 g, 6.13 mmol) in water (3 mL). The reaction mixture was refluxed for 52 h, and then cooled to room temperature. After pouring into 5% hydrochloric acid (30 mL), the reaction mixture was left in a refrigerator for two days. A white precipitate formed which was filtered and washed with deionized water until the washings were neutral to pH paper, and then dried under vacuum. The crude product was crystallized from 95% ethanol to afford 20 as a white powder (0.42 g, 15%). mp 256-275 °C (with decomposition); ¹H NMR (DMSO-d₆): 4.00 (s, 4H, H-12, H-32), 4.44 (s, 4H, H-2, H-22) 6.63 (s, 4H, H-41, H-42, H-43, H-44), 7.27 (m, 4H, H-8, H-18, H-28, H-38), 7.94 (d, J=9, 4H, H-9, H-19, H-29, H-39), 8.06 (d, J=9, 4H, H-7, H-
17, H-27, H-37): $^{13}$C NMR (DMSO-$d_6$): 29.2 (C-2), 35.5 (C-12), 121.4 (C-10),
124.2 (C-44), 124.8 (C-3), 126.2 (C-7), 127.0 (C-11), 127.8 (C-8), 130.8 (C-6),
133.6 (C-9), 142.6 (C-10), 150.4 (C-5); MS (ESMS), Intensity (%): 537.3
([M+6Na-8H]$^{+}$, 15), 471.5 ([M-4H]$^{+}$, 15), 358.0 ([M+6Na-9H]$^{+}$, 63), 321.0
([M+Na-4H]$^{+}$, 13), 313.7 ([M-4H]$^{+}$, 65), 287.4 ([M-3H-SO$_3$H]$^{+}$, 51), 235.3 ([M-
4H]$^{+}$, 100), 229.7 ([M-4H-H$_2$O]$^{+}$, 72).

Phenyl (1-hydroxy-6-naphthyl) sulphone (27).

![Phenyl (1-hydroxy-6-naphthyl) sulphone](image)

To dry diethyl ether (25 mL) were added magnesium turnings (2.4 g, 100 mmol) and one third of the calculated amount of bromobenzene (23.4 mL, 100 mmol) in diethyl ether (25 mL). After stirring for 5 min, the solution became cloudy and exothermic with resulting reflux of the solvent. The rest of the bromobenzene was added dropwise. The solution was maintained at gentle boiling for an additional hour after the addition of the bromobenzene was completed. A benzene solution (50 mL) of 6 (2.50 g, 12.14 mmol) was added to the Grignard reagent solution. The reaction mixture was refluxed for 4 h, and after cooling to room temperature, 5% hydrochloric acid (50 mL) was added to
the solution. After stirring for 15 min, the aqueous and organic layers were separated. The aqueous layer was extracted with benzene. The benzene extracts (20 mL x2) were combined and dried over anhydrous magnesium sulphate. After filtering and evaporating the solvent, the residue obtained was crystallized from benzene. Sulphone 27 was obtained as colourless needles (2.05 g, 59%): lit. mp 140 °C; δ 134.5-135.0 °C; ¹H NMR (CDCl₃): 7.19 (d, J=7.3, 1H, H-2), 7.51 (m, 6H, phenyl, and H-4), 7.81 (m, 1H, H-6), 7.84 (m, 1H, H-3), 8.13 (q, J₆,₈=8.4, J₆,₇=1.2, 1H, H-5), 8.58 (q, J₇,₅=7.5, J₇,₆=1.2, 1H, H-7); ¹³C NMR (DMSO-d₆): 112.2, 119.4, 120.0, 124.6, 125.4, 127.9, 130.7, 131.7, 135.2, 136.2, 144.7, 152.4; MS (m/z), Intensity (%): 285 (M⁺+1, 18), 284 (M⁺, 100), 219 (18), 218 (14), 206 (27), 189 (6), 142 (38).

¹¹-Bis-(1-hydroxy-8-naphthylsulphonato)ethane (28).

![Diagram]

To a solution of 6 (2.0 g, 10 mmol) in dry benzene (50 mL) was added ethylmagnesium bromide (3.0 M ether solution, 8 mL) over 30 min. The reaction mixture was refluxed for 4 h. After cooling to room temperature, 5% hydrochloric acid (50 mL) was added to the solution. After stirring for 15 min, the
aqueous and organic layers were separated. The aqueous layer was extracted with benzene (20 mL x2). The benzene extracts were combined and dried over anhydrous magnesium sulphate. Filtration and evaporation of the solvent gave a residue, which was crystallized from benzene. The product 26 was obtained as colourless needles (0.95 g, 44%): mp 197-198°C; IR (KBr, cm⁻¹): 3300 (s, br, OH), 1510 (m), 1496 (s), 1400 (s), 1353 (s) 1250, 1120; ¹H NMR (CDCl₃): 2.11 (d, J=7.2, 3H, H-12), 6.54 (m, 1H, H-11), 6.89 (m, 2H, H-4, H-4'), 7.31 (m, 6H, H-2, H-2', H-3, H-3', H-6, H-6'), 7.81 (d, J=8.4, 2H, H-5, H-5'), 8.07 (d, J=7.5, 2H, H-7, H-7'); ¹³C NMR (CD₃COCD₃): 149.5 (C-8, C-8'), 136.9 (C-7, C-7'), 135.8 (C-1, C-1'), 133.0 (C-5, C-5'), 131.0 (C-10, C-10'), 128.3 (C-9, C-9'), 127.9 (C-6, C-6'), 123.4 (C-3, C-3'), 122.8 (C-4, C-4'), 118.4 (C-2, C-2'), 78.4 (C-11), 8.3 (C-12); MS (m/2), Intensity (%): 443 (M⁺+1, 15), 442 (M⁺, 55), 236 (7), 234 (6), 191 (22), 190 (100), 174 (21), 171 (12), 162 (20), 144 (36).

Bis-(1,8-sultonyl-4-naphthyl)methane (28) and 2,4-di-(1',8'-sultonyl-4'-naphthylimethyl)-1,8-naphthalene sultone (29).
To a solution of 6 (206 mg, 1.30 mmol) and paraformaldehyde (120 mg, 4.0 mmol) in glacial acetic acid (10 mL) was carefully added concentrated sulphuric acid (0.3 mL). The clear solution was refluxed for 2.5 h. After cooling to room temperature, the reaction solution was poured onto crushed ice (10 g). A white precipitate formed which was filtered, washed with water until the washings were neutral to pH paper and dried under vacuum. A crude product was obtained (202 mg), which was purified by preparative thin layer chromatography (PLC) using 50% dichloromethane / petroleum ether (30-60 °C) as eluent. The dimer 28 (148.1 mg, 54%) and the trimer 29 (21.4 mg, 8%) were obtained as white powders. Dimer 28: mp 296-298 °C; \(^1\)H NMR (DMSO-\(d_6\) / CDCl₃ (4:1)): 4.95 (s, 2H, H-11), 7.26 (d, \(J=7.8\), 2H, H-2, H-2'), 7.36 (d, \(J=7.8\), 2H, H-3, H-3'), 7.96 (m, 2H, H-6, H-6'), 8.41 (d, \(J=8.6\), 2H, H-7, H-7'), 8.49 (d, \(J=8.4\), 2H, H-5, H-5'); \(^13\)C NMR (DMSO-\(d_6\) / CDCl₃): 32.4 (C-11), 106.5, 121.0, 121.7, 127.9, 129.5 (x2), 129.8, 130.5, 131.2, 145.0 (aromatic). MS (m/z), Intensity (%): 425 (M⁺+1, 25), 424 (M⁺, 100), 360 (M⁺-SO₂, 16), 296 (M⁺-2SO₂, 24), 268 (26), 267 (12), 240 (24), 239 (81), 238 (12), 237 (20), 120 (66), 118 (14). Trimer 29: mp>300 °C (with decomposition); \(^1\)H NMR (DMSO-\(d_6\)) 4.58, 4.87 (s, 4H, H-11, H-11'), 7.07 (s, 1H, H-3), 7.24 (d, \(J=9\), 7.26 (d, \(J=6\), 7.36 (d, \(J=6\), 7.48 (d, \(J=9\) (4H, H-2', H-3', H-2'', H-3''), 7.73, 7.82, 7.97 (m, 3H, H-6, H-6', H-6''), 8.24 (d, \(J=9\), 8.35 (d, \(J=9\), 8.39 (d, \(J=9\), 8.41 (d, \(J=9\), 8.49 (d, \(J=9\), 8.52 (d, \(J=9\) (6H, H-5, H-7, H-5', H-7', H-5'', H-7''); \(^13\)C NMR (DMSO-\(d_6\)): 29.9, 32.3
(C-11, C-11'), 106.5, 106.6, 106.7, 106.8, 121.9, 122.0, 122.4, 129.3, 129.5,
129.8, 129.9, 130.1, 130.8, 131.0 (d, C-3, C-5, C-6, C-7, C-2', C-3', C-5', C-6', C-
7', C-2", C-3", C-5", C-6", C-7"), 118.9, 120.7, 120.8, 121.1, 127.7 (x2), 128.7,
129.4, 129.7, 130.5, 131.2, 131.7, 132.1, 142.2, 144.8, 144.9 (s, C-1, C-2, C-4,
C-8, C-9, C-10, C-1', C-4', C-8', C-9', C-10', C-1", C-4", C-8", C-9", C-10")}: MS
(m/z), Intensity (%): 642 (M+, 18), 424 (11), 363 (8), 239 (34), 237 (15), 226 (7),
213 (8), 203 (7), 187 (4), 182 (5), 155 (9), 127 (15), 119 (11).

**Oxa-calix[4]naphthalene sultone (30).**

To a solution of 6 (7.9 g, 50 mmol) and paraformaldehyde (4.8 g, 160
mmol) in glacial acetic acid (200 mL) was carefully added concentrated sulphuric
acid (6.0 mL). The clear solution was refluxed for 6 days. After cooling to room
temperature, the reaction solution was poured onto crushed ice (200 g). The
white precipitate was filtered, washed with water until the washing were neutral
to pH paper, and dried under vacuum. A crude product was obtained (202 mg),
which was purified by column chromatography (CC) using dichloromethane as eluent. Evaporation of the solvent left a residue, which was purified by CC using 70% dichloromethane / petroleum ether (30-60 °C) as eluent. Calixnaphthalene 30 was obtained as a white solid (1.81 g, 14%): mp 265-270 °C (with decomposition); $^1$H NMR (CDCl$_3$/DMSO-d$_6$): 4.84 (s, 4H, H-13, H-33), 5.24 (s, 4H, H-3, H-23), 7.05 (d, J=7.8, 2H, H-41, H-44), 7.21 (d, J=7.8, 2H, H-42, H-45), 7.32 (s, 2H, H-43, H-46), 7.79-7.89 (m, 4H, H-9, H-17, H-29, H-37), 8.06 (m, 4H, H-8, H-18, H-28, H-38), 8.14 (d, J=8.4, 8.24 (d, J=8.1, 4H, H-10, H-16, H-30, H-36); $^{13}$C NMR (DMSO-d$_6$): 30.5 (C-13, C-33), 57.2 (C-3, C-23), 104.6, 104.7, 120.1, 120.5, 127.2, 127.3, 127.6, 127.7, 127.9 (d, C-8, C-9, C-10, C-16, C-17, C-18, C-28, C-29, C-30, C-36, C-37, C-38, C-41, C-42, C-43, C-44, C-45, C-46), 113.3, 118.9, 119.0, 125.7, 125.8, 125.9, 128.2, 129.4, 129.7, 140.7, 143.0 (s, C-1, C-4, C-5, C-6, C-7, C-11, C-12, C-14, C-15, C-16, C-19, C-20, C-21, C-24, C-25, C-26, C-27, C-31, C-32, C-34, C-35, C-39, C-40); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 517 (M$^{+}$, C$_{44}$H$_{30}$O$_{16}$S$_{4}$Na$_{4}$, 1), 494 (2.2), 436 (4), 395 (7), 367 (6).

Attempted functionalization of the 2-position of bis-(1,8-sultonyl-4-naphthyl)methane (28).

A. Bromomethylation of 28. To a solution of the sultone dimer 28 (800 mg, 1.88 mmol) and paraformaldehyde (400 mg, 13.3 mmol) in glacial acetic acid (50
mL) were added 30%HBr in glacial acetic acid (50 mL) and anhydrous ZnBr₂ (700 mg, 3.14 mmol). The reaction mixture was heated to 90-100 °C and maintained at that temperature for one week. After cooling to room temperature, the reaction solution was poured onto crushed ice (20 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. TLC revealed at least five spots. The crude product was separated by CC with dichloromethane as eluent. The major fraction was re-chromatographed with 30% ethyl acetate / hexanes as eluent. A cream coloured crystalline product was obtained (103 mg, 9%), whose structure was assigned to be 4-bromomethyl-1,8-naphthalene sultone (34): lit. mp 145-146 °C,¹¹ mp 143-145 °C; ¹H NMR (CDCl₃): 4.92 (s, 2H, H-11), 7.10 (d, J=7.8, 1H, H-2), 7.69 (d, J=7.8, 1H, H-3), 7.95 (q, J₈.₇=7.2, J₉.₅=8.1, 1H, H-6), 8.06 (d, J=7.2, 1H, H-7), 8.42 (d, J=8.1, 1H, H-5); ¹³C NMR (CDCl₃): 29.1 (C-11), 106.2, 121.2, 128.8, 129.2, 130.5 (C-2, C-3, C-5, C-6, C-7), 122.1, 128.6, 129.4, 144.8, 147.4 (C-1, C-4, C-8, C-9, C-10); MS (m/z), Intensity (%): 300 (M⁺, 4), 298 (M⁺, 4), 219 (100), 155 (35).
B. Formylation of 28. To a solution of the sultone dimer 28 (100 mg, 0.24 mmol) in dry dichloromethane (5 mL) cooled to 0-5 °C in a salt-ice bath were added TiCl₄ (0.10 mL, 0.90 mmol) and α,α-dichloromethyl methyl ether (0.10 mL, 1.10 mmol). After removing the ice bath, the reaction mixture was warmed to room temperature and stirred for 3 h. When the crude reaction mixture was checked by TLC, the starting material remained unchanged with no evidence of product formation.

Bis-(1-hydroxy-8-sulphonato-4-naphthyl)methane (25b).

The sultone dimer 28 (500 mg, 1.18 mmol) was dissolved in a mixture of absolute ethanol (40 mL) and water (20 mL) containing KOH (530 mg, 9.4 mmol). After refluxing for 2 h under N₂, the starting material disappeared as evidenced by TLC. The solvent was evaporated under vacuum and the residue was suspended in hot water (80-90 °C, 6 mL), filtered, and dried under vacuum. Compound 25b was obtained (510 mg, 94%) as a reddish solid: mp>300 °C (with decomposition); ¹H NMR (D₂O): 4.42 (s, 2H, H-1), 6.92 (m, 4H, H-2, H-3, H-2', H-3'), 7.34 (m, 2H, H-6, H-6'), 7.98 (d, J=8.4, 2H, H-7, H-7'), 8.23 (d, J=7.5, 2H,
H-5, H-5'); $^{13}$C NMR (D$_2$O): 35.6 (C-11), 114.7, 124.4, 127.0, 128.9, 129.3, 129.5 (x2), 134.2, 136.6, 149.3 (aromatic).

Complexation Studies.

A series of aqueous peri-sulfonatocalixarene (20) solutions of different concentrations were prepared. Naphthalene (215.0 mg) was suspended in each solution of 20 (10.00 mL) in capped test tubes and sonicated for 1 h at room temperature. Residual undissolved naphthalene solid was removed by centrifugation followed by filtration. The intensities of fluorescence emissions of the saturated aqueous naphthalene solutions were measured on a Varian SF-330 Spectrofluorometer at 340 nm with excitation at 285 nm. The results are summarized in Table 3.1.
Chapter 4.

Calix[4]naphthalenes Derived from 3-Hydroxy-2-Naphthoic Acid

4.1. Introduction.

Intra-annular hydroxy groups which are in close proximity to one another in calixarenes play a very important role in supramolecular chemistry. They form intramolecular hydrogen bonds, which hold the conformation of calixarenes in the "cone" and serve as a "cap" for the cavity of calixarenes so that stable inclusion complexes with guests can be formed.

As described in Chapter 3, peri-sulphonatocalix[4]naphthalene (20) did not form an inclusion complex with neutral guests possibly because of the absence of intra-annular hydroxy groups. Since calixnaphthalenes 8, 10 and 11 do not have intra-annular hydroxy groups, they are not expected to form inclusion complexes.

The calix[4]naphthalene 35, which would meet this basic requirement for complexation was therefore designed. A retrosynthesis of 35 gives 2-hydroxy-3-hydroxymethylnaphthalene (36), which can be prepared from commercially available 3-hydroxy-2-naphthoic acid (7a). The corresponding chemical transformation of 36 to 35 is a self-condensation / cyclization.
4.2. Synthesis of Calixnaphthalenes.

4.2.1. Self-Condensation of 36 under Basic Conditions.

Lithium aluminum hydride (LAH) reduction of 3-hydroxy-2-naphthoic acid (7a) in dry THF produced 2-hydroxy-3-hydroxymethylnaphthalene (36) in 61% yield (Scheme 4.2) in addition to several by-products. Chaulk has identified these by-products as 3-methyl-2-hydroxynaphthalene (37) and 2-formyl-3-hydroxynaphthalene (38).75

Benzyl alcohol-type compounds have been suggested as intermediates for the formation of calixarenes in Gutsche's procedure.12 However, when the self-condensation of 36 was carried out under the conditions similar to those of
Gutsche, a light brown powder was isolated from the dark brown reaction mixture in 22% yield (Scheme 4.3). Its $^1$H NMR spectrum showed a singlet (equivalent to two protons) at $\delta$ 4.60 ppm in the normal methylene proton region and a doublet (equivalent to two protons) at $\delta$ 5.07 ppm. When D$_2$O was added to the sample solution in CDCl$_3$, this doublet became a singlet, allowing it to be assigned as a hydroxymethyl group. Its $^{13}$C NMR spectrum shows two secondary carbon signals at $\delta$ 25.01, and 62.00 ppm, which confirmed the existence of the methylene and hydroxymethyl groups. In its mass spectrum, $m/z=312$ is the molecular ion peak (100%). Based on this evidence, the structure of this compound was assigned as 39, a pyran ring-containing bis-naphthalene. A mechanism for the formation of 39 is suggested in Scheme 4.3. Under strongly basic and high temperature conditions, compound 36 was likely converted to naphthaquinone methide 40. An apparent hetero [4+2] cycloaddition of the hetero diene 40, with the dieneophile 36 gives compound 39.
4.2.2. Self-Condensation of 36 under Acidic Conditions.

Conditions similar to those of Högberg\textsuperscript{13} were used in the synthesis of calix[4]resorcinarenes by self-condensation of 36. Treatment with hydrochloric acid in ethanol afforded only 2-hydroxy-3-naphthylmethyl ethyl ether (41) in good yield (Scheme 4.4).

When 36 was treated with 5% TFA in chloroform by stirring for 14 h at room temperature, trifluoroacetate 41\textsuperscript{a} was isolated in 37% yield. When 36 was refluxed in dry chloroform in the presence of 5% TFA, a purple solution was formed. After workup, the crude product was subjected to flash column
chromatography with dichloromethane as eluent and subjected to PLC with 50% dichloromethane / petroleum ether (30-60 °C) as eluent to give a product as colourless fine crystals in 15% yield (Scheme 4.4). The mass spectrum shows a molecular ion peak at m/z = 624. Its 1H NMR spectrum revealed a singlet methylene signal, and its 13C NMR spectrum revealed eleven carbon signals. All data are consistent with the calix[4]naphthalene, structure 35, which has also been reported by Andreetti et al.\textsuperscript{75a}

Scheme 4.4.

Compound 35 is conformationally flexible at room temperature, as evidenced by a methylene singlet at δ 4.57 ppm. As the temperature was decreased, this signal became broader with coalescence temperature of ca. -10 °C. Cooling to -40 °C gave an AB quartet (Fig. 4.1), suggesting a
Fig. 4.1. VT $^1$H NMR Spectra of 35 in CDCl$_3$. 

![NMR Spectra of 35 in CDCl$_3$ at various temperatures]
rigid conformation.

Similarly to calix[4]naphthalenes 8, 10 and 11, as discussed in Chapter 2, tetramer 35 can adopt “cone”, “partial cone”, “1,3-alternate” and “1,2-alternate” conformations. The singlet $^1$H NMR signal of the methylene bridge indicates a symmetrical conformation. The unusually high chemical shift at $\delta$ 10.95 ppm and the low IR absorption at 3135 cm$^{-1}$ for the hydroxy groups are consistent with the existence of intramolecular hydrogen bonding. This indicates that 35 most likely exists in a “cone” conformation.

The by-products of self-condensation of 36 under acidic conditions were unidentified oligomers or polymers, whose formation is due to the great reactivity of 36. In order to control the reactivity of 36, methylation of naphthoic acid 7a was considered. The reaction sequence outlined in Scheme 4.5 was employed to produce 43. However, when 43 was reacted under similar conditions used to form 35, the $^1$H NMR of the crude product obtained was very broad and poorly resolved. After crystallizing three times from acetonitrile, the $^1$H NMR signals were still found to be very broad. These broad $^1$H NMR signals could be a result of slow interconversion of conformations (see Chapter 2). However, when the sample solution in DMF-$d_7$ was heated to 100 °C, its $^1$H NMR signals did not become any sharper. Thus, it appears as though many oligomers form in the self-condensation product, as verified by TLC. No evidence for the presence of any well-defined cyclic oligomer was formed.
Examination of molecular models revealed a strong steric repulsive methoxy group interaction with one another, which may inhibit the formation of a cyclic tetramer. Another reason for failure to form a cyclic tetramer could be the absence of hydrogen bonding in the penultimate precursor of 43a, such hydrogen bonding being presumed to be a strong driving force to form calixarenes.\textsuperscript{12}


2-Hydroxy-3-hydroxymethylnaphthalene (36) is an ideal building block for supramolecular compounds since calixnaphthalenes derived from it will have intra-annular hydroxy groups which, as discussed previously, appear to be
necessary for host-guest chemistry.

In order to alter the cavity size and the conformation of macrocyclic compounds derived from 7a, the methylene bridge can be replaced with a longer carbon chain, e.g. to form dihomocalix[4]naphthalene (46), in which two methylene bridges are substituted by two ethylene bridges. Due to the large size, a sulphur atom is often used as a temporary template to facilitate cyclization in the synthesis of strained carbocycles and this procedure was adopted in the synthesis of 46. The complete approach for the synthesis of 46 is illustrated in Scheme 4.6.

Condensation of 3-hydroxy-2-naphthoic acid 7a with formaldehyde in glacial acetic acid containing 5% concentrated sulphuric acid gave dimer 47 in a quantitative yield. This compound is also commercially available under the trivial name of pamoic acid. Starting from 47, sequential methylation, reduction and bromination gave bis-(2-methoxy-3-bromomethyl-4-naphthyl)methane (49). Reaction of 49 with thiourea formed a bis(isothiocyanate) salt, which was subsequently hydrolysed to produce bis-(2-methoxy-3-mercaptopropyl-4-naphthyl)-methane (50). The coupling reaction of 49 and 50 under basic and high dilution conditions gave dithiadihomocalix[4]naphthalene (51).

The sulphur extrusion reaction is a key step in this synthetic approach.
Among many sulphur extrusion approaches available, the direct photochemical reaction is one of the most attractive, as it has the fewest number of steps and occurs under neutral conditions. Thus, 46 was produced in 22% yield when 51 was subjected to photochemical irradiation for 18 h in the presence of the
sulphur scavenger trimethyl phosphite in a Pyrex® tube placed in a Rayonet®
photochemical reactor fitted with RPR 3500 Å lamps. Trimethyl phosphite reacts
with the dithia compound to form an intermediate with an S-P bond. This
intermediate undergoes a homolytic fission to give a carbon diradical, whose
recombination gives the product with C-C bond formation. The reaction is
facilitated if the sulphur compound is tethered.\textsuperscript{23}

\textbf{Scheme 4.7.}

\begin{equation}
\begin{array}{c}
\text{R} \quad \text{S} \\
\text{R} \quad \text{S} \\
\end{array}
\begin{array}{c}
\xrightarrow{\text{P(OCH₃)₃}} \\
\xrightarrow{\text{hv}} \\
\xrightarrow{\text{P(OCH₃)₃}} \\
\xrightarrow{\text{hv}} \\
\end{array}
\begin{array}{c}
\text{R} \\
\text{R} \\
\end{array}
\end{equation}

Trimethyl phosphite also serves as a reaction medium to form a
suspension of substrate 51. As a dispersed solid, the resulting carbon diradical
is relatively immobile,\textsuperscript{23} which thus favours cyclization over linear polymerization.

A Wittig-rearrangement sulphur extrusion procedure failed to give any
desired product, forming a dark brown residue instead. It is possible that the
naphthalene carbanion generated by \textit{n}-butyllithium undergoes a tautomeration
and methylation instead of a Wittig rearrangement (Scheme 4.8).

Ambient temperature \textit{¹}H NMR spectrum of 51 (Figure 4.2) suggests that it
is conformationally flexible since all signals are sharp and well-defined. The
VT $^1$H NMR spectra (Figure 4.2) show the signals due to the sulphide methylene bridges at $\delta$ 3.86 ppm with a coalescence temperature at approximately -40 °C. The signals due to the *para-para* methylene bridge at $\delta$ 4.68 ppm are, however
Fig. 4.2. $^1$H NMR Spectra of 51 in CDCl$_3$. 
Fig. 4.3. VT $^1$H NMR Spectra of 46 in CDCl$_3$. 

8
6
4
2 PPM

20°C
0°C
-15°C
-20°C
-25°C
-30°C
-40°C
-50°C
not split even at -55 °C. The methoxy signal at δ 3.29 ppm separates into three broad signals at δ 4.00, 3.38 and 2.85 ppm in a 1:1:2 ratio. The lower-field signals at δ 2.85 ppm suggest a conformer in which two methoxy groups are shielded by the two opposing naphthalene rings.

The ambient temperature ¹H NMR spectrum of 46 (Figure 4.3) indicates similar conformational flexibility. However, the coalescence temperature of the signal due to the ethylene bridges at δ 3.06 ppm is at approximately -20 °C. Unlike 51, the position of the signal for the methoxy groups does not change, even on cooling to -60 °C. The para-para methylene bridge at δ 4.68 ppm does not split. The methoxy groups appear as a broad singlet at δ 2.91 ppm, which suggests that the conformation of 51 is symmetric, "cone", "1,2-alternate", and/or "1,3-alternate". The unusual upfield chemical shift suggests shielding by the naphthalene rings, which excludes the possibility of the "cone".

The single crystal X-ray diffraction structure of 46 is depicted in Figure 4.4. In the solid state, the structure of 46 contains a center of symmetry as its only symmetry element and has a "1,2-alternate" type of orientation of the naphthalene rings. Fig.4.4 also shows that one pair of symmetry-related methoxy groups (C-47 and C-49) is situated closer (3.52 Å) to its opposite symmetry-related naphthalene planes than the other pair (6.26 Å). This supports the arguments presented above concerning the unusual upfield chemical shifts observed for the methoxy groups in the ¹H NMR spectrum of 46.
Fig. 4.4. ORTEP Diagram of the Molecular Structure of 46.

(The numbering system is not the same as the one in experimental.)
4.4. Summary.

Self-condensation of 2-hydroxy-3-hydroxymethylnaphthalene (36) under TFA-catalysis in chloroform affords a cyclic tetramer 35 in 14.5% yield. VT $^1$H NMR studies showed that the coalescence temperature of 35 was -10 °C and it existed in a "cone" conformation at -60 °C. Self-condensation of 36 under basic conditions gave a pyran ring-containing compound 40 through an apparent [4+2] cycloaddition, but did not give a corresponding calixnaphthalene.

Self-condensation of 2-methoxy-3-hydroxymethylnaphthalene (45) under acidic conditions gave linear oligomers, but did not produce a calixnaphthalene-type product.

Starting from 3-hydroxy-2-naphthoic acid (7a), a convergent synthetic procedure afforded a dihomocalix[4]naphthalene 46, which is the first example of this class of compounds. VT $^1$H NMR studies showed that at -60 °C the preferred conformation of 46 was a "1,2-alternate" or "1,3-alternate" in solution. X-ray crystallography showed that it prefers a "1,2-alternate" or centrosymmetric, box-like conformation in the solid state.
4.5. Experimental.

For general experimental conditions and instrumentation employed, see Chapter 2.

*Methyl 3-methoxy-2-naphthoate (44).*

![Chemical Structure](image)

To a solution of 3-hydroxy-2-naphthoic acid (7a) (1.88 g, 10 mmol) in dichloromethane (50 mL) and water (38 mL) under vigorous stirring, were added Adogen® 464 (0.5-1.0 mL) all at once and then dimethyl sulphate (6.48 mL, 60 mmol) dropwise over 15 min. The reaction mixture was stirred at room temperature for 10 h. The two layers were separated, and the aqueous layer was extracted with two 20 mL portions of dichloromethane. The combined dichloromethane extracts were dried over MgSO₄ and filtered. The solvent was removed and the residue was diluted with water (10 mL) and then extracted with ether (50 mL). The organic layer was washed with 2.0 M aqueous ammonia solution (20 mL) to remove the excess dimethyl sulphate, and then washed with aqueous saturated sodium chloride solution until the washings were neutral to pH paper. After drying over anhydrous MgSO₄ and filtering, the solvent was evaporated. Compound 44 was obtained as a colourless solid (2.05 g, 95%) by flash column chromatography using 40% ethyl acetate / hexanes as eluent: mp
80-82 °C; 'H NMR (CDCl₃): 3.96 (s, 3H, OCH₃), 4.00 (s, 3H, CO₂CH₃), 7.21 (s, 1H, H-4), 7.37, 7.52 (m, 2H, H-6, H-7), 7.74 (d, J=8.4, 1H, H-5 or H-8), 7.82 (d, J=7.8, 1H, H-5 or H-8), 8.31 (s, 1H, H-1); ¹³C NMR (CDCl₃): 52.0 (OCH₃), 55.7 (CO₂CH₃), 106.5, 121.5, 124.2, 126.2, 128.2, 128.4, 132.5, 135.9 (C-1, C-2, C-4-C-10), 155.5 (C-3), 166.5 (CO₂CH₃); MS (m/z), Intensity (%): 216 (M⁺, 100), 185 (83), 183 (31), 155 (23), 142 (18), 128 (13), 27 (53), 115 (12), 114 (25).

2-Hydroxy-3-hydroxymethylnaphthalene (36).

LAH (10 g, 263 mmol) was suspended in dry THF (100 mL). 3-Hydroxy-2-naphthoic acid (7a) (10 g, 53.2 mmol) in THF (50 mL) was added over a period of 1 h to the vigorously stirred reaction mixture which was cooled in a Dry Ice-acetone bath. When the addition was completed, the cooling bath was removed, and the reaction mixture was refluxed for 10 h. After cooling to room temperature, water was carefully added to the reaction mixture to destroy the excess LAH. The reaction mixture was diluted with ether (50 mL) and then added to 5% sulphuric acid (50 mL). The two layers were separated and the aqueous layer was extracted with ether (50 mL x2). The combined organic extracts were dried over MgSO₄, filtered and the solvent was evaporated. The
crude product was recrystallised twice from ethyl acetate / hexanes. A cream coloured crystalline product 36 was obtained (5.60 g, 61%): lit. mp 190-191 °C.\(^6\) mp 191-193 °C; \(^1\)H NMR (CD\(_3\)COCD\(_3\)): 4.51 (t, J=5.7, 1H, H-12), 4.88 (d, J=5.7, 1H, H-11), 7.19 (s, 1H, H-1), 7.27 (m, 1H, H-6 or H-7), 7.35 (m, 1H, H-6 or H-7), 7.66 (d, J=7.8, 1H, H-5 or H-8), 7.77 (d, J=7.8, 1H, H-5 or H-8), 7.83 (s, 1H, H-4), 8.79 (s, 1H, H-13); \(^{13}\)C NMR (CD\(_3\)COCD\(_3\)): 61.7 (C-11), 109.7, 123.9, 126.5, 126.7, 126.9, 128.4, 129.5, 131.7, 135.1, 155.6 (aromatic); MS (m/2), Intensity (%): 174 (M\(^+\), 33), 156 (43), 128 (100), 127 (15), 115 (11), 64 (13).

2-Methoxy-3-hydroxymethylinaphalene (45).

\[
\begin{array}{c}
\text{OCH}_3 \\
\text{CH}_2\text{OH}
\end{array}
\]

LAH (151 mg, 3.97 mmol) was suspended in dry THF (1.5 mL). Compound 44 (261 mg, 1.29 mmol) in THF (2 mL) was added over a period of 1 h to the vigorously stirred reaction mixture, which was cooled in a Dry Ice-acetone bath. When the addition was completed, the cooling bath was removed, and the reaction mixture was refluxed for 4 h. After cooling to room temperature, water was carefully added to the reaction mixture to destroy the excess LAH. The reaction mixture was diluted with ether (10 mL) and then added to 5% sulphuric acid (10 mL). The two layers were separated and the aqueous layers
were extracted with ether (10 mL x2). The combined organic extracts were dried over MgSO₄, filtered and the solvent was evaporated. The crude product was recrystallised twice from ethyl acetate/hexanes. A colourless crystalline product, 45, was obtained (218 mg, 90%): lit. mp 71-72°C, 87 mp 70-71 °C; IR (Nujol, cm⁻¹), 3602 (s, br, OH), 1650 (s), 1640, 1550, 1500 (s); ¹H NMR (CDCl₃): 2.39 (t, J=6, 1H, H-12), 3.98 (s, 3H, OCH₃), 4.83 (d, J=6, 2H, H-11), 7.13 (s, 1H, H-1), 7.35 (m, 1H, H-6 or H-7), 7.44 (m, 1H, H-6 or H-7), 7.73-7.78 (m, 3H, H-4, H-5, H-8); ¹³C NMR (CDCl₃): 55.4 (OCH₃), 62.5 (C-11), 105.2, 123.9, 126.3, 126.4, 127.5, 127.6, 128.6, 130.5, 134.1, 155.9 (aromatic carbons); MS (m/z), intensity (%): 188 (M⁺, 100), 172 (10), 159 (52), 155 (13), 144 (22), 128 (23), 127 (36), 115 (30).

1-Hydroxymethyl-dibenzo[c,j]-10H-9-oxaanthracene (39).

To a solution of 36 (1.0 g, 5.75 mmol) in xylenes (60 mL) under N₂ was added NaOH (8 mg, 0.2 mmol) in water (5 mL). Upon heating, the colourless emulsion turned a cream colour. The reaction mixture was refluxed for one week. After cooling to room temperature, the solvent was removed under
vacuum. The dark brown residue was extracted with chloroform (250 mL) for 6 h using a Soxhlet extraction apparatus. After evaporating the solvent, the residue was purified by PLC using 40% ethyl acetate/hexanes as solvent. The pyran compound 39 was obtained as a colourless powder (401 mg, 22%): mp 140-142 °C; $^1$H NMR (CD$_2$Cl$_2$): 4.58 (s, 2H, H-11), 5.04 (s, 2H, H-12), 7.41-7.96 (m, 11H, aromatic); $^{13}$C NMR (CD$_2$Cl$_2$): 24.9 (C-11), 61.9 (C-12), 121.0, 122.0, 124.5, 124.6, 126.2, 126.4, 126.7, 126.9, 127.2, 128.2, 128.5, 128.8, 129.1, 129.7, 130.5, 133.3, 145.2 (aromatic); MS (m/z), Intensity (%): 312 (M$^+$, 100), 311 (M$^+$-1, 79), 294 (16), 282 (22), 281 (89), 265 (12).

2-Hydroxy-3-naphthylmethyl trifluoroacetate (41a)

To a solution of 36 in chloroform (8 mL) was added TFA (0.4 mL). The reaction mixture was stirred for 14 h at room temperature. The reaction mixture was washed with water until the washings were neutral to pH paper. After drying with MgSO$_4$, filtering, and evaporating the solvent, the crude product was purified by PLC using dichloromethane as eluent. Compound 41a was obtained as a light brown solid (56 mg, 37%): mp 113-115 °C; $^1$H NMR (CDCl$_3$): 5.58 (s, 2H, H-11), 7.16 (s, 1H, H-1), 7.36 (m, 1H, H-6, H-7), 7.46 (m, 1H, H-6 or H-7).
7.66 (d, J=8.1, 1H, H-5 or H-8), 7.78 (d, J=7.8, 1H, H-5 or H-8), 7.83 (s, 1H, H-4).


To a solution of 36 (200 mg, 1.15 mmol) in chloroform (15 mL) was added trifluoroacetic acid (TFA, 0.75 mL). After refluxing for 48 h, the reaction mixture was transferred to a separatory funnel and washed with water until the washings were neutral to pH paper. After drying over MgSO₄ and filtering, the solvent was evaporated. The crude product was purified by flash column chromatography using dichloromethane as eluent followed by re-chromatography with PLC using 50% dichloromethane / petroleum ether (30-60 °C) as eluent.

*Calix[4]naphthalene 35* was obtained as a colourless product (26 mg, 15%): mp>250°C (with decomposition); IR (Nujol, cm⁻¹): 3135 (s, br, OH); ¹H NMR (CDCl₃): 4.47 (s, 8H, H-11, H-11', H-11", H-11"'), 7.23 (m, 4H, H-7, H-7', H-7", H-7"'), 7.50 (m, 4H, H-8, H-8', H-8", H-8"'), 7.60 (d, J=7.8, 4H, H-6, H-6', H-6", H-6"'), 7.85 (s, 4H, H-4, H-4', H-4", H-4"'), 8.38 (d, J=8.7, 4H, H-5, H-5', H-5", H-5"'),
To a solution of 36 (100 mg, 0.53 mmol) in 95% ethanol (20 mL) was added concentrated hydrochloric acid (5 mL). The reaction mixture was stirred at room temperature for 10 h, during which no change was observed on checking by TLC. The reaction mixture was then heated to 70-75°C and kept at that temperature for 3 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice (25 g). A purple precipitate formed. After filtering, the precipitate was washed with water until the washings were neutral to pH paper and then dried under vacuum. The crude product was extracted with 50 mL of ether. After evaporating the solvent, the crude product was purified by PLC with dichloromethane as eluent to afford 41 as a colourless solid (395 mg, 68%): mp 80-82°C; ¹H NMR (CDCl₃): 1.29 (t, J=6.9, 3H, H-13), 4.86 (s, 2H, H-
11). 7.25 (s, 1H, H-1), 7.30 (m, 1H, H-6 or H-7), 7.40 (m, 1H, H-6 or H-7), 7.53 (s, 1H, H-4), 7.64 (q, J=6.9, 2H, H-12), 7.68-7.72 (m, 2H, H-5, H-8), 7.78 (s, OH);

$^{13}$C NMR (CDCl$_3$): 15.1 (q, C-13), 66.2 (t, C-12), 72.3 (t, C-11), 110.0 (d, C-1), 123.6, 126.3 (x2), 127.4, 127.5 (d, C-4, C-5, C-6, C-7, C-8), 124.9, 128.2, 134.7, 154.2 (s, C-2, C-3, C-9, C-10); MS (m/z), Intensity (%): 202 (M$^+$, 26), 157 (15), 156 (59), 129 (12), 128 (100), 127 (11), 115 (6).

**Attempted synthesis of calixnaphthalenes from 2-methoxy-3-hydroxy-methylnaphthalene (45).**

To a solution of 45 (100 mg, 0.53 mmol) in dry chloroform (10 mL) was added TFA (0.5 mL). After refluxing for 48 h, the reaction mixture was transferred to a separatory funnel and washed with water until the washings were neutral. After drying over MgSO$_4$ and filtering, the solvent was evaporated. The crude product was crystallized from ethanol to give a purple powder (67 mg). The $^1$H NMR of the crude product showed that it consists of many oligomers, and it was not further purified and characterized.

**4,4'-Bis-(methyl 3-methoxy-2-naphthylcarboxylate)methane (48a).**
A solution of 3-hydroxy-2-naphthoic acid (7a) (2.0 g, 10.6 mmol) and paraformaldehyde (0.43 g, 14.2 mmol HCHO) in glacial acetic acid (20 mL) containing concentrated sulphuric acid (0.1 mL) was refluxed for 10 h. After cooling to room temperature, a light yellow precipitate formed, which was filtered and washed with aqueous saturated NaCl solution (5 mL x2). The product was dried under vacuum to give 3.9 g (95%) of bis(3-hydroxy-2-naphthoyl)methane (47) as a light yellow powder, mp>300°C (with decomposition). This was used directly in the following step without further purification.

To a solution 47 (3.9 g) in CH₂Cl₂ (15 mL) was added water (30 mL), Adogen® 464 (0.5 mL), and aqueous 10% NaOH (10 mL). To the vigorously stirred mixture at room temperature was added dimethyl sulphate (6.5 mL, 68.8 mmol) dropwise over a period of 15 min at room temperature. The mixture was stirred at room temperature for 10 h. After separation of the two layers, the aqueous layer was extracted with CH₂Cl₂ (20 mL x2). The solvent was removed on a rotary evaporator and the residue was mixed with water (10 mL) and diethyl ether (50 mL). The ether extracts were separated and washed with aqueous 2.0 M NH₄OH (10 mL x2) in order to remove the excess dimethyl sulphate. The ether extracts were washed with aqueous saturated NaCl (60 mL x2) and then was dried over anhydrous MgSO₄, filtered and evaporated on a rotary evaporator. After drying under vacuum, the crude product was flash chromatographed using 40% ethyl acetate / hexanes as eluent to give 48a (4.1
g. 92%) as a cream coloured solid: lit. mp 133 °C, mp 113-115 °C; "H NMR (CDCl₃): 3.81 (s, 6 H, H-12, H-12'), 3.99 (s, 6 H, H-13, H-13'), 5.01 (s, 2 H, H-11, H-11'), 7.30-7.43 (m, 4 H, H-6, H-6', H-7, H-7'), 7.76 (q, J₆,₇=8.1, J₈,₉=0.8, 2 H, H-8, H-8'), 8.17 (q, J₅,₆=8.1, J₆,₇=0.8, 2 H, H-5, H-5'), 8.26 (s, 2 H, H-1, H-1'); NOED (%): *H-5 / H-11 (3.65), H-11 / H-5 (20.97), H-8 / H-1 (14.81); 13C NMR (CDCl₃): 22.6 (t, C-11, C-11'), 52.3 (s, C-13, C-13'), 62.7 (q, C-12, C-12'), 123.7 (s, C-4, C-4'), 124.7 (d, C-8, C-8'), 125.2 (d, C-7, C-7'), 128.3 (d, C-6, C-6') 129.3 (d, C-5, C-5'), 129.8 (s, C-2, C-2'), 130.0 (s, C-9, C-9'), 132.3 (d, C-1, C-1'), 135.2 (s, C-10, C-10'), 153.6 (s, C-3, C-3'), 166.8 (s, C-14, C-14'); MS (m/z): intensity (%): 444 (100, M⁺), 412 (81), 397 (76), 381 (8), 353 (56), 337 (43), 324 (50), 280 (20); HRMS: M⁺ 444.1578, calcd for C₂₇H₂₄O₆ 444.1573.

Bis-(2-methoxy-3-hydroxymethyl-1-naphthyl)methane (48).

* The 'H NMR signal of the protons indicated in boldface type was irradiated.
To a suspension of LAH (0.64 g 16.8 mmol) in anhydrous THF (30 mL) under Ar at -78 °C, was added dropwise a solution of 48a (4.9 g, 11 mmol) in THF (40 mL) over 30 min. After the addition was complete, the cooling bath was removed and the reaction mixture was allowed to warm to room temperature. The mixture was stirred for an additional 4 h at room temperature and was worked up by adding water dropwise until the excess LAH was decomposed, followed by the addition of 10% sulphuric acid (40 mL). The organic layer was separated, washed with aqueous 5% NaHCO₃ solution, followed by saturated NaCl (20 mL x2). After drying over anhydrous MgSO₄ and filtering, the solvent was removed to afford, after vacuum drying, crude 48 (4.3 g, 67% yield). The crude product was sufficiently pure by TLC to be used for the subsequent step without further purification. For characterization, the crude reaction product (50 mg) was purified by PLC using 30% ethyl acetate/hexanes as eluent. Isolation of the major band afforded colourless crystalline 48 (42 mg): mp 89-90 °C; \(^1\)H NMR (CDCl₃): 2.38 (br, 2H, OH), 3.86 (s, 6H, H-12, H-12'), 4.93 (two overlapping singlets, 4H, H-11, H-11', H-13, H-13'), 7.25-7.28 (m, 4H, H-6, H-6', H-7, H-7'), 7.66-7.68 (m, 2H, H-5, H-5'), 7.69 (s, 2H, H-4, H-4'), 8.10-8.13 (m, 2H, H-8, H-8'); \(^13\)C NMR (CDCl₃): 22.7 (t, C-11, C-11'), 61.5 (q, C-12, C-12'), 62.2 (t, C-13, C-13'), 124.4 (d, C-8, C-8'), 124.8 (d, C-6, C-6'), 126.0 (d, C-7, C-7'), 127.1 (d, C-4, C-4'), 128.3 (d, C-5, C-5'), 126.6 (s, C-1, C-1'), 131.1 (s, C-3, C-3'), 133.1 (s, C-10, C-10'), 153.8 (s, C-9, C-9'), 166.6 (s, C-2, C-2'); MS (m/z), Intensity (%): 388
To a solution of 48 (0.50 g, 1.3 mmol) in CH₂Cl₂ (30 mL) was added PBr₃ (0.40 mL, 4.1 mmol) dropwise over 30 min. The reaction solution was stirred at room temperature for 4 h. The reaction was worked up by diluting the mixture with an additional 20 mL-portion of dichloromethane, and washing with water (30 mL x3). After drying over MgSO₄ and filtering, the solvent was evaporated to afford, after flash chromatography with 30% ethyl acetate / hexanes as eluent, 49 (0.49 g, 74%) as a colourless powder: mp 191-193 °C; ¹H NMR (CDCl₃): 4.05 (s, 6H, H-12, H-12'), 4.80 (s, 4H, H-13, H-13'), 4.95 (s, 2H, H-11, H-11'), 7.22-7.29 (m, 4H, H-6, H-6', H-7, H-7'), 7.63 (m, 2H, H-5, H-5'), 7.75 (s, 2H, H-4, H-4'), 8.11 (m, 2H, H-8, H-8'); NOED(%): H-8 / H-11 (4.55), H-8 / H-7 (2.73), H-11 / H-8 (18.14); ¹³C NMR (CDCl₃): 23.0 (t, C-11, C-11'), 29.4 (t, C-13, C-13'), 62.9 (q, C-12, C-12'), 124.5 (d, C-8, C-8'), 124.8, 126.5 (d, C-6, C-6', C-7, C-7'), 128.1(d, C-5, C-5'), 129.1(s, C-1, C-1'), 130.4 (d, C-4, C-4'), 130.5 (s, C-3, C-3'),
130.9 (s, C-10, C-10'), 133.7 (s, C-9, C-9'), 153.6 (s, C-2, C-2'); MS (m/z). Intensity (%): 514 (M⁺, 70), 512 (M⁺, 35), 435 (20), 433 (18), 412 (7), 309 (18), 265 (61), 263 (63), 155 (100); HRMS: M⁺ 511.9994, calcd for C_{25}H_{22}O_{2}Br_{2}, 511.9986.

Bis-(2-methoxy-3-mercaptomethyl-1-naphthyl)methane (50).

A solution of 49 (2.0 g, 3.9 mmol) and thiourea (0.59 g, 7.8 mmol) in THF (100 mL) was refluxed for 4 h under N₂. The solvent was evaporated on a rotary evaporator and the residue was dissolved in aqueous 1% NaOH (250 mL). The mixture was refluxed for 4 h, cooled to room temperature and neutralized with aqueous 3 M HCl. The resulting white precipitate was filtered and dried under vacuum. Flash chromatography of the crude product using 20% ethyl acetate / hexane as eluent afforded 50 (1.4 g, 85%) as colourless crystals: mp 134-135 °C; ¹H NMR (CDCl₃): 3.95 (s, 6H, H-12, H-12'), 3.96 (s, 4H, H-13, H-13'), 3.99 (s, 2H, SH, exchangeable with D₂O), 4.95 (s, 2H, H-11, H-11'), 7.21-7.26 (m, 4H, H-6, H-6', H-7, H-7'), 7.60-7.63 (m, 2H, H-5, H-5'), 7.64 (s, 2H, H-4, H-4'), 8.12-
4, 8.12-8.15 (m, 2H, H-8, H-8'); NOED (%): H-8 / H-12 (4.29), H-8 / H-7 (3.87), H-11 / H-8 (16.81), H-11 / H-12 (1.94); 13C NMR (CDCl3): 23.0 (t, C-11, C-11'), 24.7 (t, C-13, C-13'), 62.7 (q, C-12, C-12'), 124.7 (d, C-5, C-5'), 124.8 (d, C-6, C-6'), 125.9 (d, C-7, C-7'), 127.8, 127.9 (d, C-4, C-8, C-8'), 129.0 (s, C-1, C-1'), 131.1 (s, C-3, C-3'), 132.9 (s, C-10, C-10'), 133.8 (s, C-9, C-9'), 153.6 (s, C-2, C-2'); MS (m/z), intensity (%): 420 (M+, 100), 355 (20), 352 (22), 309 (16), 308 (14), 265 (12), 217 (24), 185 (180) 171 (61); HRMS: M+ 420.1235, calcd for C25H24O2S2 420.1218.

45, 46, 47, 48-Tetramethoxy-3,25-dithia[3.1.3.1]naphthalenophane (51).

Into a solution of KOH (230 mg) in 95% ethanol (120 mL) under vigorous stirring was added dropwise a solution 50 (300 mg, 0.71 mmol) and 49 (370 mg, 0.72 mmol) in benzene (50 mL) over 10 h. The reaction mixture was stirred at room temperature for 12 h and then neutralized with concentrated sulphuric acid until the pH was 5-6. Removal of the solvent on a rotary evaporator afforded a residue, which was dissolved in dichloromethane (200 mL)
and washed with water (100 mL) to remove inorganic salts. The aqueous washings were re-extracted with dichloromethane (50 mL x2). The combined organic extracts were dried over anhydrous MgSO₄. Filtration and evaporation of the solvent to dryness left a solid product. Crystallization from chloroform / hexanes gave 51 (342 mg, 62%) as colourless fine needles: mp>300 °C (with decomposition); ¹H NMR (CDCl₃): 3.29 (s, 12H, OCH₃), 3.86 (s, 8H, H-2, H-4, H-24, H-26), 4.81 (s, 4H, H-14, H-36), 7.26-7.36 (m, 8H, H-9, H-10, H-18, H-19, H-31, H-32, H-40, H-41), 7.71 (s, 4H, H-6, H-22, H-28, H-44), 7.72-7.75 (m, 4H, H-8, H-20, H-30, H-42), 7.93-7.96 (m, 4H, H-11, H-17, H-33, H-39); NOED (%): H-11 / H-14 (6.60), H-11 / H-10 (6.01), H-14 / H-11 (21.55), H-14 / OCH₃ (1.18); ¹³C NMR (CDCl₃): 24.1(t, C-14, C-36), 32.1(t, C-2, C-4, C-24, C-26), 61.7 (q, OCH₃), 123.9 (d, C-11, C-17, C-33, C-39), 124.4 (d, C-9, C-19, C-31, C-41), 125.9 (d, C-10, C-18, C-32, C-40), 128.4 (d, C-6, C-22, C-26, C-44), 128.9 (s, C-13, C-15, C-35, C-37), 129.1 (d, C-8, C-20, C-30, C-42), 130.9 (s, C-1, C-5, C-23, C-27), 131.3 (s, C-7, C-21, C-29, C-43), 132.9 (s, C-12, C-16, C-34, C-38), 155.5 (s, C-45, C-46, C-47, C-48); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 794 ((M + Na)+, 3) 772 (M+, 1).

A solution of 51 (200 mg, 0.26 mmol) in trimethyl phosphite (10 mL) in a Pyrex® tube was fitted with a reflux condenser and placed in a Rayonet® photochemical reactor fitted with RPR 3500 Å lamps. The solution was maintained under argon and was stirred vigorously while irradiating for 18 h. The solvent was removed by vacuum distillation and the residue was crystallized from dichloromethane / hexanes to give 46 (41 mg, 22%) as colourless fine crystals: mp 163-165 °C; ¹H NMR (CDCl₃): 2.91 (br, s, 12H, OCH₃), 3.06 (br, s, 8H, H-2, H-3, H-23, H-24), 4.68 (s, 4H, H-13, H-34), 7.26-7.28 (m, 8H, H-8, H-9, H-17, H-18, H-29, H-30, H-38, H-39), 7.52 (s, 4H, H-5, H-21, H-26, H-42), 7.63-7.65 (m, 4H, H-7, H-19, H-28, H-40), 7.97-7.98 (m, 4H, H-10, H-16, H-31, H-37); NOED (%): H-10 / H-13 (8.29), H-10 / H-9 (4.33), H-7 / H-8 (3.01), H-5 / H-7 (4.56), H-5 / H-3 (3.42), H-13 / OCH₃ (2.35), H-13 / H-10 (23.43), CH₃O, H-3 / H-5 (2.64), CH₃O, H-3 / H-13 (2.70); ¹³C NMR (CDCl₃): 23.7 (t, C-13, C-34), 30.2 (t, C-2, C-3, C-23, C-24), 60.3 (q, OCH₃), 123.5 (d, C-10, C-16, C-31, C-37), 123.6 (d, C-8, C-18, C-29, C-39), 124.7(d, C-9, C-17, C-30, C-36), 127.5 (d, C-5, C-21, C-26,
C-7, C-19, C-28, C-40), 128.3 (s, C-12, C-14, C-33, C-35), 130.7 (s, C-1, C-4, C-22, C-25), 132.2 (s, C-6, C-20, C-27, C-41), 134.7 (s, C-11, C-15, C-32, C-36), 156.2 (s, C-43, C-44, C-45, C-46); MS (m/z), Intensity (%): 709 (M' +1, 100), 677 (6), 537 (8), 354 (25), 308 (11), 265 (9), 185 (18); HRMS: M' 708.3130, calcd for C_{50}H_{44}O_{4}; 708.3240.

X-ray Data for 46.

Crystal data for 46: C_{50}H_{44}O_{4}, triclinic, space group P1 (#2), a=10.343 (3) Å, b= 11.240 (6) Å, c= 8.992 (4) Å, α= 96.15 (4)°, β= 110.13 (3)°, γ= 104.46 °, Z= 1, D_{calcd} = 1.267 g/cm³, crystal size = 0.400 x 0.200 x 0.400 mm. Intensity data were measured at 299 K on a Rigaku AFC6S diffractometer with MoKα (λ = 0.71069 Å) to 2θ_{max} (deg) = 50.2°; 3304 unique reflections converged to a final R = 0.042, for 2392 reflections with l>2.00σ(l); R_w=0.038, G.O.F. = 2.54.

Additional details of the structure solution are given in Appendix I.

Attempted sulphur extrusion of 51 via Wittig Rearrangement.

To a solution of 51 (100 mg, 0.13 mmol) in dry THF (10 mL) cooled to -10 °C with an ice-NaCl bath was added n-butyllithium (0.2 mL, 1.6 M in hexane, 3.2 mmol) at such a rate that the light blue color was maintained. After the addition was completed, the reaction mixture was stirred until the temperature reached to ambient temperature. Methyl iodide (0.45 mL, 7.25 mmol) was added
to quench the reaction. After ether (10 mL) was added, the reaction mixture was washed with aqueous saturated NaCl solution until the washings were neutral to pH paper. After drying over MgSO₄ and filtering, the solvent was evaporated to afford a dark brown residue. TLC of the crude product revealed at least five spots, which were not further separated and characterized.
Chapter 5.

Calix[4]naphthalenes Derived from 2,3-Dihydroxynaphthalene

5.1. Introduction.

The choice to use 2,3-dihydroxynaphthalene as a building block for calixnaphthalenes was based on the following considerations: (1) the electron-donating effect of the two hydroxy groups should make electrophilic substitution at the C-1 and C-4 positions facile; (2) the number of possible isomers is limited; (3) the cyclic tetramer will possess eight intra-annular oxygen atoms as potential complexation sites; and (4) the intramolecular hydrogen bonding effect should hold cyclic oligomers in a "cone" conformation.

Dreiding molecular models suggest that the structure of a calix[4]-naphthalene derived from 2,3-dihydroxynaphthalene would be very rigid. This conformational rigidity is required for supramolecular applications. On the other hand, the same rigidity could also create difficulties in effecting the final cyclization step in the synthesis. The molecular rigidity and the size of the cavity of the macrocyclic compounds could be altered by replacing the methylene bridges with longer carbon chains. Hence, the homocalixnaphthalenes were also selected as synthetic targets.

5.2.1. Condensation of 2,3-Dihydroxynaphthalene with Aldehydes.

The condensation of 2,3-dihydroxynaphthalene with formaldehyde under basic conditions was studied first. A dark resinous product was obtained by using either Gutsche's procedure, or the conditions which were employed for the synthesis of calix[4]naphthalenes from 1-naphthol as described in Chapter 2. It became apparent that under basic conditions, 2,3-dihydroxynaphthalene is very easily oxidized to quinone-like products (Scheme 5.1).

Scheme 5.1.

When 2,3-dihydroxynaphthalene was treated with formaldehyde under acidic conditions, a brown precipitate formed after the reaction mixture was stirred at room temperature for 4 hours. After workup, the crude product was extracted with acetone and the extract was fractionated by flash column chromatography to afford a small portion of dimer, bis-(2,3-dihydroxy-1-naphthyl)methane (52), in 17% yield. The rest of the crude product is sparingly soluble in common organic solvents and is believed to be a mixture of longer oligomers or polymers (see Scheme 5.2). Attempted separation of these oligomers or polymers however were unsuccessful. It was anticipated that it
would be easier to separate the mixture of the corresponding acetates. Thus, the crude product was reacted with acetic anhydride and pyridine as a catalyst. Both dimer 53 and trimer 54 were isolated low yields (15% and 7% respectively). No other products from the crude product were separated or characterized.

When 2,3-dihydroxynaphthalene was treated with acetaldehyde in
ethanol in the presence of sulphuric acid at room temperature, followed by acetylation with acetic anhydride and pyridine, dimer 55 was obtained in 16% yield.

**Scheme 5.3.**

Two factors may have prevented product formation in good yield from the condensation of 2,3-dihydroxynaphthalene with aldehydes. One is the great reactivity of the dihydroxy compounds, which could lead to undefined longer linear oligomers or polymers, instead of smaller cyclic oligomers. Another factor could have been the great polarity of the oligomers from 2,3-dihydroxynaphthalene and its corresponding acetates, which would create difficulty in the fractionation of the crude product. Therefore, protection of the diol as the diether was considered to be necessary, both to reduce the reactivity and polarity of the anticipated products.

**5.2.2. Protection of 2,3-Dihydroxynaphthalene.**

One of the most convenient methods for protection of the hydroxy groups in 2,3-dihydroxynaphthalene is methylation with dimethyl sulphate under basic
conditions. Since this reaction is heterogeneous, vigorous stirring and the presence of Adogen\textsuperscript{9} as a phase transfer catalyst (PTC) is required to effect efficient synthesis. Another method of protecting of the ortho dihydroxy groups is methylation with dichloro- or dibromomethane. Bashall and Collins \textsuperscript{90} have shown that high yields of methylenated catechols may be obtained by using a phase transfer catalyst under refluxing conditions. This process required the use of strong base and the method of slow addition (three hours or more) of the reactants under a nitrogen atmosphere. Clark \textsuperscript{99} reported a methylation method for catechol and 2,3-dihydroxynaphthalene. The reaction of a catechol with a dihalogenomethane in DMF in the presence of an excess of KF or CsF provides a high yield of the corresponding methylenedioxy compound in a relatively short time period.

The methoxylolation method is easily handled. However, subsequent deprotection requires relatively harsh conditions.\textsuperscript{90} In addition, the methoxy group is bulky, which could cause problems for the subsequent cyclization steps. This effect has already been noted in Chapter 4. Emphasis was therefore
placed on the methylation approach.

When 2,3-dihydroxynaphthalene was treated with dichloromethane in the presence of large excess of anhydrous CsF in dry DMF, a colourless crystalline product 57 was obtained in 91% yield (Scheme 5.5).

**Scheme 5.5.**

![Scheme 5.5](image)

In order to reduce cost, expensive CsF was recycled by recrystallization twice from water (ca. 50%). The yield of product was not decreased when recycled CsF was used for methylation of 2,3-dihydroxynaphthalene.

**5.2.3. Synthesis of Cyclic Ethers 79, 80, 81 and 83.**

Cyclic ethers are classical supramolecular compounds. The synthesis of these compounds suffered from low yield. The methodology for the methylation of 2,3-dihydroxynaphthalene in the presence of CsF in DMF was extended to the synthesis of macrocyclic ethers. When these conditions were employed, the six-membered ring compound 79 formed in the highest yield (84%). In going from the seven-membered ring compound 80, to the twelve-membered ring compound 81, the yield was not significantly decreased (from 49% to 48%). For 1,1'-bis-naphthol (82), which was prepared by oxidative
coupling in the presence of FeCl₃, the corresponding seven-membered cyclic ether, 83, is produced in 52% yield. Since bis-naphthol plays a very important role in asymmetric catalytic hydrogenation, there is interest in any of its derivatives that could be used as chiral ligands with Lewis acids.

Scheme 5.6.

In this synthetic method, the dissociation of the protons from the hydroxy groups in 2,3-dihydroxynaphthalene was assisted by fluoride anion, which can hydrogen bond with acidic protons of naphthol. Under these conditions, 2,3-dihydroxynaphthalene is stable to oxidation, resulting in good observed yields of products.
Prevention of intermolecular reactions is a challenge in the synthesis of macrocyclic polyethers. One of the methods to overcome this is to utilize the "template effect". The large, soft cesium cation acts as a template onto which presumably the oxyanion and the halomethyl can interact to enhance the chances of intramolecular cyclization (see Figure 5.1). DMF is the reaction solvent of choice since CsF is has a high solubility in it.

Fig. 5.1. Template Effect of Cs⁺ in Ether Formation.


Retrosynthetic analysis of calix[4]naphthalene 62 gives the following possible starting materials (Scheme 5.7): 1-bromomethyl-2,3-methylenedioxy-naphthalene (58) (Approach "a"); 1,4-bis-(bromomethyl)-2,3-methylenedioxy-naphthalene (59) (Approach "b"); and bis-(1-bromomethyl-2,3-methylenedioxy-4-naphthyl)methane (60) (Approach "c").
5.2.4.a. Self-Condensation of 1-Bromomethyl-2,3-Methylenedioxy-naphthalene (58).

In Approach "a", the corresponding chemical transformation is the self-condensation-cyclization of 1-bromomethyl-2,3-methylenedioxy-naphthalene (58). Synthesis of 58 could be achieved by treatment of 57 with paraformaldehyde and HBr in glacial acetic acid (Scheme 5.8). There are two
forms of anhydrous hydrogen bromide that are commercially available, namely, as a 30% solution in glacial acetic acid and, as compressed gaseous HBr. The former reagent was found to be more convenient and cheaper and it also gave a higher yield (58%, in contrast to 41%).

Scheme 5.8.

![Scheme 5.8](image)

Self-condensation of 58 in the presence of ZnBr₂, TiCl₄, or FeCl₃, however, resulted in the formation of dark brown resins, which were insoluble in common organic solvents (Scheme 5.9).

Scheme 5.9.

![Scheme 5.9](image)

A variation of Approach “a” is the self-condensation-cyclization of 1-hydroxymethyl-2,3-methylenedioxy-naphthalene (64), which was prepared by formylation of 57, followed by NaBH₄ reduction (Scheme 5.10). Reaction of 57 with α,α-dichloromethyl methyl ether in the presence of TiCl₄ in dry
5.2.4.b. Coupling Reaction of 1,4-\textit{Bis}-\textit{(bromomethyl)}-2,3-Methylene-dioxy-naphthalene (59) with 57.

In retroanalytical Approach "b", 1,4-\textit{Bis}-\textit{(bromomethyl)}-2,3-methylenedioxy-naphthalene (59) is coupled with 57. Synthesis of 59 was effected by bromo-methylation with paraformaldehyde and HBr. However, the attempted coupling reaction of 57 and 59 in the presence of TiCl\textsubscript{4} also afforded a dark brown resin which was insoluble in common organic solvents and could not be further characterized (Scheme 5.12).

\textbf{Scheme 5.12.}

\begin{center}
\includegraphics[width=0.5\textwidth]{Scheme_5.12.png}
\end{center}

5.2.4.c. Convergent Synthesis of Calixnaphthalene 62.

Synthesis of calix[4]naphthalene 62 using the convergent Approach "c" shown in Scheme 5.13 was attempted. The key step is the synthesis of dimer 61, for which three different procedures were evaluated.

In the first route shown in Scheme 5.14, compound 57 was reacted with
5.2.4.b. Coupling Reaction of 1,4-Bis-(bromomethyl)-2,3-Methylene-dioxynaphthalene (59) with 57.

In retroanalytical Approach "b", 1,4-bis-(bromomethyl)-2,3-methylenedioxy-naphthalene (59) is coupled with 57. Synthesis of 59 was effected by bromo-methylation with paraformaldehyde and HBr. However, the attempted coupling reaction of 57 and 59 in the presence of TiCl₄ also afforded a dark brown resin which was insoluble in common organic solvents and could not be further characterized (Scheme 5.12).

Scheme 5.12.

5.2.4.c. Convergent Synthesis of Calixnaphthalene 62.

Synthesis of calix[4]naphthalene 62 using the convergent Approach "c" shown in Scheme 5.13 was attempted. The key step is the synthesis of dimer 61, for which three different procedures were evaluated.

In the first route shown in Scheme 5.14, compound 57 was reacted with
dimer 61 in 35% yield and trimer 65 18% yield (Scheme 5.15).

Treated with formaldehyde in 3% sulphuric acid/glacial acetic acid to give both

in the second route to the synthesis of dimer 61, compound 57 was

58 under thermal conditions to give dimer 61 in 54% yield.
In the third route to dimer 61, the bromo group was used as a blocking group by taking advantage of the high chemoselectivity of bromination. The brominated compound 66 was easily synthesized in 56% yield by treatment of 57 with bromine/dioxane complex. Condensation of 66 with paraformaldehyde in 3% sulphuric acid / glacial acetic acid gave the dimer 67 in 83% yield. Removal of
the bromo group in 1,1'-bis-bromo dimer 67 was effected by using LAH reduction in THF with sonication at 30-40 °C. The desired dimer 61 was obtained in 64% yield (see Scheme 5.16).

**Scheme 5.16.**

With dimer 61 in hand, bis-(1-bromomethyl-2,3-methylenedioxy-4-naphthyl)methane (60) was prepared in 71% yield by reacting 61 with paraformaldehyde in the presence of HBr in glacial acetic acid (Scheme 5.13). The coupling reaction of 60 with 61 in p-dioxane using TiCl₄ as a catalyst gave a small amount (4%) of the cyclic tetramer 62.

In spite of the low yield, cyclic tetramer 62, a novel calix[4]naphthalene, gave promising information. Its ¹H NMR spectrum shows the methylene bridge
as an AB quartet centred at $\delta$ 4.19 ppm, which indicates that it is conformationally rigid, even at room temperature. The signal due to the methylenedioxy groups appears at $\delta$ 5.36 ppm, due to strong shielding by the naphthalene rings. The $^1$H NMR spectrum reveals two multiplets centred at $\delta$ 3.66 and 3.98 ppm, most likely due to $p$-dioxane, the reaction solvent. Since “free” $p$-dioxane demonstrates a singlet at $\delta$ 3.53 ppm, the chemical shifts of the included $p$-dioxane suggests that it is situated within the deshielding field of the naphthalene ring. The dioxane could not be removed under high vacuum (1 mm Hg) and heating with refluxing toluene. The MS (FAB+) confirmed the presence of $p$-dioxane, showing a peak of the complex of 62 plus $p$-dioxane (m/z= 932). This evidence is strongly suggestive that the dioxane molecule complexes with calix[4]naphthalene 62. Attempts to obtain suitable crystals of 62 for X-ray diffraction studies failed.


Since dihomocalix[4]naphthalenes from 3-hydroxy-2-naphthoic acid (36), were successfully synthesized by using the dithia intermediated approach, similar methodology was employed to synthesize dihomocalixnaphthalene 70 from 2,3-dihydroxynaphthalene. Scheme 5.16 outlines the approach used to synthesize 70.
The bis-bromomethyl compound 60 was treated with thiourea to form a urea salt, which was subsequently hydrolysed to produce the corresponding bis-(1-mercaptomethyl-2,3-methyleneedioxy-4-naphthyl)methane (68) in 69% yield. The coupling reaction of 60 and 68 under basic and high dilution conditions gave the dithiacalixnaphthalene 69. Sulphur extrusion of 69 was effected by photolysis to produce the dihomocalixnaphthalene 70, in 11% yield from 60 and 68.

Its $^1$H NMR spectrum shows the methylenedioxy groups as four singlets at $\delta$ 5.99, 6.05, 6.09, and 6.17 ppm. The two methylene bridges appear as four doublets centred at $\delta$ 3.02, 3.30, 3.36 and 3.39 ppm. The ethylene bridges appear as eight sets of multiplets centred at $\delta$ 1.25, 3.60, 1.25, 4.11, 1.63, 2.23, 4.16, and 4.61 ppm. These $^1$H NMR data indicate that 70 is conformationally fixed or rigid at ambient temperature.

Examination of Dreiding models revealed four possible conformations for 70: "cone", "partial cone", "1,2-alternate", and "1,3-alternate". The "cone", "1,3-alternate" and "1,2-alternate" conformations have $C_4$ symmetry so that the four methylenedioxy groups would be equivalent, and therefore only one singlet is expected in the $^1$H NMR spectrum. The dissymmetrical "partial cone" conformer is expected to show four methylenedioxy groups as four discrete singlets. This was indeed observed in the $^1$H NMR spectrum, and therefore, the suggested
conformation of dihomocalix[4]naphthalene 70 is a "partial cone".

A similar procedure using 1,4-bis-bromomethyl compound 59 led to a
dithiacyclonaphthalenophane 71, in 31% yield. Under high dilution conditions,
compound 59 also reacted with the solvent (ethanol) to give a diethyl ether 72 in
37% yield.
The $^1$H NMR spectrum of 71 shows the methylene bridge as a pair of doublets centred at δ 3.88 and 4.63 ppm. The methylenedioxy group appears as two singlets at δ 5.67 and 6.19 ppm, confirming the conformational rigidity of 71. NOED experiments were conducted to establish the conformation in solution state. When one of the methylenedioxy proton signals was irradiated, the other is enhanced strongly and vice versa (33% and 26%). This indicates that the two singlets are due to geminal methylenedioxy groups. However, the signals of methylene bridges are not enhanced at all. At this stage, the conformation of 71 is determined although the “anti” conformation in a unfunctionalised dithia[3.3](1,4)naphthalenophane is predominant one.

Scheme 5.18.

Two approaches can be used to achieve high dilution conditions. Use of large volumes of solvent, as was used in the syntheses of dihomocalix[4]-
naphthalene 70, and thiacyclonaphthalenophane 71, or use of heterogeneous conditions, are possible \(^a\) (Scheme 5.18a). However, when compound 59 was reacted under heterogeneous conditions with sodium sulphide dispersed onto silica, a polymer was formed rather than cyclonaphthaleneophane 71.

**Scheme 5.18a.**

![Scheme 5.18a](image)

5.4. Dilithiation of 2,3-Dimethoxynaphthalene.

Regioselectivity is a major problem in conventional electrophilic substitution reactions of aromatic compounds. Snieckus \(^b\) has developed a "directed ortho metallation" (DoM) process to enhance the regioselectivity of the electrophilic substitution of aromatic compounds. In DoM reactions, the substrates should possess a "Directing Metallation Group" (DMG) which usually contains an oxygen or nitrogen atom. A methoxy group can serve as such a DMG group. Shirley \(^c\) reported that the carbanion of 1-methoxynaphthalene can be selectively generated at C-2 or C-8 by choosing different lithium reagents. Sundberg \(^d\) reported that the carbodianion of 1,2-dimethoxybenzene can be generated at the C-3 and C-6 positions by use of an excess of \(n\)-butyllithium.
Eustache reported a coupling reaction of phenylmagnesium bromide with allyl bromide. McMurry and Shih* reported coupling reactions of phenyllithium with allyl bromide.

In order to test the possibility that coupling reactions of carbanions with suitable electrophiles would be a method to synthesize calixnaphthalenes, the reactions shown in Scheme 5.19 were investigated. The generation of the 1,4-carbodianion of 2,3-methoxynaphthalene was first effected by treatment of 56 with 4 equivalents of n-butyllithium and TMEDA in dry diethyl ether. The reaction mixture was stirred at room temperature for one hour, followed by refluxing for another hour. Trimethylsilyl chloride or methyl iodide as good electrophiles, were added to trap the carbodianion species and quench the reactions. After workup, the crude product was purified by flash column chromatography to afford 1,4-bis-(trimethylsilyl)-2,3-dimethoxynaphthalene (77) in 55% yield. Due to the ortho-methoxy group, the C-1 and C-4 protons are very weakly acidic, requiring a stronger base to remove them. TMEDA can increase the basicity of n-butyllithium by complex formation.

Three factors can affect the lithiation of naphthalene 56: (1) steric hindrance of the protons being removed; (2) electron density at the carbon to which the proton is attached and (3) the DoM effect. Since the protons on C-1 and C-4 of 56 are in the peri positions they are sterically hindered and due to the presence of the ortho-methoxy group, the H-1, and H-4 will be less acidic.
Scheme 5.19.
Both factors (1) and (2) make lithiation at the C-1 and C-4 positions unfavourable. On the other hand, the DoM effect of the methoxy group favours lithiation in the C-1 and C-4 positions. The results reported herein show that the DoM effect is dominant, and can overcome factors (1) and (2).

Alternatively, carbanions can be generated via metal-halogen exchange. With this in mind, 1,4-dibromo-2,3-dimethoxynaphthalene (74) was prepared by bromination of 56 in chloroform. After 4-6 hours of stirring at room temperature, 74 was obtained in good yield. The conditions used for the metal-exchange reaction were very mild (-78 °C) and did not require TMEDA. The yield obtained (75%) is higher than that resulting from direct lithiation (55%), as determined by the amount of the product obtained when 75 was quenched with trimethylsilyl chloride. When the reaction was quenched with an excess of methyl iodide, 1,4-dimethyl-2,3-methylenedioxy napthalene (76) was obtained in 72% yield.

The coupling reaction of 1,4-bis-bromomethyl-2,3-dimethoxynaphthalene (78) with 1,4-dilithia-2,3-methoxynaphthalene (75) was carried out in the same flask used for the lithiation reaction, by adding 78 to 75. However, only brown resins which were insoluble in common organic solvents and could not be characterized were obtained. It was concluded that the coupling reaction between 78 and 75 formed polymeric products.
5.5. Attempted Synthesis of allhomocalixinaphthalenes.

Högberg reported a synthesis of [2,4]cyclophane in 22% yield via a one-pot Wittig reaction procedure. This report suggested that it should be feasible to synthesize an analogous allhomocalixinaphthalene via a Wittig procedure.

Since it was not possible to introduce formyl groups in the 1-, and 4-positions of 57 by Lewis acid-catalysed reactions, 1,4-bis-(bromomethyl)-2,3-methylenedioxynaphthalene (59) was instead considered as a starting material. Compound 59 was converted to the corresponding hydroxymethyl compound 84 in the presence of calcium carbonate. Oxidation by PCC-molecular sieve converted hydroxy groups to the corresponding formyl groups. With 85 in hand, we turned our attention toward the efficient preparation of bis-phosphonium salt, 86, the precursor of the required bis-ylide. Scheme 5.20 outlines this approach. Since the monophosphonium salt was insoluble in THF, ether, or benzene, the formation of bis-phosphonium salt 86 could not be achieved when the reaction was conducted in these solvents. When the reaction was carried out in dry DMF, bis-phosphonium salt 86 was obtained in 95% yield. The Wittig reaction of 85 and 86 was carried out in dry DMF at -40 °C with very slow addition of lithium ethoxide over 16 h. After workup, TLC analysis showed that the crude highly fluorescent product consists of many components. Two major products were isolated in 9.1% and 14% yields. The former is assigned as 1,4-dimethyl-
Scheme 5.20.

2,3-methylenedioxyphthalene (87) and the latter as the linear trimer 88 with cis double bonds \( J = 6 \text{ Hz} \). No cyclic oligomer was isolated. The methyl groups in 87 and in 88 appear to be formed by the hydrolysis of unreacted bis-phosphonium salts during the aqueous workup, as shown in Scheme 5.21.
5.6. Summary.

Condensation of 2,3-dihydroxynaphthalene with paraformaldehyde under acidic conditions gave linear oligomers or polymers, but did not produce any calixnaphthalene. The TiCl₄-catalysed coupling reaction of bis-(1-bromomethyl-2,3-methylenedioxy-4-naphthyl)methane (60) with bis-(2,3-methylenedioxy-1-naphthyl)methane (61) gave calix[4]naphthalene 62 in 4% yield. The conformational mobility of 62 appeared restricted even at ambient temperature.

Starting from 2,3-dihydroxynaphthalene, a convergent synthetic procedure afforded dihomocalix[4]naphthalene 70, which was also fixed in a “partial cone” conformation at ambient temperature. Condensation of 1,4-bis-(mercaptomethyl)-2,3-methylenedioxy naphthalene (73) with 1,4-bis-(bromomethyl)-2,3-methylenedioxy naphthalene (59) gave a cyclic dimer (71).

The Wittig reaction of 1,4-diformyl-2,3-methylenedioxy naphthalene (85)
with 1,4-bis-(bromomethy)-2,3-methylenedioxyxynaphthalene (59) gave linear oligomers. The anticipated allhomocalixnaphthalene precursor was not isolated from the reaction mixture.

Cyclic naphthalene ethers 79, 80, 81, and 83 were synthesized in the presence of CsF. In these reactions, the hydrogen-bonding effect of fluoride ion and the template effect of the cesium cation play key roles.

5.7. Experimental.

For General experimental conditions and instrumentation employed, see Chapter 2.

Condensation of 2,3-dihydroxynaphthalene with formaldehyde under basic conditions.

To a solution of 2,3-dihydroxynaphthalene (0.80 g, 5.0 mmol) in xylenes (10 mL) were added formalin (37% formaldehyde, 0.5 mL, 6.2 mmol) and 10% aqueous KOH (0.2 mL, 1.45 mmol). After refluxing for 10 h, a dark brown solution which revealed at least six spots on TLC with 50% acetone / hexanes as eluent was obtained. This crude product was not further purified or characterized.

Condensation of 2,3-dihydroxynaphthalene with formaldehyde under acidic
conditions.

To a solution of 2,3-dihydroxynaphthalene (1.60 g, 10 mmol) in a mixture of 95% ethanol (4 mL) and water (4 mL) were added formalin (37% formaldehyde, 0.70 mL, 8.6 mmol) and concentrated hydrochloric acid (1 mL) under N₂. The milky emulsion was stirred at room temperature for 40 h, and then the reaction mixture was poured onto crushed ice (50 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The crude product was purified by flash column chromatography with 50% acetone/hexanes as eluent. The dimer 52 was obtained as a colourless powder (0.28 g, 17%): mp 204-207 °C; IR (nujol, cm⁻¹): 3261 (br, OH), 1697 (w), 1607 (m), 1519 (m), 1460 (s), 1409 (s), 1377 (s); ¹H NMR (CD₂COCD₃): 4.91 (s, 2H, H-11), 7.08 (m, 4H, H-6, H-6', H-7, H-7'), 7.12 (s, 2H, H-1, H-1'), 7.49 (m, 2H, H-8, H-8'), 8.25 (m, 2H, H-5, H-5'); ¹³C NMR (CD₂COCD₃): 22.2 (t, C-11), 108.7, 123.6, 123.7, 124.8, 127.2 (d, C-1, C-5-C-8, C-1', C-5'-C-8'), 120.7, 129.8, 130.4, 144.4, 146.0 (s, C-2-C-4, C-9, C-10, C-2'- C-4', C-9', C-10'); MS (m/z), Intensity (%): 332 (M⁺, 2), 172 (5), 162 (1), 160
Acetylation of crude condensation product from the reaction of 2,3-dihydroxynaphthalene with formaldehyde.

A crude condensation product was obtained (1.33 g), starting from 2,3-dihydroxynaphthalene (1.60 g, 10 mmol). It was dissolved in acetic anhydride (50 mL) and pyridine (0.5 mL) and was refluxed for 4 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice (50 g). The resulting white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The crude product was column chromatographed using 60% ethyl acetate / hexanes as eluent. Dimer 53 (375 mg, 15% from 2,3-dihydroxynaphthalene) and trimer 54 (167 mg, 7% from 2,3-dihydroxynaphthalene) were obtained. Dimer 53: mp 202-205 °C; IR (KBr, cm⁻¹): 1771 (s, CH₃COO), 1665 (w), 1550 (m), 1445 (s), 1440 (s); ¹H NMR (CDCl₃): 1.89, 2.26 (sx2, COCH₃), 4.74 (s, 2H, H-11, 7.43-7.49 (m, 4H, H-6, H-7, H-6', H-7'), 7.63 (s, 2H, H-1, H-1'), 7.79-7.82, 8.04-8.07 (m, 4H, H-5, H-5', H-8, H-8'); ¹³C NMR (CDCl₃): 19.9, 20.8 (COCH₃), 24.6 (C-11), 120.0, 124.0, 126.2,
Condensation of 2,3-dihydroxynaphthalene with acetaldehyde and acetylation of the crude condensation product.

2, 3-Dihydroxynaphthalene (1.60 g, 10 mmol) was dissolved in aqueous 10% sulphuric acid (25 mL), and heated to 95-100 °C. A mixture of aqueous
10% acetaldehyde (4.5 mL) and aqueous 10% sulphuric acid (5 mL) was slowly added into the 2,3-dihydroxynaphthalene solution over 5 h. After an induction time of 5-10 min, the reaction mixture became cloudy. The reaction mixture was stirred for three days at 95-100 °C. After cooling to room temperature, a brown precipitate formed, which was filtered, washed with aqueous saturated sodium chloride and dried under vacuum, to afford a dark crude product (1.30 g).

A portion of this crude condensation product (400 mg, equivalent to 3.1 mmol of 2,3-dihydroxynaphthalene) was dissolved in acetic anhydride (10 mL) and three drops of pyridine were added. The reaction mixture was refluxed for 2.5 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice (10 g). The white precipitate was filtered, washed with water until the washings are neutral to pH paper, and dried under vacuum. The crude product was column chromatographed with 60% ethyl acetate/hexanes as eluent. Dimer 55 was obtained (120 mg, 16% from 2,3-dihydroxynaphthalene) as a colourless solid: mp 205-207 °C; \(^1\)H NMR (CDCl\(_3\)): 1.64 (d, J=6.9, 3H, H-12), 2.35 (s, 3H, H-14), 2.46 (s, 6H, H-13, H-15), 5.45 (q, J=6.9, 1H, H-11), 7.48, 7.60 (mx2, 4H, H-6, H-7, H-6', H-7'), 7.55 (s, 2H, H-1, H-1'), 7.82 (d, J=8.1, 2H, H-5, H-5' or H-8, H-8'), 8.20 (d, J=8.4, 2H, H-5, H-5' or H-8, H-8'); \(^1^3\)C NMR (CDCl\(_3\)): 20.7 (C-11), 20.8, 23.4, 26.9 (C-12, C-13, C-14), 119.5, 120.6, 120.9, 122.1, 125.1, 126.4, 126.6, 127.4, 128.6, 129.1, 130.4, 131.5, 138.5, 141.3 (aromatic), 168.6 (CH\(_3\)COO); MS (m/z, Intensity (%): 472 (M\(^+\), 1), 456 (20), 415
To a solution of 2,3-dihydroxynaphthalene (8.0 g, 50 mmol) in aqueous 7% NaOH (60 mL, 175 mmol) was added dimethyl sulphate (9.4 mL) over 1 h. The solution was stirred at 70-80 °C for 4 h. After the crude reaction mixture was cooled to room temperature, a pale brown precipitate formed. The precipitate was filtered and washed with aqueous 10% NaOH (100 mL) followed by water until the washings were neutral to pH paper. Dimethoxynaphthalene 56 was obtained (7.5 g, 80%) as a colourless fine powder: lit. mp 115-116 °C, 102 mp 114-115 °C; 1H NMR (CDCl3): 4.00 (s, 6H, OCH3), 7.12 (s, 2H, H-1, H-4), 7.34 (m, 2H, H-6, H-7), 7.69 (m, 2H, H-5, H-8).

2,3-Methylenedioxynaphthalene (57).
This compound was prepared according to a literature procedure.\textsuperscript{69} CsF was recycled by recrystallization twice from water and drying at 200 °C for 24 h before re-use (ca. 50%). Product 57 was obtained (91%) as colourless fine needles: lit. mp 96-97 °C, mp 96-98 °C; IR (KBr, cm\textsuperscript{-1}): 1515 (m), 1464 (s), 1450 (m), 1216 (-OCH\textsubscript{2}O-); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 6.03 (s, 2H, H-11), 7.12 (s, 2H, H-1, H-4), 7.31 (m, 2H, H-6, H-7), 7.66 (m, 2H, H-5, H-8); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): 100.9 (C-11), 103.8 (C-1, C-4), 124.3 (C-6, C-7), 127.0 (C-5, C-8), 130.4 (C-9, C-10), 147.5 (C-2, C-3); MS (m/z), Intensity (%): 173 (M\textsuperscript{\textdagger} + 1, 11), 172 (M\textsuperscript{\textdagger}, 100), 115 (12), 114 (35), 87 (5), 66 (18);

1-Bromomethyl-2,3-methylenedioxy-\textit{naphthalene} (58).

\textit{Method A.} To a solution of 57 (2.0 g, 11.6 mmol) and paraformaldehyde (350 mg, 11.7 mmol) in glacial acetic acid (50 mL) was added dropwise 33% HBr in glacial acetic acid (20 mL). The reaction mixture was stirred at room temperature for 15 h, and was then poured onto crushed ice (70 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper and dried under vacuum. The crude product was purified by flash column
chromatography using 20% ethyl acetate / hexanes as eluent. The bromomethyl compound 58 was obtained (1.78 g, 58%) as a cream-coloured powder: mp 130-132 °C; \(^1\)H NMR (CDCl\(_3\)): 4.89 (s, 2H, H-12), 6.09 (s, 2H, H-11), 7.09 (s, 1H, H-4), 7.37, 7.46 (m, 2H, H-6, H-7), 7.66 (d, J=6.9, 1H, H-5 or H-8), 7.90 (d, J=8.4, 1H, H-5 or H-8); \(^{13}\)C NMR (CDCl\(_3\)): 23.8 (C-12), 101.5 (C-11), 105.0, 122.5, 124.7, 124.9, 127.8 (C-4, C-5, C-6, C-7, C-8), 110.7, 125.3, 130.8, 146.3, 146.7 (C-1, C-2, C-3, C-9, C-10); MS (m/z), Intensity (%): 266 (M\(^+\), 9), 264 (M\(^+\), 7), 186 (11), 185 (100), 127 (30).

Method B. Into a solution of 57 (2.0 g, 11.6 mmol) and paraformaldehyde (350 mg, 11.7 mmol) in glacial acetic acid (50 mL) HBr gas was bubbled for 20 min. The reaction mixture was stirred at room temperature for 15 h, and was then poured onto crushed ice (70 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The crude product was purified by flash column chromatography with 20% ethyl acetate / hexanes as eluent. Compound 58 was obtained (1.30 g, 41%) as a cream-coloured powder.

Self-condensation of 1-bromomethyl-2,3-methylenedioxynaphthalene (58).

To a solution of 58 (500 mg, 1.89 mmol) in dry chloroform (20 mL) was added anhydrous FeCl\(_3\) (400 mg, 2.45 mmol). The reaction mixture turned dark brown. This dark solution was refluxed under N\(_2\) for 3 d. A dark brown
precipitate was obtained after workup, which was insoluble in common organic solvents and was not further characterized.

*N-Methylformanilide (MFA) (88a).*

![Methylformanilide](image)

This compound was prepared according to a literature procedure.\(^{103}\)

Compound 88a (94%) was obtained as a colourless liquid: lit. bp. 114-121 °C/8 mm Hg, bp. 90-93 °C/1 mm Hg; IR (KBr, cm\(^{-1}\)), 1678 (s, CHO), 1600 (s), 1500 (s); \(^1\)H NMR (CDCl\(_3\)): 3.31 (s, 3H, H-7), 7.15-7.18 (m, 2H, H-2, H-6), 7.23-7.29 (m, 1H, H-4), 7.34-7.44 (m, 2H, H-3, H-5), 8.47 (s, CHO).

1-Formyl-2,3-methylenedioxy naphthalene (63).

![1-Formyl-2,3-methylenedioxy naphthalene](image)

*Via a Vilsmeier reaction procedure.* To a solution of 57 (200 mg, 1.16 mmol) and 88a (0.25 mL, 1.18 mmol) cooled to 0 °C was added phosphorus
oxychloride (POCl₃, 0.16 mL, 1.73 mmol). The reaction mixture was heated to 95-100 °C and kept at that temperature for 6 h. After cooling to room temperature, aqueous saturated sodium acetate solution was added until a pH 6-7 was attained. The resulting precipitate was filtered and purified by flash column chromatography using 30% ethyl acetate/hexanes as eluent. A colourless crystalline product 63 was obtained (96 mg, 42%): mp 126-127 °C; IR (nujol, cm⁻¹): 1681 (s, CHO), 1636 (m), 1614 (m), 1510 (m), 1495 (s); ¹H NMR (CDCl₃): 6.20 (s, 2H, H-11), 7.31 (s, 1H, H-4), 7.41, 7.50 (m, 2H, H-6, H-7), 7.67 (m, 1H, H-5), 9.07 (d, J=7.8, 1H, H-8), 10.6 (s, CHO); ¹³C NMR (CDCl₃): 102.6 (C-11), 110.5, 111.1, 124.8, 125.6, 127.0, 127.5 (aromatic), 187.8 (CHO); MS (m/z): intensity (%): 201 (M⁺+1, 55), 200 (M⁺, 100), 199 (M⁺-1, 75), 173 (16), 172 (61), 171 (69), 170 (28), 169 (29), 157 (16), 142 (48).

Via a Lewis acid catalyzed reaction procedure. To a solution of 57 (0.46 g, 2.67 mmol) in dry dichloromethane (2 mL) cooled to 0 °C were sequentially added TiCl₄ (0.45 mL, 8 mmol) and α,α-dichloromethyl methyl ether (0.38 g, 4.20 mmol). After stirring at room temperature for 2 h, water (1 mL) was added to quench the reaction. Dichloromethane (5 mL) was added to increase the volume of the organic layer, which was then separated from the aqueous layer, and washed with water until the washings were neutral to pH paper. After drying over MgSO₄ and filtering, the solvent was evaporated. The crude product was subjected to flash column chromatography with 30% ethyl acetate/hexanes as
eluent. Compound 63 was obtained as colourless crystals (376 mg, 70%).

*1-Hydroxymethyl-2,3-methylenedioxy-naphthalene (64).*

![Chemical Structure](image)

To a solution of 63 (260 mg, 1.3 mmol) in methanol (30 mL) was added NaBH₄ in small portions at such a rate that the reaction flask was not hot. The reaction mixture was stirred at room temperature for 23 h and the methanol was evaporated under vacuum. The residue was extracted with ether (30 mL) and the organic layer was washed with two 10 mL-portions of water. After drying over MgSO₄ and filtering, the solvent was evaporated. The crude product was subjected to column chromatography using 60% ethyl acetate / hexanes as eluent. Hydroxymethyl compound 64 was obtained as a white powder (216 mg, 82%): mp 129-131 °C; IR (KBr, cm⁻¹): 3607(s, b. OH), 1600 (w), 1500 (w), 1450 (m), 1400 (s); ¹H NMR (CDCl₃): 5.10 (d, 2H, H-12), 6.07 (s, 2H, H-11), 7.11 (s, 1H, H-4), 7.32-7.45 (m, 2H, H-6, H-7), 7.69 (d, 1H, H-5), 8.02 (d, 1H, H-8); ¹³C NMR (CDCl₃): 56.2 (C-12), 101.0 (C-11), 104.2, 122.9, 124.3, 124.7, 127.2, 127.5, 128.7, 130.7, 145.8 (aromatic); MS (m/²). Intensity (%): 202 (M⁺, 100), 185 (47), 173 (38), 144 (40), 127 (37), 115 (66).
**Self-condensation of 1-hydroxymethyl-2,3-methylenedioxynaphthalene (64).**

To a solution of 64 (50 mg, 0.24 mmol) in dry chloroform (3 mL) was added TFA (0.50 mL) in CHCl₃ (2 mL) over 20 min. The reaction mixture turned dark purple. After refluxing for 2 d, a dark purple precipitate was formed (35 mg), which was insoluble in common organic solvents and was not further characterized.

**1,4-Bis-(bromomethyl)-2,3-methylenedioxynaphthalene (59).**

![Chemical Structure](image)

To a solution of 57 (0.34 g, 2.0 mmol) and paraformaldehyde (130 mg, 4.3 mmol) in glacial acetic acid (10 mL) was added dropwise 21% HBr in glacial acetic acid (8 mL). The reaction mixture was heated to 60-70 °C over 30 min and kept at that temperature for an additional 2 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice (20 g). The resulting white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The crude product was purified by column chromatography using 20% ethyl acetate / hexanes as eluent. Compound 59 was obtained (0.62 g, 87%) as a colourless powder: mp 202-204
°C; IR (KBr, cm⁻¹): 1514 (m), 1452 (s), 1400 (s), 1300 (s), 1215 (s, -OCH₂O-); ¹H NMR (CDCl₃): 4.87 (s, 4H, CH₂Br), 6.18 (s, 2H, -OCH₂O-), 7.53 (m, 2H, H-6, H-7), 7.96 (m, 2H, H-5, H-8); ¹³C NMR (CDCl₃): 23.3 (C-12, C-13), 102.1 (C-11), 111.8, 123.3, 125.3, 128.4, 143.0 (C-1-C-10); MS (m/z), Intensity (%): 358 (M⁺, 12), 280 (82), 279 (56), 278 (83), 277 (59), 199 (18), 198 (100), 185 (14), 169 (77), 142 (85), 141 (26), 139 (30), 115 (95).

**Attempted coupling reaction of 59 and 57.**

To a solution of 59 (1.79 g, 5 mmol) and 57 (0.86 g, 5.0 mmol) in dry p-dioxane (250 mL) was added TiCl₄ (2.0 mL, 10 mmol). A dark brown solution was produced. The reaction mixture was refluxed for 1 week. After evaporating the solvent under vacuum, a dark brown residue which was insoluble in organic solvents was obtained, and was not further characterized.

**1,4-Bis-bromomethyl-2,3-dimethoxynaphthalene (78).**

![Chemical Structure](image)

To a solution of 56 (0.47 g, 2.5 mmol) and paraformaldehyde (0.16 g, 5.3 mmol) in glacial acetic acid (10 mL) was added 21% HBr in glacial acetic acid (8
mL). After stirring at room temperature for 5 h, the reaction mixture was poured into cold water (50 mL). The resulting precipitate was filtered, dried under vacuum, and purified by flash column chromatography with 30% ethyl acetate/hexanes as eluent. Compound 78 was obtained (0.63 g, 77%) as a colourless powder: mp 182-183 °C; 1H NMR (CDCl3): 4.05 (s, 6H, H-13, H-14), 5.04 (s, 4H, H-11, H-12), 7.59 (m, 2H, H-6, H-7), 8.07 (m, 2H, H-5, H-8); 13C NMR (CDCl3): 23.9 (C-11, C-12), 60.9 (C-13, C-14), 124.1, 126.2 (C-5-C-8), 127.3, 129.2 (C-1, C-4, C-9, C-10), 150.5 (C-2, C-3).

Bis-(2,3-methylenedioxy-1-naphthyl)methane (61) and 1,4-di(2',3'-methylenedioxy-naphthyl-methyl)-2,3-methylenedioxy naphthalene 65.

Method A. To a solution of 57 (3.38 g, 19.6 mmol) and paraformaldehyde (295 mg, 9.8 mmol) in glacial acetic acid (160 mL) was carefully added concentrated sulphuric acid (3.4 mL). The reaction mixture was stirred at room temperature for 54 h. The reaction mixture was poured onto crushed ice (150 g). The resulting white precipitate was filtered, washed with water until the washings
were neutral to pH paper, and dried under vacuum. The crude product was purified by column chromatography using 50% dichloromethane / petroleum ether (30-60 °C) as eluent. Dimer 61 (1.22 g, 35%), trimer 65 (636 mg, 18%) and starting material 57 (507 mg, 15%) were obtained. Dimer 61: mp 146-149 °C; 1H NMR (CDCl₃): 4.64 (s, 2H, H-11), 6.06 (s, 4H, H-12, H-12'), 7.02 (s, 2H, H-1, H-1'), 7.24-7.27 (m, 4H, H-6, H-7, H-6', H-7'), 7.59-7.62, 8.01-8.04 (m, 2H, H-5, H-5', H-5''), 13C NMR (CDCl₃): 23.1 (C-11), 100.7 (C-12, C-12'). 103.0 (C-1, C-1'), 123.4, 124.0, 124.2, 127.6 (C-5-C-8, C-5'-C-8'), 123.7, 123.8, 125.9, 130.9 (C-2, C-3, C-9, C-10, C-2', C-3', C-9', C-10'); MS (m/z). Intensity (%): 357 (M'+1, 23), 356 (M+, 100), 355 (15), 297 (4.8), 268 (4), 240 (6), 239 (18), 186 (11), 185 (86), 149 (5), 134 (15), 127 (10), 119 (45); HRMS: M' 356.1058, cald for C₂₃H₁₆O₄: 356.1048. Trimer 58: mp 263-265 °C; 1H NMR (CDCl₃): 4.61 (4H, H-16, H-16'), 6.00 (4H, H-17, H-17'), 6.11 (2H, H-18), 7.00 (2H, H-1, H-1'), 7.17-7.26 (m, 6H, H-6, H-7, H-13, H-6', H-7', H-13'), 7.58-7.61 (m, 2H, H-8, H-8'), 7.97-8.04 (m, 4H, H-5, H-14, H-5', H-14'); 13C NMR (CDCl₃): 23.1 (C-16, C-16'), 100.4 (C-18), 100.6 (C-17, C-17'), 102.9 (C-1, C-1'), 123.4, 123.5, 123.8, 123.9, 124.0, 124.1 (C-5-C-8, C-13, C-14, C-5'-C-8', C-13', C-14'), 112.3, 113.7, 129.8, 130.3, 130.9, 144.9, 145.7, 146.5 (C-2, C-3, C-4, C-9, C-10, C-11, C-12, C-15, C-2', C-3', C-4', C-9', C-10', C-11', C-12', C-15'); MS (m/z). Intensity (%): 541 (31), 540 (M+, 83), 369 (2), 355 (3), 337 (2), 325 (1), 310 (1), 297 (2), 270 (5), 252 (3), 237 (1), 199 (1), 196 (2), 186 (14), 185 (100).
Method B. To a refluxing solution of 57 (2.0 g, 11.62 mmol) in chlorobenzene (45 mL) was added dropwise a solution of 58 (1.50 g, 5.68 mmol) in chlorobenzene (15 mL) over 2 h. The reaction mixture was refluxed for 12.5 h. The solvent was removed by vacuum distillation. The residue was column chromatographed with dichloromethane as eluent. The major fraction was further purified by flash column chromatography using 50% dichloromethane / petroleum ether (30-60°C) as eluent. Dimer 61 (1.10 g, 54%), and starting material 57 (516 mg, 26%) were obtained.

1,4-Dibromo-2,3-dimethoxynaphthalene (74).

These two compounds were prepared according to a literature procedure.\textsuperscript{101} Compound 74 (81%) and 1,4,6-tribromo-2,3-methylenedioxyxynaphthalene (74a)(11%) were obtained as colourless fine crystals. Dibromo compound 74: lit. mp 76-78 °C, mp 180-181 °C; \textsuperscript{1}H NMR (CDCl\textsubscript{3}): 4.01 (s, 6H, -OCH\textsubscript{3}), 7.57 (m, 2H, H-6, H-7), 8.24 (m, 2H, H-5, H-8); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): 61.1 (OCH\textsubscript{3}), 116.1 (C-1, C-4), 127.1, 127.2 (C-5-C-8), 130.1 (C-
9, C-10), 150.4 (C-3, C-3); MS (m/z), Intensity (%): 348 (M'+2, 50), 347 (M'+1, 13), 346 (M*, 100), 344 (M'-2, 51), 301 (9), 250 (8), 222 (16), 115 (27).

Tribromo compound 74a: lit. mp 190 °C, mp 190-192 °C; \(^1\)H NMR (CDCl₃): 4.06 (s, 6H, OCH₃), 7.46 (m, 3H, H-5, H-7, H-8). \(^{13}\)C NMR (CDCl₃): 56.1 (OCH₃), 106.4, 120.6, 128.2, 128.6, 151.0 (aromatic); MS (m/z), Intensity (%): 426 (M'+2, 20), 424 (M*, 21), 348 (50), 346 (100), 302 (27), 288 (11), 250 (14), 126 (13).

1-Bromo-2,3-methylenedioxyzynaphthalene (66).

\[
\begin{array}{c}
\begin{array}{c}
\text{Br} \\
\mid \\
\text{O} \\
\mid \\
\end{array}
\end{array}
\]

To a solution of 57 (1.0 g, 5.81 mmol) in chloroform (10 mL) was added a solution of bromine / dioxane complex (1.43 g, 5.81 mmol) in chloroform (5 mL) over 30 min. After stirring for 14 h at room temperature, the reaction mixture was washed with water until the washings were neutral to pH paper. After the organic layer was separated, dried over MgSO₄, and filtered, the solvent was evaporated. The crude product was crystallized twice from aqueous ethanol.

Compound 66 was obtained as colourless needles (613 mg, 56%): mp 84-85 °C; \(^1\)H NMR (CDCl₃): 6.09 (s, 2H, H-11), 7.05 (s, 1H, H-4), 7.33-7.46 (m, 2H, H-6, H-7), 7.63 (d, J=7.5, 1H, H-5 or H-8), 8.01 (d, J=8.1, 1H, H-5 or H-8); \(^{13}\)C NMR
(CDCl₃): 101.3 (C-11), 103.5 (C-4), 125.1, 125.3, 125.4, 127.3 (C-5-C-8), 125.8, 126.3, 128.4, 128.6, 131.0 (C-1, C-2, C-3, C-9, C-10); MS (m/z), Intensity (%): 252 (M⁺ 98), 250 (M⁺ 100), 194 (12), 192 (12), 115 (31), 113 (56).

*Bis-(1-bromo-2,3-methylenedioxy-4-naphthyl)methane (67).*

To a solution of 66 (594 mg, 2.38 mmol) and paraformaldehyde (85.8 mg, 2.86 mmol) in glacial acetic acid (20 mL) was slowly added concentrated sulphuric acid (0.4 mL). The reaction mixture was heated to 60-70°C and kept at that temperature for 3.5 h. After cooling to room temperature, the reaction mixture was poured onto crushed ice (20 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper and dried under vacuum. The crude product was recrystallized from ethyl acetate / hexanes. Dimer 67 was obtained (510 mg, 82%) as a colourless powder; mp 167-170°C; ¹H NMR (CDCl₃): 4.59 (s, 2H, H-11), 6.14 (s, 4H, H-12, H-12'), 7.29-7.44 (m, 4H, H-6, H-7, H-6', H-7'), 7.98, 8.05 (d, 4H, H-5, H-8, H-5', H-8'); ¹³C NMR (CDCl₃): 30.0 (C-11), 101.1 (C-12, C-12'), 123.5, 125.2, 125.4, 126.0 (C-5-C-8, C-5'-C-8').
Bis-(2,3-methylenedioxy-1-naphthyl)methane (61) via debromination of 67.

A flask fitted with a condenser and containing a suspension of LAH (300 mg, 7.89 mmol) in dry THF (15 mL) under N₂ was set up in a sonicator. A solution of 67 (917 mg, 1.79 mmol) in THF (15 mL) was added over 20 min. The reaction mixture was sonicated for 20 h at 35-40°C. The reaction was quenched by adding water dropwise. Diethyl ether (30 mL) and 5% sulphuric acid (20 mL) were added. The aqueous layer was washed with two 20 mL-portions of ether. The combined organic extracts were dried over MgSO₄, and filtered, and the solvent was evaporated. The crude product was purified by flash column chromatography using 30% ethyl acetate / hexanes as eluent to afford 61 as a colourless powder (408 mg, 64%), whose properties were identical to those described above.

Bis-(1-bromomethyl-2,3-methylenedioxy-1-naphthyl)methane (60).
To a solution of 61 (579 mg, 1.63 mmol) and paraformaldehyde (147 mg, 4.89 mmol) in dichloromethane (60 mL) was added a solution of 30% HBr in glacial acetic acid (4 mL). The reaction mixture was stirred at room temperature for 10 h and then washed with water until the washings were neutral to pH paper. After drying over anhydrous MgSO₄ and filtering, the solvent was evaporated. The crude product was purified by column chromatography using 30% ethyl acetate/hexanes as eluent. A colourless powder was obtained (629 mg, 71%): mp 250-252 °C; ¹H NMR (DMSO-d₆/CDCl₃): 4.59 (s, 2H, H-11), 4.92 (s, 4H, H-13, H-13'), 6.26 (s, 4H, H-12, H-12'), 7.31-7.43 (m, 4H, H-6, H-7, H-6', H-7'), 7.87-8.07 (m, 4H, H-5, H-8, H-5', H-8'); ¹³C NMR (DMSO-d₆/CDCl₃): 23.9 (C-11), 24.0 (C-13, C-13'), 78.1 (C-12, C-12'), 101.1, 109.1, 113.8, 122.3, 122.7, 123.3, 124.2, 124.3, 127.8, 129.3, 144.6 (aromatic); MS (m/z), Intensity (%): 540 (M⁺, 3), 463 (11), 461 (11), 384 (3), 279 (21), 277 (22), 265 (2.7), 252 (3), 198 (27), 141 (6), 132 (5), 126 (6), 80 (100); HRMS: M⁺ 539.9684, calcd for C₂₅H₁₆O₄Br₂: 539.9684.

To a solution of 60 (1.79 g, 3.31 mmol) and 61 (0.86 g, 5 mmol) in dry 
$p$-dioxane (250 mL) under $N_2$ was slowly added $\text{TiCl}_4$ (2.0 mL, 10 mmol). A dark 
brown solution was produced. The reaction mixture was refluxed for 1 week.

After evaporating the solvent, the dark brown residue was extracted with 
chloroform (200 mL) using a Soxhlet extraction apparatus. The crude product 
was purified twice by flash column chromatography using dichloromethane and 
50% dichloromethane / hexanes sequentially as eluents. Calix[4]naphthalene 
62 was obtained (111 mg, 4%) as a light brown solid: mp $>$ 300°C (with 
decomposition); $^1$H NMR (CDCl$_3$): 3.29 (m, 4H, H-11"$_a$, H-11"$_a$, H-11"$_a$, H-11"$_a$), 
4.18 (m, 4H, H-11$_e$, H-11$_e$, H-11$_e$, H-11$_e$), 3.66 (m, 8H, H$_a$(dioxane)), 3.98 (m, 
8H, H$_a$(dioxane)), 3.88 (m, 4H, H-12$_a$, H-12$_a$, H-12$_a$, H-12$_a$), 4.41 (m, 4H, H- 
12$_e$, H-12$_e$, H-12$_e$, H-12$_e$), 7.38 (m, 8H, H-6, H-7, H-6', H-7', H-6", H-7", H-6", 
H-7'"), 7.70 (m, 8H, H-5, H-8, H-5', H-8', H-5", H-8", H-5'"., H-8'"), $^{13}$C NMR 
(CDCl$_3$): 27.3 (C-11, C-11', C-11", C-11"), 59.5, 59.7, 66.3, 68.7 (C-dioxane), 
99.9(C-12, C-12', C-12", C-12"'), 109.6, 122.2, 124.2, 129.2, 160.8 (aromatic); 
MS (FAB+, m/z), Intensity (%): 932 (M$^+$+2H+2 dioxane+H$_2$O, 0.2), 826 
(M$^+$+2H+dioxane, 0.2), 752 (0.2), 697 (0.2), 606 (0.3), 540 (0.5), 458 (0.5), 431 
(0.6), 408 (0.5), 352 (0.5), 340 (1.0), 325 (0.8), 318 (1.3), 309 (1.1), 297 (1.1), 

* "H$_a$" is perpendicular to the naphthalene ring; "H$_a$" is parallel with the 
naphthalene ring.

** The integration is not accurate.
To a solution of 60 (798 mg, 1.48 mmol) in THF (50 mL) was added thiolourea (249 mg, 3.3 mmol). The reaction mixture was refluxed for 10 h. After cooling to room temperature, the solvent was evaporated and the residue was dissolved in water (60 mL) containing aqueous 10% NaOH (6 mL). The reaction mixture was refluxed under N₂ for 12 h. After cooling to room temperature, concentrated sulphuric acid was carefully added until the pH of the reaction mixture was 5-6. A white precipitate formed, which was filtered, washed with water and dried under vacuum. The crude product (580 mg) was chromatographed using 40% ethyl acetate / hexanes as eluent. Compound 68 was obtained as pale crystals (456 mg, 69%): mp 217-220 °C; ¹H NMR (CDCl₃): 2.02 (t, J=7.2, 2H, SH), 4.20 (d, J=7.2, 4H, H-13, H-13'), 4.73 (s, 2H, H-11). 6.19 (s, 4H, H-12, H-12'), 7.36-7.55 (m, 4H, H-6, H-7, H-6', H-7'), 7.96 (d, J=8.4, 2H, H-5, H-5' or H-8, H-8'), 8.19 (d, J=8.1, 2H, H-5, H-8 or H-5', H-8'); ¹³C NMR
(CDCl₃): 18.9 (C-13), 23.1 (C-11), 100.9 (C-12, C-12'), 113.1, 121.2, 122.9, 124.2, 124.3, 124.4, 124.6, 128.3, 145.0 (aromatic); MS (m/z). Intensity (%): 448 (M⁺, 62), 434 (3), 415 (24), 401 (5), 381 (4), 369 (11), 265 (5), 239 (4), 231 (100), 215 (3), 207 (4), 198 (23), 191 (51).


A solution of 68 (448 mg, 1.0 mmol) and 60 (540 mg, 1.0 mmol) in benzene (200 mL) was very slowly added into a Erlenmeyer flask containing 95% ethanol (500 mL) and KOH (280 mg, 4.8 mmol) in water (5 mL). The addition of the benzene solution took 10-15 h. The reaction mixture was vigorously stirred for 72 h after the addition was completed. Concentrated sulphuric acid was carefully added to the reaction mixture until the pH value of the reaction mixture reached 5-6. After evaporating the solvent, the residue was extracted with dichloromethane (300 mL). The organic layer was washed with water until the washings were neutral to pH paper, dried over MgSO₄,
filtered and the solvent was evaporated. The residue was chromatographed using 80% dichloromethane / petroleum ether (30-60 °C) as eluent. The major fraction was recrystallized from chloroform / hexanes. A colourless crude product was obtained (356 mg, mp>300 °C with decomposition), which was not further purified or characterized due to low solubility in common organic solvents and presumed to be the cyclic sulphur-bridged tetramer. It was used in the subsequent step.

The cyclic sulphur-bridged tetramer (100 mg) was suspended in trimethyl phosphite (5 mL). The suspension was irradiated with an ultraviolet lamp (RPR 3500 Å) for 69 h (for detailed conditions see Chapter 4). After the solvent was removed by vacuum distillation, the residue was purified by PLC using 40% ethyl acetate / hexanes as eluents. Dhomocalixnaphthalene 70 was obtained as colourless fine crystals (22 mg, 11% from 60, and 68): mp 295-300 °C; 'H NMR (CDCl₃): 1.25 (m, 2H, H-2α, H-2β), 1.64 (m, 1H, H-3α), 2.32 (m, 1H, H-3β), 3.00 (d, 1H, H-12α), 3.29 (d, 1H, H-12β), 3.39 (d, 1H, H-31α), 3.60 (m, 1H, H-2α), 4.11 (m, 1H, H-21α), 4.18 (m, 1H, H-22α), 4.22 (d, 1H, H-31β), 4.60 (m, 1H, H-22β), 6.00, 6.07, 6.09, 6.17 (sx4, 8H, H-47-H-50), 7.18-8.01 (not resolved, 16H, aromatic); ¹³C NMR (CDCl₃): 21.2, 22.0, 24.9 (C-2, C-3, C-12, C-21, C-22, C-31), 99.6, 100.1, 100.4, 100.7 (C-48, C-49, C-50), 122.5, 122.7, 123.3, 123.5, 123.7,

*** See the previous footnote in page 173 of this chapter.
123.9, 127.1, 124.2, 124.3, 129.4, 130.2, 144.9 (aromatic); MS (FAB+, m/z).
Intensity (%): 763 (M+1, 4), 329 (3), 307 (11), 289 (11).

1,4-Bis-mercaptomethyl-2,3-methylene dioxy naphthalene (73).

![Chemical structure](image)

To a solution of 59 (500 mg, 1.40 mmol) in THF (50 mL) was added thiourea (234 mg, 3.07 mmol). The reaction mixture was refluxed for 10 h. After cooling to room temperature, the solvent was evaporated and the residue was dissolved in water (50 mL) containing aqueous 10% NaOH (5 mL). The reaction mixture was refluxed under N₂ for 12 h. After cooling to room temperature, concentrated sulphuric acid was carefully added until the pH of the reaction mixture reached 6-7. After the solvent was evaporated, the residue was extracted with dichloromethane (50×3 mL). The combined dichloromethane extracts were dried over MgSO₄, filtered and the solvent was evaporated, the residue was chromatographed with 40% ethyl acetate / hexanes as eluent. Compound 73 was obtained as a cream-coloured powder (300 mg, 81%): mp 150-152°C; IR (KBr, cm⁻¹): 3530 (s, br, SH), 1550 (m), 1450 (s), 1400 (m); 'H NMR (CDCl₃): 1.94 (t, J=7.2, 2H, SH), 4.09 (d, 4H, J=7.2, H-11, H-13), 6.13 (s,
(s, 2H, H-12), 7.47 (m, 2H, H-6, H-7), 7.90 (m, 2H, H-5, H-8); 13C NMR (CDCl₃): 18.8 (C-11, C-13), 101.4 (C-12), 123.2, 124.7 (C-5-C-8), 113.8, 128.4, 144.2 (C-1-C-4), C-9, C-10); MS (m/z), intensity (%): 264 (M⁺, 100), 231 (78), 198 (20), 185 (41), 157 (12), 139 (11), 127 (10), 115 (11).

Dithia[3.3](1,4) cyclonaphthaleneophane (71).

A solution of 59 (243 mg, 0.68 mmol) and 73 (177 mg, 0.67 mmol) in benzene (100 mL) was very slowly added into a Erlenmeyer flask containing 95% ethanol (250 mL) and KOH (182 mg, 3.3 mmol) in water (3 mL) under N₂. The addition of the benzene solution took 10-15 h. The reaction mixture was vigorously stirred for another 72 h after the addition was completed. Concentrated sulphuric acid was carefully added until the pH of the reaction mixture reached 5-6. After evaporating the solvent, the residue was extracted with dichloromethane (100 mL x2). The dichloromethane extracts were washed with water until the washings were neutral to pH paper. After drying over MgSO₄ and filtering, the solvent was evaporated. The residue was chromatographed
using 50% dichloromethane / petroleum ether (30-60 °C) as eluent. The major fraction was re-chromatographed using 30% ethyl acetate / hexanes as eluent. The cyclic dimer 71 was obtained (72 mg, 31%) as colourless needles. In addition, 1,4-diethoxymethyl-2,3-methylenedioxy naphtalene (72) (65 mg, 37%) was also obtained as colourless fine crystals. Compound 71: mp 280 °C (with decomposition); ¹H NMR (CDCl₃): 3.88 (d, J=15, 4H, H-1₁, H-1₂, H-1₁', H-1₂'), 4.63 (d, 4H, J=15, H-1₁, H-1₂, H-1₁', H-1₂'), 5.67 (s, 2H, H-1₃, H-1₃'), 6.19 (s, 2H, H-1₃, H-1₃'), 6.94 (m, 4H, H-6, H-7, H-6', H-7'), 7.74 (m, 4H, H-5, H-8, H-5', H-8'); NOED (%): H-1₁, H-1₁' / H-1₂, H-1₂' (33), H-1₃, H-1₃' / H-1₃, H-1₃'; H-1₃, H-1₃' (26), H-6, H-7, H-6', H-7' / H-5, H-8, H-5', H-8' (7.5), H-5, H-8, H-5', H-8' / H-1₁, H-1₂, H-1₁', H-1₂' (6.9); ¹³C NMR (CDCl₃): 27.7 (C-1₁, C-1₂, C-1₂'), 100.1 (C-1₃, C-1₃'), 108.9, 123.1, 124.1, 128.6, 143.9 (aromatic); MS (m/z), Intensity (%): 462 (11), 461(23), 460(M⁺, 88), 229 (100), 199 (85).

Compound 72: mp 87-88 °C; ¹H NMR (CDCl₃): 1.23 (t, J=6.9, 6H, H-1₃, H-1₄), 3.59 (q, J=6.9, 4H, H-1₂, H-1₅), 4.88 (s, 4H, H-1₁, H-1₆), 6.06 (s, 2H, H-1₇), 7.41 (m, 2H, H-6, H-7), 8.02 (m, 2H, H-5, H-8); ¹³C NMR (CDCl₃): 15.2 (C-1₁, C-1₂, C-1₂'), 63.1 (C-1₃, C-1₅), 65.5 (C-1₃, C-1₆), 101.0 (C-1₇), 111.6, 124.0, 124.6, 130.0, 147.0 (C-1-C-10); MS (m/z), Intensity (%): 288 (M⁺, 100), 243 (39), 198 (41), 185 (37).

Attempted synthesis of Dihomocalixnaphthalene 70 via a supported Na₂S
procedure.

To a solution of Na₂S·9H₂O (1.60 g, 10.9 mmol) in water (10 mL) was added basic Al₂O₃ (Alumina Fluka, Type 5016 A, 1.70 g). After vigorous stirring for 10 min and evaporating the solvent, the residue was dried under vacuum to give an alumina-supported sodium sulphide reagent (3.96 g, 2.75 mmol / g).

To a solution of 59 (1.0 g, 2.8 mmol) in dichloromethane (90 mL) and 95% ethanol (10 mL) was added freshly prepared alumina-supported sodium sulphide reagent (2.75 mmol / g, 2.04 g, 5.62 mmol). The reaction mixture was stirred at room temperature for 5 d. Dichloromethane (50 mL) was added to the reaction mixture and the sodium sulphide reagent was filtered off. The filtrate was washed with water until the washings were neutral to pH paper. The organic layer was dried over MgSO₄ and filtered. After evaporating the solvent, the residue was dried under vacuum. A yellowish crude product was obtained (588 mg), which could not be re-dissolved in common organic solvents and was not further characterized.

1,4-Bis-(trimethylsilyl)-2,3-dimethoxynaphthalene (77).
Method A. To a solution of 56 (376 mg, 2 mmol) in dry diethyl ether (10 mL) under argon added dropwise TMEDA (1.6 mL, 10 mmol) and n-butyllithium (2.0 M in hexane, 5.0 mL, 10 mmol). This reaction mixture was stirred for 1 h at room temperature, and then heated to refluxing and kept refluxing for another 1 h. The reaction mixture was cooled to room temperature. Trimethylsilyl chloride (5.0 mL) was added through a syringe into the reaction mixture solution and the resulting mixture was stirred for 15 min. A mixture of ice (10 g) and aqueous saturated NH₄Cl (20 mL) was added, and the mixture was stirred for 15 min. After separating the aqueous layer, the ether layer was washed with water until the washings were neutral to pH paper. The ether extracts were dried with MgSO₄ and filtered. After the solvent was evaporated, the residue was purified by flash column chromatography using 30% ethyl acetate / hexanes as eluent. The product 77 was obtained (0.37 g, 55%) as a light brown solid: mp 75-82°C; 'H NMR (CDCl₃): 0.52 (s, 18H, -SiMe₃), 3.83 (s, 6H, OCH₃), 7.36 (m, 2H, H-6, H-7), 8.12 (m, 2H, H-5, H-8); MS (m/z), Intensity (%): 332 (M⁺, 100), 287 (25), 260 (12), 188 (39).

Method B. n-Butyllithium (0.5 M in hexane, 4 mL) was added dropwise to a solution of 1,4-dibromo-2,3-dimethoxynaphthalene (74) (173 mg, 0.50 mmol) in dry diethyl ether (5 mL) cooled to -78 °C under Ar. This reaction mixture was stirred for 3 h at -78 °C. Into this reaction mixture was added by a syringe trimethylsilyl chloride (2 mL). The reaction mixture was stirred for 15 min at
room temperature. A mixture of ice (3 g) and aqueous saturated NH₄Cl (5 mL) was added, and the mixture was stirred for 15 min. The ether layer was separated, washed with water until the washings were neutral to pH paper, dried over MgSO₄ and filtered. After the ether was evaporated, the residue was purified by flash column chromatography using 20% ethyl acetate / hexanes as eluent to afford 77 (125 mg, 75%).

1,4-Dimethyl-2,3-dimethoxynaphthalene (76).

To a solution of 74 (173 mg, 0.50 mmol) in dry diethyl ether (5 mL) cooled to -78 °C was added under argon dropwise n-butyllithium (0.5 M in hexane, 4 mL). This reaction mixture was stirred for 3 h at -78 °C. Methyl iodide (1 mL) was added, and the mixture was stirred for 15 min at room temperature. A mixture of ice (3 g) and aqueous saturated NH₄Cl (5 mL) was added, and the mixture was stirred for 15 min. The ether layer was separated, washed with water until the washings were neutral to pH paper, dried over MgSO₄ and filtered. After the ether was evaporated, the residue was purified by flash column chromatography using 20% ethyl acetate / hexanes as eluent to afford
76 (77.8 mg, 72%) as a light brown oil: 'H NMR (CDCl₃): 2.57 (s, 6H, H-11, H-12), 3.88 (s, 6H, H-13, H-14), 7.44 (m, 2H, H-6, H-7), 7.91 (m, H-5, H-8); ¹³C NMR (CDCl₃): 11.0 (C-11, C-12), 60.8 (C-13, C-14), 124.3, 124.6 (C-5-C-8), 126.6, 127.8, 130.6 (C-1, C-2, C-3, C-4, C-9, C-10); MS (m/z), Intensity (%): 216 (M⁺, 100), 205 (22), 201 (27), 173 (47), 158 (34), 141 (21), 115 (20).

Attempted coupling reaction of 1,4-dilithio-2,3-dimethoxynaphthalene (75) with 1,4-bis-bromomethyl-2,3-methoxynaphthalene (78).

To a solution of 74 (346 mg, 1.0 mmol) in dry diethyl ether (10 mL) cooled to -78°C was added under Ar dropwise n-butyllithium (2.0 M in hexane, 2 mL). The reaction mixture was stirred for 3 h at -78°C. Bis-bromomethyl compound 78 (372 mg, 1.0 mmol) was added, and the reaction mixture was stirred for a further 12 h at -78°C, during which a suspension formed. The ether was evaporated and the residue was washed with aqueous saturated NH₄Cl solution followed by water, and dried under vacuum. A brown solid product (mp>250°C) was obtained (509 mg), which was insoluble in common organic solvents and not further characterized.

Synthesis of cyclic naphthalene ethers 79, 80, 81 and 83.

General procedure:

Into a three-necked 500 mL flask fitted with a condenser and calcium
chloride drying tube, were added dry DMF, 2,3-dihydroxynaphthalene and anhydrous CsF. Under vigorous stirring, the dibromo- or ditosyl reagents were added via a dropping funnel over 30 min. The reaction mixture was heated to reflux and kept at reflux for 2-3 h. After cooling to room temperature, CsF was removed by filtration and recovered by recrystallisation twice from water. The mother liquor was diluted with water and extracted with diethyl ether. After drying over MgSO₄, filtering and evaporating the ether, the crude product was purified by column chromatography using 40% ethyl acetate/hexane as eluent to afford 79, 80, 81 or 82.

Cyclic ether 79 was obtained in 84% yield: mp 78.0-79.5 °C; IR (Kbr, cm⁻¹): 1600 (m), 1505 (s), 1495 (s), 1445 (s), 1400 (s), 1292.0(s, -OCH₂⁻); ¹H NMR (CDCl₃): 4.34 (s, 4H, H-11, H-12), 7.25 (s, 2H, H-1, H-4), 7.29 (m, 2H, H-6, H-7), 7.64 (m, H-5, H-8); ¹³C NMR (CDCl₃): 64.4 (C-11, C-12), 112.5 (C-1, C-4), 124.1, 126.3 (C-5-C-8), 129.4 (C-9, C-10), 143.9 (C-2, C-3); MS (m/z), Intensity (%): 186 (M⁺, 100), 171 (35), 130 (17); HRMS: M⁺ 186.0661, calcd for C₁₂H₁₀O₂:186.0680.
Cyclic ether 80 was obtained in 49% yield: mp 122-124 °C; IR (KBr, cm⁻¹): 
1600 (m), 1502 (s), 1497 (s), 1495 (s), 1445 (s), 1400 (s), 1292 (s, -OCH₂-); ¹H 
NMR (CDCl₃): 2.25 (m, 2H, H-12), 4.28 (t, J=5.7, 4H, H-11, H-13), 7.35 (m, 2H, 
H-6, H-7), 7.41 (s, 2H, H-1, H-4), 7.69 (m, 2H, H-5, H-8); ¹³C NMR (CDCl₃): 
31.9(C-12), 70.9 (C-11, C-13), 117.7, 124.9, 126.6, 130.5, 180.3 (aromatic); MS 
(m/z), Intensity (%): 200 (M⁺, 100), 171 (52), 159 (10), 131 (14); HRMS: M⁺ 

Cyclic polyether 81 was obtained in 48% yield: mp 102-103.5 °C; IR (KBr, 
cm⁻¹): 1610 (w), 1600 (w), 1503 (s), 1498 (s), 1490 (s), 1400 (m), 1250 (s, - 
OCH₂-); ¹H NMR (CDCl₃): 3.84 (s, 4H, H-13, H-14), 3.94 (m, 4H, H-12, H-15), 
4.27 (m, 4H, H-11, H-16), 7.30 (s, 2H, H-1, H-4), 7.35 (m, 2H, H-6, H-7), 7.69 (m, 
2H, H-5, H-8); ¹³C NMR (CDCl₃): 69.8, 71.3, 71.7 (C-11-C-16), 124.5, 126.5, 
130.1, 150.6 (aromatic); MS (m/z), Intensity (%): 274 (M⁺, 66), 186 (M⁺- 
dioxane,100), 171 (57), 160 (16), 130 (12); HRMS: M⁺ 274.1205, calcd for
Cyclic ether 83 was obtained in 52% yield: mp 178-179 °C; IR (nujol, cm⁻¹): 1204 (s), 1225 (s, -OCH₂O-); ¹H NMR (CDCl₃): 5.67 (s, 2H, H-11), 7.26 (m, 2H, H-7, H-7'), 7.40 (m, 2H, H-6, H-6'), 7.45 (d, J=8.7, 2H, H-3, H-3'), 7.51 (d, 2H, H-4, H-4'), 7.90 (d, J=8.1, 2H, H-8, H-8'), 7.94 (d, J=8.7, 2H, H-5, H-5'); ¹³C NMR (CDCl₃): 103.1 (C-11), 120.9, 124.9, 126.0, 126.8, 128.3, 130.3 (C-3-C-8, C-2'-C-8'), 131.7 (x 2), 132.1, 151.2 (C-1, C-2, C-9, C-10, C-1', C-2', C-9', C-10'); MS (m/z), Intensity (%): 298 (M⁺, 100), 270 (49), 269 (71), 268 (15), 253 (14), 252 (13), 241 (13), 240 (11), 239 (33), 237 (16), 134 (21), 120 (62), 118 (21); HRMS: M⁺ 298.0989, calcd for C₂₁H₁₄O: 298.0993.

(±)-1,1'-Bis-2-naphthol (82).
1,1'-Bis-2-naphthol was prepared according to a literature procedure \(65a\) in 61.3% yield as almost colourless crystals: lit. mp 218 °C, mp 216-217 °C; \(^1H\) NMR (CDCl\(_3\)): 5.05 (s, 2H, exchangeable with D\(_2\)O, OH), 7.16 (d, J=8.4, 2H, H-3, H-3'), 7.30 (m, 4H, H-6, H-6', H-7, H-7'), 7.40 (d, J=8.4, 2H, H-4, H-4'), 7.90 (d, J=7.8, 2H, H-8, H-8'), 7.99 (d, J=9.0, 2H, H-5, H-5').

1,4-bis-(hydroxymethyl)-2,3-methylenedioxy naphthalene (84).

Bis-(bromomethyl)-2,3-methylenedioxy naphthalene (59) (100 mg, 0.28 mmol) was dissolved in aqueous 50% \(\rho\)-dioxane (40 mL) and CaCO\(_3\) (2.8 g, 2.8 mmol) was added to the solution. The reaction mixture was refluxed for 10 h. After cooling to room temperature, the unreacted CaCO\(_3\) was filtered off. The filtrate was evaporated to dryness and the residue was crystallized from 95% ethanol. Bis-hydroxymethyl compound 84 was obtained as a colourless powder (59.8 mg, 92%): mp 219-221 °C; IR (KBr, cm\(^{-1}\)): 3356 (s, br, OH), 1671 (w), 1638 (w), 1443 (s); \(^1H\) NMR (CDCl\(_3\)): 5.09 (s, 4H, H-12, H-13), 6.07 (s, 2H, H-11), 7.39 (m, H-6, H-7), 8.14 (m, H-5, H-8); \(^{13}C\) NMR (CDCl\(_3\)): 56.3 (C-12, C-13), 101.2 (C-11), 123.7, 128.0 (C-5-C-8); MS (m/z), Intensity (%): 232 (M\(^+\), 100), 215 (14),
To a vigorously-stirred suspension of PCC (0.4 g, 1.86 mmol) and molecular sieves (Type 3 Å, 0.6 g) in dichloromethane (6 mL) was added 84 (100 mg, 0.43 mmol). After stirring at room temperature for 1 h, the dichloromethane solution was decanted, and filtered through a pad of florisil®. After evaporating the solvent, the residue was chromatographed using 30% ethyl acetate / hexanes as eluent. The product 85 was obtained as yellow needles (67.7 mg, 70%): mp 186-187 °C; IR (KBr, cm⁻¹): 1675 (s, CHO), 1600 (m), 1505 (m), 1495 (s); ¹H NMR (DMF-d₆) at 100 °C: 6.57 (s, 2H, H-11), 7.58 (m, H-7), 8.00 (m, H-5, H-6), 10.7 (s, 2H, CHO); MS (m/z), Intensity (%): 228 (M⁺, 100), 200 (43), 184 (11), 170 (17), 142 (5.9), 114 (35); HRMS: M⁺ 228.0422, calcd for C₁₉H₈O₄: 228.0422.

1,4-Diformyl-2,3-methylene dioxy naphthalene (85).
1,4-Bis-phosphonium salt 86.

To a solution of 59 (200 mg, 0.56 mmol) in dry DMF (2 mL) was added triphenylphosphine (Ph₃P) (323 mg, 1.23 mmol). The reaction mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was cooled to 0 °C 30 min. A white precipitate formed, which was filtered and washed with DMF (2 mL), followed by diethyl ether (10 mL). The precipitate was dried under vacuum to afford 86 as a colourless powder (377 mg, 76%): mp 296-298 °C; 'H NMR (DMSO-d₆): 5.26 (s, 2H, H-11), 5.34 (d, J=14, H-12, H-13), 6.84 (m, 2H, H-6, H-7), 7.42 (m, 2H, H-5, H-8), 7.56-7.94 (m, 30H, aromatic).

Wittig reaction of 85 and 86.

In dry DMF (10 mL) under argon were dissolved 85 (200 mg, 0.888 mmol) and 86 (783 mg, 0.89 mmol). The reaction flask was cooled down to -42 °C with a dry ice-acetonitrile bath. A mixture of lithium ethoxide (0.4 M in ethanol, 5 mL, 2.0 mmol) and DMF (5 mL) was added over 12 h. After the addition was completed, the reaction mixture was stirred for 30 min. After warming to room temperature, water (10 mL) was added, and the reaction mixture was extracted with three 50 mL-portions of diethyl ether. The ether extracts showed a strong yellow fluorescence. The combined ether extracts
were washed with water, dried over MgSO₄, filtered, and the ether was evaporated. The yellow residue was purified through flash column chromatography using 80% dichloromethane/hexanes as eluent. 1,4-Dimethyl compound 87 (16 mg, 9%) and the conjugated trimer 88 (74 mg, 14%) were obtained.

![Compound 87](image)

![Compound 88](image)

Compound 87 was obtained as colourless needles: mp 87-89 °C; ¹H NMR (CDCl₃): 2.48 (s, 6H, H-12, H-12'), 3.01 (s, 2H, H-11), 7.39 (m, 2H, H-6, H-7). 7.82 (m, H-5, H-8); ¹³C NMR (CDCl₃): 10.8 (C-12, C-13), 100.2 (C-11), 108.9, 123.4, 123.7, 130.4, 144.6 (aromatic); MS (m/z), Intensity (%): 200 (M⁺, 100), 199 (16), 169 (5), 142 (15), 141 (23), 129 (4), 115 (15). Trimer 88 was a yellow powder: mp >300 °C; ¹H NMR (CDCl₃): 2.56 (s, 6H, H-12, H-12'), 6.23 (s, 4H, H-11, H-11'), 6.40 (s, 2H, H-25), 7.26 (H-13, H-13' or H-14, H-14', overlap with CHCl₃), 7.45-7.50 (m, 6H, H-6, H-7, H-20, H-21, H-6', H-7'), 7.85-7.88 (m, 2H, H-19, H-22), 8.10 (d, J=6, 2H, H-13, H-13' or H-14, H-14'), 8.19-8.23 (m, 4H, H-5,
H-8, H-5', H-8'); MS (m/z), Intensity (%): 592 (M⁺, 38), 590 (11), 198 (36), 141 (7), 138 (4), 119 (5), 115 (3), 105 (4), 97 (4), 87 (10), 85 (70), 84 (8), 83 (100);

HRMS: M⁺ 592.1847, calcd for C₃₀H₂₆O₆: 592.1884.
Chapter 6.

Other Calixnaphthalenes, Functionalized Calixresorcinarenes, and Calixspherands


Among compounds which can be considered to be analogues of 1-naphthol are 1,5-, and 1,3-dihydroxynaphthalene. Calixnaphthalenes derived from these two compounds would have more hydroxy groups to serve as complexation binding sites, and to be functionalized. The other commercially available dihydroxynaphthalene, 2,7-dihydroxynaphthalene is an analogue of 2-naphthol. Although the condensation reaction of 2-naphthol with formaldehyde affords only a single product, bis(2-hydroxy-1-naphthyl)methane (89),\textsuperscript{104,105} it was likely that 2,7-dihydroxynaphthalene would be more reactive than 2-naphthol due to the extra hydroxy group, and that condensation with formaldehyde would go further, to produce linear or cyclic oligomers.

The possibility that the corresponding calixnaphthalenes could be formed from these three dihydroxynaphthalenes was investigated and the results are described in this chapter.
6.1.1. Condensation of 1,5- or 1,3-Dihydroxynaphthalene with Formaldehyde.

When the condensation of 1,5-, 1,3-dihydroxy naphthalene or the benzyl-protected naphthalene 90 with formaldehyde was carried out under acidic conditions, polymeric products were obtained (Scheme 6.1).

Scheme 6.1.

When the conditions which were employed for the formation of calix[4]naphthalenes from 1-naphthol in Chapter 2 were applied to the
condensation of 1,5- or 1,3-dihydroxynaphthalene with formaldehyde, a dark brown powder was obtained. The condensation of benzyl-protected naphthalene 90 with formaldehyde also did not afford any defined products (Scheme 6.2).

Scheme 6.2.

Both 1,5- and 1,3-dihydroxynaphthalene are electron-rich aromatic compounds. Therefore, they are highly reactive towards electrophiles, with the result that their condensation with formaldehyde under acidic conditions produces polymeric products. Under basic conditions, they are very labile to oxidation by molecular oxygen and form quinone-like compounds.

6.1.2. Condensation of 2,7-Dihydroxynaphthalene with Formaldehyde.

When 2,7-dihydroxynaphthalene was treated with formaldehyde either in the presence of acid or base, a dimer 91 is obtained (Scheme 6.3). Since the two reactive positions, C-1, and C-8, are peri, steric hindrance presumably
prevented the second condensation reaction from occurring at the C-8 or C-8' of 91. This suggested that in 2,7-dihydroxynaphthalene only positions C-1 and C-8 are chemically reactive, as confirmed by the fact that only 91 was formed, under a variety of conditions.

Scheme 6.3.


As previously indicated, calixresorcinarenens are another major class of calixarenes. Compared with calixarenes derived from phenols, few derivatized calixresorcinarenens have been reported. The condensation of aldehydes with 2,6-dihydroxyacetophenone (92) was investigated to try to form the corresponding calixresorcinarenene 93.

When 92 was treated with acetaldehyde, formaldehyde, or benzaldehyde in the presence of hydrochloric acid in ethanol solution, a white precipitate was formed. The $^1H$ NMR spectrum of the crude product indicated it to be a complex mixture with no clearly defined products. Several recrystallizations from
acetonitrile / water did not afford any defined product.

**Scheme 6.4.**

Examination of Dreiding models suggested strong steric repulsion between the aceto groups, which could limit formation of any cyclic oligomer. Another factor could be that strong hydrogen bonding between the aceto and hydroxy groups could be formed, which could diminish any intramolecular hydrogen bonding between the *meta* hydroxy groups. Such intramolecular hydrogen bonding is suggested to be a driving force to form calixresorcin-arenes.$^{43}$

### 6.3. Calixspherands.

Among the calixarene derivatives that have been reported, calixspherands are some of the most important. One of the most extensively studied calixspherands is 94. Reinhoudt$^{30}$ found that in its free ligand state, calixspherand 94 is fixed in a cone conformation while its complexes with sodium, potassium, or rubidium cation are in "partial-cone" conformations. The
complexes with Na⁺ and K⁺ at room temperature in chloroform saturated with water have decomplexation half-life times of 37 and 2.2 years respectively. Due to the large size of Rb⁺ which forces the methoxy groups of the calixspherand to rotate away from the cavity, the complex of 94 with Rb⁺ has a decomplexation half-life time of 2.8 hours. This low stability of the Rb⁺ complex does not meet the requirements for the immobilization of rubidium for organ imaging purposes. In order to achieve such biomedical applications of the rubidium complex, much effort has been spent on trying to increase the stability of the rubidium complexes, with kinetic stabilities on a human-time scale as a final goal.

Since the naphthalene ring is larger than benzene, a calixspherand having naphthalene tethers might be more rigid, and, therefore, its complexes with alkaline cations would be more stable.
6.3.1. Synthesis of Calixspherands.

Calixspherands made from \( p\text{-}t\text{er}t\text{-}b\text{u}t\text{y}l\text{c}a\text{l}i\text{x}[4]\text{ar}\text{e}n\text{e} \) (1) and naphthalene tethers derived from 49, 59, and 60 were studied. Calixarene 1 was prepared according to Gustche's procedure. The preparation of 49 was described in Chapter 4, and those of 59, and 60 were described Chapter 5. The major synthetic task was to effect the coupling of 1 with 49, 59, or 60.

When calixarene 1 was reacted with 49 in the presence of sodium hydride and 18-crown-6, calixspherand 95 was obtained in good yield (Scheme 6.5). However, the coupling reaction of 1 with 59, or 60 failed to yield any corresponding calixspherand.

The challenge for the synthesis of calixspherands is the regioselectivity of O-alkylation. The second alkylation can be at the adjacent or at the opposite hydroxy groups leading to the lower rim 1,2- or 1,3-dialkylated calixarenes; or
intermolecularly to give bridged di-calixarenes. Examination of Dreiding models suggested that the lower rim 1,3-dialkylated product of calixarene with 49 is relatively flexible, but that the 1,2-dialkylated product is very rigid. As a result, the former would be expected to be favoured over the latter. The high yield of intramolecular versus intermolecular products without requiring high dilution conditions is possibly due to the template effect of a sodium cation. The ligand sites of the naphthalene tether 49 and the calixarene 1 can fold together around Na⁺. Reinhout found that when the larger K⁺ was used, only a small amount of calixspherand was obtained as K⁺ is too large to act as a good template ion.\(^3\)

Examination of Dreiding molecular models revealed that the structures of calixspherands derived from 1 and 59 or 60 are very rigid. This could be the reason that calixspherands from 1 and 56, or 60 were not obtained.
Fig. 6.2. NOED Spectra of 95 in CDCl₃.
Fig. 6.1. HH COSY Spectrum of 95 in CDCl₃.
6.3.2. Conformation of Calixspherand 95.

Examination of Dreiding models also revealed that in the "cone" conformation of 95, one of two geminal protons in all the methylene and oxymethylene bridges is approximately perpendicular to the adjacent aromatic rings, which we call the *pseudo* equatorial proton (Hₚ); the other which we call the *pseudo* equatorial proton (Hₑ) is approximately parallel to the adjacent aromatic rings.

The 300 MHz COSY spectrum of 95 is shown in Fig. 6.1. There are five pairs of doublets due to the four methylene bridges (A, B, C, and D) of calixarene, and one of the oxymethylene bridges (F). There are two sets of AB quartets, one of which is due to the methylene bridge (E) of the bisnaphthalene methane, and the other due to the other oxymethylene bridge (G). These signals indicate that the calixspherand 95 is conformationally fixed in solution even at ambient temperature. Further studies on the conformation of 95 were conducted by NOED experiments (Fig. 6.2). In the NOED spectra, there are four discrete signals (δ 0.70, 1.12, 1.27, and 1.39 ppm) due to the tert-butyl groups. Irradiation of any of these tert-butyl signals did not enhance any of the signals due to the methylene bridges and the methoxy protons. This confirms that the calixspherand is in a "cone" conformation. In this rigid conformation, the oxymethylene groups are different: (a) oxymethylene group G appears as an AB
Table 6.1. Assignments of the $^1$H NMR Spectrum of Calixspherand 95.

<table>
<thead>
<tr>
<th>tert-butyl</th>
<th>$^1$H</th>
<th>0.696 (s)</th>
<th>1.12 (s)</th>
<th>1.27 (s)</th>
<th>1.39 (s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>31.3 (q)</td>
<td>31.7 (q)</td>
<td>32.0 (q)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$H_a$ (A)</td>
<td>$H_a$ (A)</td>
<td>$H_a$ (B)</td>
<td>$H_a$ (B)</td>
<td></td>
</tr>
<tr>
<td>$^1$H</td>
<td></td>
<td>2.54 (d, J=14.1)</td>
<td>3.99 (d, J=14.1)</td>
<td>3.20 (d, J=13.8)</td>
<td>4.08 (d, J=13.8)</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>28.74 (t)</td>
<td></td>
<td>32.14 (t)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$H_a$ (C)</td>
<td>$H_a$ (C)</td>
<td>$H_a$ (D)</td>
<td>$H_a$ (D)</td>
<td></td>
</tr>
<tr>
<td>$^1$H</td>
<td></td>
<td>3.33 (d, J=12.6)</td>
<td>4.48 (d, J=12.6)</td>
<td>3.54 (d, J=13.6)</td>
<td>4.14 (d, J=13.6)</td>
</tr>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>32.3 (t)</td>
<td></td>
<td>34.7 (t)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>$H_a$ (E)</td>
<td>$H_a$ (E)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ph-CH$_2$-Ph</td>
<td>$^1$H</td>
<td>4.99 (q, 16.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>24.96 (t)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCH$_2$</td>
<td>$^1$H</td>
<td>4.44 (d, J=11.7)</td>
<td>5.76 (d, J=11.7)</td>
<td>4.59 (q, J=8.4)</td>
<td></td>
</tr>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>75.7 (t)</td>
<td></td>
<td>74.5 (t)</td>
<td></td>
</tr>
<tr>
<td>OCH$_3$</td>
<td>$^1$H</td>
<td>3.21 (s)</td>
<td></td>
<td>3.09 (s)</td>
<td></td>
</tr>
<tr>
<td>$^{13}$C</td>
<td></td>
<td>63.4 (q)</td>
<td></td>
<td>62.5 (q)</td>
<td></td>
</tr>
</tbody>
</table>

Quartet centred at δ 4.59 ppm, which indicates that the pseudo equatorial protons are less deshielded by the naphthalene ring and the pseudo axial protons are less shielded by the naphthalene ring; (b) oxymethylene group F
appears as a pair of doublets (AX) with one centred at δ 4.44 and the other at 5.76 ppm. This indicates that the pseudo equatorial protons are more deshielded by the naphthalene ring, and that the pseudo axial ones are more shielded by the naphthalene ring. Therefore, the conformation does not appear as a perfect "cone". These assignments are summarized in Table 6.1.

6.4. Summary.

Condensation of 1,5- or 1,3-dihydroxynaphthalene with formaldehyde under basic conditions gave oxidized products such as quinones, and under acidic conditions gave linear oligomers. Condensation of formaldehyde with 2,7-dihydroxynaphthalene under either basic or acidic conditions gave the dimer 91.

Condensation of 2,6-dihydroxyacetophenone with aldehydes such as acetaldehyde and benzaldehyde under acidic conditions gave polymers, but did not give cyclic the anticipated calixresorcinarene.

The naphthalene-tethered calixspherand 95 was synthesized in 77% yield without requiring high dilution conditions. The conformation was assigned to be a "cone" by using 2D NMR (COSY, NOED and HETCOR) experiments.
6.5. **Experimental.**

For general experimental conditions and instrumentation employed see Chapter 2.

**1-Hydroxy-5-naphthyl benzyl ether (90).**

![Chemical Structure]

To a solution of 1,5-dihydroxynaphthalene (800 mg, 5 mmol) in dry DMF (20 mL) was added potassium carbonate (0.69 g, 5 mmol). After heating to 85-90°C, benzyl chloride (0.60 mL, 4.3 mmol) was added over 20 min. The reaction mixture was stirred for 5 h at 85-90 °C. After cooling to room temperature, the reaction mixture was poured into a mixture of crushed ice (20 g) and concentrated hydrochloric acid (20 mL). A dark brown precipitate formed. After filtering, washing with water until the washings were neutral to pH paper, and drying under vacuum, a crude product was obtained (1.2 g), which, after purification by PLC, afforded the product **90** (770 mg, 60%) as a light brown solid: MP 164-166 °C; IR (KBr, cm⁻¹): 3509 (s, OH), 1620 (s), 1516 (s), 1414 (s), 1271 (s); ¹H NMR (CD₂COCD₂): 5.30 (s, 2H, H-11), 6.95 (q, J₈₋₇=7.5, J₆₋₅=0.9,
1H, H-6), 7.05 (q, J_{2,3}=7.8, J_{2,4}=0.3, 1H, H-2), 7.26-7.47 (m, 5H, phenyl-H), 7.59-7.62 (m, 2H, H-4, H-8), 7.78-7.85 (m, 2H, H-3, H-7), 9.04 (s, 1H, OH); MS (m/z). Intensity (%): 250 (M⁺, 7), 159 (5), 131 (12), 103 (8), 102 (5), 91 (100).

Condensation of 1,5-dihydroxynaphthalene, 1-hydroxy-5-naphthyl benzyl ether (90) or 1,3-dihydroxynaphthalene with formaldehyde.

Under acidic conditions. To a solution of 1,5-dihydroxynaphthalene (1.6 g, 10 mmol) and formalin (aqueous 37% formaldehyde solution, 0.7 mL, 8.6 mmol) in 95% ethanol (18 mL) and water (4 mL) was added concentrated hydrochloric acid (1 mL). After refluxing for 1 h, a dark blue solution formed. After cooling to room temperature, the precipitate was filtered, washed with aqueous 1M NaOH solution (6 mL), followed by water until the washings were neutral to pH paper. A brown powder was obtained, which was only sparingly soluble in common organic solvents, and was not further characterized.

When the reaction of 1-hydroxy-5-naphthyl benzyl ether (90) or 1,3-dihydroxynaphthalene with formaldehyde was carried out under the same conditions as described above, similar polymeric products were obtained, and were not further characterized.

Under basic conditions. To a solution of 1,5-dihydroxynaphthalene (1.60 g, 10 mmol) in DMF (15 mL) were added formalin (aqueous 37% formaldehyde solution, 0.70 mL, 8.6 mmol) and aqueous 10% K₂CO₃ solution (1 mL, 0.72
mmol). The reaction mixture was refluxed for 40 h. After cooling to room temperature, the reaction mixture was poured into aqueous 5% hydrochloric acid (20 mL). A dark brown precipitate formed, which was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum to afford quantitative brown powder. The $^1$H NMR spectrum of the crude product showed it to be a mixture of many products, which were not further fractionated or characterized.

When the reaction of 1-hydroxy-5-naphthyl benzyl ether (90) or 1,3-dihydroxynaphthalene with formaldehyde was carried out under the same conditions as described above, similar polymeric products were obtained, which were not further purified or characterized.

*Bis(2,7-dihydroxy-1-naphthyl)methane (91).*

*Under basic conditions.* To a solution of 2,7-dihydroxynaphthalene (1.60 g, 10 mmol) in DMF (10 mL) were added formalin (aqueous 37% formaldehyde solution, 0.70 mL, 8.6 mmol) and aqueous 10% potassium carbonate solution
(1.0 mL, 0.72 mmol). The blue solution was refluxed under N₂ for 30 h and then cooled to room temperature. When the reaction mixture was poured into a mixture of ice (50 g) and aqueous 5% hydrochloric acid (10 mL), a brown precipitate formed, which was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The crude product was purified by flash chromatography using 40% ethyl acetate/hexanes as eluent to afford 91 (0.64 g, 59%) as a colourless powder: MP 255-256°C; IR (nujol, cm⁻¹), 3319 (s, br, OH), 1629 (m), 1518 (m), 1500 (s), 1377 (m), 1216 (s); ¹H NMR (CD₃COCD₃): 4.67 (s, 2H, H-11), 6.82 (q, J₆,₆=8.7, J₇,₇=2.1, 2H, H-6, H-6'), 7.00 (d, J=8.7, 2H, H-3, H-3'), 7.51 (d, J=8.7, 2H, H-5, H-5'), 7.55 (d, J=8.7, 2H, H-4, H-4'), 7.62 (d, J=2.4, 2H, H-8, H-8'); ¹³C NMR (CD₃COCD₃) 21.9 (C-11), 107.2, 115.5, 115.8, 128.4, 130.6 (C-3-C-6, C-8, C-3'-C-6', C-8'), 118.0, 125.0, 136.7, 153.2, 156.2 (C-1, C-2, C-7, C-9, C-10, C-1', C-2', C-7', C-9', C-10'); MS (m/z), intensity (%): 332 (M⁺, 3), 313 (3), 172 (26), 160 (100), 144 (20).

Under acidic conditions. To a solution of 2,7-dihydroxynaphthalene (1.60 g, 10 mmol) in a mixture of absolute ethanol (4 mL) and water (4 mL) were added formalin (aqueous 37% formaldehyde solution, 0.70 mL, 8.6 mmol) and concentrated hydrochloric acid (1 mL) under N₂. The milky emulsion was heated to 50°C and kept at that temperature for 1 h. The reaction mixture was then poured onto ice (50 g). The white precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum. The
crude product was purified by flash chromatography using 40% ethyl acetate / hexanes as eluent to afford compound 91 as a white powder (1.34 g, 81%).

Condensation of 2,6-dihydroxyacetophenone (92) with aldehydes.

Crude 2,6-dihydroxyacetophenone (92) was prepared according to a literature procedure.\textsuperscript{107} The crude product showed two spots on TLC. Flash column chromatography was carried out using 30% ethyl acetate / hexanes as eluent to purify it.

To a solution of purified 92 (0.79 g, 5 mmol) in 95% ethanol (10 mL) was added aqueous 10% acetaldehyde solution (2.2 mL). During refluxing for 12 h, a white precipitate formed. After cooling to room temperature, the precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum to afford a crude product (1.45 g). The \textsuperscript{1}H NMR spectrum of this crude product showed poorly resolved signals. The crude product was crystallized three times from acetonitrile / water to give a colourless fine powder whose \textsuperscript{1}H NMR signals were still very broad, and were not resolved.

When formaldehyde or benzaldehyde were used instead of acetaldehyde in the same molar ratio, similar intractable products were obtained, which were not further characterized.
p-tol-Bulthcalixarene (1).

_p-tol_-Butylcalixarene was prepared according to Gutsche's procedure\textsuperscript{167} in 42% yield. MP >300 °C (with decomposition); IR (Nujol, cm\textsuperscript{-1}): 3135 (s, br, OH), 1665 (w), 1600 (w), 1550 (w); \textsuperscript{1}H NMR (CDCl\textsubscript{3}): \textdelta 1.21 (s, 36H, C(CH\textsubscript{3})\textsubscript{3}), 3.52 (d, 4H, (CH\textsubscript{2})\textsubscript{a}), 4.28 (d, 4H, (CH\textsubscript{2})\textsubscript{a}), 7.05 (s, 8H, aromatic), 10.3 (s, 4H, OH); \textsuperscript{13}C NMR (CDCl\textsubscript{3}): 31.4 (CH\textsubscript{3}), 32.6 (CH\textsubscript{2}), 34.0 (C(CH\textsubscript{3})\textsubscript{3}), 125.9, 127.6, 144.3, 146.6 (aromatic).

Calixspherand 95.

A mixture of 1 (389 mg, 0.6 mmol), NaH (50% oil-dispersion, 144 mg, 3 mmol), and 18-crown-6 (5 mg) in dry THF (140 mL) was stirred at room temperature for 30 min and heated to reflux. A solution of bisbromomethyl compound 49 in dry THF (30 mL) was added into the above refluxing solution over 3.5 h. Refluxing for another 3 h was followed by the addition of water (5 mL) to quench the reaction. After evaporating the solvent under vacuum, the residue was redissolved in dichloromethane (100 mL) and washed with water until the
washings were neutral to pH paper. Further purification was carried out through PLC with 50% dichloromethane / petroleum ether (30-60 °C) as eluent. Calixspherand 95 was obtained as cream-coloured crystals (452 mg, 77%): MP 230-235 °C; \(^1\)H NMR (CDCl\(_3\)): 0.70, 1.12, 1.27, 1.39 (sx4, 36H, C(CH\(_3\))\(_3\)), 3.32, 3.09 (sx2, 6H, OCH\(_3\)), 2.54, 3.20, 3.33, 3.54, 3.99, 4.08, 4.14, 4.48 (dx8, 8H, Ph-CH\(_2\)-Ph), 4.99 (q, 2H, Naph-CH\(_2\)-Naph), 4.44, 5.76 (dx2, 2H, OCH\(_2\)), 4.59 (q, 2H, OCH\(_2\)), 6.41, 6.47, 6.80, 6.88, 6.89, 6.95, 7.07, 7.15, 7.24, 7.41, 7.44, 7.53, 7.55, 7.57, 7.60, 7.63, 7.66, 7.76, 7.92, 7.95, 8.40, 8.44, 8.47 (aromatic); \(^13\)C NMR (CDCl\(_3\)): 31.28, 31.68, 32.02 (q, C(CH\(_3\))\(_3\)), 28.74, 32.14, 32.33, 34.68 (t, Ph-CH\(_2\)-Ph), 25.0 (t, Naph-CH\(_2\)-Naph), 63.4, 62.5 (q, OCH\(_3\)), 74.5, 75.7 (t, OCH\(_2\)), 123.3, 124.0, 124.7, 125.0, 125.6, 125.7, 125.8, 126.1, 126.5, 126.6, 126.7, 128.0, 128.7, 129.0, 129.4, 129.6, 129.8, 130.8, 131.1, 131.3, 131.4, 131.5, 133.0, 133.1, 134.4, 134.7, 138.1, 141.1, 143.2, 144.6, 147.1, 147.5, 149.6, 150.4, 152.2, 154.6, 156.1 (aromatic); MS (FAB+, NOBA as a matrix, m/z), Intensity (%): 1024 ((M +1+Na)\(^+\), 7), 1023 ((M+Na)\(^+\), 9), 1000 (M\(^+\), 9), 999 (7), 968 (10), 967 (8).
References


(d) p 190; and (e) pp 197-200.


76. Öki, M, *Application of Dynamic NMR Spectroscopy to Organic*


87a. Failla, S., Finocchiaro, P., Belsky, V. K., Zavodnik, V. E., Sobolev, A. N.,


Appendix I

Data of X-ray Crystallography of Compound 46.
This page appears to contain scientific or technical text, possibly related to experimental data and methodology. Due to the complexity and density of the text, a full transcription is not feasible here. If you need specific information extracted from the document, please provide a section or part of the text for more accurate transcription and analysis.
References


(4) Least-Squares:
Function minimized: \[ \sum (|F_o| - |F_c|)^2 \]
where: \[ \sum = 4F_o^2/\sigma^2 = (S^2 + C + R^2 + B)/P \]
\[ S = \text{Scan rate} \]
\[ C = \text{Total Integrated Peak Count} \]
\[ R = \text{Ratio of Scan Time to background counting time} \]
\[ B = \text{Total Background Count} \]
\[ P = \text{Lorentz-polarization factor} \]
(5) Standard deviation of an observation of unit weight:
\[ \left( \sum (|F_o| - |F_c|)^2 / (N_o - N_v) \right)^{1/2} \]
where: \[ N_o = \text{number of observations} \]
\[ N_v = \text{number of variables} \]


EXPERIMENTAL DETAILS

A. Crystal Data

<table>
<thead>
<tr>
<th>Empirical Formula</th>
<th>C_{35}H_{34}O_{4}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formula Weight</td>
<td>788.90</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>colourless, irregular</td>
</tr>
<tr>
<td>Crystal Dimensions (nm)</td>
<td>0.400 X 0.200 X 0.400</td>
</tr>
<tr>
<td>Crystal System</td>
<td>triclinic</td>
</tr>
<tr>
<td>No. Reflections Used for Unit Cell Determination (20 range)</td>
<td>19</td>
</tr>
<tr>
<td>Omega Scan Peak Width at Half-height</td>
<td>0.32</td>
</tr>
</tbody>
</table>

Lattice Parameters:
| a     | 10.343 (3) |Å |
| b     | 11.260 (6) |Å |
| c     | 8.992 (4)  |Å |
| \( b \) | 96.12 (4)  |Å |
| \( b \) | 110.13 (3) |Å |
| \( b \) | 104.46 (3) |Å |
| \( b \) | 92.07 (7)  |Å |

| Space Group       | P1 (#1) |

| Z value | 1 |

\( \rho_{\text{calc}} \) |

| 1.267 g/cm³ |

| \( P_{(\text{MoKα})} \) | 375 |

\( 0.73 \text{ cm}^{-1} \)

B. Intensity Measurements

| Diffractometer | Rigaku AFC65 |

| Radiation      | MoKα (\( \lambda = 0.71069 \text{ Å} \) ) |

| Temperature    | 293°C |

| Take-off Angle | 5.0° |
Detector Aperture

4.5 mm horizontal
3.0 mm vertical

40 cm

υ = 2θ

4.0°/min (in omega)
(2 scans)

(1.73 + 0.35 tanθ)*

50.2°

Total: 3501
Unique: 3304 (Rint = 0.021)

Lorenz-polarization
Absorption
(two factors: 0.91 - 1.00)
Secondary Extinction
(coefficient: 0.35228E-05)

C. Structure Solution and Refinement

Structure Solution

Refinement

Function minimized
Least-squares Weights

p-factor
Anomalous Dispersion

No. Observations (1>2.00σ(I))
No. Variables
Reflection/Parameter Ratio

Residuals: R Fx

Goodness of fit Indicator

Max Shift/Error in final cycle

Maximum Peak in Final Diff. Map

0.18 e Å⁻³

Minimum Peak in Final Diff. Map

-0.14 e Å⁻³

Intramolecular Bond Angles Involving the Nonhydrogen Atoms

<table>
<thead>
<tr>
<th>Atom Atom Atom</th>
<th>Angle</th>
<th>Atom Atom Atom</th>
<th>Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C(45) O(3) C(49)</td>
<td>113.3(2)</td>
<td>C(15) C(14) C(45)</td>
<td>118.4(2)</td>
</tr>
<tr>
<td>C(46) O(4) C(50)</td>
<td>115.0(2)</td>
<td>C(14) C(15) C(16)</td>
<td>124.4(2)</td>
</tr>
<tr>
<td>C(4) C(11) C(23)</td>
<td>114.2(2)</td>
<td>C(14) C(15) C(20)</td>
<td>118.5(2)</td>
</tr>
<tr>
<td>C(3) C(4) C(51)</td>
<td>119.4(2)</td>
<td>C(16) C(15) C(20)</td>
<td>117.0(2)</td>
</tr>
<tr>
<td>C(3) C(4) C(46)</td>
<td>123.0(2)</td>
<td>C(15) C(16) C(17)</td>
<td>121.5(2)</td>
</tr>
<tr>
<td>C(5) C(4) C(46)</td>
<td>117.5(2)</td>
<td>C(16) C(17) C(18)</td>
<td>120.9(2)</td>
</tr>
<tr>
<td>C(4) C(5) C(6)</td>
<td>121.7(2)</td>
<td>C(17) C(18) C(19)</td>
<td>119.6(2)</td>
</tr>
<tr>
<td>C(5) C(6) C(7)</td>
<td>120.1(2)</td>
<td>C(18) C(19) C(20)</td>
<td>121.1(2)</td>
</tr>
<tr>
<td>C(5) C(6) C(11)</td>
<td>119.7(2)</td>
<td>C(15) C(20) C(19)</td>
<td>119.7(2)</td>
</tr>
<tr>
<td>C(7) C(6) C(11)</td>
<td>120.1(2)</td>
<td>C(15) C(20) C(21)</td>
<td>119.7(2)</td>
</tr>
<tr>
<td>C(4) C(7) C(8)</td>
<td>119.2(2)</td>
<td>C(19) C(20) C(21)</td>
<td>120.5(2)</td>
</tr>
<tr>
<td>C(7) C(8) C(9)</td>
<td>120.2(2)</td>
<td>C(20) C(21) C(22)</td>
<td>122.1(2)</td>
</tr>
<tr>
<td>C(8) C(9) C(10)</td>
<td>121.5(3)</td>
<td>C(21) C(22) C(23)</td>
<td>122.5(2)</td>
</tr>
<tr>
<td>C(9) C(10) C(11)</td>
<td>120.3(2)</td>
<td>C(21) C(22) C(45)</td>
<td>117.2(2)</td>
</tr>
<tr>
<td>C(6) C(11) C(11)</td>
<td>117.7(2)</td>
<td>C(23) C(22) C(45)</td>
<td>120.2(2)</td>
</tr>
<tr>
<td>C(6) C(11) C(12)</td>
<td>119.8(2)</td>
<td>C(3) C(22) C(22)</td>
<td>117.2(2)</td>
</tr>
<tr>
<td>C(10) C(11) C(12)</td>
<td>123.5(2)</td>
<td>C(3) C(45) C(14)</td>
<td>118.2(1)</td>
</tr>
<tr>
<td>C(11) C(12) C(13)</td>
<td>124.2(2)</td>
<td>C(3) C(45) C(22)</td>
<td>118.0(2)</td>
</tr>
<tr>
<td>C(11) C(12) C(16)</td>
<td>118.3(2)</td>
<td>C(14) C(45) C(22)</td>
<td>123.6(2)</td>
</tr>
<tr>
<td>C(13) C(12) C(16)</td>
<td>119.5(2)</td>
<td>C(4) C(46) C(4)</td>
<td>120.3(2)</td>
</tr>
<tr>
<td>C(12) C(13) C(14)</td>
<td>116.1(2)</td>
<td>C(4) C(46) C(12)</td>
<td>115.9(2)</td>
</tr>
<tr>
<td>C(12) C(14) C(15)</td>
<td>121.5(2)</td>
<td>C(4) C(46) C(12)</td>
<td>123.6(2)</td>
</tr>
<tr>
<td>C(13) C(14) C(45)</td>
<td>120.1(2)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.
### Intramolecular Distances Involving the Nonhydrogen Atoms

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC(*)</th>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC(*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)</td>
<td>C(45)</td>
<td>1.397(3)</td>
<td>1</td>
<td>C(12)</td>
<td>C(13)</td>
<td>1.513(3)</td>
<td>1</td>
</tr>
<tr>
<td>O(3)</td>
<td>C(49)</td>
<td>1.441(3)</td>
<td>1</td>
<td>C(12)</td>
<td>C(46)</td>
<td>1.382(4)</td>
<td>1</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(46)</td>
<td>1.391(3)</td>
<td>1</td>
<td>C(13)</td>
<td>C(14)</td>
<td>1.522(3)</td>
<td>1</td>
</tr>
<tr>
<td>O(4)</td>
<td>C(50)</td>
<td>1.431(4)</td>
<td>1</td>
<td>C(14)</td>
<td>C(15)</td>
<td>1.437(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(4)</td>
<td>1.524(4)</td>
<td>1</td>
<td>C(14)</td>
<td>C(45)</td>
<td>1.374(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(3)</td>
<td>C(23)</td>
<td>1.539(3)</td>
<td>55602</td>
<td>C(15)</td>
<td>C(16)</td>
<td>1.421(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(5)</td>
<td>1.371(3)</td>
<td>1</td>
<td>C(15)</td>
<td>C(20)</td>
<td>1.414(2)</td>
<td>1</td>
</tr>
<tr>
<td>C(4)</td>
<td>C(46)</td>
<td>1.406(3)</td>
<td>1</td>
<td>C(15)</td>
<td>C(17)</td>
<td>1.369(4)</td>
<td>1</td>
</tr>
<tr>
<td>C(5)</td>
<td>C(6)</td>
<td>1.437(4)</td>
<td>1</td>
<td>C(17)</td>
<td>C(18)</td>
<td>1.392(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(6)</td>
<td>C(7)</td>
<td>1.421(3)</td>
<td>1</td>
<td>C(18)</td>
<td>C(19)</td>
<td>1.359(4)</td>
<td>1</td>
</tr>
<tr>
<td>C(6)</td>
<td>C(11)</td>
<td>1.417(3)</td>
<td>1</td>
<td>C(19)</td>
<td>C(20)</td>
<td>1.423(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(7)</td>
<td>C(8)</td>
<td>1.363(4)</td>
<td>1</td>
<td>C(20)</td>
<td>C(21)</td>
<td>1.424(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(8)</td>
<td>C(9)</td>
<td>1.392(4)</td>
<td>1</td>
<td>C(21)</td>
<td>C(22)</td>
<td>1.367(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(9)</td>
<td>C(10)</td>
<td>1.371(4)</td>
<td>1</td>
<td>C(22)</td>
<td>C(23)</td>
<td>1.518(3)</td>
<td>1</td>
</tr>
<tr>
<td>C(10)</td>
<td>C(11)</td>
<td>1.427(4)</td>
<td>1</td>
<td>C(22)</td>
<td>C(45)</td>
<td>1.416(2)</td>
<td>1</td>
</tr>
</tbody>
</table>

### Intermolecular Distances Involving the Nonhydrogen Atoms

<table>
<thead>
<tr>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC(*)</th>
<th>atom</th>
<th>atom</th>
<th>distance</th>
<th>ADC(*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>O(3)</td>
<td>C(50)</td>
<td>3.356(4)</td>
<td>55401</td>
<td>C(19)</td>
<td>C(21)</td>
<td>3.544(4)</td>
<td>55602</td>
</tr>
<tr>
<td>C(18)</td>
<td>C(21)</td>
<td>3.596(4)</td>
<td>55602</td>
<td>C(49)</td>
<td>C(50)</td>
<td>3.528(5)</td>
<td>55401</td>
</tr>
<tr>
<td>C(19)</td>
<td>C(19)</td>
<td>3.426(5)</td>
<td>55602</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Distances are in angstroms. Estimated standard deviations in the least significant figure are given in parentheses.
Appendix II

$^1H$ NMR Spectra of Compounds.

(In Order of Compound Number)