SYNTHESIS AND PROPERTIES OF CALIX[4]NAPHTHALENES

ZHAOPENG LI

Synthesis and Properties of Calix[4]naphthalenes

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

ISBN 0-612-17612-6

Abstract

This work describes the synthesis and some properties of a new class of cyclic formaldehyde-naphthol tetramers which are analogous to the better-known calixarenes and resorcinarenes. These new compounds are of interest for their potential supramolecular properties. The "calixnaphthalenes", 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 calixnaphthalenes which could enhance potential receptor abilities. Furthermore, fixed conformations of most calixnaphthalenes are dissymmetric and have potential applications as chiral hosts, or chiral ligands.

The prototype calixnaphthalenes **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 "*pseudo*calixnaphthalene" 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]naphthalene (**20**) was synthesized from 1,8-naphthalene sultone (**6**) under basic conditions. Under acidic conditions, **6** formed only *oxy*calix[4]naphthalene (**30**) and linear oligomeric compounds **28** and **29**.

Synthesis of calixnaphthalene **35** was effected by a self-condensation reaction of 2-hydroxy-3-hydroxymethylnaphthalene (**36**) under TFA catalysis. Calixnaphthalene **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]naphthalene **46** was synthesized from 3-hydroxy-2-naphthoic acid (**7a**) via a convergent synthetic procedure. VT ^{1}H NMR studies suggest that in $CDCl_3$ 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]naphthalene **62** and dihomocalixnaphthalene **70** were both synthesized from the precursor 2,3-dihydroxynaphthalene (**7b**) by convergent syntheses. Both **62** and **70** have rigid conformations at ambient temperature.

Finally, a novel naphthalene-tethered calixspherand **95** which possesses a "cone" conformation was synthesized. Attempted synthesis of other calixnaphthalenes from 1,5- and 1,3-dihydroxynaphthalene 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

List of Figures

List of Tables

List of Symbols, Abbreviations, and Acronyms

Ac	Acetyl
APT	Attached proton test
bp	Boiling point
CC	Column chromatography
COSY	Correlated spectroscopy
disy	Dissymmetric
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulphoxide
EI	Electron impact
ESMS	Electrospray mass spectrometry
FAB	Fast atom bombardment mass spectrometry
Hetcor	Hetero atom correlation
hv	Irradiation, photoreaction
IR	Infrared spectoscopy
J	Coupling constant
mp	Melting point
MS	Mass spectrometry

NOED	Nuclear Overhauser effect Difference spectroscopy
NOBA	*p*-Nitrobenzyl alcohol
NMR	Nuclear magnetic resonance spectroscopy
p	*para*
PCC	Pyridinium chlorochromate
PLC	Preparative thin layer chromatography
r.t.	Room temperature
sy	Symmetric
tert	tertiary
THF	Tetrahydrofuran
TFA	Trifluoroacetic acid
TLC	Thin-layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TPE	1,1,2,2-Tetraphenylethene
VT	Variable temperature

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 group[2] has shown that cyclodextrin derivatives can catalyze the hydrolysis of certain esters. Sanders[3] 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]

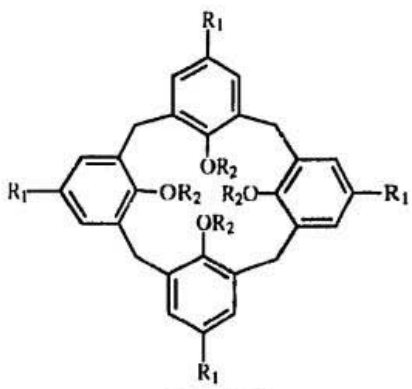
Organic chemists also try to create novel organic compounds, which will have wide applications in industry. Typical examples include: (1) efficient homogenous solution catalysts; (2) receptors and molecular sensors having unprecedented sensitivities; (3) separation techniques; (4) electronic devices 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,[5] 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]

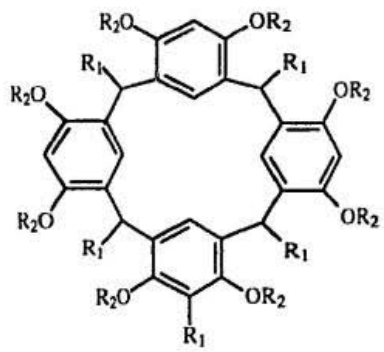
In the 1970s, Gutsche[12] reinvestigated the condensation *of para*-substituted phenols with formaldehyde. He obtained cyclictetra-, hexa-, and octamers, which were named "calix[*n*]arenes" as typified by structure **1**. In the term calix[*n*]arene, "calix" describes the cup-like shape or conformation 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[13] and Cram.[14] These cyclic tetramers as depicted by stucture **2**, are named as calix[4]resorcinarenes, although they do not have the same shape with calixarene **1**.



R_1= *tert*-Bu
R_2=H
1



R_1=CH_3, Ph.
R_2=H
2

1.2. Synthesis of Calixarenes and homocalixarenes.

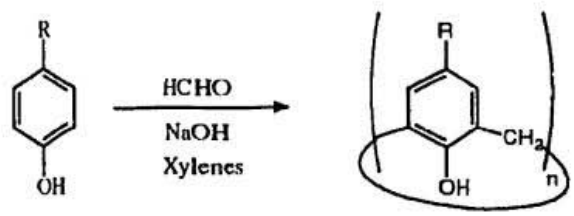
1.2.1. Synthesis of Calixarenes.

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 [15] describing this condensation reaction. In 1902, Leo Baekeland filed for a patent [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.[17] 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.[12] 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*]arenes 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).[12]

Scheme 1.1.



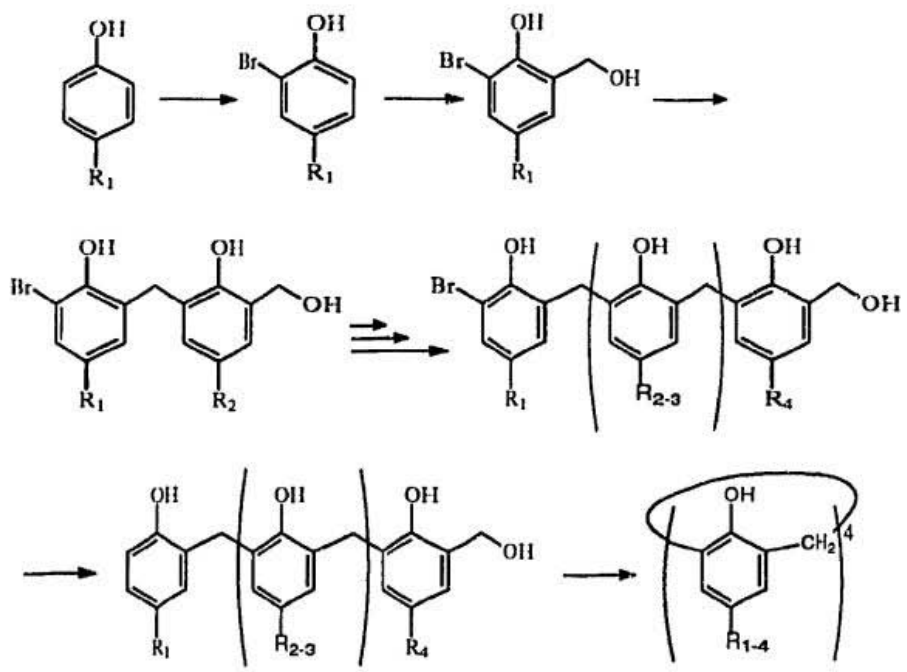
1

R= *tert*-butyl

n= 4-16

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,[18a] as depicted in Scheme 1.2. Starting with an

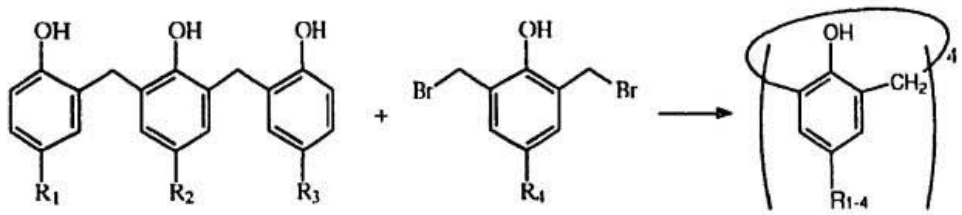
Scheme 1.2.



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.

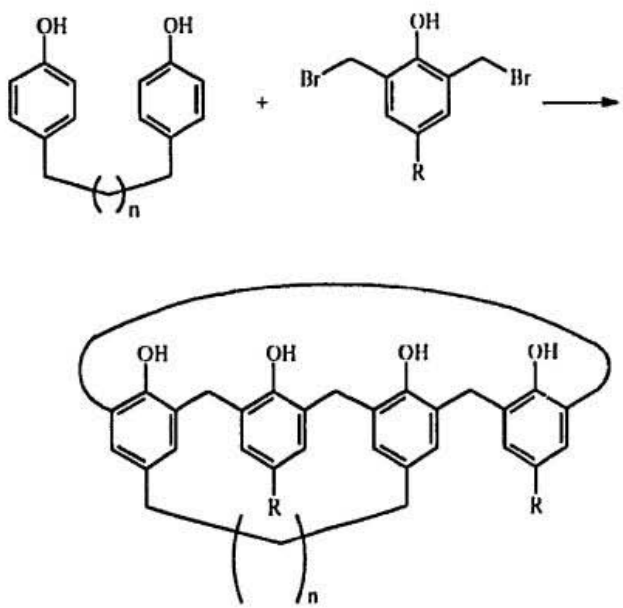
Scheme 1.3.



Such a procedure was successful in the synthesis of various calix[4]arenes, where the yields in the cyclization step may reach 30-35%.[18b]

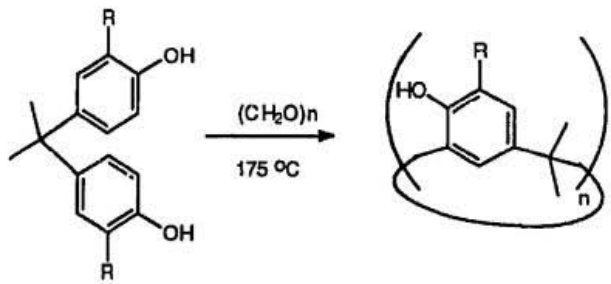
Bridged calix[4]arenes in which two opposite phenolic units are linked by an aliphatic chain have analogously been synthesized by reaction of *bis*bromomethylated phenols with suitable diphenols such as α,ω-(4)-hydroxy-phenylalkanes (Scheme 1.4).

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).[19]

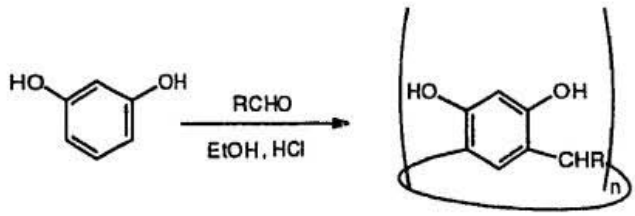
Scheme 1.5.



R= *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.[12] In contrast to phenol-derived calix[4]arenes, larger cyclic oligomers are rarely observed (Scheme 1.6).

Scheme 1.6.



2

R= alkyl or aryl

n= 4

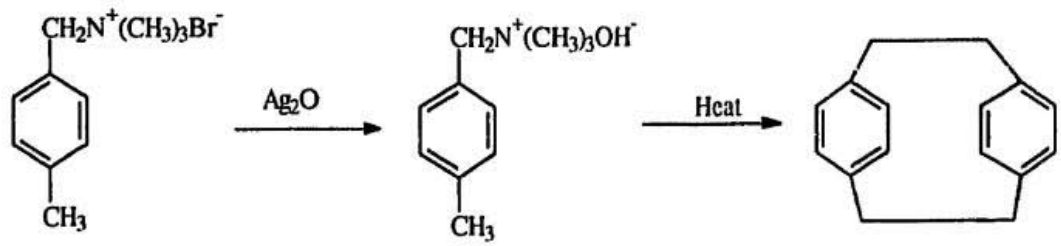
1.2.2. Synthesis of homocalixarenes.

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$_n$]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.

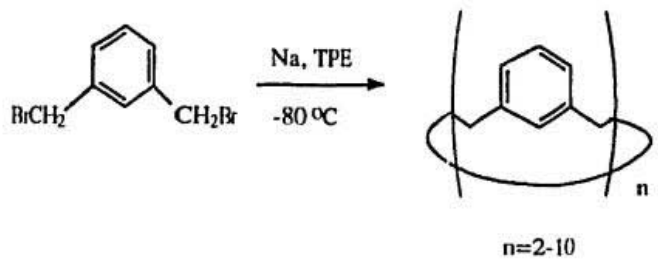


pyrolysis to produce a polyene intermediate, which cyclizes to give [2,2]paracyclophanes via an apparent [6+6] process.[20]

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 [2$_n$]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.



n=2-10

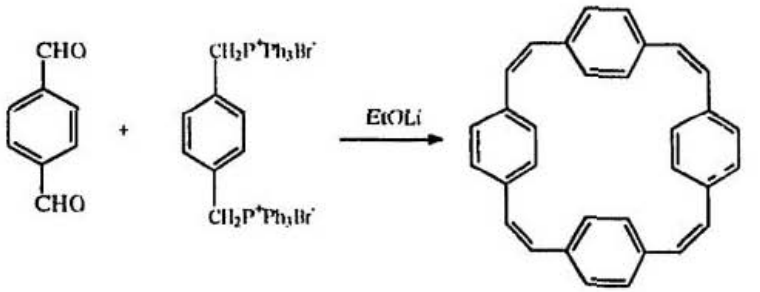
1.2.2.c. Wittig Reaction Procedure.

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 *all*homocalixarene.[22]

1.2.2.d. Dithia-Intermediated Cyclization Procedure.

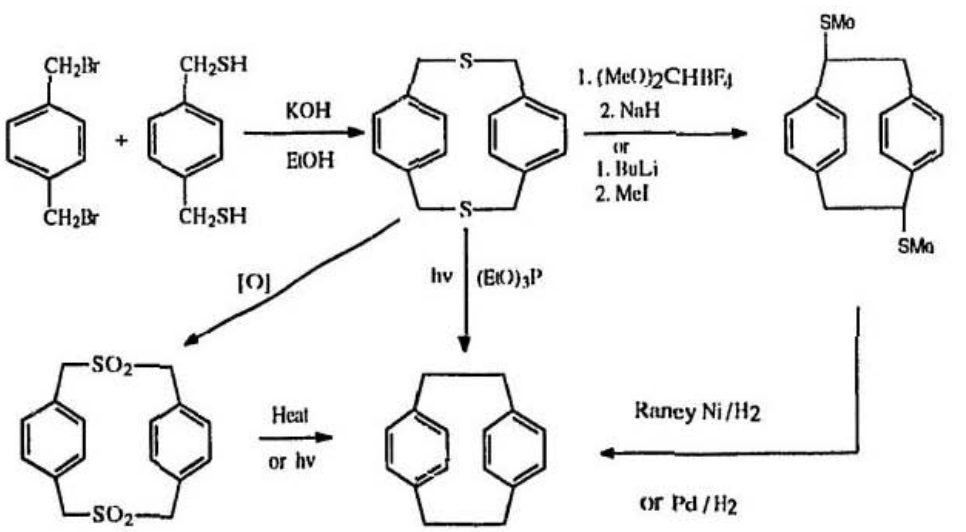
A general synthetic route to [2.2]cyclophanes uses dithia[3.3]cyclophanes as key intermediates . Such intermediates can be subjected directly to photochemical sulphur extrusion,[23] or be oxidized to sulphone compounds

Scheme 1.9.



which are pyrolyzed to the same [2.2]cyclophane.[24] From the dithia-[3.3]-cyclophane intermediate, a second choice involves carrying out a Wittig rearrangement followed by Raney-Ni reduction.[25] A third choice involves a Stevens rearrangement followed by Raney Ni reduction.[26] Scheme 1.10 outlines these procedures.

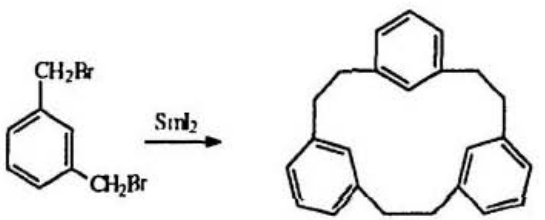
Scheme 1.10.



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

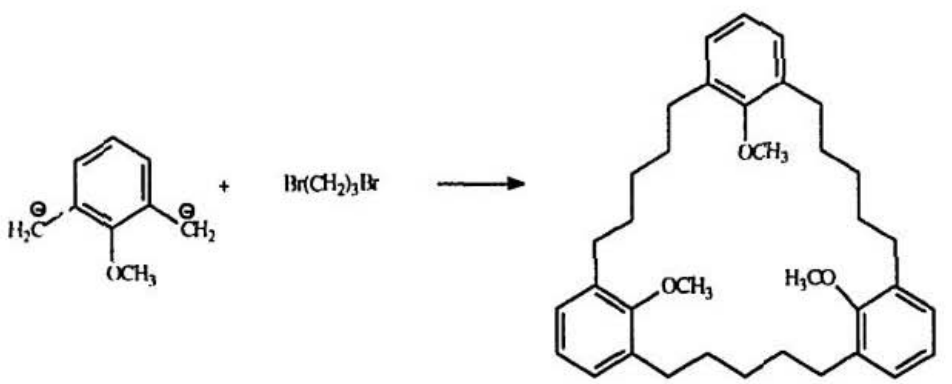
Self-coupling reaction of 1,3-*bis*(bromomethyl)benzene in the presence of five equivalents of SmI_2 in THF gave [2$_3$]metacyclophane in 10% yield.[27]

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 α,ω-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. Reihoudt[29] 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 calixcrowns. Reinhoudt[30] joined the hydroxy group by another aromatic tether to form calixspherands. Shinkai [31] 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[32] introduced a sulphonic acid group at the *upper* rim to afford water-soluble calixarenes. Böhmer [33] produced bridged calixarenes by introducing an aliphatic tether at the *upper* rim. Cram [34] modified both the *lower* and *upper* rim of calixresorcinarenes to produce cavitands, carcerands and *hemi*carcerands.

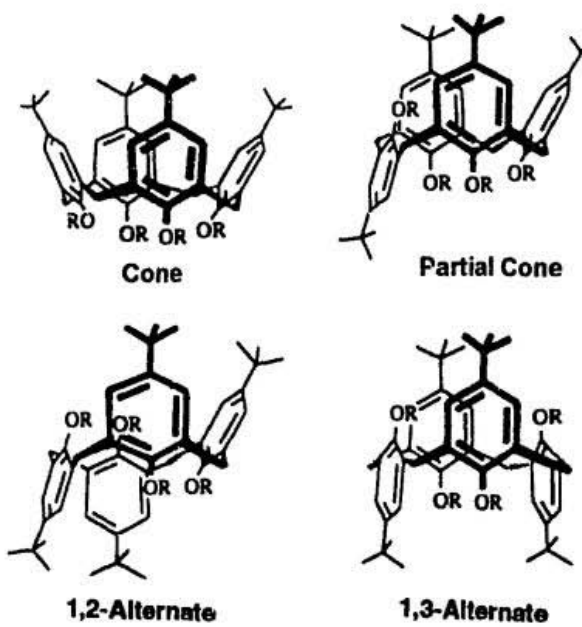
1.4. Confomational Properties of Calixarenes.

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 *p-tert*-butylcalix[4]arene exists in the "calix" or "cone" conformation in the crystalline state as Gutsche predicted.[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.

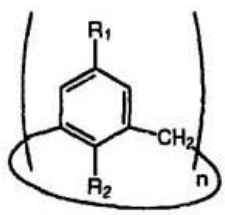
Fig.1.1. Four Possible Conformations of *p-tert*-Butylcalix[4]arenes.



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 [36] 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-tert*-butylcalix[4]arene is 14.7 kcal/mol in chloroform, while it is 11.8 kcal/mol in pyridine. Pochini [37] 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[38] found the tetraacetate of *p-tert*-butylcalix[4]arene is fixed in the "partial cone" conformation while McKervey [39] found that most of the ether derivatives of *p-tert*-butylcalixarene are fixed in cone conformations. Shinkai [40] found that the metal cation present in the base strongly affects the conformational distribution

in the *tetra-O*-alkylation of *p-tert*-butylcalix[4]arene by ethyl bromoacetate. The "cone" conformer predominates when the base contains small sized metal cations such as Li^+, Na^+, and K^+ in DMF whereas "partial cone" and "1,3-alternate" conformers result when the base contains non-template metal cations such as Cs^+ in acetone. Reinhoudt [41] synthesized *tetra-O*-alkylated calix[4]arenes **3a** fixed in the "1,3-alternate" conformation in 77% isolated yield by using Cs_2CO_3 in DMF. The only example of an unbridged calix[4]arene that adopts the "1,2-alternate" conformation is the *tetra-N,N*-dimethylthiocarbamoyl compound **3b**.[12a]



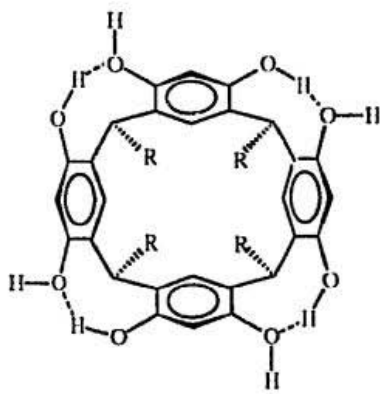
3a R_1= *tert*-butyl
R_2=$OCH_2CH_2OCH_3$
n= 4

3b R_1=*tert*-Butyl
R_2=$OCSCN(CH_3)_2$
n=4

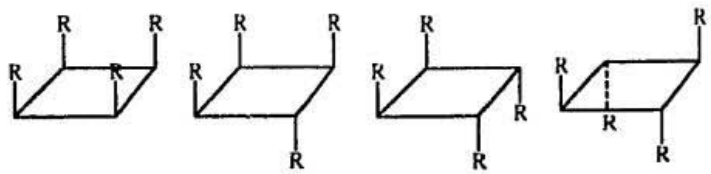
Due to the dissymmetrical bridging -CHR- groups in calixresorcinarenes (**2**) four different diastereomers are possible, which are (1) *cis-cis-cis* (*ccc*); (2) *cis-trans-trans* (*ctt*); (3) *trans-cis-trans* (*tct*); (4) *trans-trans-trans* (*ttt*). Fortunately, in many cases, the *ccc* isomer is the predominant one and has been obtained in batch reactions[12b] in yields higher than 50% with acetaldehyde,

dodecylaldehyde, benzaldehyde, thiophenecarboxaldehyde or ferrocenecarboxaldehyde.[42] 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 [43] 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 NO_2 in the C-2 position.

Fig.1.2. Four Possible Stereoisomers of Calix[4]resorcinarenes (2).



ccc



ccc *cct/ctt* *ctc/tct* *ttt*

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_{4v} 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[48] 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 UO_2^{2+} from seawater.[12d,18d] Calixarenes can form kinetically stable complexes for diagnostic or other medical applications.[51] Ion-sensitive electrodes and ion-sensitive field-effect transistors for Na^+, K^+, and 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 (Ag^+, Cu^{2+}, Cd^{2+}, Hg^{2+}, 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.[18c] 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 C_{60}- and C_{70}-fullerenes.

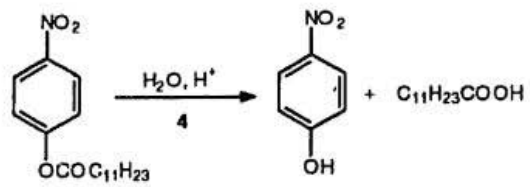
Calixarenes have many potential applications for optical, electronic and

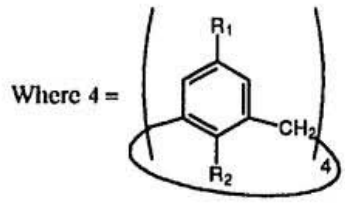
magnetic sensors. Resorcinol-based calixarenes show strong and specific interactions via hydrogen bonding with certain sugars. These interactions may lead to specific sensors.[57] Calixarenes mayl open possibilities to various chromogenic,[58] fluorogenic[59] and "light-switchable" ionophores.[60] New liquid crystalline materials have been obtained from tungsten-capped calix[4]arenes.[61] The *p*-nitro derivatives of calixarene ethers show nonlinear optical properties useful for frequency doubling of laser light.[62] They may be ordered within polymer material by strong electric fields or by the Langmuir-Blodgett method.[63] The latter technique has also been used to produce "perforated" monolayers leading to membranes with permeabilities defined at the molecular level.[64] Calixarene derivatives are also potential enzyme mimics. Gutsche has designed an aldolase and a heme mimic[12e] from calixarenes. Shinkai[65] found that the *p*-alkylcalixarene 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 1989, Poh [66] reported a cyclic tetramer formed by condensation of formaldehyde with 4,5-dihydroxy-2,7-

Scheme 1.13.





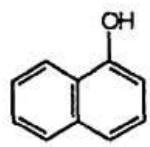
R_1= *tert*-butyl

R_2=$N^+(Me)_3Cl^-$

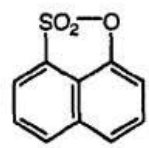
naphthalenedisulphonic acid (chromotropic acid). The evidence which they used to support their assignment however is ambiguous. In an earlier report, Georghiou[67] concluded instead from similar evidence that linear oligomers and/or polymers were formed.

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,

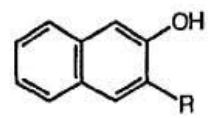
the B ring in naphthol has four free positions available to be functionalised. As stated before, one of the main reasons for the ever increasing interest in calixarenes is their ability to act as enzyme mimics. A main feature of enzymes is their chirality. Unsubsituted or *para*-subsituted calixarenes 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.



5



6



7a: R=CO_2H

7b: R=OH

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.

Chapter 2.

Calix[4]naphthalenes Derived from 1-Naphthol

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.[68] 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.[69] 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 [70] 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 [71] 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.

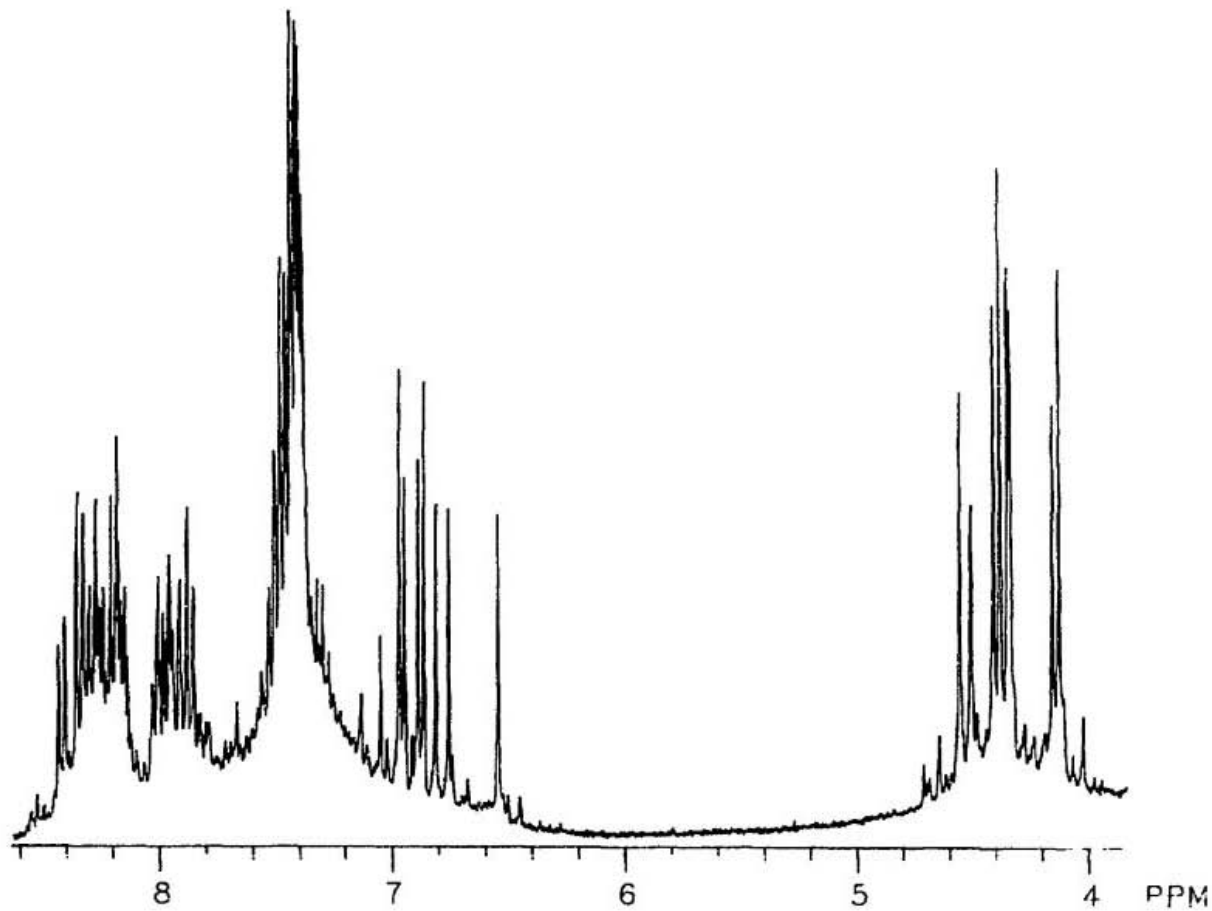
It was rationalized that due to its great reactivity, the condensation of 1-naphthol with formaldehyde under acidic conditions is so fast that it forms a polymer. Under basic conditions, the condensation is not so fast. However, 1-naphthol is sensitive to oxygen especially in aqueous basic media leading 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.

2.2. Synthesis of Calix[4]naphthalenes.

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 δ 4.0-4.8

Fig. 2.1. ^1H NMR Spectrum of the Crude Product from the Condensation of 1-Naphthol with Formaldehyde in CD_3COCD_3.

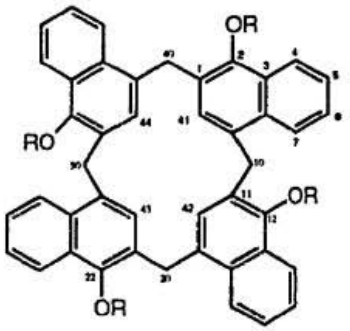


ppm region resemble those usually seen for the methylene bridge protons of the various isomers of calixarene derivatives.

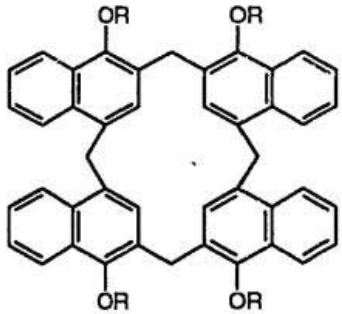
The limited solubility of the crude product in the usual organic solvents prohibited purification by chromatographic techniques. However, fractional crystallization of the crude reaction mixture afforded three crystalline products. Mass spectra indicated that these products were isomeric tetramers, each 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}C NMR resonance signals. Isomer **11**, the least symmetrical of the isomers, could be expected to show forty-four carbon signals.

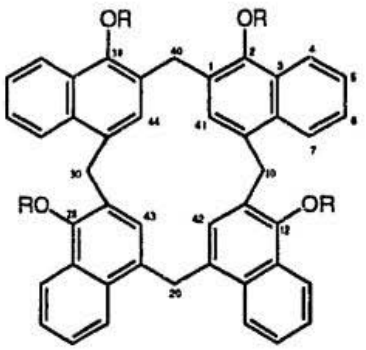
The initial substance to precipitate from the crude reaction mixture consists of at least two compounds as ascertained by TLC. Crystallization from acetone yielded a homogeneous product whose ^{13}C NMR (DMSO-d_6) spectrum shows eleven signals consisting of five quaternary aromatic carbon signals, five methine aromatic carbon signals, and a single aliphatic methylene carbon signal.



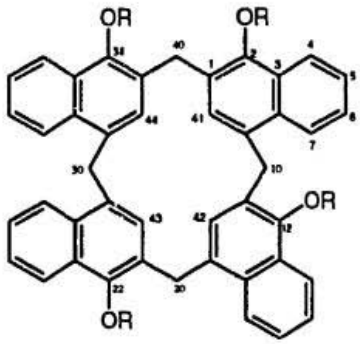
8 R= H
8a R=Bz
8b R=Ac



9
R=H



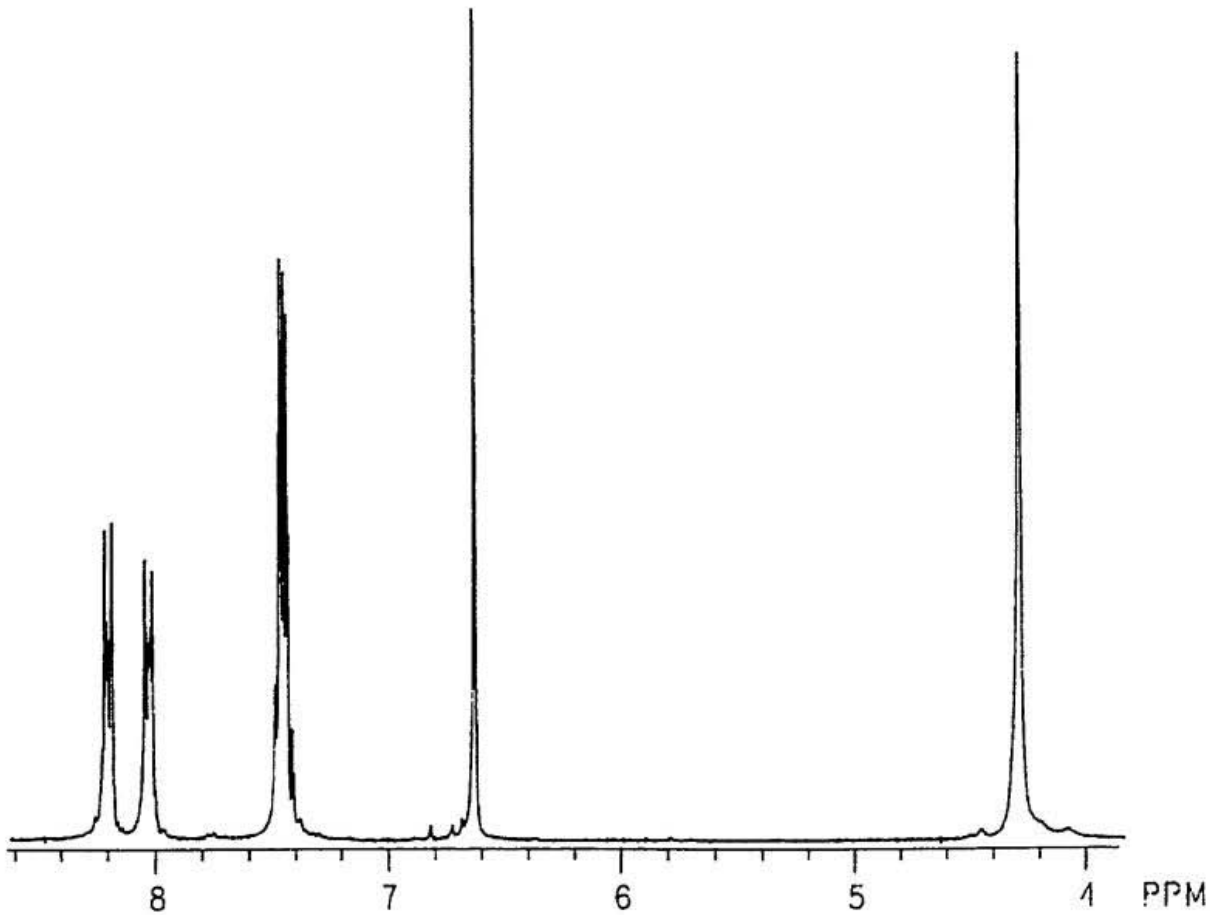
10 R= H
10a R= Bz
10b R= Ac



11 R=H
11a R=Bz
11b R=Ac

The ^{1}H NMR spectrum of **8** (Figure 2.2) includes a relatively high-field aromatic signal which is a four-proton singlet at δ 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 δ 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.

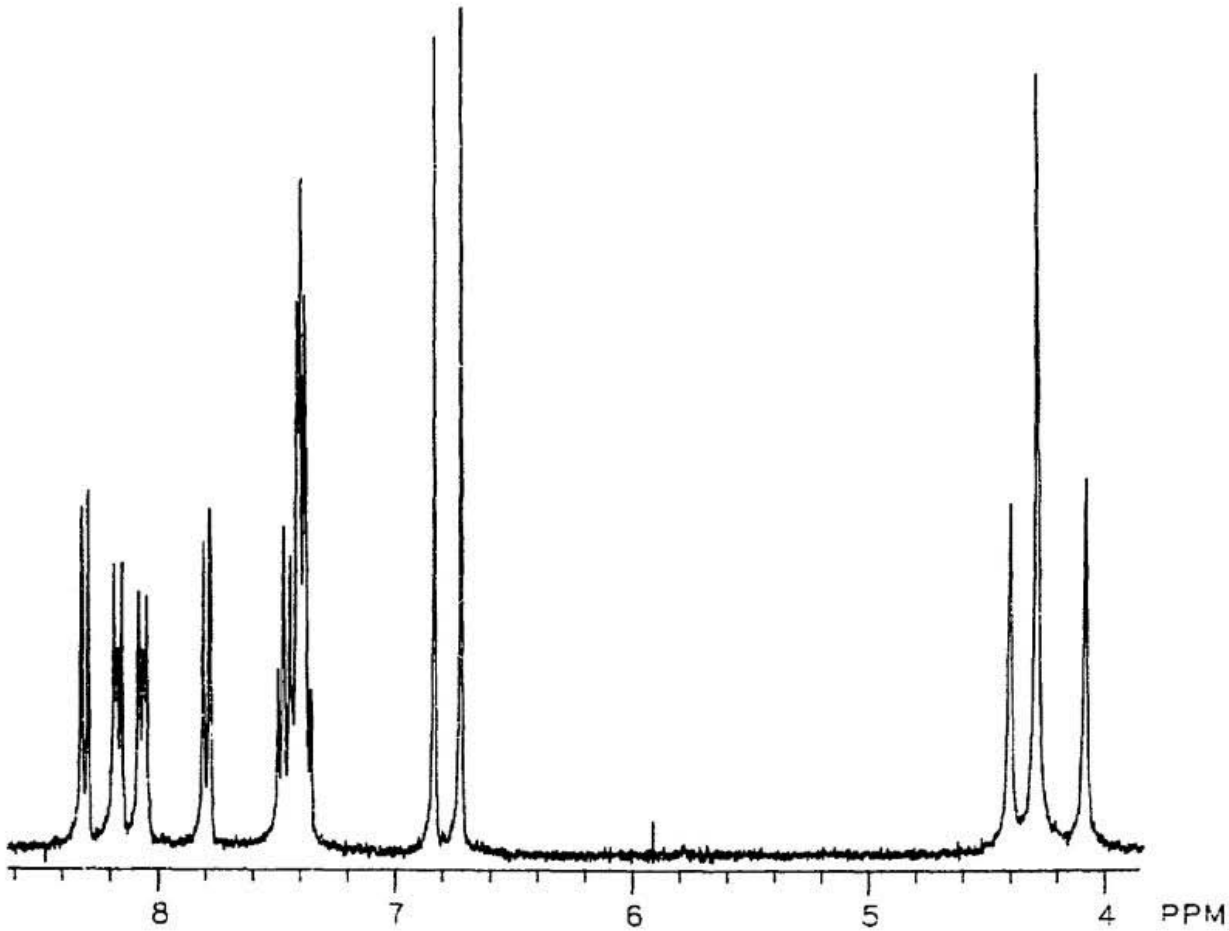


consistent for structure **8** which possesses C_4 symmetry. The relatively higher-field aromatic signal in this and the other isomers can be accounted for by examination of molecular models which reveal that the intra-annular protons can be situated in the shielding region of the naphthalene ring. That 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 ^{13}C NMR (DMSO-d_6) spectrum of this pure product reveals only twenty-one clearly defined signals of the expected twenty-three. However, the APT-^{13}C 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

Fig. 2.3. ^{1}H NMR Spectrum of Calix[4]naphthalene 10 in DMSO-d_6.

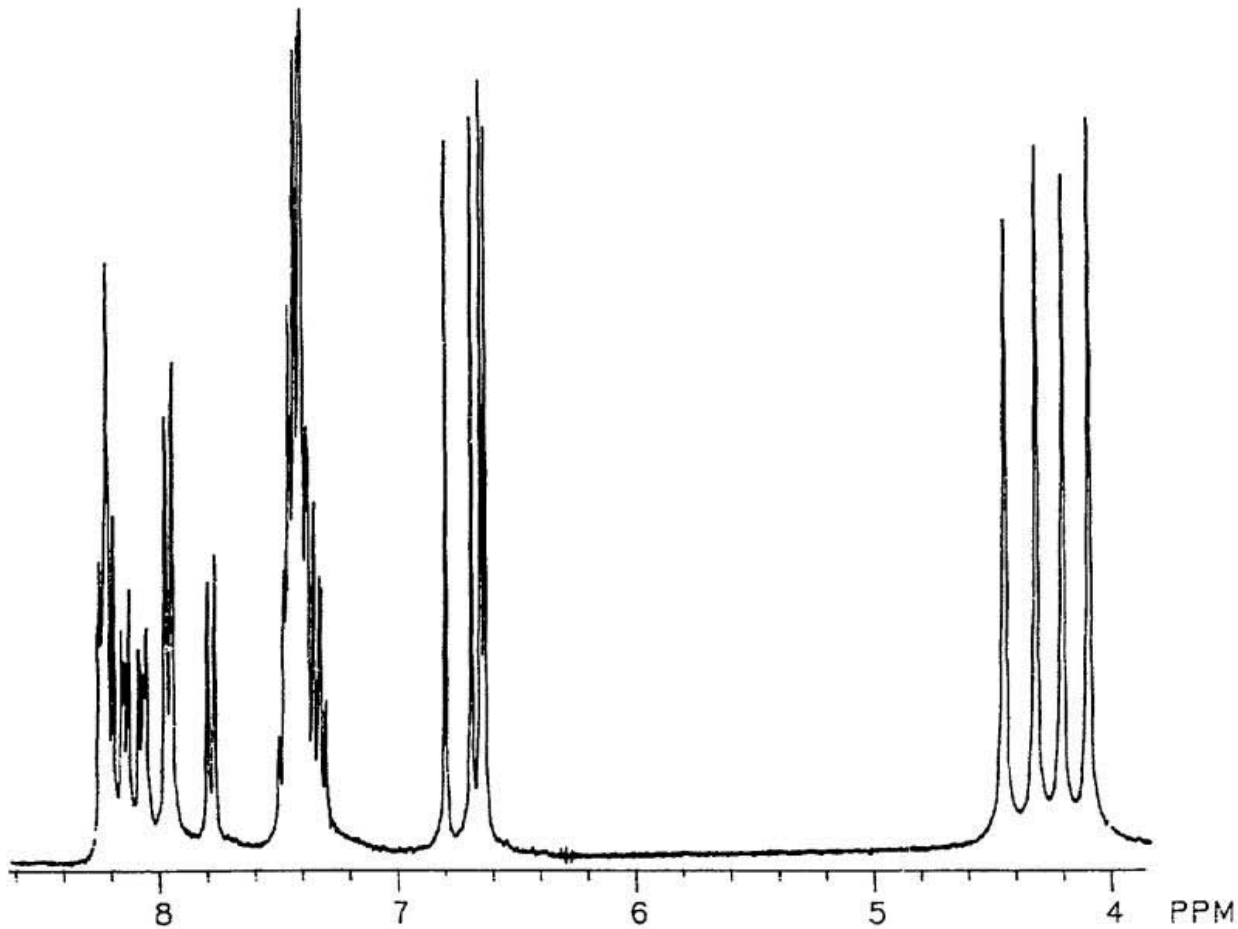


structure **10** which has a plane of symmetry through the C-20 and C-40 methylene groups which are perpendicular to the macrocyclic ring. This isomer is also conformationally flexible at ambient temperature.

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 δ 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 δ 124.5 ppm was not clearly resolved, and four aliphatic methylene carbon signals.

The ^1H NMR spectrum of **11** (Figure 2.4) shows four relatively high-field aromatic (one-proton) singlets of equal intensities, at δ 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 δ 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 ^1H 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 δ 6.5-6.9 ppm

Fig. 2.4. ^{1}H NMR Spectrum of Calix[4]naphthalene 11 in DMSO-d_6.



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.

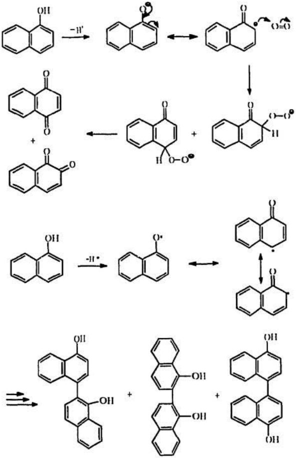
In basic solution open to the air and at high temperature, 1-naphthol undergoes many changes due to oxidation by molecular oxygen to form quinone-like products and biphenols.[72] Scheme 2.1 shows some possible oxidations of 1-naphthol by molecular oxygen under basic conditions.

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.

Temperature (°C)	**Time** (h)	**Results**
20.5	100	No reaction (TLC).
60-70	100	Starting material disappeared, and a small amount of products formed (TLC).
90-100	20	Starting material disappeared, and a small amount of products formed (TLC).
	30	Yield 25% (isolated)
	35	Yield 31% (isolated)
	40	Yield 27% (isolated)

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 N_2 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 ($CO_3^{2-} > OH^-$). A possible reason could be the higher

solubility of Cs_2CO_3 over other bases, in DMF.

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

Base	NaOH	Na_2CO_3	KOH	K_2CO_3	Cs_2CO_3
Yield (%)	trace	5	10	25	35

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/H_2O, 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, N_2 was bubbled into the reaction solution, and in the other, no N_2 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).

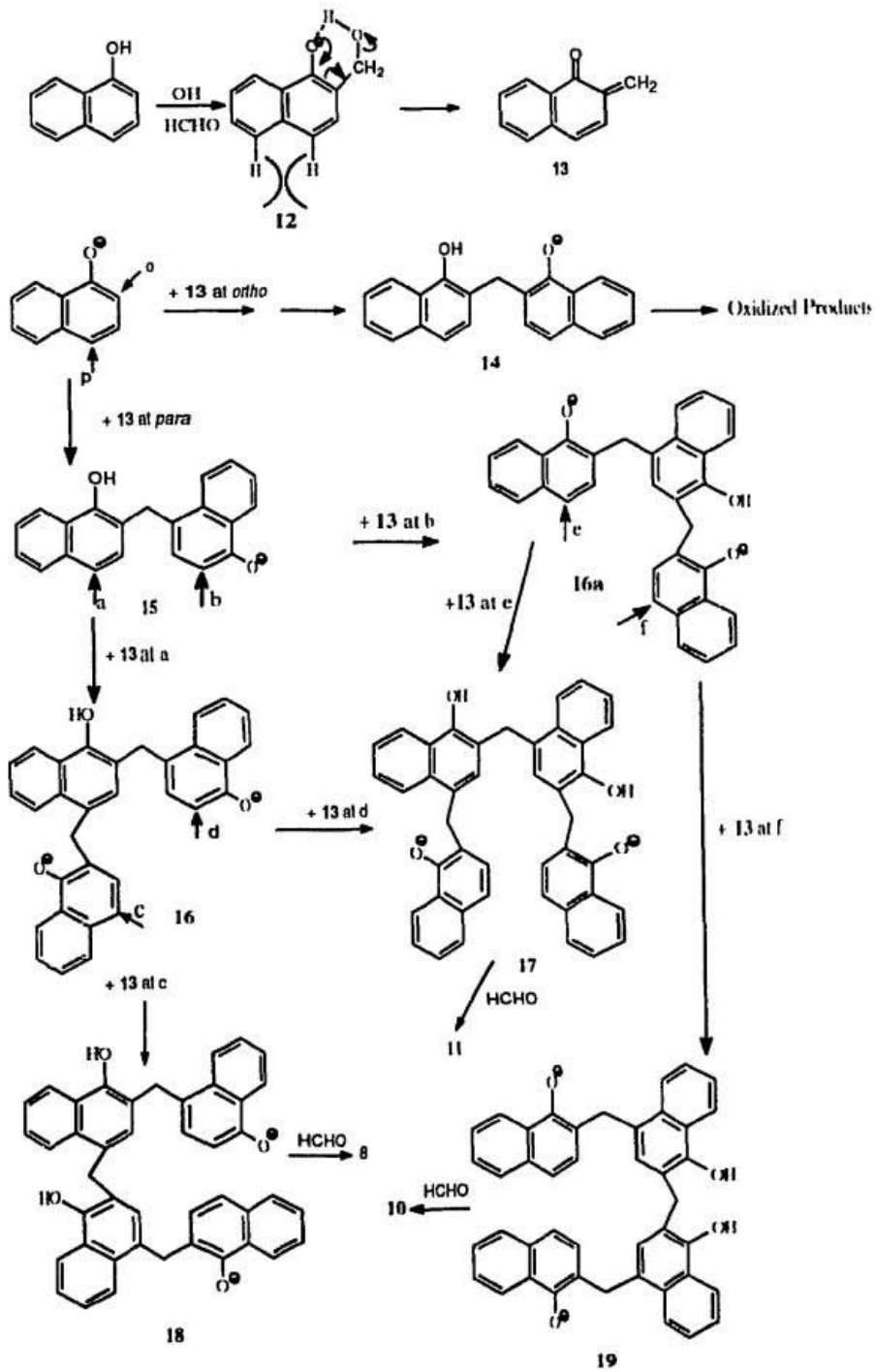
2.3. Mechanism of the Formation of Calix[4]naphthalenes.

Gutsche [12] has proposed two mechanisms for the formation of calixarenes. One is the "*pseudo*calixarene" pathway, in which a linear tetramer is the

precursor of calixarenes. The other is the "*hemi*calixarene" 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.[73] 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-naphthol, 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 dinaphthylmethyl 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.[74] 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.


OH
HCHO
CH2
12
13
+ 13 at ortho
14
Oxidized Products
+ 13 at para
15
+ 13 at b
16a
+13 at e
+ 13 at a
16
+ 13 at d
17
+ 13 at f
HCHO
11
+ 13 at c
HCHO
8
HCHO
10
18
19

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 C_{2v} 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 [75] 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 "*pseudo*calixnaphthalene" pathway, rather than the "*hemi*calixnaphthalene" pathway.

2.4. Conformational Studies on Calix[4]naphthalenes and Their Derivatives.

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 tetrabenzoylations 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 tetrabenzoates 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]arenes, 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.

Characteristics	Intra-annular Protons			Methylene Protons					
	8	10	11	8		10		11	
	s	s	s	s	q	s	q	s	q
flexible	1(br)	2(br)	4(br)	1		3		4	
cone	1	2	4		1		3		4
partial cone(sy)	4	4	4		4		4		4
partial cone(dissy)		4	4				4		4
1,3-alternate	1	4	4	1		2	1		4
1,2-alternate(sy)	1	2	4		2	2	2		4
1,2-alternate(dissy)		4	4				3		4

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 hydroxy 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".

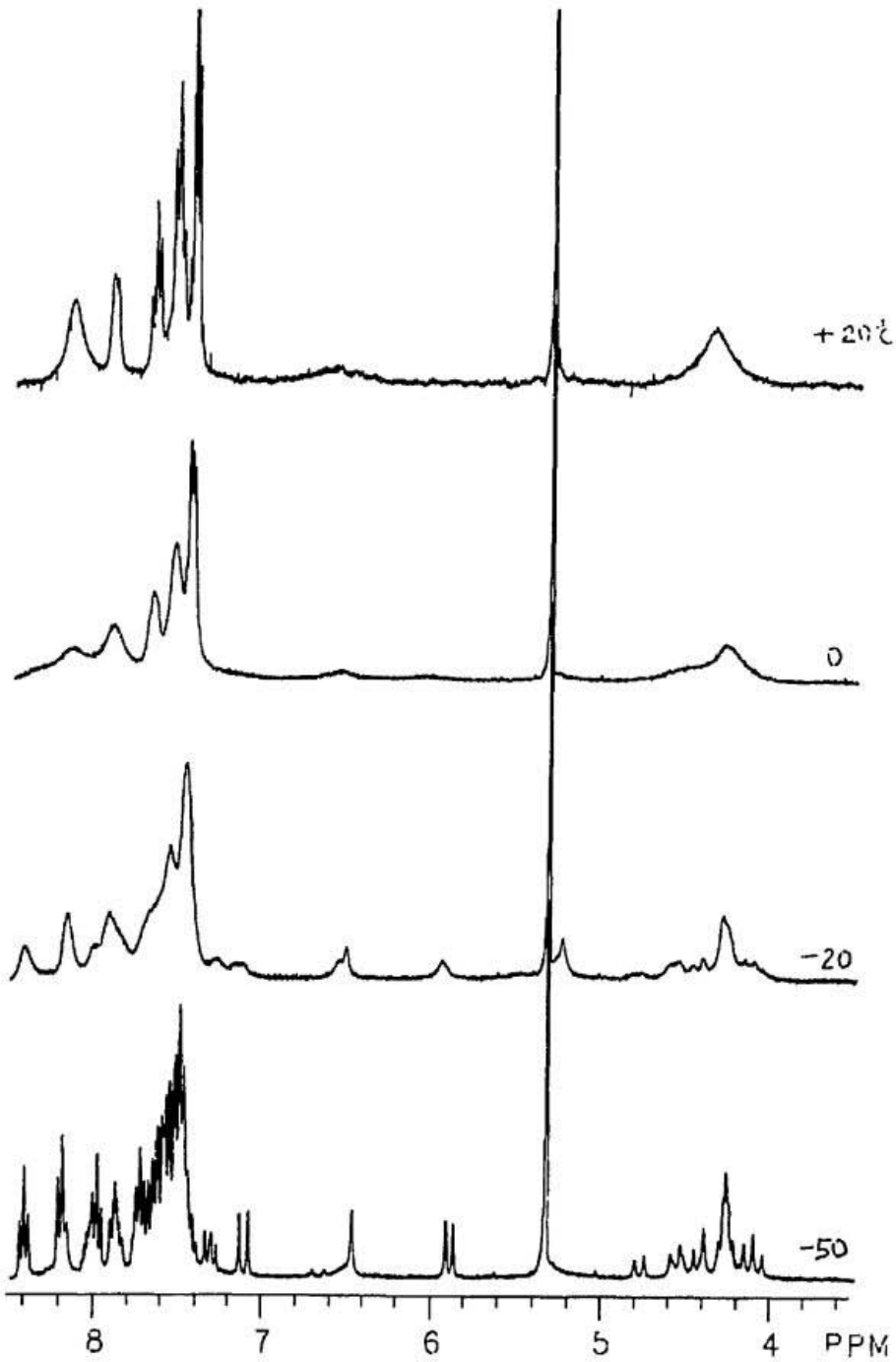
The former has two types of intra-annular protons which would appear as two singlets. The methylene bridge protons would appear as two singlets and two AB quartets. Finally, the dissymmetric "1,2-alternate" conformation has four different intra-annular protons, which would appear as four singlets. It 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_2Cl_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 interconvertion 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

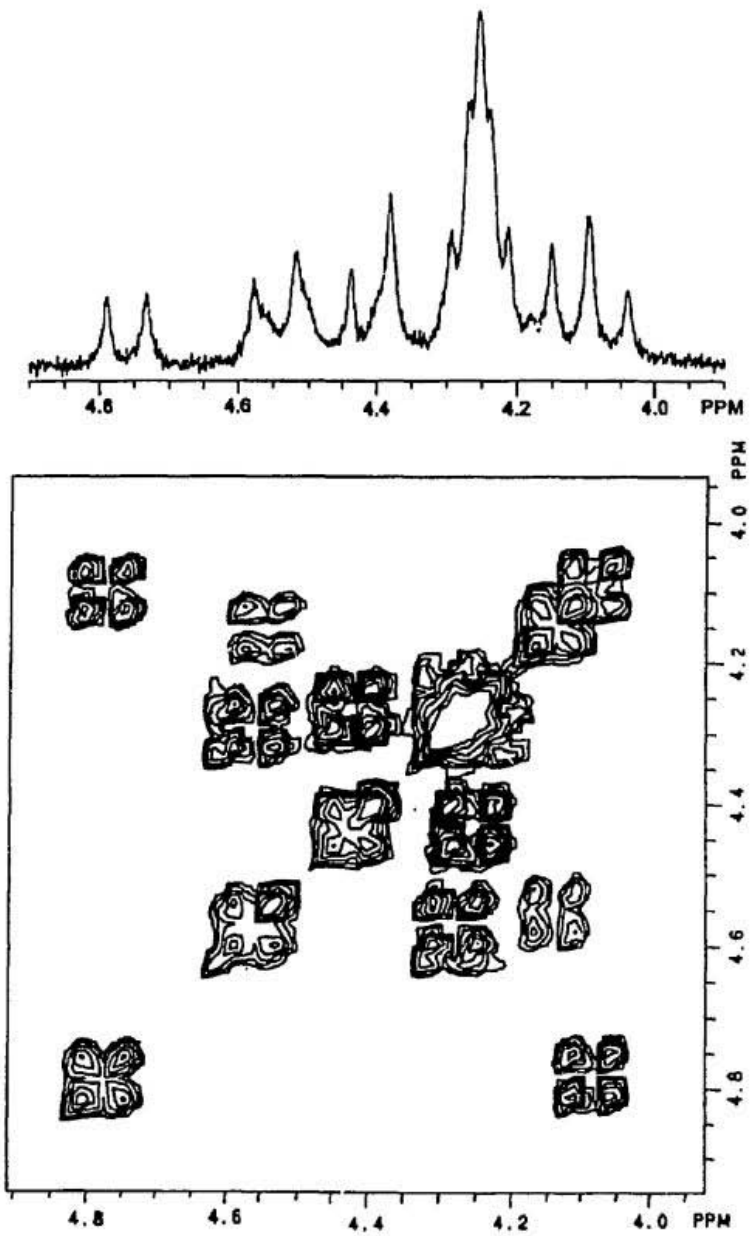
Fig. 2.5. VT ^{1}H NMR Spectra of 8a in CD_2Cl_2.



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**.[76] 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.[12,18] 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_2Cl_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

Table 2.4. Potential Energies (kcal/mol) of 8a, and 10a Calculated by Alchemy III®.[77]

	8a	**10a**
cone	32.22	32.25
partial cone (sy)	27.44	36.01
partial cone (dissy)		35.20
1,3-alternate	22.92	33.89
1,2-alternate (sy)	28.28	37.99
1,2-alternate (dissy)		39.57

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

Fig. 2.7. VT ^{1}H NMR Spectra of 10a in $CDCl_3$.

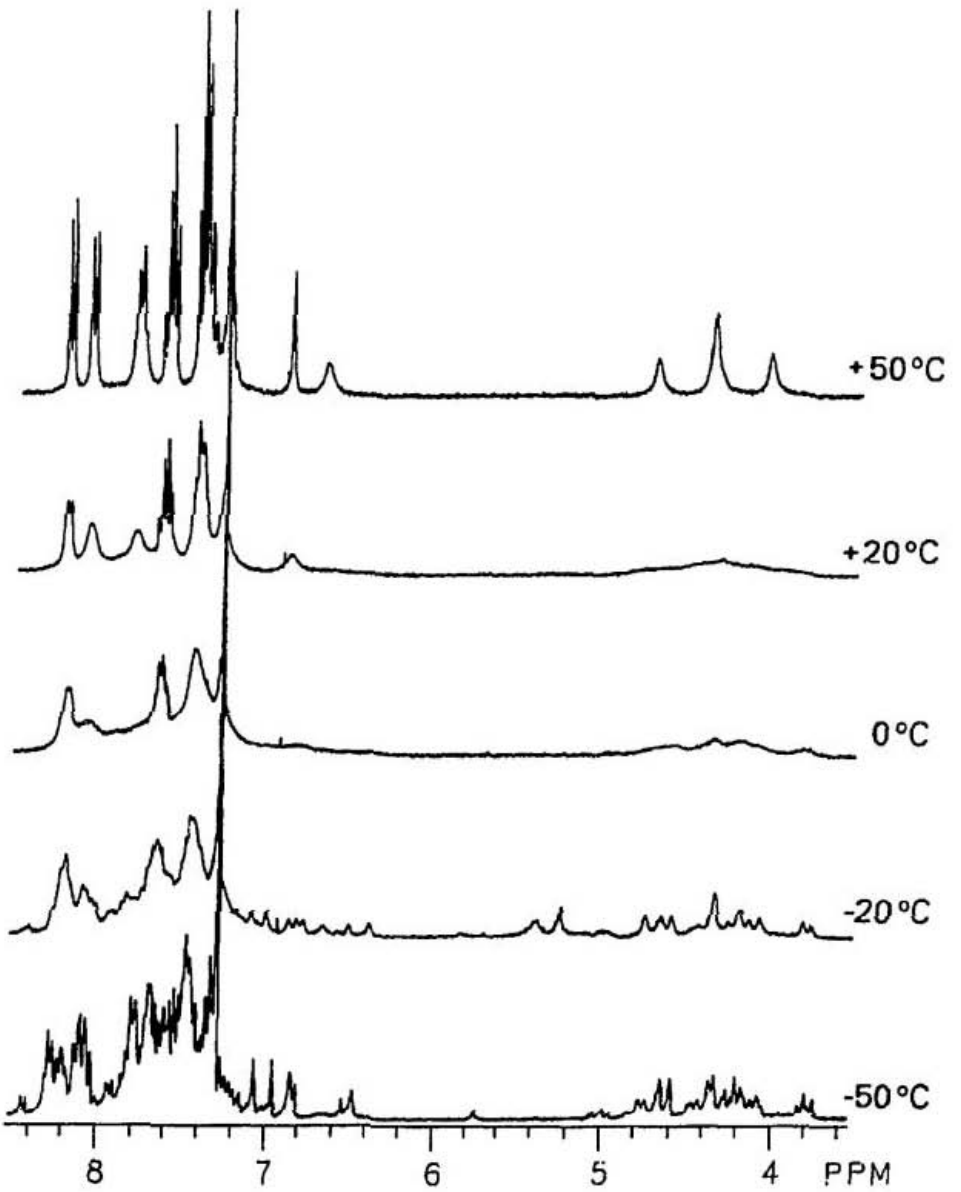


Fig. 2.8. HH COSY Spectrum of Methylene in 10a at -50 °C in $CDCl_3$.

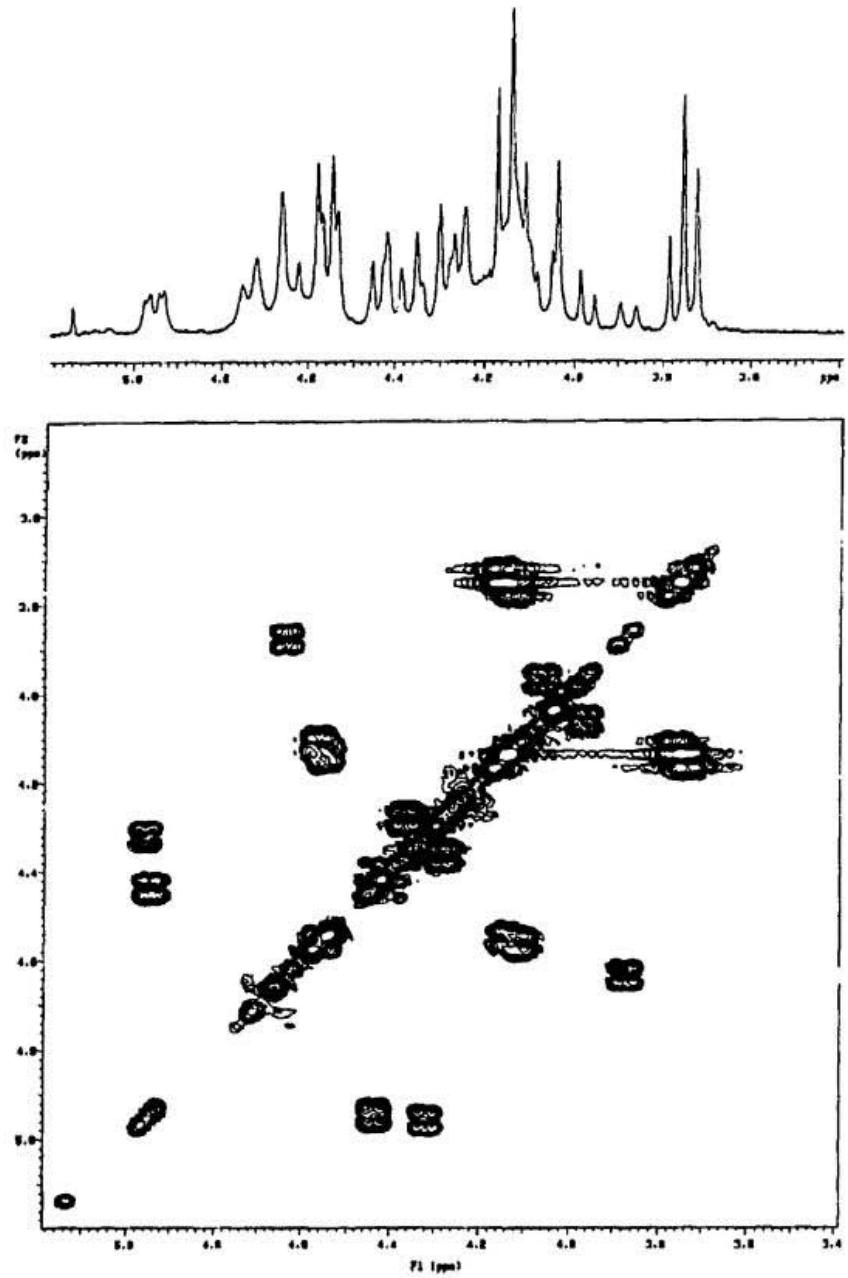
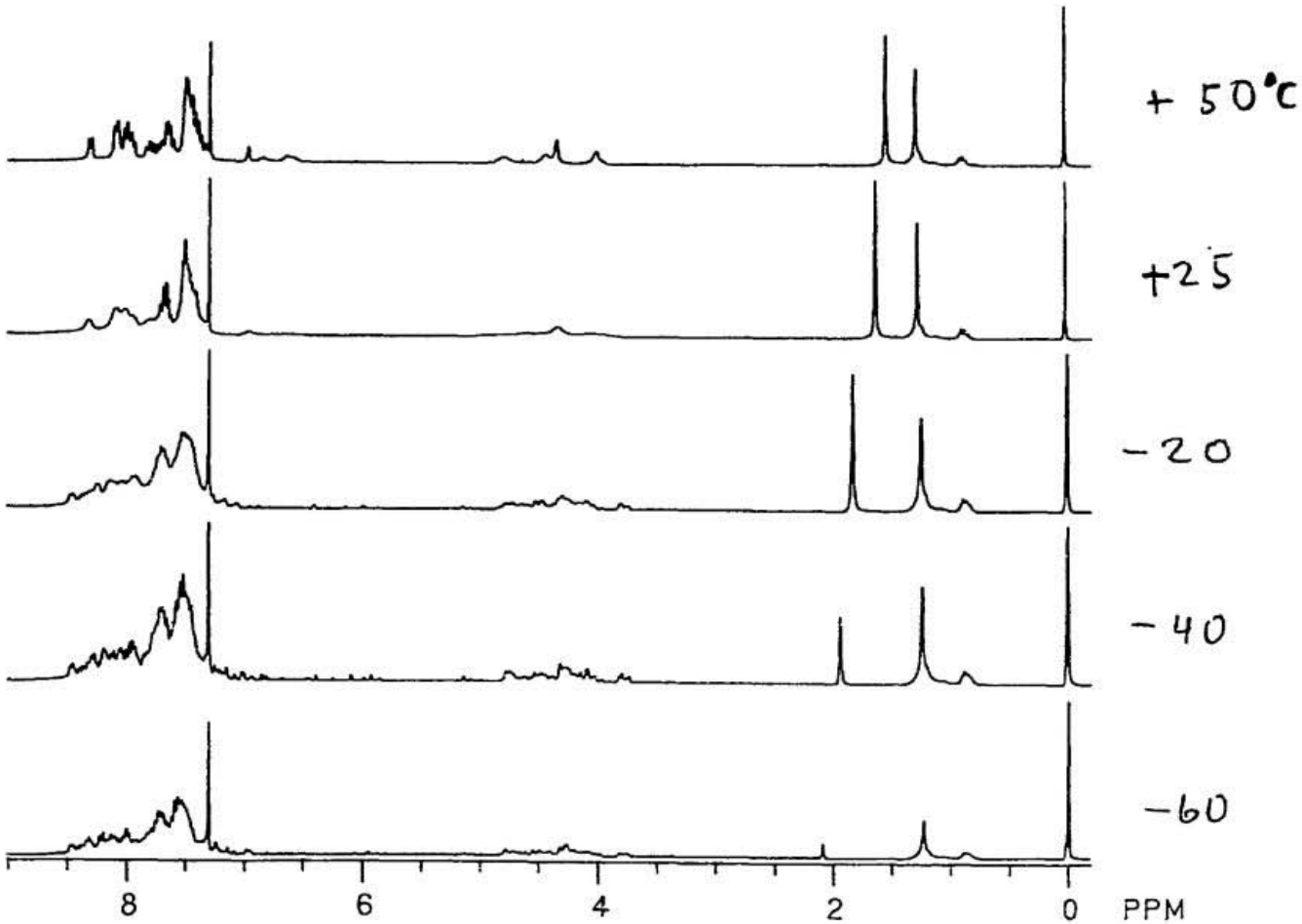


Fig. 2.9. VT ^{1}H NMR Spectra of 11a in $CDCl_3$.



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**, tetraacatates **8b**,**10b** and **11b** have sharper signals at the same temperature, and have lower coalescence temperatures (-10 °C).

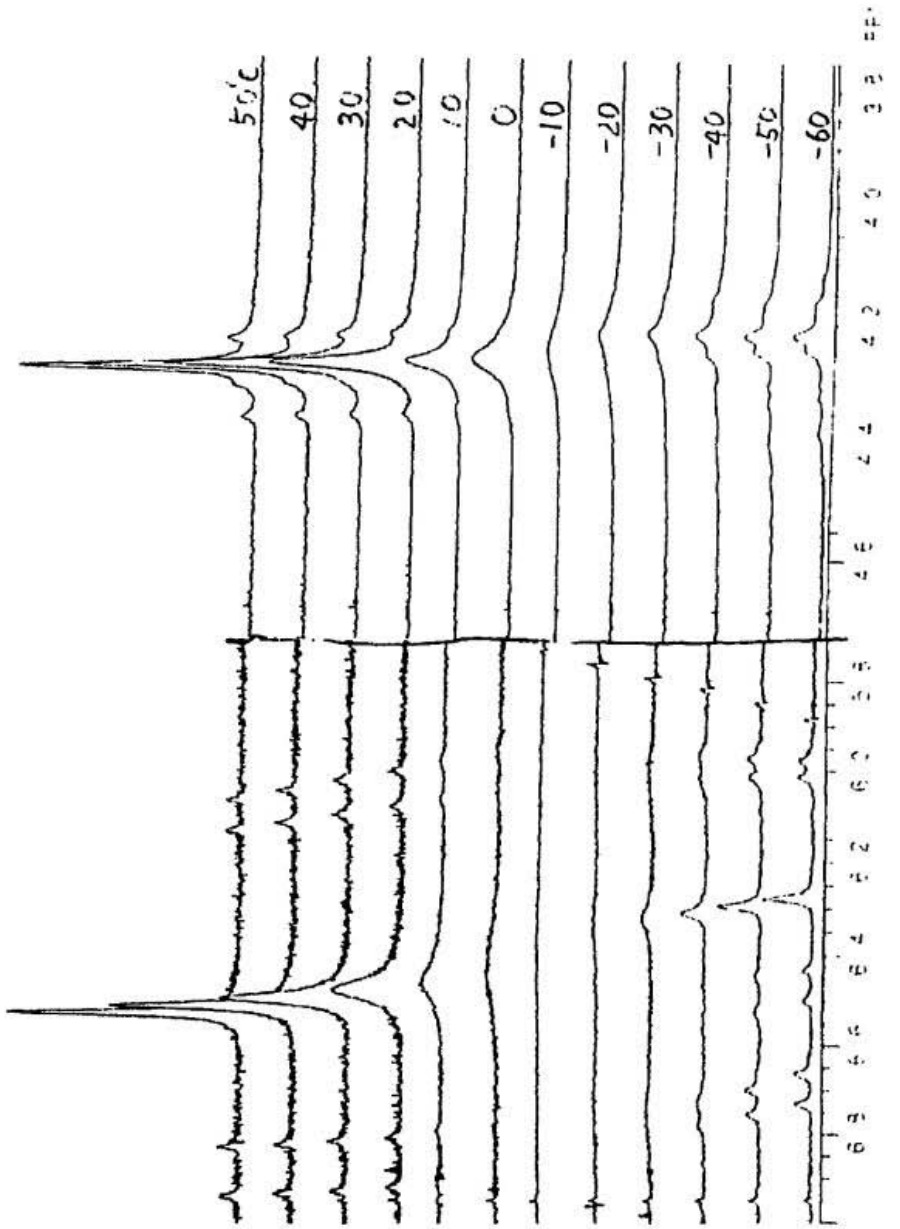


Fig. 2.10. VT ^{1}H NMR Spectra of 8b in $CDCl_3$.

Fig. 2.11. VT ^{1}H NMR Spectra of 10b in $CDCl_3$.

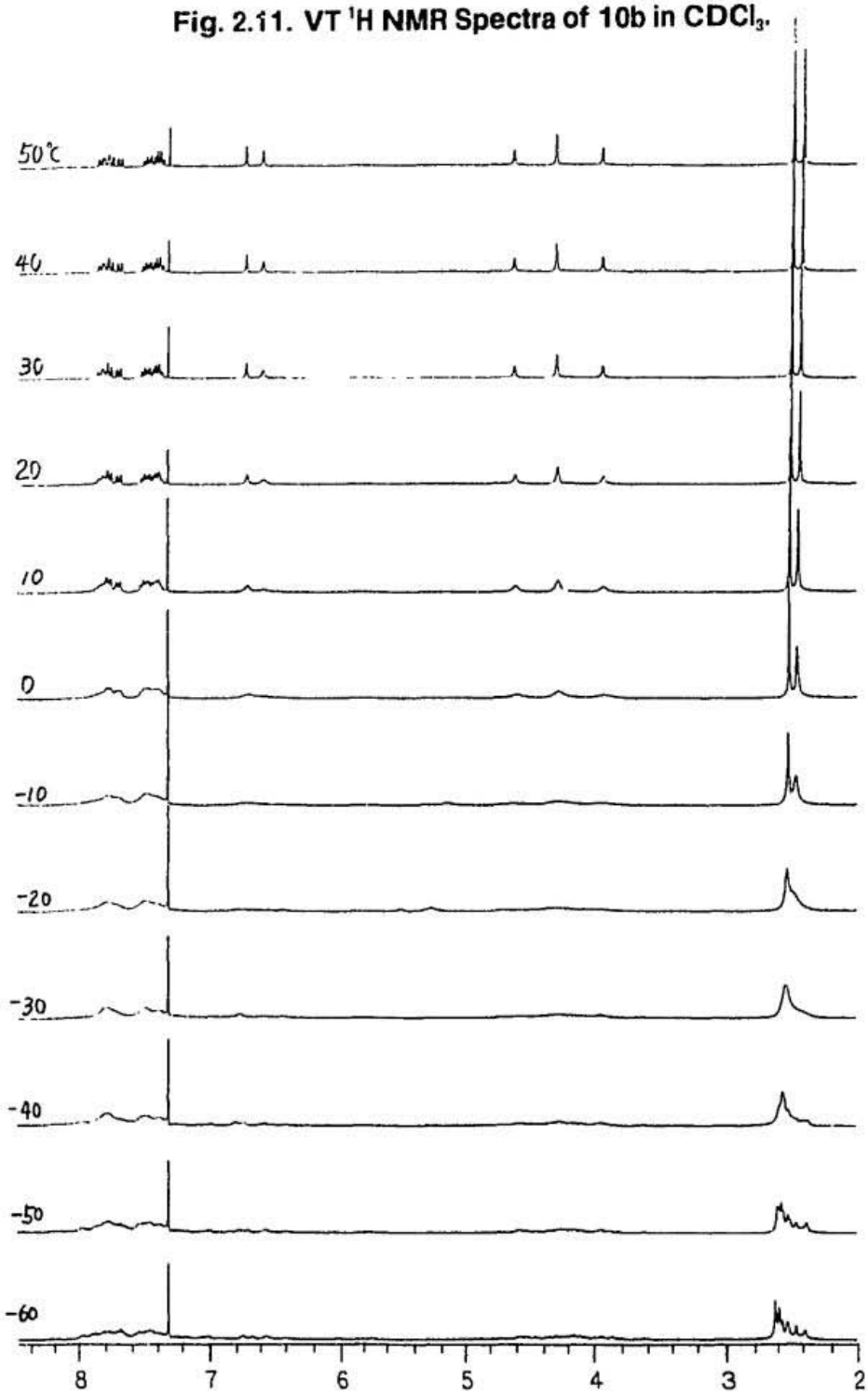
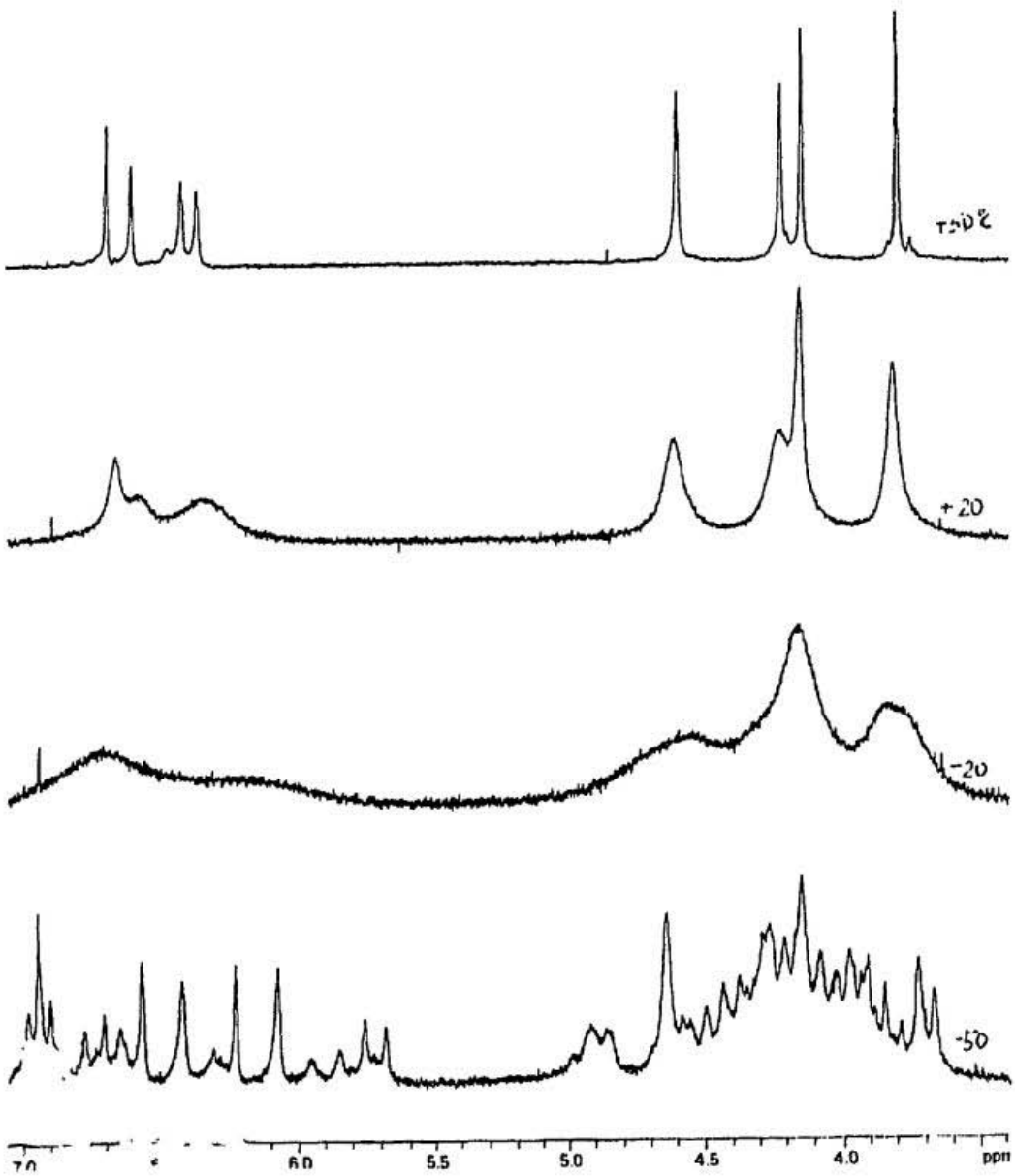


Fig. 2.12. VT ^{1}H NMR Spectra of 11b in $CDCl_3$.



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 "*pseudo*calixnaphthalene" pathway, rather than the "*hemi*calixnaphthalene" 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 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_{254} plates (Merck, Darmstadt, FRG).

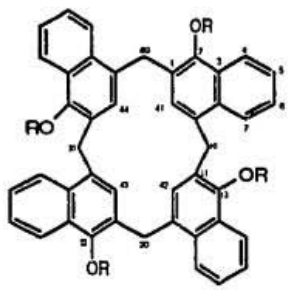
Materials. Chemical reagents and solvents whose synthesis are not described were purchased from Aldrich or Fluka and were used as received with the following exceptions. Dry dichloromethane was obtained by distillation of ACS grade dichloromethane from calcium hydride. Dry chloroform was obtained from 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 N_2.

Instrumentation. Melting points (mp) were determined on a Fisher-Johns apparatus and are uncorrected. Infrared (IR) spectra were recorded on a

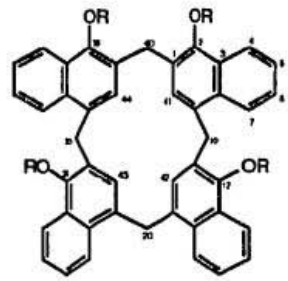
Mattson Polaris FT instrument. Data are presented as follows: frequency of absorption (cm^{-1}), intensity (s=strong, m=medium, w=weak, br=broad), and assignment (when appropriate). Low resolution and high resolution (HRMS) mass spectral (MS) data were obtained using a V.G. Micromass 7070HS instrument. 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. ^{1}H 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 assigments are based on HH COSY, CH Hetcor, and NOED. ^{13}C 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 ^{13}C NMR spectra are relative to the respective solvents (δ 77.0 for $CDCl_3$; δ 53.8 for CD_2Cl_2). The assigments 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.

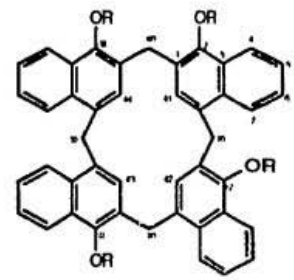
*Calix[4]naphthalenes **(8)**, **(10)** and **(11)**.*



8 R= H
8a R=Bz
8b R=Ac



10 R= H
10a R=Bz
10b R=Ac



11 R=H
11a R=Bz
11b R=Ac

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 N_2 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-d_6): 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); ^{13}C NMR (DMSO-d_6): 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,

OH), 1690 (w), 1665 (w), 1600 (w), 1500 (s), 1404 (s); ^{1}H NMR (DMSO-d_6): δ 4.08 (s, 1H, H-20), 4.29 (s, 2H, H-10, H-30), 4.40 (s, 2H, H-40), 6.72 (s, 2H, H-41, H-44), 6.83 (s, 2H, H-42, H-43), 7.40 (m, 8H, H-5, H-6, H-15, H-16, H-24, H-25, H-34, H-35), 7.78 (d, 2H, H-7, H-33), 8.08 (m, 2H, H-17, H-23), 8.18 (m, 2H, H-14, H-26), 8.31 (d, 2H, H-4, H-36); NOED (%): *__H-40__ / H-41 (H-44) (0.99), __H-20__ / H-42 (H-43) (0.98), __H-30 (H-10)__ / H-41 (H-44) (1.05), __H-40__ / H-41(H-44) (0.99); ^{13}C NMR (DMSO-d_6): δ 31.6 (t, C-10, C-30), 33.6 (t, C-20), 36.7 (t, C-40), 120.3 (s, C-1, C-39), 120.9 (s, C-11, C-29), 122.2 (d, C-14, C-26), 122.8 (d, C-4, C-36), 123.7 (d, C-7, C-33), 123.9 (d, C-17, C-23), 124.6, 124.8 (d, C-5, C-6, C-34, C-35), 125.3, 125.4 (d, C-15, C-16, C-24, C-25), 125.9 (s, C-13, C-17), 127.6 (s, C-3, C-37), 127.7 (s, C-18, C-22), 128.5 (d, C-41, C-44), 128.7 (s, C-8, C-32), 129.4 (d, C-42, C-43), 131.2 (s, C-19, C-21), 131.4 (s, C-9, C-31), 147.3 (s, C-12, C-28), 147.8 (s, C-2, C-28); MS (*m/z*), Intensity (%): 624 (M$^+$, 18), 606 (4), 480 (3), 468 (3), 313 (7), 312 (10), 311 (3), 282 (10), 281 (16), 144 (100).

Compound **11**: mp>300°C (with decomposition); IR (Kbr, cm^{-1}), 3404 (s, br, OH), 1695 (m), 1668 (w), 1602 (m), 1500 (s), 1402 (s); ^{1}H NMR (DMSO-d_6): δ 4.09 (s, 1H, H-40), 4.21 (s, 1H, H-20), 4.32 (s, 1H, H-10), 4.45 (s, 1H, H-30), 6.64 (s, 1H, H-41), 6.66(s, 1H, H-44), 6.70 (s, 1H, H-43), 6.80 (s, 1H, H-42), 7.40 (m, 8H, H-5, H-6, H-15, H-16, H-25, H-26, H-34, H-35), 7.79 (d, 1H, H-33), 7.97 (d, 1H, H-

---

* The ^{1}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** / H42 (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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) 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^++1, 2.5), 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 ($CDCl_3$) 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); ^{13}C NMR ($CDCl_3$) at 50 °C: 34.70, 32.80, 30.40 (methylene), 121.3-143.4 (aromatic), 164.6, 164.9 (carbonyl); MS, (FAB+ ,NOBA as a matrix, *m/z*), Intensity (%):1062 ($(M-1+Na)^+$, 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); ^1H 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, 33.1, 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 ($CDCl_3$) at 50 °C: δ 2.40 (s, 12H, $COCH_3$), 4.24 (s, br, 8H, methylene), 6.45 (s, br, 4H, intra-annular), 7.26-7.92 (m, 16 H, other aromatic); ^{13}C NMR ($CDCl_3$): 20.6 ($CO\mathbf{C}H_3$), 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 ($CDCl_3$) at 50 °C: 2.45, 2.38 (sx2, br, 12H, $COCH_3$), 3.88, 4.61, 4.25 (sx3, br, 8H, methylene), 6.52 (s, br), 6.66 (d, br, 4H, intra-annular), 7.33-7.80 (m, 16H, aromatic); ^{13}C NMR ($CDCl_3$) at 50 °C: 20.7 ($COCH_3$), 34.7, 32.8, 30.7 (methylene), 121-4-143.6 (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 ($CDCl_3$) at 50 °C: 2.22, 2.32, 2.40, 2.42 (sx4, br, 12H, $COCH_3$), 3.85, 4.18, 4.26, 4.63 (sx4, br, 8H, methylene), 6.37, 6.42, 6.60, 6.69 (sx4, br, 4H, intra-annular), 7.36-7.88 (m, 16H, other aromatic); ^{13}C NMR ($CDCl_3$) at 50 °C: 20.7, 20.5 ($CO\mathbf{C}H_3$), 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.

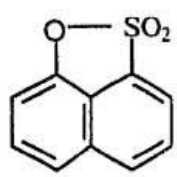
Calix[4]naphthalenes Derived from 1,8-Naphthalene Sultone

3.1. Introduction.

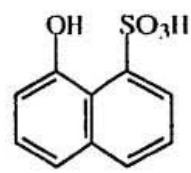
One of Gutsche's original motivations for studying calixarene chemistry was to try to develop enzyme mimics. The design and synthesis of hosts for suitable enzyme mimics are strong driving forces for the further development of calixarene chemistry.[78] Most biological processes take place in an aqueous 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 [79] 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 [80] has synthesized some calixarenes which are much more water-soluble by first removing the *tert*-butyl group of the *p-tert*-butylcalixarenes with $AlCl_3$ 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.



6

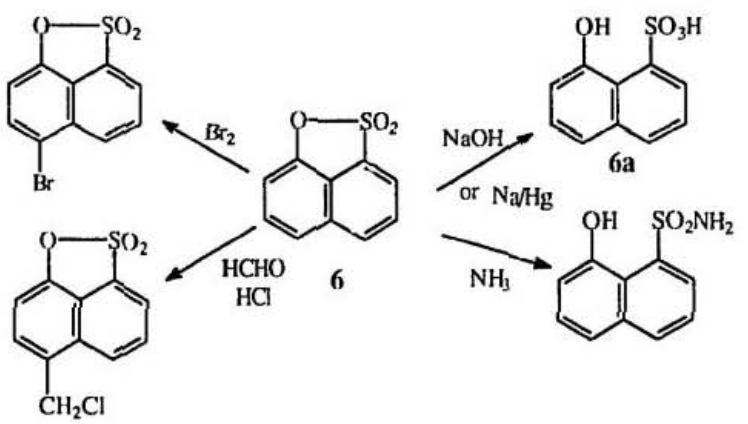


6a

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 sulphonic 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.*

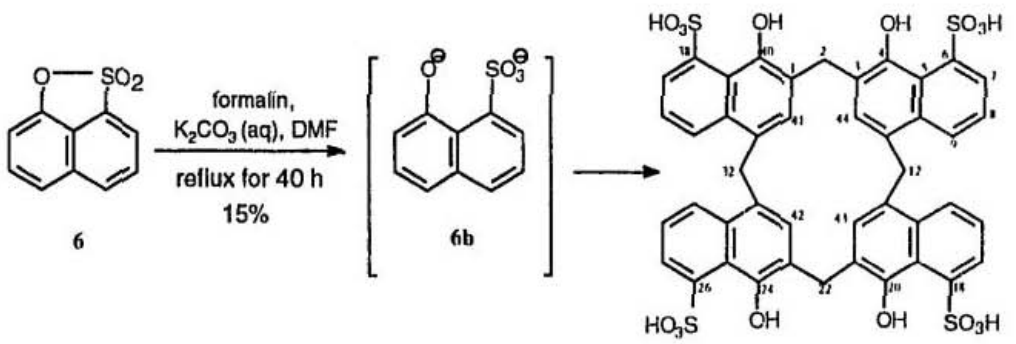
3.2.1. Synthesis of *peri*-Sulphonatocalixnaphthalenes under Basic Conditions.

Commercially available 1,8-naphthalene sultone (**6**) is a 50:50 aqueous dark brown paste. Attempts to remove the 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.

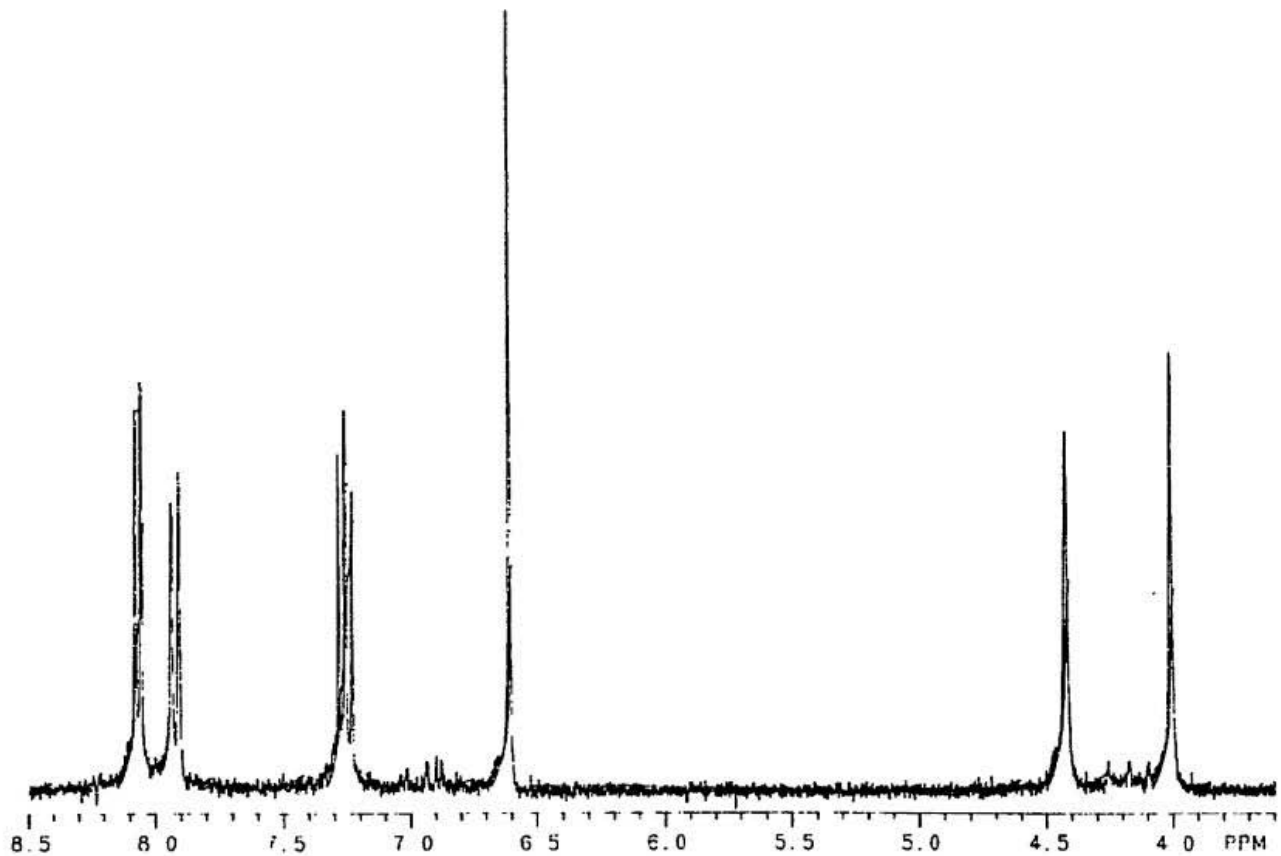
When **6** was treated with potassium carbonate, the corresponding *sulphonate dianion* ***6b***, *was presumably formed in situ. Condensation of* ***6b*** with formaldehyde gave, after acidification, the cyclic tetrameric product **20** in 15% yield as shown in Scheme 3.2.

Scheme 3.2.



The ^{1}*H NMR spectrum (Fig. 3.1) of* **20** *shows two sharp singlets at* δ 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}H NMR spectrum indicates that there is conformational flexibility at ambient temperature. Its ^{13}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.

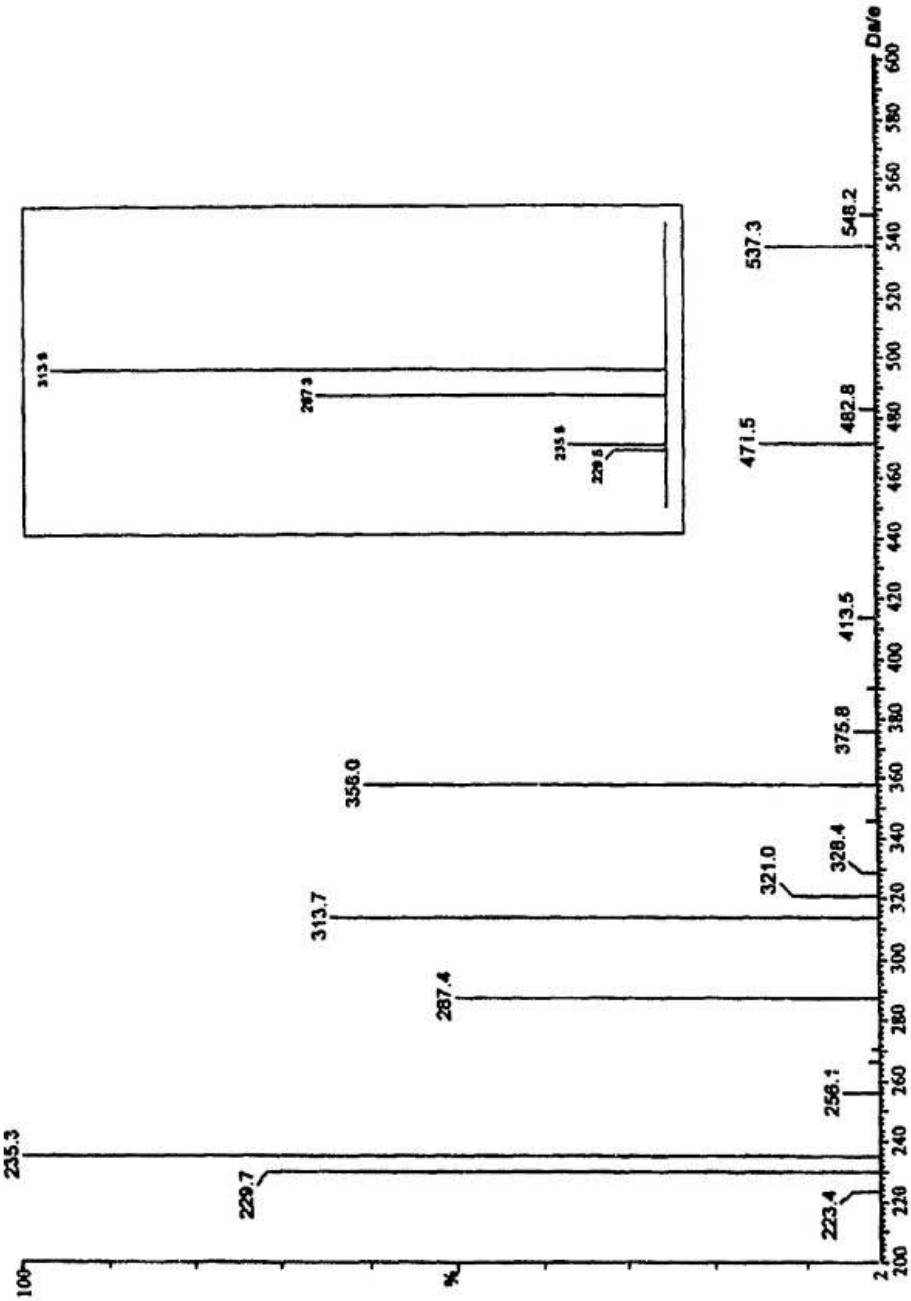


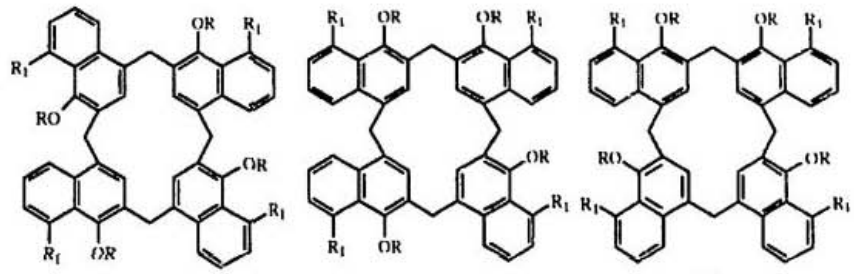
Further characterization of **20** was carried by using electrospray mass spectrometry (ESMS). In the positive ion mode, an aqueous solution of **20** did not electrospray. In the negative ion mode the mass spectrum shown in Fig. 3.2 was obtained.

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 $[M-3H-SO_3H]^{3-}$ 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.

Fig. 3.2. ESMS Spectrum of 20.





21
R= H
R1= SO_3H

22
R=H
R1= SO_3H

23
R= H
R1= SO_3H

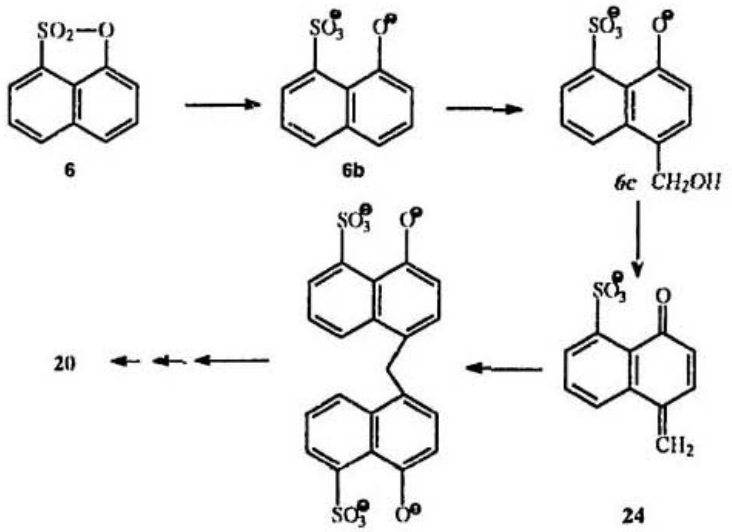
In the sulphonate dianion (**6b**), the 4-position is much more electron-rich than the 2-position.[81] The condensation of **6b** with formaldehyde occurs at the 4-position with great preference to give the α,γ-dienone **24**. This intermediate **24** can react with another molecule of sulphonate dianion **6b** to form a *para-para* dimer **25**. Following the hemicalixnaphthalene pathway, dimer **25** will lead only to **20**, the observed C_{2v} compound.

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

The isolated yield of **20** is low, because of the diffucuty of seperation 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 ^{1}H and ^{13}C NMR.

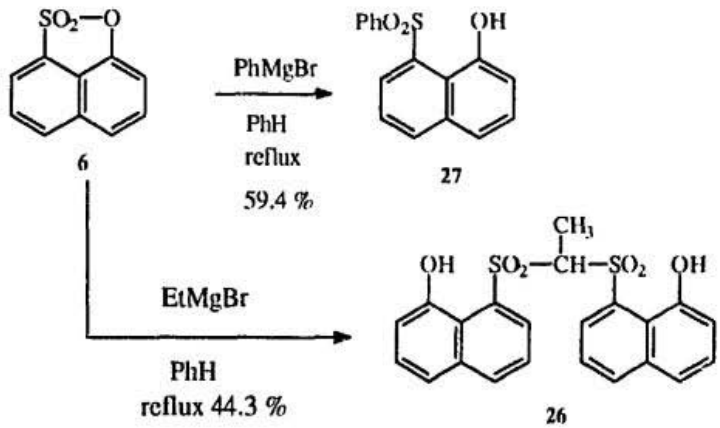
Scheme 3.3.



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,[82] 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.

Scheme 3.4.



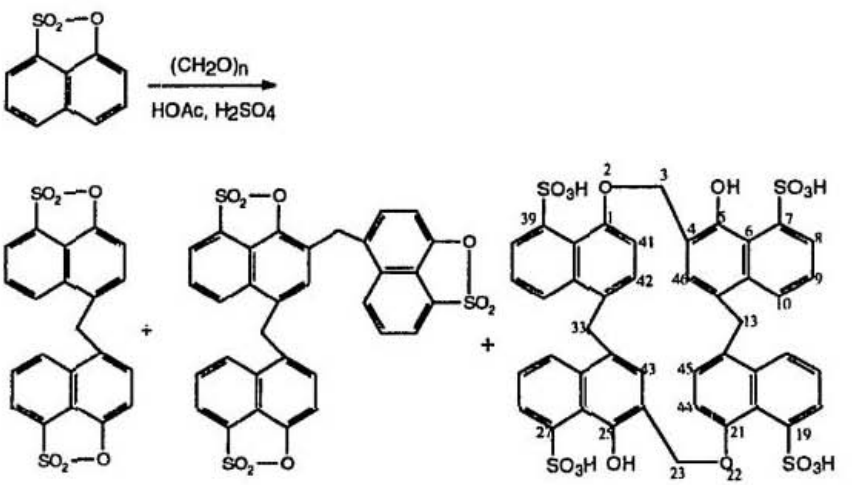
3.2.3. Synthesis of *peri*-Sulphonatocalixnaphthalene under Acidic Conditions.

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*-sulphonatocalix-naphthalene, **30**, was obtained (Scheme 3.5).

In the ^{1}H NMR spectrum of **30**, two singlets appear at δ 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 (δ 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 (δ 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

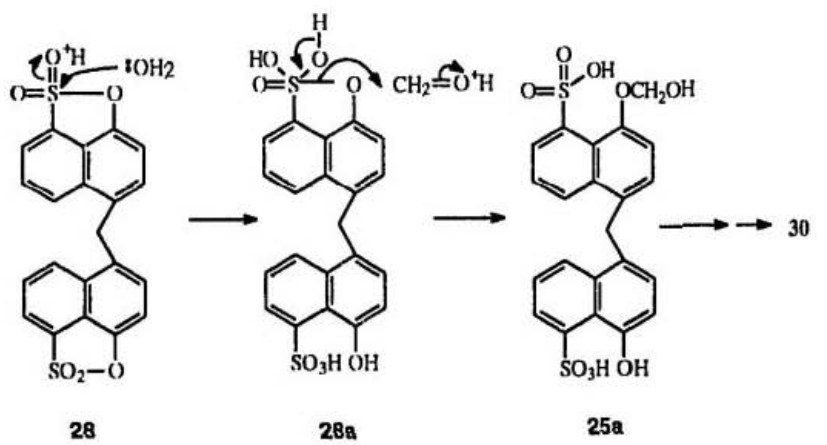
evident. Under strong acidic conditions the dimer **28** can hydrolyse to **28a**, which undergoes O-alkylation to give **25a**. Self-condensation of **25a** produced **30** (Scheme 3.6).

Scheme 3.5.



28 **29** **30**

Scheme 3.6.



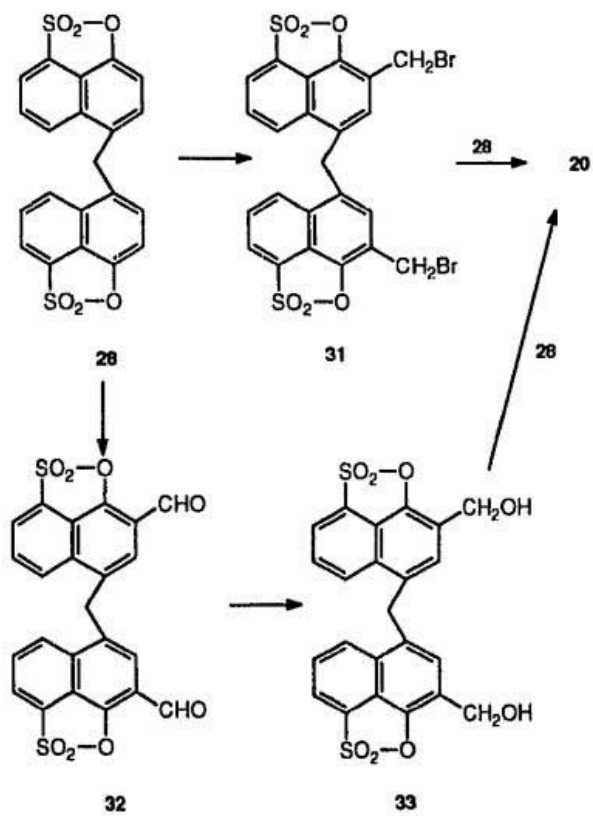
28 **28a** **25a**

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

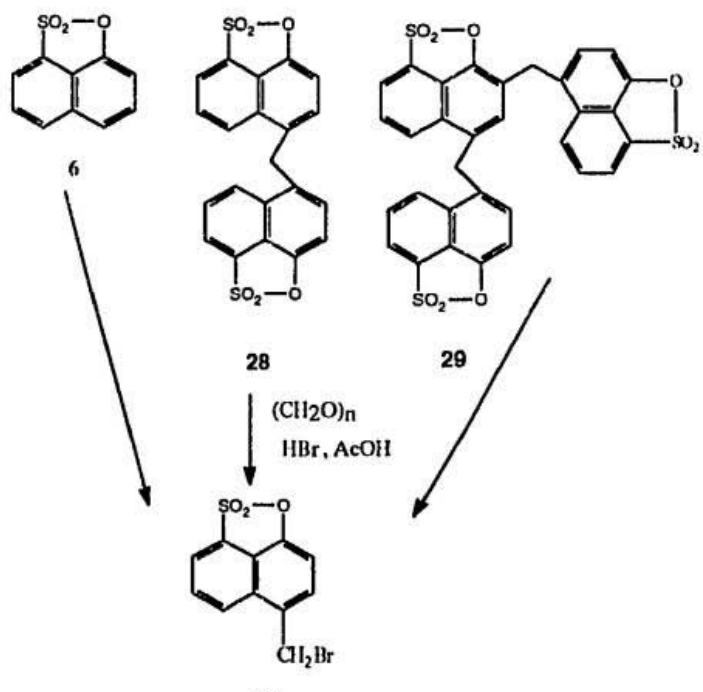
of **31** with **28** would give a cyclic tetramer **20** as outlined in Scheme 3.7.

Scheme 3.7.



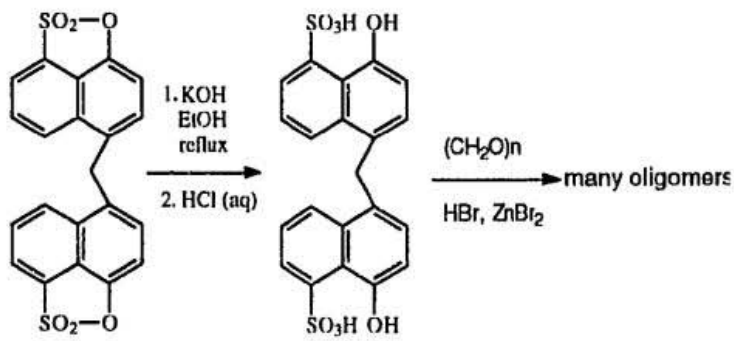
When the sultone **6**, sultone dimer **28** or sultone trimer **29** were treated with paraformaldehyde in the presence of HBr, only 4-bromomethyl-1,8-naphthalene sultone (**34**) was obtained in each case (Scheme 3.8). Thus, for **6**, substitution of a naphthalene ring by a bromomethyl cation only 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 $TiCl_4$ 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 $ZnBr_2$ 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.



28 **25b**

3.3. Complexation studies.

Water-soluble calixarene hosts can form complexes with neutral aromatic

guests in aqueous solution. Shinkai [32] 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.[83]

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

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

Entry	1	2	3	4	5
$C_{host} \times 10^{-3} M$	2.0402	1.0201	0.5101	0.2267	0.0000
Intensity	0	0	0	0	200

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.

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*-sulphonato-calix[4]naphthalene (**20**) follows the "*hemi*calixnaphthalene" pathway, but does not follow the "*pseudo*calixnaphthalene" 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".

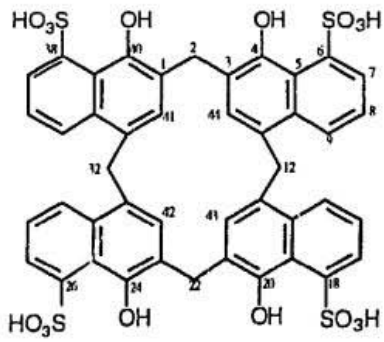
3.5. Experimental.

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

Electrospray mass spectra (ESMS) in the negative mode were recorded on a Fisons VG-Quattro triple quadrupole mass spectrometer, equipped with an electrospray ionization source, capable of analysing ions up to *m/z* 4000. A 486, 66 MHZ personal computer equipped with a Fisons MASSLYNX Mass Spectrometry Data System Software was used for data acquisition and processing. The temperature of the ES ionization source was maintained at 70 °C. The operating voltage of the ES capillary was 3.00 KV and the HV lens was at 0.50 KV throughout the operation. ESMS were obtained by scanning in the Multi Channel Analysis mode (MCA) with a scan dwell time of 1s. Spectra were an average of 3-4 scans. The mass scale was calibrated in the negative ion mode using a Horse heart Myoglobin solution. MS/MS experiments were conducted on the same instrument. Fragment ion spectra of mass-selected ions were produced by collision with argon in the second (RF only) hexapole. Argon collision gas was added in the enclosed chamber of the hexapole to give a pressure of 2×10^{-5} mBar for collisional activation of the sample ions. The resulting fragments were analysed by the third quadrupole. Collision energies of 50 eV were used in MS-MS experiments. Precursor ion scans were obtained by scanning the first quadrupole while selecting a given *m/z* value with the third

quadrupole.

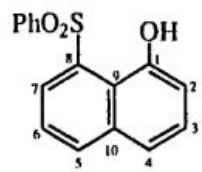
*peri-Sulphonatocalix[4]naphthalene (**20**).*



To a solution of freshly sublimed 1,8-naphthalene sultone (**6**) (2.06 g, 10 mmol) in DMF(10 mL) under N_2 were added formalin (aqueous 37% formaldehyde solution, 0.70 mL, 8.6 mmol) and Cs_2CO_3 (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); ^{1}H NMR (DMSO-d_6): 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 ($[M+6Na-8H]^{2-}$, 15), 471.5 ($[M-4H]^{4-}$, 15), 358.0 ($[M+6Na-9H]^{3-}$, 63), 321.0 ($[M+Na-4H]^{3-}$, 13), 313.7 ($[M-4H]^{4-}$, 65), 287.4 ($[M-3H-SO_3H]^{3-}$,51), 235.3 ($[M-4H]^{4-}$, 100), 229.7 ($[M-4H-H_2O]^{4-}$, 72).

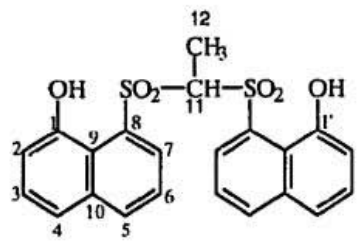
*Phenyl (1-hydroxyl-8-naphthyl) sulphone (**27**).*



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,[82] mp 134.5-135.0 °C; ^{1}H NMR ($CDCl_3$): 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, $J_{5,6}$=8.4, $J_{5,7}$=1.2, 1H, H-5), 8.58 (q, $J_{7,6}$=7.5, $J_{7,5}$=1.2, 1H, H-7); ^{13}C NMR (DMSO-d_6): 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).

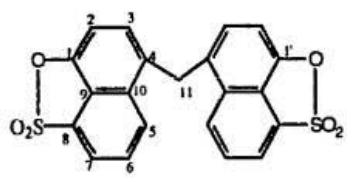
*1',1'-Bis-(1-hydroxl-8-naphthylsulphonato)ethane (**25**).*



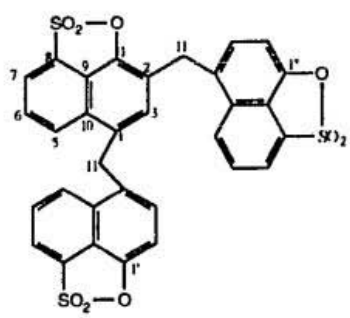
To a solution of **6** (2.0 g, 10 mmol) in dry benzene (50 mL) was added ethylmagnesium bromide (3.0 M ether solution, 8 mL) over 30 min. The reaction mixture was refluxed for 4 h. After cooling to room temperature, 5% hydrochloric acid (50 mL) was added to the solution. After stirring for 15 min, the

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. Fitration 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 ($CDCl_3$): 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'); ^{13}C NMR (CD_3COCD_3): 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/z*), 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'-naphthylmethyl)-1,8-naphthalene sultone (**29**).*



28

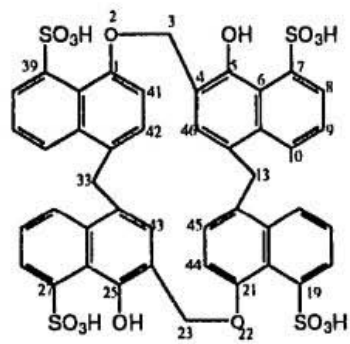


29

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 / $CDCl_3$ (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 / $CDCl_3$): 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^+-SO_2, 16), 296 (M^+-2SO_2, 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 (mx3, 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**).*



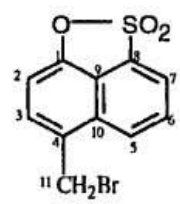
To a solution of **6** (7.9 g, 50 mmol) and paraformaldehyde (4.8 g, 160 mmol) in glacial acetic acid (200 mL) was carefully added concentrated sulphuric acid (6.0 mL). The clear solution was refluxed for 6 days. After cooling to room temperature, the reaction solution was poured onto crushed ice (200 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^{2+}, $C_{44}H_{30}O_{16}S_4Na_4$, 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 $ZnBr_2$ (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,[84] mp 143-

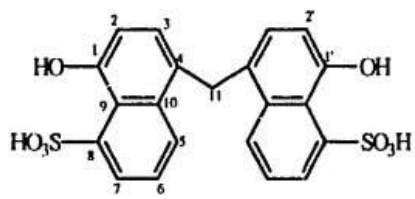


34

145 °C; ^{1}H NMR ($CDCl_3$): 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, $J_{6,7}$=7.2, $J_{6,5}$=8.1,1H, H-6), 8.06 (d, J=7.2, 1H, H-7), 8.42 (d, J=8.1, 1H, H-5); ^{13}C NMR ($CDCl_3$): 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 $TiCl_4$ (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 N_2, 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 redish solid: mp>300 °C (with decomposition); ^{1}H NMR (D_2O): 4.42 (s, 2H, H-11), 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_2O): 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.[83] The results are summarized in Table 3.1.

Chapter 4.

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

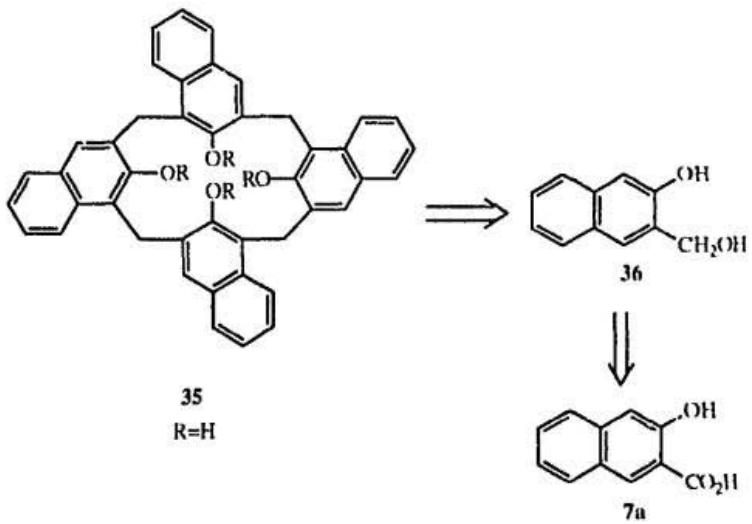
4.1. Introduction.

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.

Scheme 4.1.



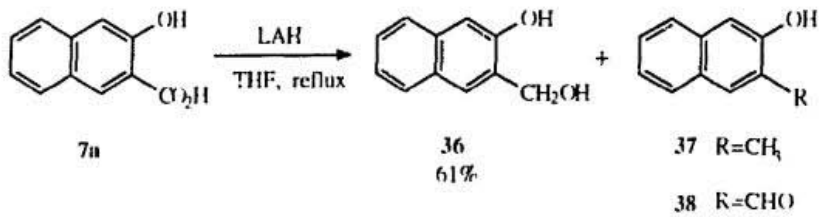
4.2. Synthesis of Calixnaphthalenes.

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]

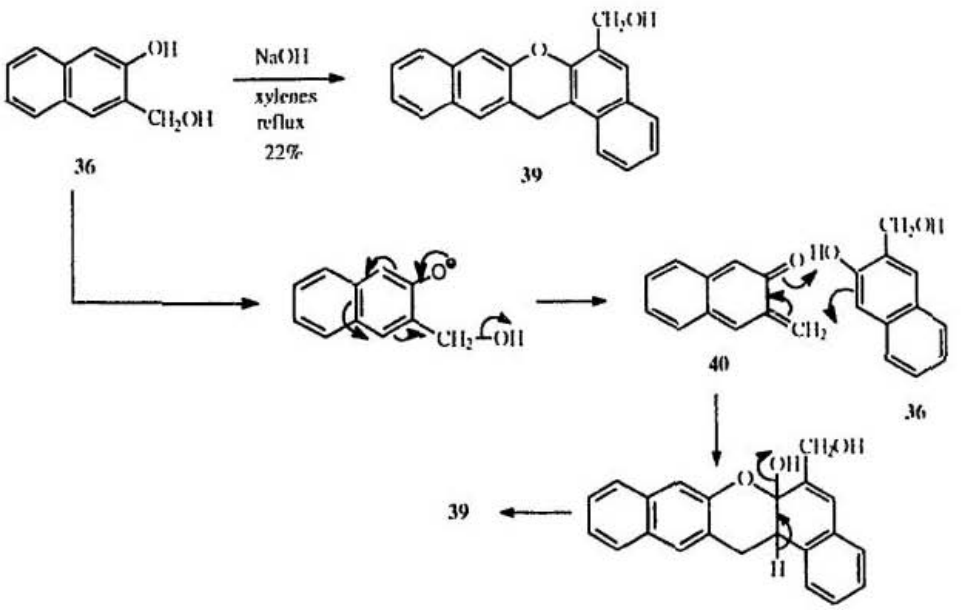
Benzyl alcohol-type compounds have been suggested as intermediates for the formation of calixarenes in Gutsche's procedure.[12] However, when the self-condensation of **36** was carried out under the conditions similar to those of

Scheme 4.2.



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 δ 4.60 ppm in the normal methylene proton region and a doublet (equivalent to two protons) at δ 5.07 ppm. When D_2O 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 δ 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 apprent hetero [4+2] cycloaddition of the hetero diene **40**, with the dieneophile **36** gives compound **39**.

Scheme 4.3.



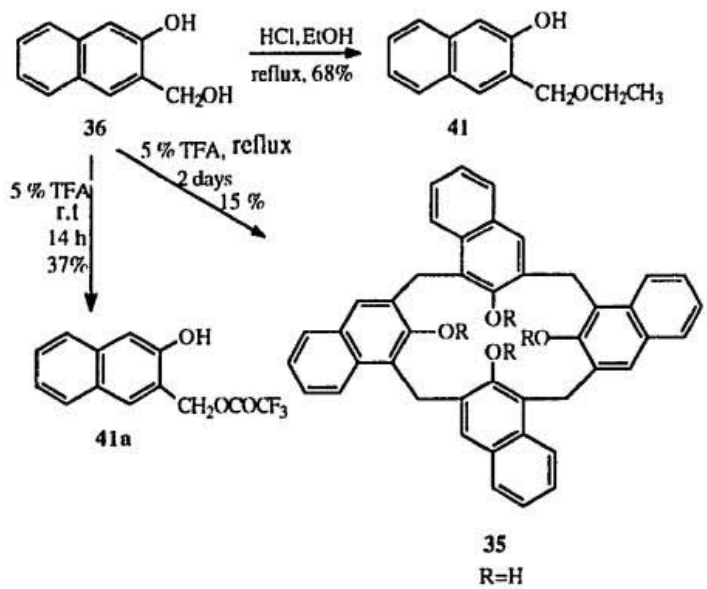
4.2.2. Self-Condensation of 36 under Acidic Conditions.

Conditions similar to those of Högberg[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 **41a** 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

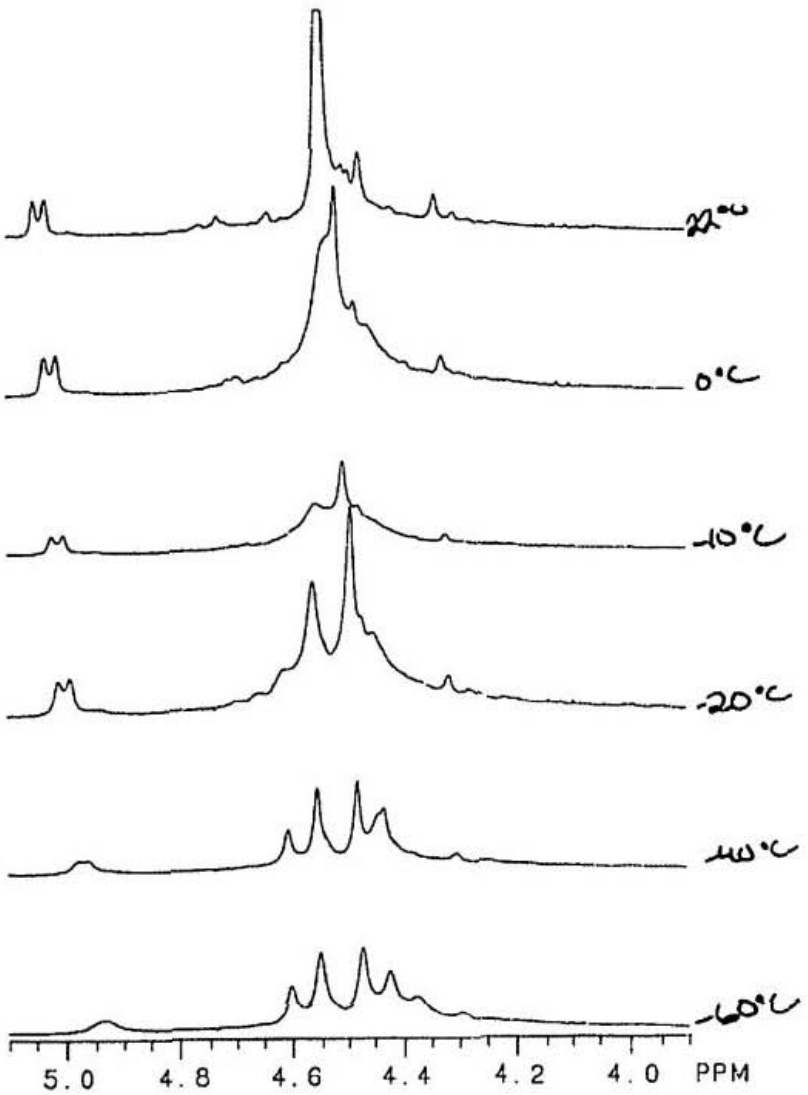
chromatography with dichloromethane as eluent and subjected to PLC with 50% dichloromethane / petroleum ether (30-60 °C) as eluent to give a product as colourless fine crystals in 15% yield (Scheme 4.4). The mass spectrum shows a molecular ion peak at *m/z* =624. Its ^{1}H NMR spectrum revealed a singlet methylene signal, and its ^{13}C 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.*[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 $CDCl_3$.

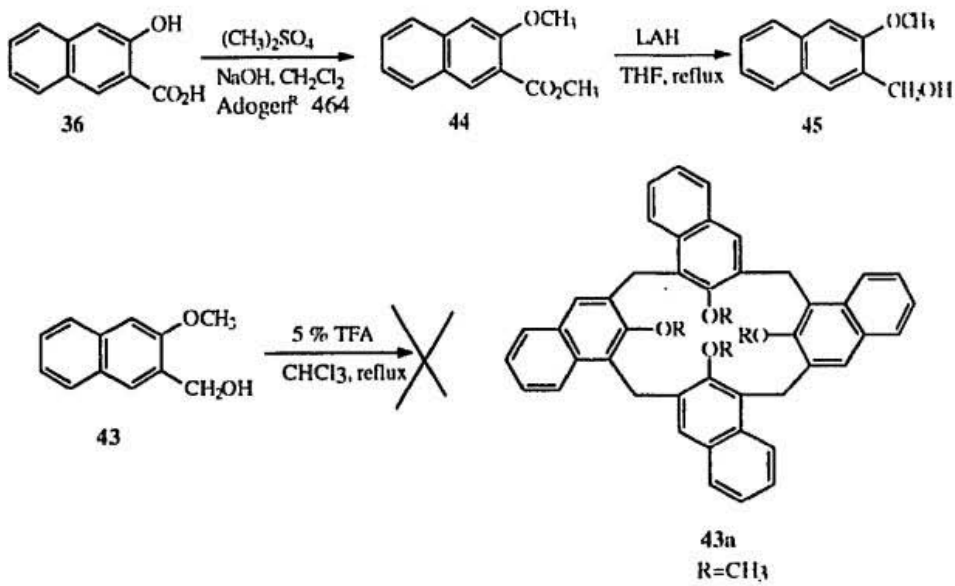


rigid conformation.

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 δ 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.

Scheme 4.5.



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.[12]

4.3. Synthesis of Dihomocalix[4]naphthalene 46.

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

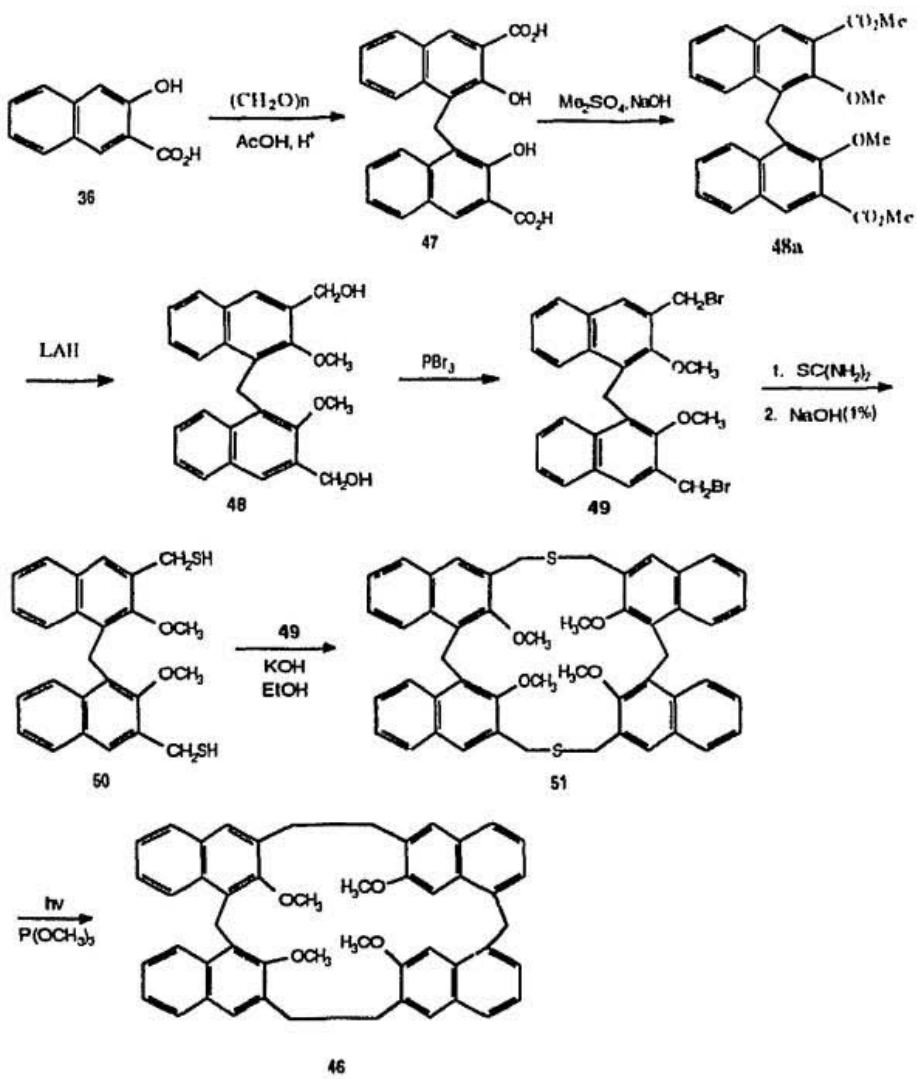
necessary for host-guest chemistry.

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[85] 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*isothiouronium salt, which was subsequently hydrolysed to produce *bis*-(2-methoxy-3-mercaptomethyl-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.

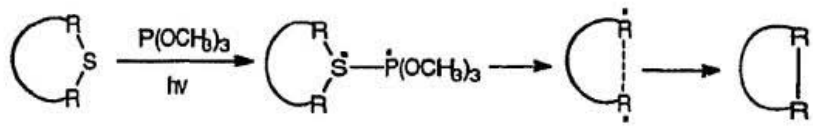
Scheme 4.6.



Among many sulphur extrusion approaches available,[85] 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.[23]

Scheme 4.7.

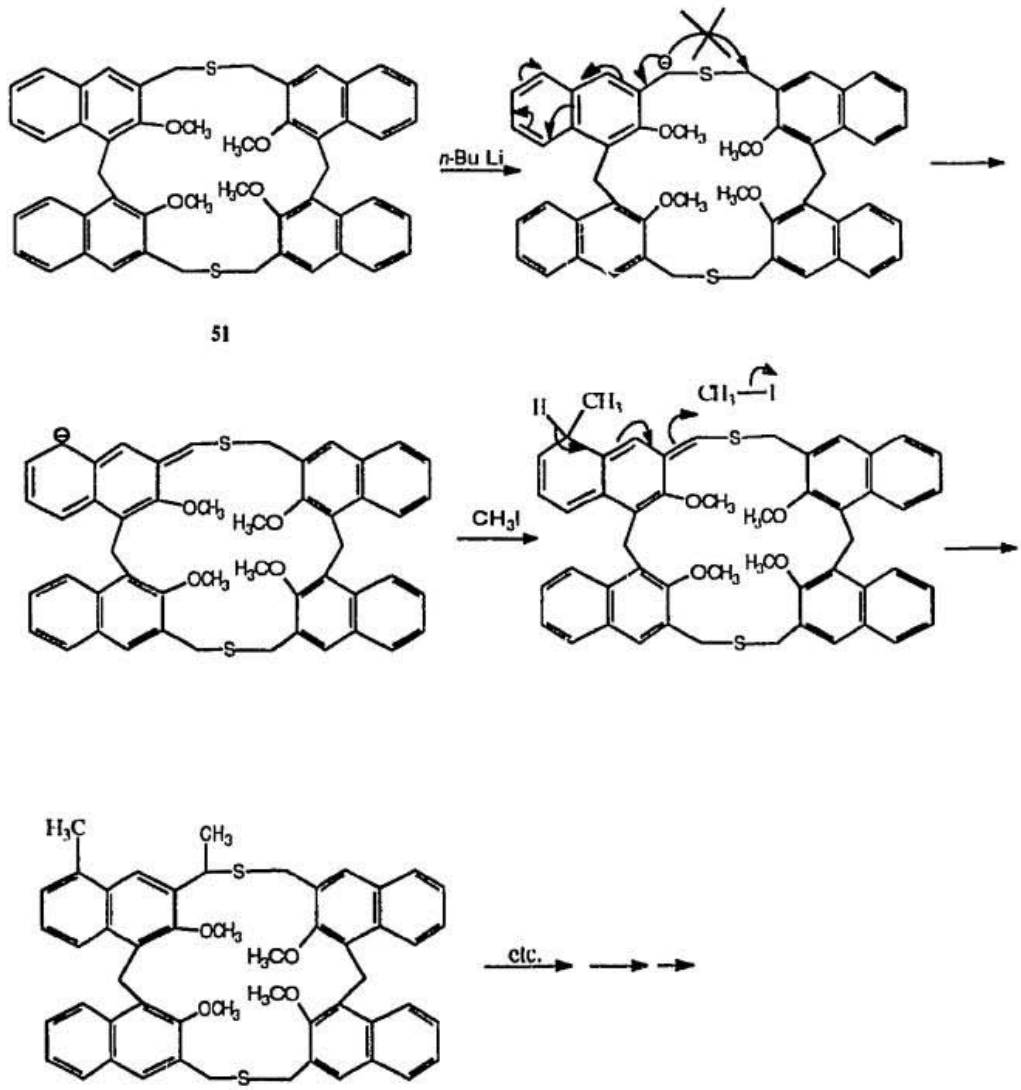


Trimethyl phosphite also serves as a reaction medium to form a suspension of substrate **51**. As a dispersed solid, the resulting carbon diradical is relatively immobile,[23] which thus favours cyclization over linear polymerization.

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 *n*-butyllithium undergoes a tautomerisation and methylation instead of a Wittig rearrangement (Scheme 4.8).

Ambient temperature ^{1}H NMR spectrum of **51** (Figure 4.2) suggests that it is conformationally flexible since all signals are sharp and well-defined. The

Scheme 4.8.



VT ^{1}H NMR spectra (Figure 4.2) show the signals due to the sulphide methylene bridges at δ 3.86 ppm with a coalescence temperature at approximately -40 °C. The signals due to the *para-para* methylene bridge at δ 4.68 ppm are, however

Fig. 4.2. ^{1}H NMR Spectra of 51 in $CDCl_3$.

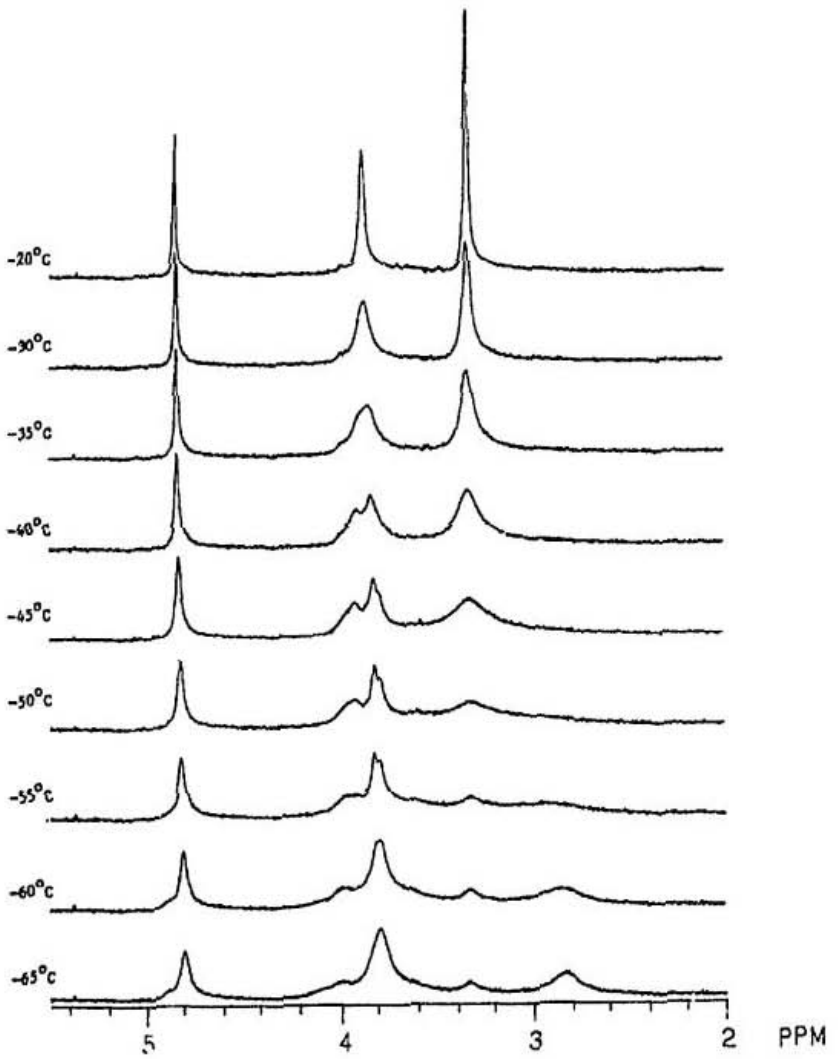
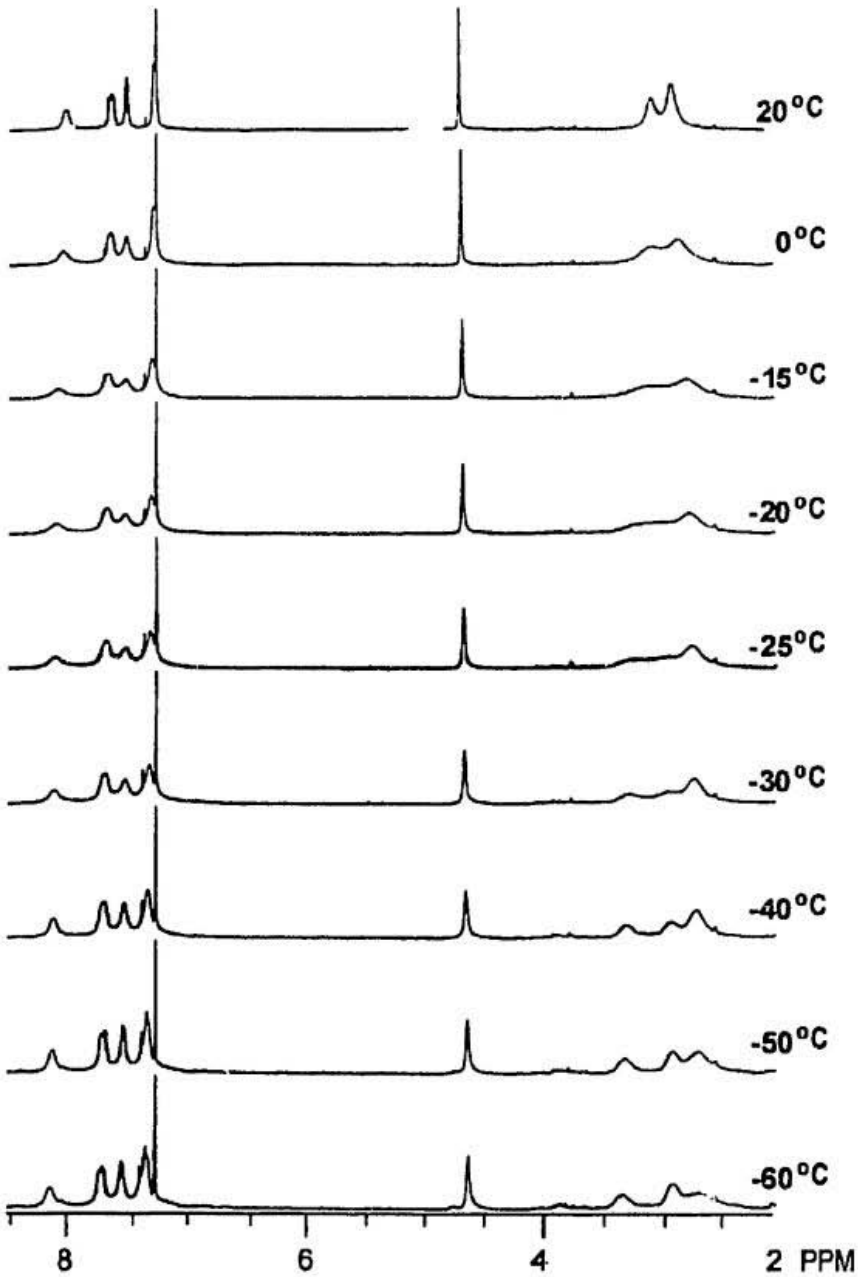


Fig. 4.3. VT ^{1}H NMR Spectra of 46 in $CDCl_3$.

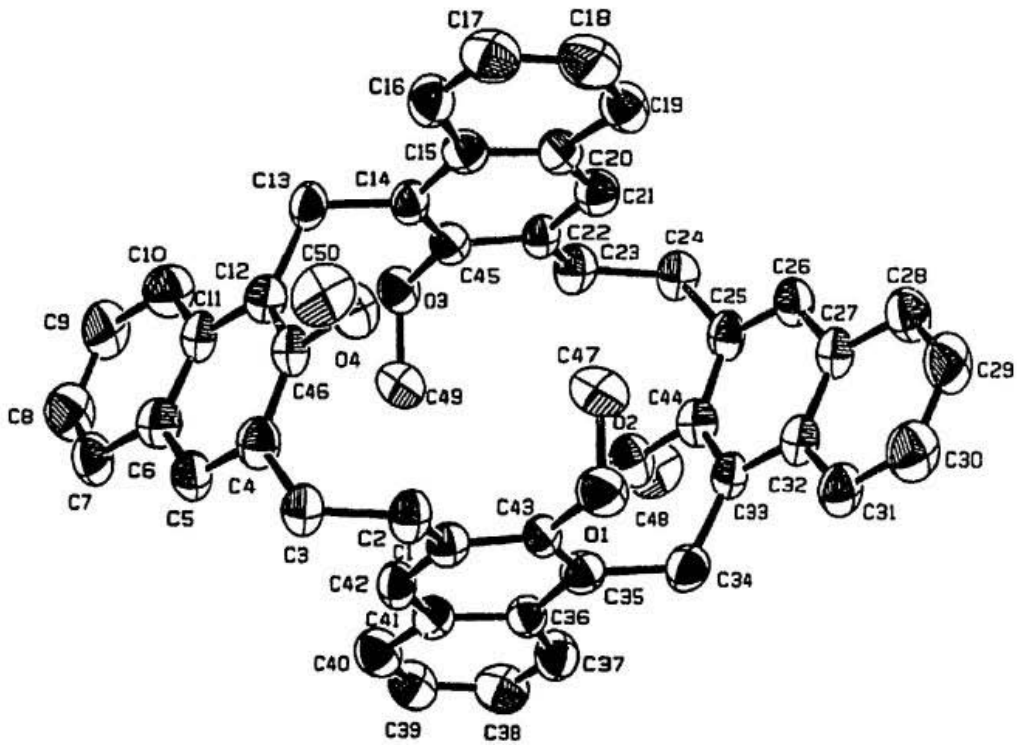


not split even at -55 °C. The methoxy signal at δ 3.29 ppm separates into three broad signals at δ 4.00, 3.38 and 2.85 ppm in a 1:1:2 ratio. The lower-field signals at δ 2.85 ppm suggest a conformer in which two methoxy groups are shielded by the two opposing naphthalene rings.

The ambient temperature ^{1}H 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 ^{1}H 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.

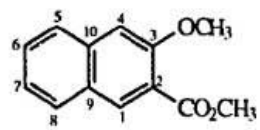
Self-condensation of 2-methoxy-3-hydroxymethylnaphthalene (**45**) under acidic conditions gave linear oligomers, but did not produce a calixnaphthalene-type product.

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.

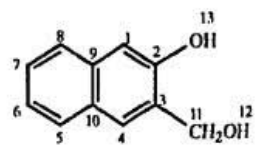
*Methyl 3-methoxy-2-naphthoate (**44**).*



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 potions of dichloromethane. The combined dichloromethane extracts were dried over $MgSO_4$ 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 $MgSO_4$ 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; ^{1}H NMR ($CDCl_3$): 3.96 (s, 3H, OCH_3), 4.00 (s, 3H, CO_2CH_3), 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); ^{13}C NMR ($CDCl_3$): 52.0 (OCH_3), 55.7 (CO_2CH_3), 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 (CO_2CH_3); MS (*m/z*), Intensity (%): 216 (M^+, 100), 185 (83), 183 (31), 155 (23), 142 (18), 128 (13), 27 (53), 115 (12), 114 (25).

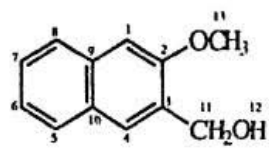
*2-Hydroxy-3-hydroxymethylnaphthalene (**36**).*



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 $MgSO_4$, 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,[86] mp 191-193 °C; ^{1}H NMR (CD_3COCD_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_3COCD_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/z*), Intensity (%): 174 (M^+, 33), 156 (43), 128 (100), 127 (15), 115 (11), 64 (13).

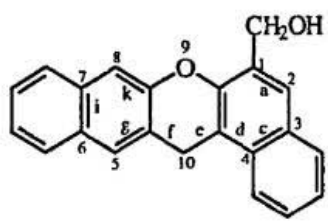
*2-Methoxy-3-hydroxymethylnaphalene (**45**).*



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 $MgSO_4$, 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 ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 55.4 (OCH_3), 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).

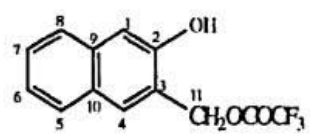
*1-Hydroxymethyl-dibenzo[c,j]-10H-9-oxaanthracene (**39**).*



To a solution of **36** (1.0 g, 5.75 mmol) in xylenes (60 mL) under N_2 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_2Cl_2): 4.58 (s, 2H, H-11), 5.04 (s, 2H, H-12), 7.41-7.96 (m, 11H, aromatic); ^{13}C NMR (CD_2Cl_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(x2) (aromatic); MS (*m/z*), Intensity (%): 312 (M^+, 100), 311 (M^+-1, 79), 294 (16), 282 (22), 281 (89), 265 (12).

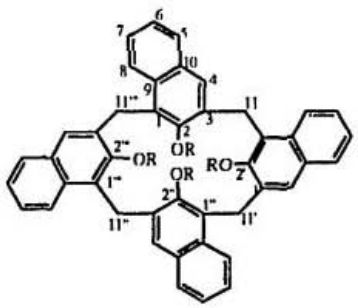
*2-Hydroxy-3-naphthylmethyl trifluoroacetate (**41a**)*



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).

Calix[4]naphthalene ***35***.



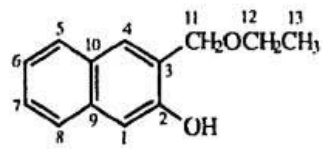
R=H

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 $MgSO_4$ 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 / peroleum 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 ($CDCl_3$): 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''), 10.95 (s, 4H, OH); ^{13}C NMR ($CDCl_3$): 25.7 (C-11), 119.7, 122.8, 123.5, 126.2, 128.7, 129.2, 129.8, 131.6, 147.9 (aromatic); MS (*m/z*), Intensity (%): 625 (M^++1,46), 624 (M^+, 100), 606 (17), 467 (10), 449 (12), 311(22), 265 (11), 252 (14), 169 (34), 157 (50).

*2-Hydroxy-3-naphthylmethyl ethyl ether (**41**).*



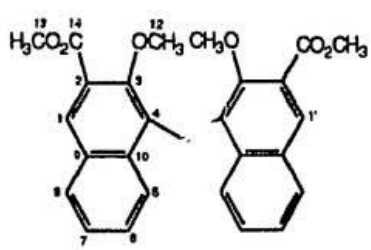
To a solution of **36** (100 mg, 0.53 mmol) in 95% ethanol (20 mL) was added concentrated hydrochloric acid (5 mL). The reaction mixture was stirred at room temperature for 10 h, during which no change was observed on checking by TLC. The reaction mixture was then heated to 70-75 °C and kept at that 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; ^{1}H NMR ($CDCl_3$):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 ^1H 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**).*

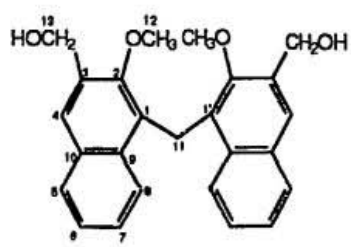


A solution of 3-hydroxy-2-naphthoic acid (**7a**) (2.0 g, 10.6 mmol) and paraformaldehyde (0.43 g, 14.2 mmol HCHO) in glacial acetic acid (20 mL) containing concentrated sulphuric acid (0.1 mL) was refluxed for 10 h. After cooling to room temperature, a light yellow precipitate formed, which was filtered 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 CH_2Cl_2 (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 CH_2Cl_2 (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 NH_4OH (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 $MgSO_4$, 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,[87a] mp 113-115 °C; ^{1}H NMR ($CDCl_3$): 3.81 (s, 6H, H-12, H-12'), 3.99 (s, 6H, H-13, H-13'), 5.01 (s, 2H, H-11, H-11'), 7.30-7.43 (m, 4H, H-6, H-6', H-7, H-7'), 7.76 (q, $J_{8,7}$=8.1, $J_{8,6}$=0.8, 2H, H-8, H-8'), 8.17 (q, $J_{5,6}$=8.1, $J_{5,7}$=0.8, 2H, H-5, H-5'), 8.26 (s, 2H, H-1, H-1'); NOED (%): * **H-5** / H-11 (3.65), **H-11** / H-5 (20.97), **H-8** / H-1 (14.81); ^{13}C NMR ($CDCl_3$): 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 $C_{27}H_{24}O_6$ 444.1573.

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

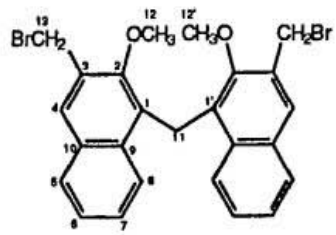


* The ^{1}H NMR signal of the protons indicated in **boldface** type was irradiated.

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% $NaHCO_3$ solution, followed by saturated NaCl (20 mL x2). After drying over anhydrous $MgSO_4$ 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 ($CDCl_3$): 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 ($CDCl_3$): 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

(M^+, 32), 352 (18), 339 (13), 337 (28), 325 (11), 323 (13), 321 (19), 309 (24) 265 (19), 252 (21), 42 (100); HRMS: M^+ 388.1667, calcd for $C_{25}H_{24}O_4$: 388.1673.

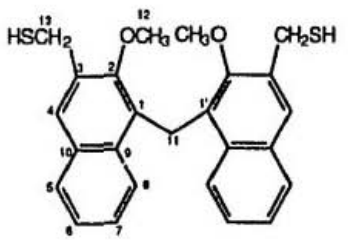
*Bis-(2-methoxy-3-bromomethyl-1-naphthyl)methane (**49**).*



To a solution of **48** (0.50 g, 1.3 mmol) in CH_2Cl_2 (30 mL) was added PBr_3 (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 $MgSO_4$ 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; ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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), 308 (18), 265 (61), 263 (63), 155 (100); HRMS: M^+ 511.9994, calcd for $C_{25}H_{22}O_2Br_2$: 511.9986.

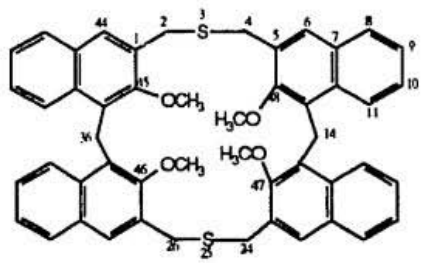
*Bis-(2-methoxy-3-mercaptomethyl-1-naphthyl)methane (**50**).*



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 N_2. 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; ^{1}H NMR ($CDCl_3$): 3.95 (s, 6H, H-12, H-12'), 3.96 (s, 4H, H-13, H-13'), 3.99 (s, 2H, SH, exchangeable with D_2O), 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)· ^{13}C NMR ($CDCl_3$): 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 $C_{25}H_{24}O_2S_2$ 420.1218.

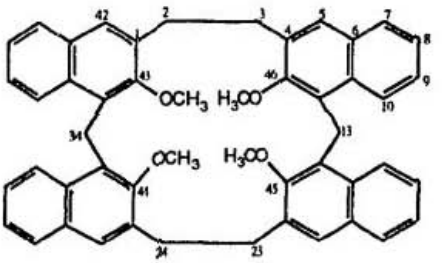
*45,46,47,48-Tetramethoxy-3,25-dithia[3.1.3.1]naphthalenophane (**51**).*



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 ar 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 $MgSO_4$. 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); ^{1}H NMR ($CDCl_3$): 3.29 (s, 12H, OCH_3), 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** / OCH_3 (1.18); ^{13}C NMR ($CDCl_3$): 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).

*Dihomocalix[4]naphthalene (**46**).*



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; ^{1}H NMR ($CDCl_3$): 2.91 (br, s, 12H, OCH_3), 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** / OCH_3 (2.35), **H-13** / H-10 (23.43), **CH_3O, H-3** / H-5 (2.64), **CH_3O, H-3** / H-13 (2.70); ^{13}C NMR ($CDCl_3$): 23.7 (t, C-13, C-34), 30.2 (t, C-2, C-3, C-23, C-24), 60.3 (q, OCH_3), 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-38), 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_{calc}= 1.267 g/cm^3, 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 $2\theta_{max}$(deg) = 50.2°; 3304 unique reflections converged to a final R = 0.042, for 2392 reflections with I>2.00σ(I); 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 $MgSO_4$ 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.

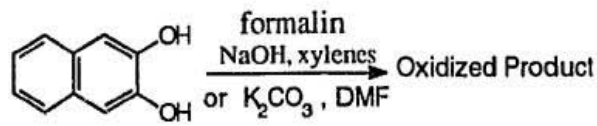
Dreiding molecular models suggest that the structure of a calix[4]-naphthalene derived from 2,3-dihydroxynaphthalene would be very rigid. This conformational rigidity is required for supramolecular applications. On the other hand, the same rigidity could also create difficulties in effecting the final 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 *homo*calixnaphthalenes were also selected as synthetic targets.

5.2. Synthesis of Calix[4]naphthalenes from 2,3-Dihydroxynaphthalene.

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

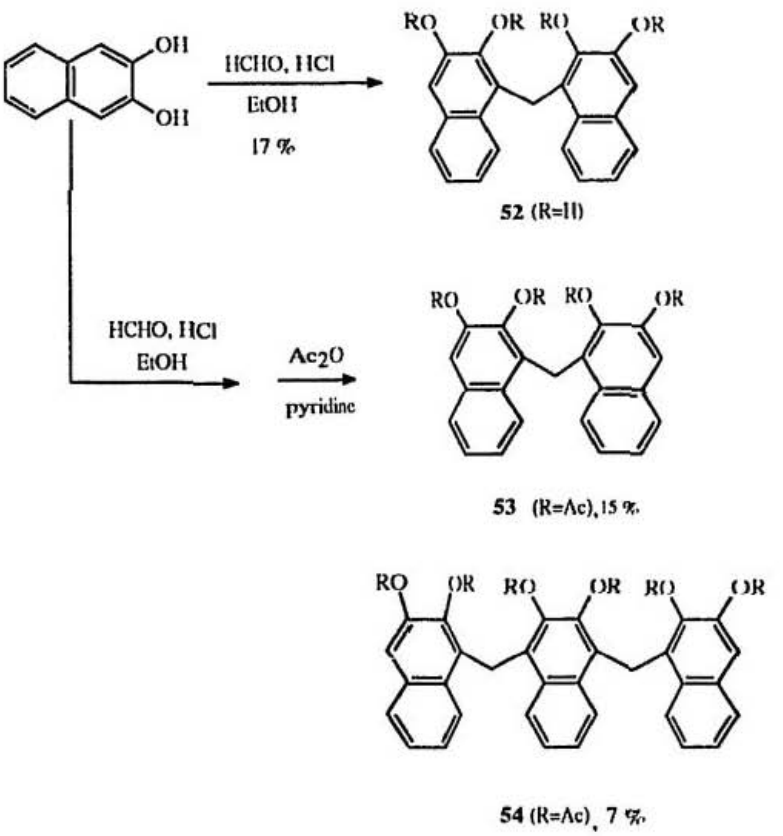
The condensation of 2,3-dihydroxynaphthalene with formaldehyde under basic conditions was studied first. A dark resinous product was obtained by using either Gutsche's procedure,[12] or the conditions which were employed for the synthesis of calix[4]naphthalenes from 1-naphthol as described in Chapter 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

Scheme 5.2.

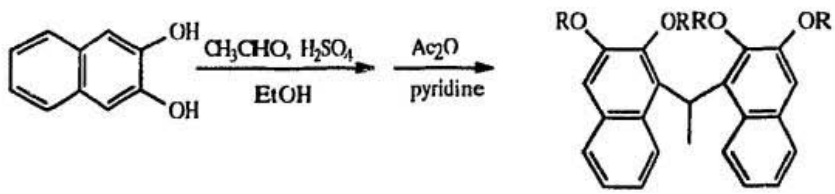


would be easier to separate the mixture of the corresponding acetates. Thus, the crude product was reacted with acetic anhydride and pyridine as a catalyst. Both dimer **53** and trimer **54** were isolated low yields (15% and 7% respectively). *No other products from the crude product were separated 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.



55 (R=Ac)

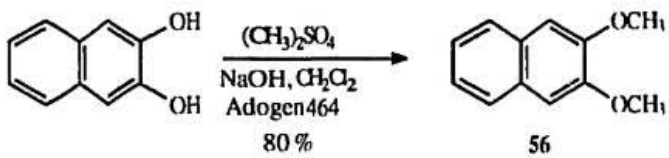
Two factors may have prevented product formation in good yield from the condensation of 2,3-dihydroxynaphthalene with aldehydes. One is the great reactivity of the dihydroxy compounds, which could lead to undefined longer linear oligomers or polymers, instead of smaller cyclic oligomers. Another factor 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®464 as a phase transfer catalyst (PTC) is required to effect efficient synthesis. Another method of protecting of the *ortho* dihydroxy groups

Scheme 5.4.



56

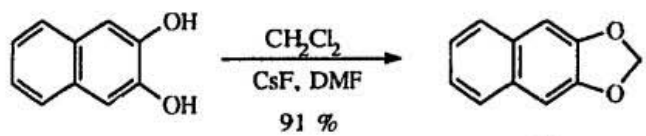
is methylenation with dichloro- or dibromomethane. Bashall and Collins [88] have shown that high yields of methylenated catechols may be obtained by using a phase transfer catalyst under refluxing conditions. This process required the use of strong base and the method of slow addition (three hours or more) of the reactants under a nitrogen atmosphere. Clark [89] reported a methylenation 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 methoxylation method is easily handled. However, subsequent deprotection requires relatively harsh conditions.[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 methylenation 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.



57

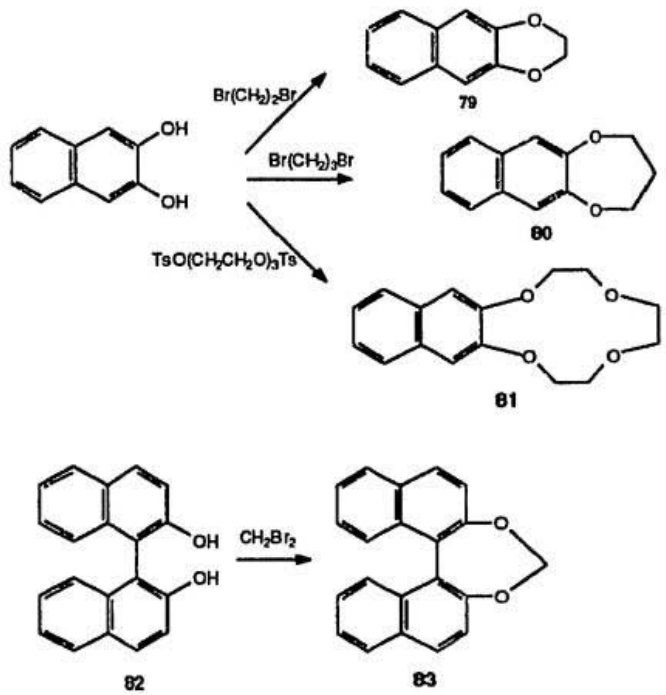
In order to reduce cost, expensive CsF was recycled by recrystallization twice from water (ca. 50%). The yield of product was not decreased when recycled CsF was used for methylenation of 2,3-dihydroxynaphthalene.

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

Cyclic ethers are classical supramolecular compounds. The synthesis of these compound suffered from low yield.[90a] The methodology for the methylenation 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 $FeCl_3$,[91] the corresponding seven-membered cyclic ether, **83**, is produced in 52% yield. Since bis-naphthol plays a very important role in asymmetric catalytic hydrogenation,[92] there is interest in any of its derivatives that could be used as chiral ligands with Lewis acids.

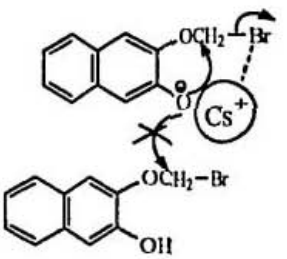
Scheme 5.6.



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".[93] 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.

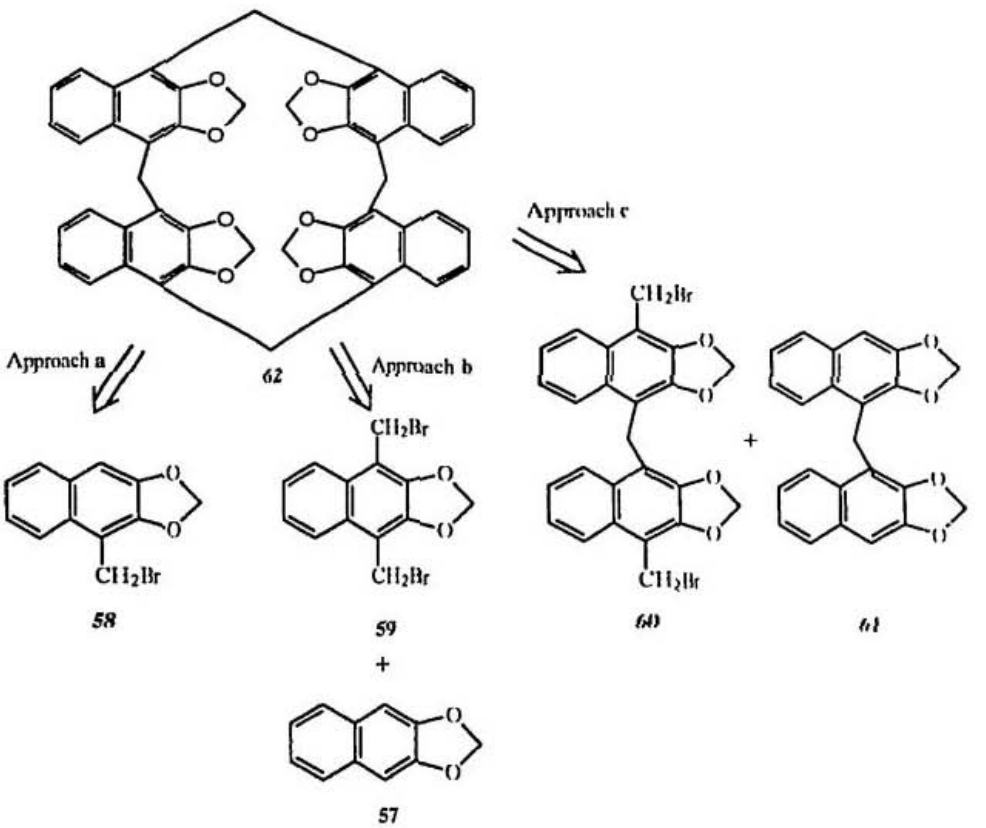
Fig.5.1. Template Effect of Cs^+ in Ether Formation.



5.2.4. Synthesis of Calix[4]naphthalene 62.

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

Scheme 5.7.

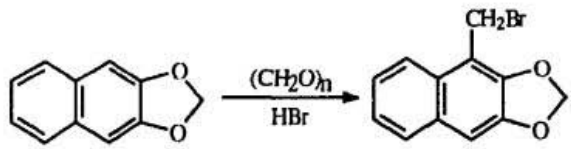


5.2.4.a. Self-Condensation of 1-Bromomethyl-2,3-Methylenedioxy-naphthalene (58).

In Approach "a", the corresponding chemical transformation is the self-condensation-cyclization of 1-bromomethyl-2,3-methylenedioxynaphthalene (**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%).

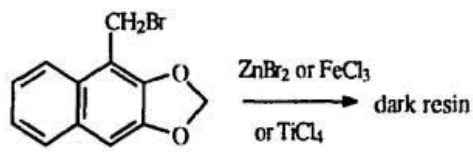
Scheme 5.8.



57 58

Self-condensation of **58** in the presence of $ZnBr_2$, $TiCl_4$, or $FeCl_3$, however, resulted in the formation of dark brown resins, which were insoluble in common organic solvents (Scheme 5.9).

Scheme 5.9.



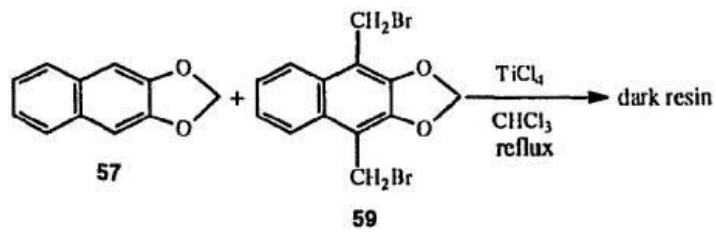
58

A variation of Approach "a" is the self-condensation-cyclization of 1-hydroxymethyl-2,3-methylenedioxynaphthalene (**64**), which was prepared by formylation of **57**, followed by $NaBH_4$ reduction (Scheme 5.10). Reaction of **57** with α,α-dichloromethyl methyl ether in the presence of $TiCl_4$ in dry

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 $TiCl_4$ 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.



57 59

5.2.4.c. Convergent Synthesis of Calixnaphthalene 62.

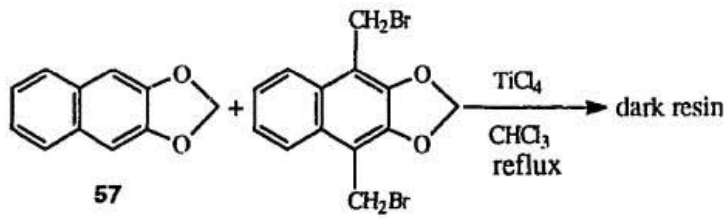
Synthesis of calix[4]naphthalene **62** using the convergent Approach "c" shown in Scheme 5.13 was attempted. The key step is the synthesis of dimer **61**, for which three different procedures were evaluated.

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 $TiCl_4$ 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.



57 **59**

5.2.4.c. Convergent Synthesis of Calixnaphthalene 62.

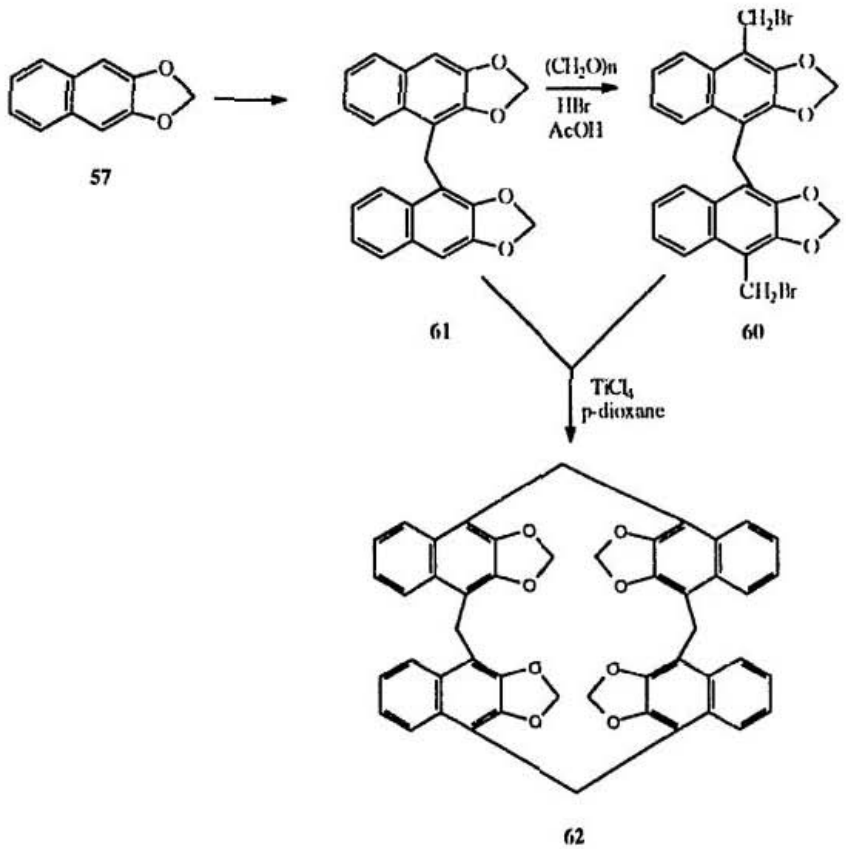
Synthesis of calix[4]naphthalene **62** using the convergent Approach "c" shown in Scheme 5.13 was attempted. The key step is the synthesis of dimer **61**, for which three different procedures were evaluated.

In the first route shown in Scheme 5.14, compound **57** was reacted with

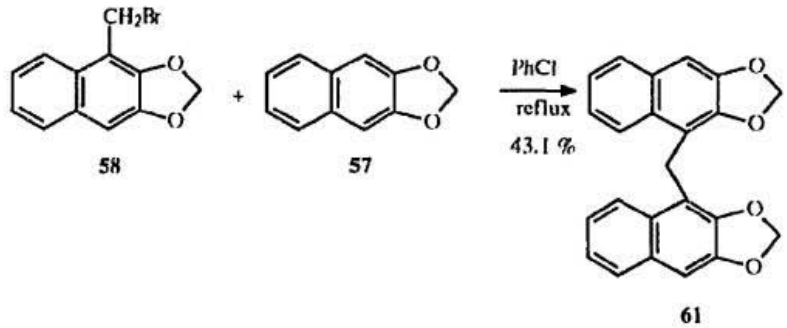
58 under thermal conditions to give dimer **61** in 54% yield.

In the second route to the synthesis of dimer **61**, compound **57** was treated with formaldehyde in 3% sulphuric acid / glacial acetic acid to give both dimer **61** in 35% yield and trimer **65** 18% yield (Scheme 5.15).

Scheme 5.13.

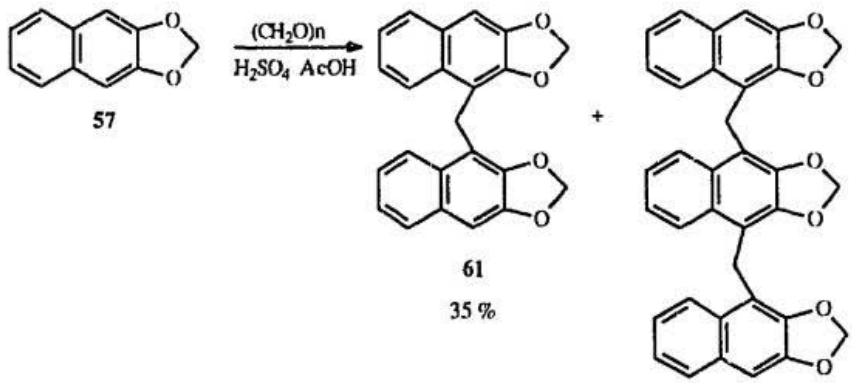


Scheme 5.14.



58 57 61

Scheme 5.15.

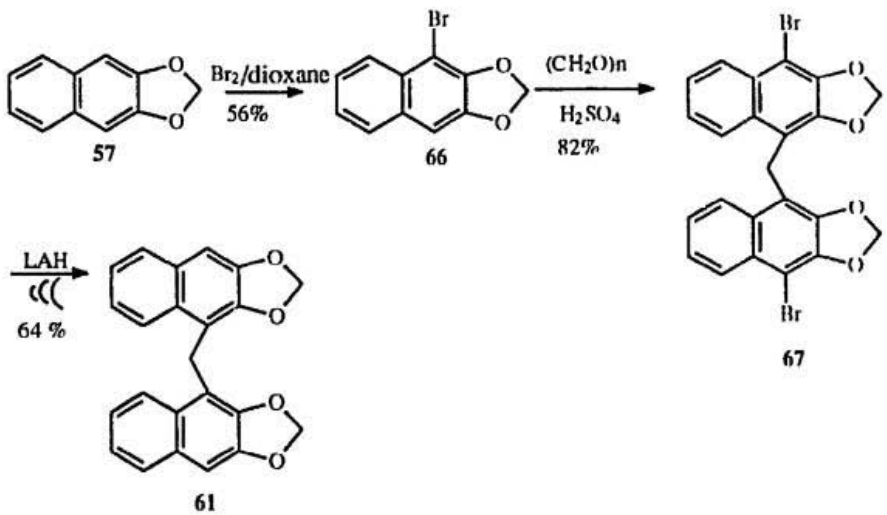


57 61 35 % 65 18 %

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 para-formaldehyde in the presence of HBr in glacial acetic acid (Scheme 5.13). The coupling reaction of **60** with **61** in *p*-dioxane using $TiCl_4$ 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 δ 4.19 ppm, which indicates that it is conformationally rigid, even at room temperature. The signal due to the methylenedioxy groups appears at δ 5.36 ppm, due to strong shielding by the naphthalene rings. The ^{1}H NMR spectrum reveals two multiplets centred at δ 3.66 and 3.98 ppm, most likely due to *p*-dioxane, the reaction solvent. Since "free" *p*-dioxane demonstrates a singlet at δ 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.

5.3. Synthesis of Dihomocalix[4]naphthalenes.

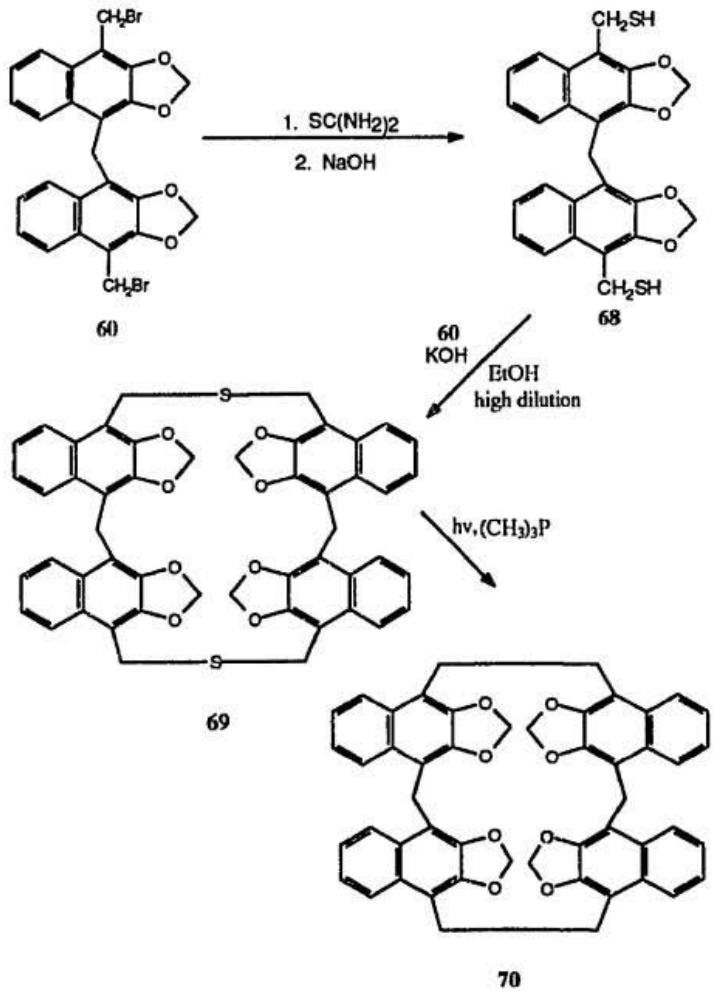
Since dihomocalix[4]naphthalenes from 3-hydroxy-2-naphthoic acid (**36**), were successfully synthesized by using the dithia intermediated approach, similar methodology was employed to synthesize dihomocalixnaphthalene **70** from 2,3-dihydroxynaphthalene. Scheme 5.16 outlines the approach used to synthesize **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-methylenedioxy-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 methylenedioxyl groups as four singlets at δ 5.99, 6.05, 6.09, and 6.17 ppm. The two methylene bridges appear as four doublets centred at δ 3.02, 3.30, 3.36 and 3.39 ppm. The ethylene bridges appear as eight sets of multiplets centred at δ 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

Scheme 5.17.

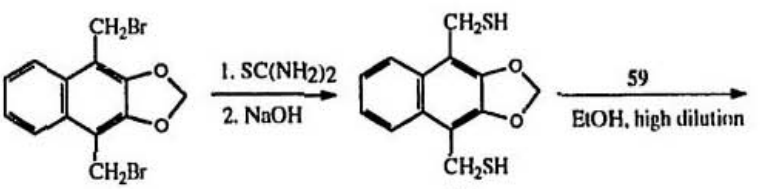


conformation of dihomocalix[4]naphthalene **70** is a "partial cone".

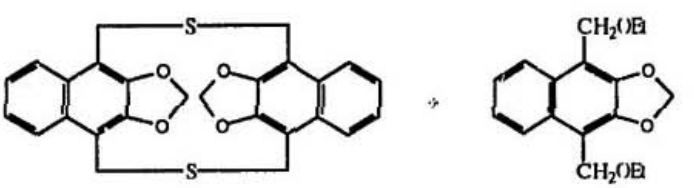
A similar procedure using 1,4-*bis*-bromomethyl compound **59** led to a dithiacyclonaphthalenophane **71**, in 31% yield. Under high dilution conditions, compound **59** also reacted with the solvent (ethanol) to give a diethyl ether **72** in 37% yield.

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 methylendioxy 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.[85]

Scheme 5.18.



59 73

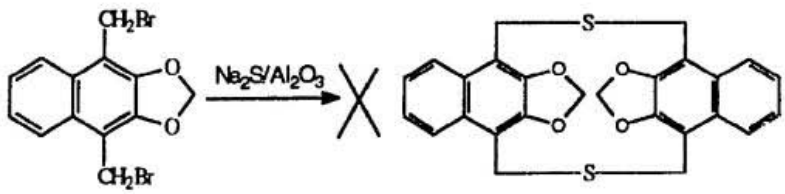


71 72

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[94] (Scheme 5.18a). However, when compound **59** was reacted under heterogenous conditions with sodium sulphide dispersed onto silica, a ploymer was formed rather than cyclonaphthaleneophane **71**.

Scheme 5.18a.



59 **71**

5.4. Dilithiation of 2,3-Dimethoxynaphthalene.

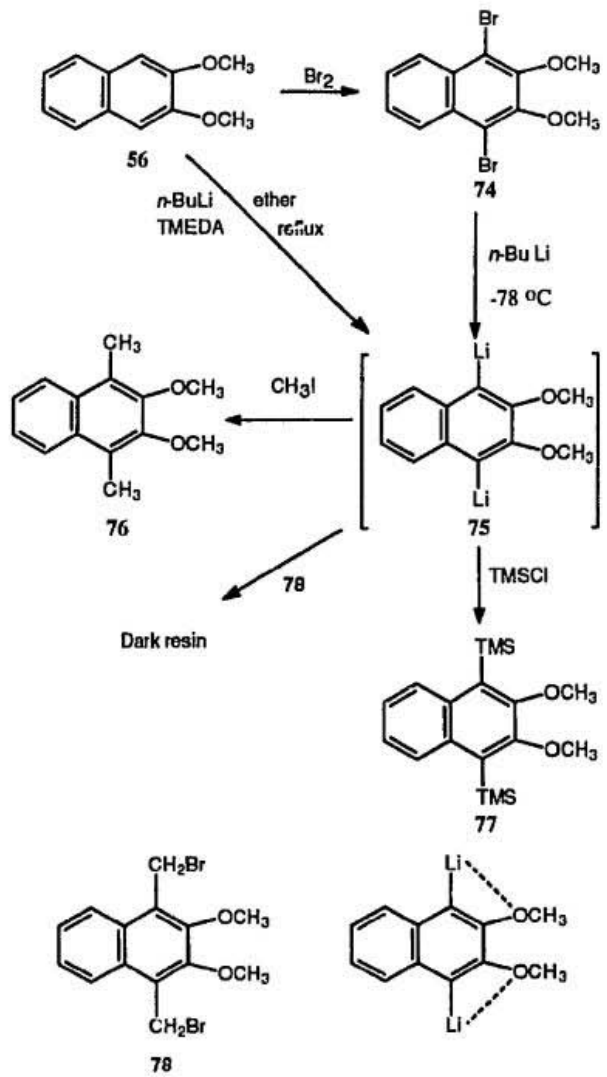
Regioselectivity is a major problem in conventional electrophilic substitution reactions of aromatic compounds. Snieckus[95] has developed a "directed ortho metallation" (DoM) process to enhance the regioselectivity of the electrophilic substitution of aromatic compounds. In DoM reactions, the substrates 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[96] reported that the carbanion of 1-methoxynaphthalene can be selectively generated at C-2 or C-8 by choosing different lithium reagents. Sundberg[97] 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 [98] reported a coupling reaction of phenylmagnesium bromide with allyl bromide. McMurry [99] and Shih [100] 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*-(trimethylsily)-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.


OCH3
OCH3
Br2
Br
OCH3
OCH3
Br
56
74
n-BuLi
TMEDA
ether
reflux
n-Bu Li
-78 °C
CH3
OCH3
OCH3
CH3
CH3I
Li
OCH3
OCH3
Li
76
75
78
TMSCl
Dark resin
TMS
OCH3
OCH3
TMS
77
CH2Br
OCH3
OCH3
CH2Br
78
Li
OCH3
OCH3
Li

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.[101] 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-methylenedioxynaphthalene (**76**) was obtained in 72% yield.

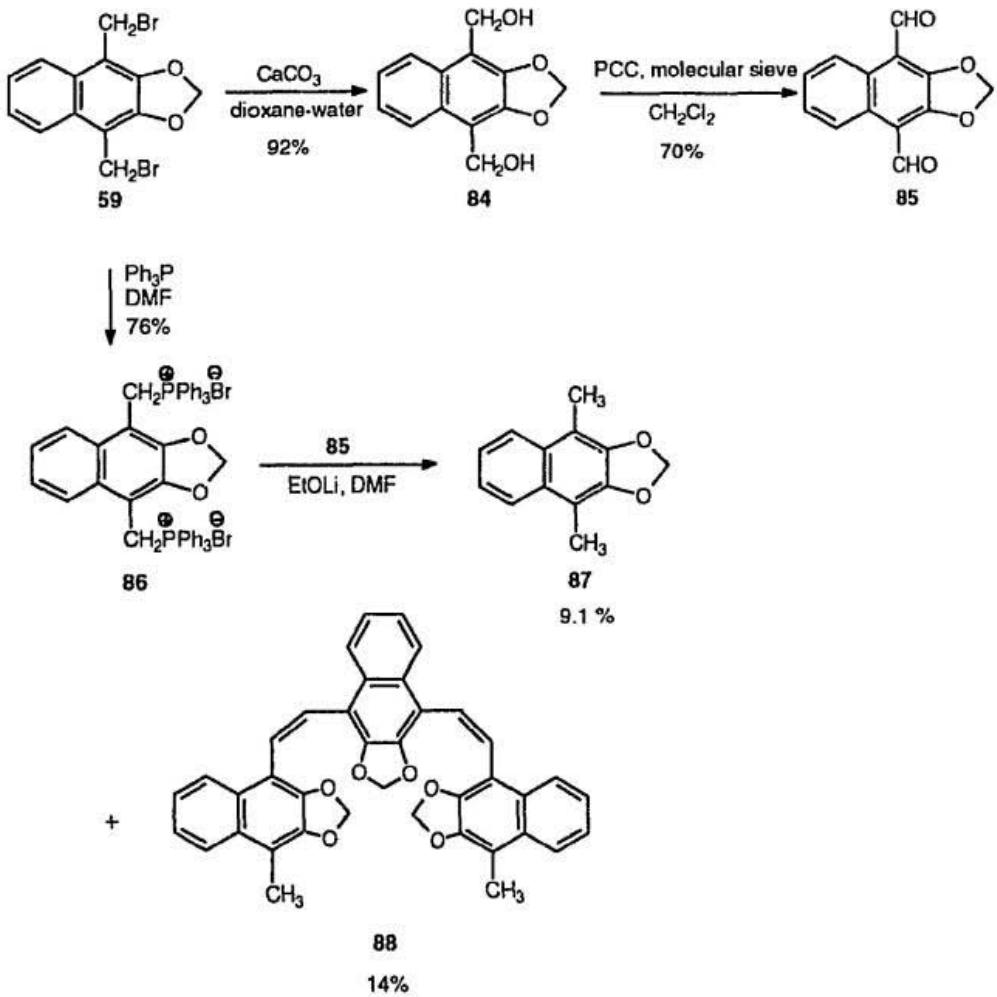
The coupling reaction of 1,4-*bis*-bromomethyl-2,3-dimethoxynaphthalene (**78**) with 1,4-dilithia-2,3-methoxynaphthalene (**75**) was carried out in the same flask used for the lithiation reaction, by adding **78** to **75**. However, only brown resins which were insoluble in common organic solvents 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 allhomocalixnaphthalenes.

Högberg [22] 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 allhomocalixnaphthalene via a Wittig procedure.

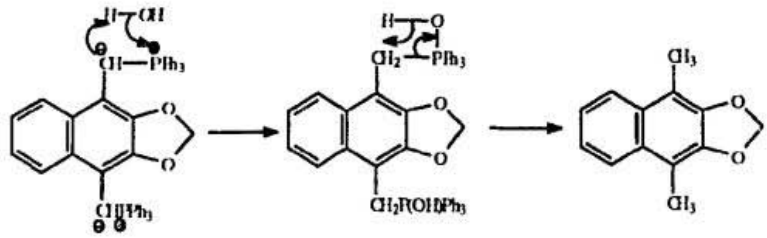
Since it was not possible to introduce formyl groups in the 1-, and 4-positions of **57** by Lewis acid-catalysed reactions, 1,4-*bis*-(bromomethyl)-2,3-methylenedioxynaphthalene (**59**) was instead considered as a starting material. Compound **59** was converted to the corresponding hydroxymethyl compound **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-methylenedioxynaphthalene (**87**) and the latter as the linear trimer **88** with *cis* double bonds *J*=6 *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.

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 $TiCl_4$-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-methylenedioxynaphthalene (**73**) with 1,4-*bis*-(bromomethyl)-2,3-methylenedioxynaphthalene (**59**) gave a cyclic dimer (**71**).

The Wittig reaction of 1,4-diformyl-2,3-methylenedioxynaphthalene (**85**)

with 1,4-*bis*-(bromomethy)-2,3-methylenedioxynaphthalene (**59**) gave linear oligomers. The anticipated *all*homocalixnaphthalene 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.

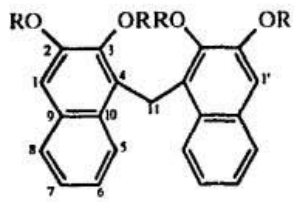
For General experimental conditions and instrumentation employed, see Chapter 2.

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.

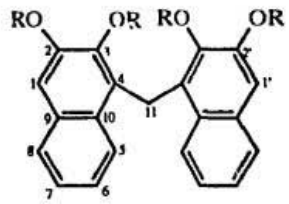


52
R=H

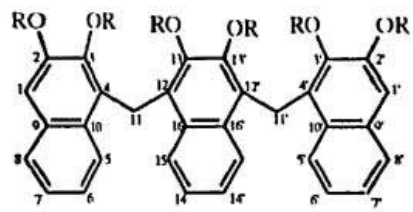
To a solution of 2,3-dihydroxynaphthalene (1.60 g, 10 mmol) in a mixture of 95% ethanol (4 mL) and water (4 mL) were added formalin (37% formaldehyde, 0.70 mL, 8.6 mmol) and concentrated hydrochloric acid (1 mL) under N_2. The milky emulsion was stirred at room temperature for 40 h, and then the reaction 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 (CD_3COCD_3): 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'); ^{13}C NMR (CD_3COCD_3): 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

(100).

Acetylation of crude condensation product from the reaction of 2,3-dihydroxynaphthalene with formaldehyde.



53
R=Ac

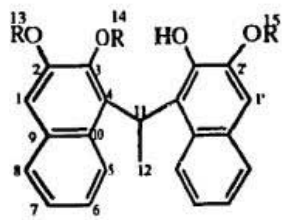


54
R=Ac

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, CH_3COO), 1665 (w), 1550 (m), 1445 (s), 1440 (s); ^1H NMR ($CDCl_3$): 1.89, 2.26 (sx2, $COCH_3$), 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'); ^{13}C NMR ($CDCl_3$): 19.9, 20.8 ($COCH_3$), 24.6 (C-11), 120.0, 124.0, 126.2,

126.6, 128.6 (C-1, C-5-C-8, C-1', C-5'-C-8'); MS (*m/z*), Intensity (%): 500 (M', 15), 458 (19), 416 (22), 398 (34), 374 (14), 356 (20), 313 (30), 215 (12), 160 (94), 43 (100). Trimer **54**: mp 235-240 °C; IR (KBr, cm^{-1}): 1794, (s, carbonyl), 1642 (m), 1550 (w), 1500 (s), 1445 (s); ^1H NMR ($CDCl_3$): 1.91, 1.94, 2.28 (sx3, 18H, $-COCH_3$), 4.69 (s, 4H, H-11, H-11'), 7.33-7.36 (m, 2H, H-14, H-14'), 7.42-7.47 (m, 4H, H-6, H-7, H-6', H-7'), 7.61 (s, 2H, H-1, H-1'), 7.76-7.80 (m, 2H, H-15, H-15'), 8.00-8.06 (m, 4H, H-5, H-8, H-5', H-8'); ^{13}C NMR ($CDCl_3$): 20.0, 20.8 (x2) ($-COCH_3$), 120.0, 124.1, 124.9, 126.1, 126.6, 128.5 (d, C-1, C-5-C-8, C-14, C-15), 124.0, 127.8, 128.9, 130.0, 131.0, 131.7, 139.8, 140.7(s, C-2, C-3, C-4, C-9, C-10, C-12, C-13, C-16), 168.0, 168.2, 168.4 ($-COCH_3$); MS (*m/z*), Intensity (%): 654 (M'-AcOH, 7), 313 (10), 202 (11), 173 (18), 160 (32), 43 (100).

Condensation of 2,3-dihydroxynaphthalene with acetaldehyde and acetylation of the crude condensation product.



55
R=Ac

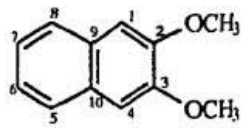
2, 3-Dihydroxynaphthalene (1.60 g, 10 mmol) was dissolved in aqueous 10% sulphuric acid (25 mL), and heated to 95-100 °C. A mixture of aqueous

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'); ^{13}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_3COO); MS (*m/z*), Intensity (%): 472 (M^+, 1), 456 (20), 415

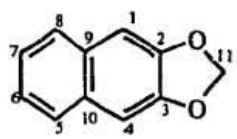
(8), 414 (31), 398 (7.6), 397 (8), 396 (6), 372 (37), 355 (19), 328 (12), 313 (100), 284 (11), 239 (10), 213 (22), 197 (27), 186 (58).

2,3-Dimethoxynaphthalene ***(56)***.



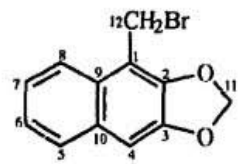
To a solution of 2,3-dihydroxynaphthalene (8.0 g, 50 mmol) in aqueous 7% NaOH (60 mL, 175 mmol) was added dimethyl sulphate (9.4 mL) over 1 h. The solution was stirred at 70-80 °C for 4 h. After the crude reaction mixture was cooled to room temperature, a pale brown precipitate formed. The precipitate 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; ^{1}H NMR ($CDCl_3$): 4.00 (s, 6H, OCH_3), 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.[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^{-1}): 1515 (m), 1464 (s), 1450 (m), 1216 (-OCH_2O-); ^1H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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^++1, 11), 172 (M^+, 100), 115 (12), 114 (35), 87 (5), 86 (18);

*1-Bromomethyl-2,3-methylenedioxynaphthalene (**58**).*



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).

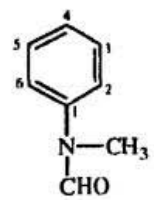
Method B. Into a solution of **57** (2.0 g, 11.6 mmol) and paraformaldehyde (350 mg, 11.7 mmol) in glacial acetic acid (50 mL) HBr gas was bubbled for 20 min. The reaction mixture was stirred at room temperature for 15 h, and was then poured onto crushed ice (70 g). The white precipitate was filtered, 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

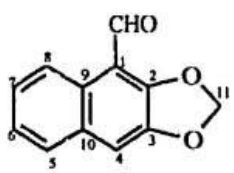
precipitate was obtained after workup, which was insoluble in common organic solvents and was not further characterized.

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



This compound was prepared accordi.. , 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); ^1H 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-methylenedioxynaphthalene (**63**).*



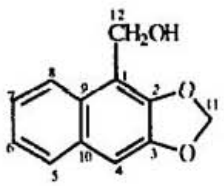
Via a Vilsmeier reaction procedure. To a solution of **57** (200 mg, 1.16 mmol) and **88a** (0.25 mL, 1.18 mmol) cooled to 0 °C was added phosphorus

oxychloride ($POCl_3$, 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 ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $TiCl_4$ (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 $MgSO_4$ 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-methylenedioxynaphthalene (**64**).*

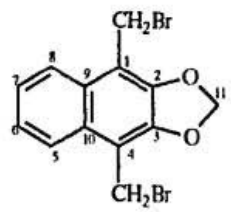


To a solution of **63** (260 mg, 1.3 mmol) in methanol (30 mL) was added $NaBH_4$ in small portions at such a rate that the reaction flask was not hot. The reaction mixture was stirred at room temperature for 23 h and the methanol was evaporated under vacuum. The residue was extracted with ether (30 mL) and the organic layer was washed with two 10 mL-portions of water. After drying over $MgSO_4$ 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 ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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/z*), 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 $CHCl_3$ (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**).*



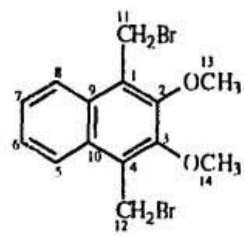
To a solution of **57** (0.34 g, 2.0 mmol) and paraformaldehyde (130 mg, 4.3 mmol) in glacial acetic acid (10 mL) was added dropwise 21% HBr in glacial acetic acid (8 mL). The reaction mixture was heated to 60-70 °C over 30 min and kept at that temperature for an additional 2 h. After cooling to room temperature, the reaction mixture was poured cnto 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, $-OCH_2O-$); ^1H NMR ($CDCl_3$): 4.87 (s, 4H, CH_2Br), 6.18 (s, 2H, $-OCH_2O-$), 7.53 (m, 2H, H-6, H-7), 7.96 (m, 2H, H-5, H-8); ^{13}C NMR ($CDCl_3$): 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 (8.2), 279 (56), 278 (8.3), 277 (59), 199 (18), 198 (100), 185 (14), 169 (7.7), 142 (8.5), 141 (26), 139 (30), 115 (9.5).

*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 $TiCl_4$ (2.0 mL, 10 mmol). A dark brown solution was produced. The reaction mixture was refluxed for 1 week. After evaporating the solvent under vacuum, a dark brown residue which was insoluble in organic solvents was obtained, and was not further characterized.

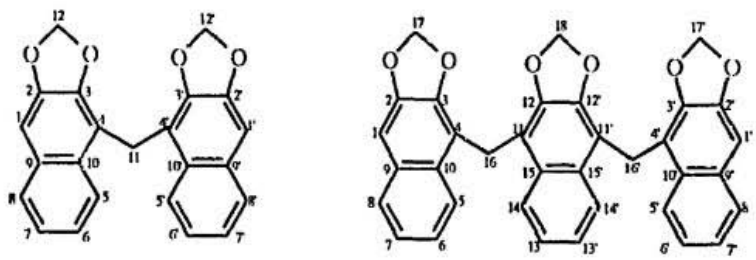
*1,4-Bis-bromomethyl-2,3-dimethoxynaphthalene (**78**).*



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; ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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-methylenedioxynaphthalene **65**.*

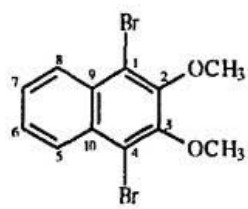


Method A. To a solution of **57** (3.38 g, 19.6 mmol) and paraformaldehyde (295 mg, 9.8 mmol) in glacial acetic acid (160 mL) was carefully added concentrated sulphuric acid (3.4 mL). The reaction mixture was stirred at room temperature for 54 h. The reaction mixture was poured onto crushed ice (150 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; ^{1}H NMR ($CDCl_3$): 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 (mx2, 4H, H-5, H-8, H-5', H-8'); ^{13}C NMR ($CDCl_3$): 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 $C_{23}H_{16}O_4$: 356.1048. Trimer **58**: mp 263-265 °C; ^{1}H NMR ($CDCl_3$): 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'); ^{13}C NMR ($CDCl_3$): 23.1 (C-16, C-16'), 100.4 (C-18), 100.6 (C-17, C-17'), 102.9 (C-1, C-1'), 123.4, 123.7, 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).



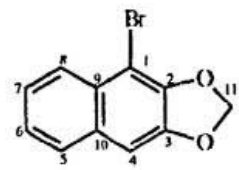
74

74a

These two compounds were prepared according to a literature procedure.[101] Compound **74** (81%) and 1,4,6-tribromo-2,3-methylenedioxynaphthalene (**74a**)(11%) were obtained as colourless fine crystals. Dibromo compound **74**: lit. mp 76-78 °C, mp 180-181 °C; ^{1}H NMR ($CDCl_3$): 4.01 (s, 6H, -OCH_3), 7.57 (m, 2H, H-6, H-7), 8.24 (m, 2H, H-5, H-8); ^{13}C NMR ($CDCl_3$): 61.1 (OCH_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 ($CDCl_3$): 4.06 (s, 6H, OCH_3), 7.46 (m, 3H, H-5, H-7, H-8), ^{13}C NMR ($CDCl_3$): 56.1 (OCH_3), 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).

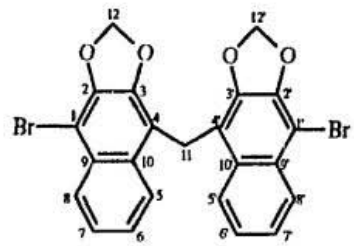
*1-Bromo-2,3-methylenedioxynaphthalene (**66**).*



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 $MgSO_4$, and filtered, the solvent was evaporated. The crude product was crystallized twice from aqueous ethanol. Compound **66** was obtained as colourless needles (813 mg, 56%): mp 84-85 °C; ^{1}H NMR ($CDCl_3$): 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

($CDCl_3$): 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**).*



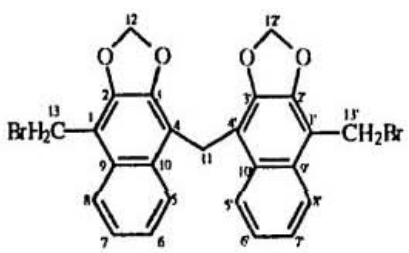
To a solution of **66** (594 mg, 2.38 mmol) and paraformaldehyde (85.8 mg, 2.86 mmol) in glacial acetic acid (20 mL) was slowly added concentrated sulphuric acid (0.4 mL). The reaction mixture was heated to 60-70°C and kept at that temperature for 3.5 h. After cooling to room temperature, the reaction 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 ($CDCl_3$): 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'); ^{13}C NMR ($CDCl_3$): 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'),

112.7, 123.9, 124.7,125.8, 129.0, 130.3 (C-1-C-4, C-9, C-10, C1'-C-4', C-9', C-10'); MS (*m/z*), Intensity (%): 516 (M^+, 34), 515 (18), 512 (35), 266 (15), 264 (13), 263 (100).

*Bis-(2,3-methylenedioxy-1-naphthyl)methane (**61**) via debromination of **67**.*

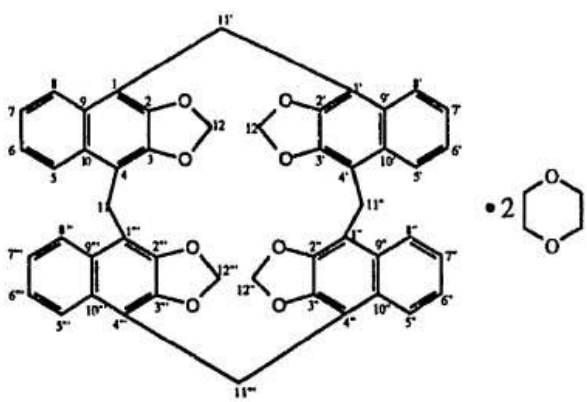
A flask fitted with a condenser and containing a suspension of LAH (300 mg, 7.89 mmol) in dry THF (15 mL) under N_2 was set up in a sonicator. A solution of **67** (917 mg, 1.79 mmol) in THF (15 mL) was added over 20 min. The reaction mixture was sonicated for 20 h at 35-40°C. The reaction was quenched 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 $MgSO_4$, 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 $MgSO_4$ 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; ^{1}H NMR (DMSO-d_6 / $CDCl_3$): 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'); ^{13}C NMR (DMSO-d_6 / $CDCl_3$): 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 $C_{25}H_{16}O_4Br_2$: 539.9684.

Calix[4]naphthalene ***62***.



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 $TiCl_4$ (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$_e$(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_2O, 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),

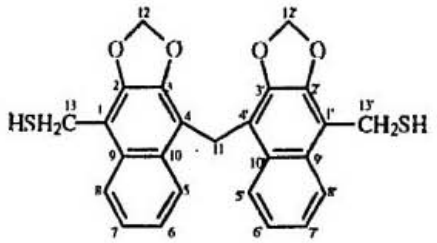
---

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

** The integration is not accurate.

290 (1.0), 283 (7.3), 273 (1.1).

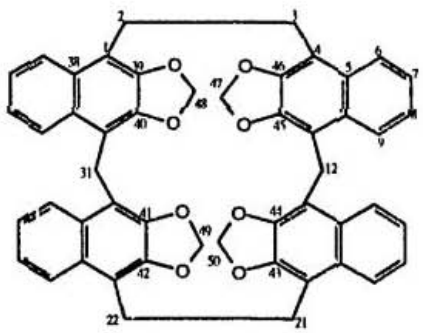
*Bis-(1-mercaptomethyl-2,3-methylenedioxy-4-naphthyl)methane (**68**).*



To a solution of **60** (798 mg, 1.48 mmol) in THF (50 mL) was added thiourea (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 N_2 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; ^{1}H NMR ($CDCl_3$): 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'); ^{13}C NMR

($CDCl_3$): 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).

Dihomocalix[4]naphthalene ***70.***



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 Erlenrmeyer 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 $MgSO_4$,

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.

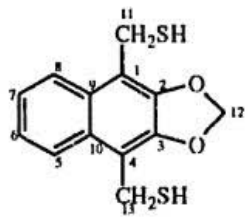
The cyclic sulphur-bridged tetramer (100 mg) was suspended in trimethyl phosphite (5 mL). The suspension was irradiated with an ultraviolet lamp (RPR 3500 Å) for 69 h (for detailed conditions see Chapter 4). After the solvent was removed by vacuum distillation, the residue was purified by PLC using 40% ethyl acetate / hexanes as eluents. *Di*homocalixnaphthalene **70** was obtained as colourless fine crystals (22 mg, 11% from **60**, and **68**): mp 295-300 °C; ^{1}H NMR ($CDCl_3$): 1.25 (m, 2H, H-2_a,*** H-21_a), 1.64 (m, 1H, H-3_a), 2.32 (m, 1H, H-3_e**), 3.00 (d, 1H, H-12_a) , 3.29 (d, 1H, H-12_e), 3.39 (d, 1H, H-31_a), 3.60 (m, 1H, H-2_e), 4.11 (m, 1H, H-21_e), 4.18 (m, 1H, H-22_a), 4.22 (d, 1H, H-31_e), 4.60 (m, 1H, H-22_e), 6.00, 6.07, 6.09, 6.17 (sx4, 8H, H-47-H-50), 7.18-8.01 (not resolved, 16H, aromatic); ^{13}C NMR ($CDCl_3$): 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).

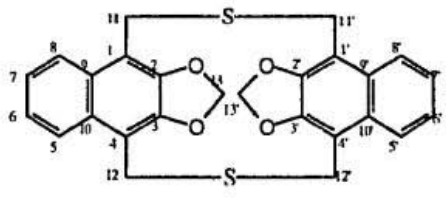
*1,4-Bis-mercaptomethyl-2,3-methylenedioxynaphthalene (**73**).*



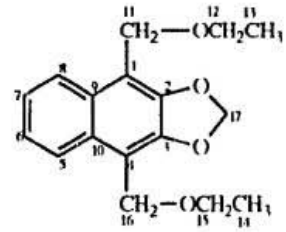
To a solution of **59** (500 mg, 1.40 mmol) in THF (50 mL) was added thiourea (234 mg, 3.07 mmol). The reaction mixture was refluxed for 10 h. After cooling to room temperature, the solvent was evaporated and the residue was dissolved in water (50 mL) containing aqueous 10% NaOH (5 mL). The reaction mixture was refluxed under N_2 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 (50x3 mL). The combined dichloromethane extracts were dried over $MgSO_4$, 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); ^1H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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**).*



71



72

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 Erlenrmeyer flask containing 95% ethanol (250 mL) and KOH (182 mg, 3.3 mmol) in water (3 mL) under N_2. 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 $MgSO_4$ 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-methylenedioxynaphthalene (**72**) (65 mg, 37%) was also obtained as colourless fine crystals. Compound **71**: mp 280 °C (with decomposition); ^{1}H NMR ($CDCl_3$): 3.88 (d, J=15, 4H, H-11_a, H-12_a, H-$11'_a$, H-$12'_a$), 4.63 (d, 4H, J=15, H-11_e, H-12_e, H-$11'_e$, H-$12'_e$), 5.67 (s, 2H, H-13_a, H-$13'_a$), 6.19 (s, 2H, H-13_e, H-$13'_e$), 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-13_e**, **H-$13'_e$** / H-13_a, H-$13'_a$ (33), **H-13_e**, **H-$13'_e$** / H-13_a, H-$13'_a$ (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_a, H-12_a, H-$11'_a$, H-$12'_a$ (6.9); ^{13}C NMR ($CDCl_3$): 27.7 (C-11, 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; ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 15.2 (C-13, C-14), 63.1 (C-12, C-15), 65.5 (C-11, 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).

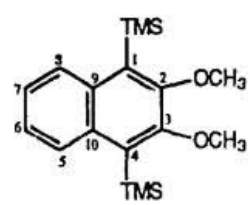
*Attempted synthesis of Dihomocalixnaphthalene **70** via a supported Na_2S*

procedure.

To a solution of $Na_2S.\ 9H_2O$ (1.60 g, 10.9 mmol) in water (10 mL) was added basic Al_2O_3 (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 $MgSO_4$ 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**).*

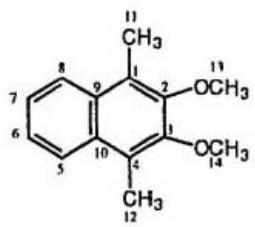


Method A. To a solution of **56** (376 mg, 2 mmol) in dry diethyl ether (10 mL) under argon added dropwise TMEDA (1.6 mL, 10 mmol) and *n*-butyllithium (2.0 *M* in hexane, 5.0 mL, 10 mmol). This reaction mixture was stirred for 1 h at room temperature, and then heated to refluxing and kept refluxing 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 NH_4Cl (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 $MgSO_4$ 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 79-82 °C; ^{1}H NMR ($CDCl_3$): 0.52 (s, 18H, -$SiMe_3$), 3.83 (s, 6H, OCH_3), 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 NH_4Cl (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 $MgSO_4$ 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 NH_4Cl (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 $MgSO_4$ 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: ^{1}H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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**).*

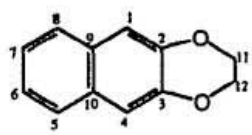
To a solution of **74** (346 mg, 1.0 mmol) in dry diethyl ether (10 mL) cooled to -78 °C was added under Ar dropwise *n*-butyllithium (2.0 M in hexane, 2 mL). The reaction mixture was stirred for 3 h at -78 °C. *Bis*-bromomethyl compound **78** (372 mg, 1.0 mmol) was added, and the reaction mixture was 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 NH_4Cl 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:

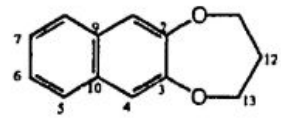
Into a three-necked 500 mL flask fitted with a condenser and calcium

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 $MgSO_4$, 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**.



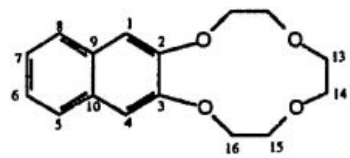
79

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, $-OCH_2-$); ^1H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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 $C_{12}H_{10}O_2$:186.0680.



80

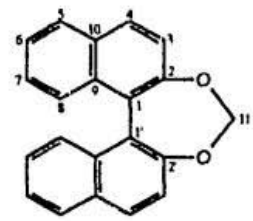
Cyclic ether **80** was obtained in 49% yield: mp 122-124 °C; IR (KBr, cm^{-1}): 1600 (m), 1502 (s), 1497 (s), 1495 (s), 1445 (s), 1400 (s), 1292 (s, $-OCH_2-$); ^1H NMR ($CDCl_3$): 2.25 (m, 2H, H-12), 4.28 (t, J=5.7, 4H, H-11, H-13), 7.35 (m, 2H, H-6, H-7), 7.41 (s, 2H, H-1, H-4), 7.69 (m, 2H, H-5, H-8); ^{13}C NMR ($CDCl_3$): 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^+ 200.0825, calcd for $C_{13}H_{12}O_2$: 200.0837.



81

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, $-OCH_2-$); ^1H NMR ($CDCl_3$): 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); ^{13}C NMR ($CDCl_3$): 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

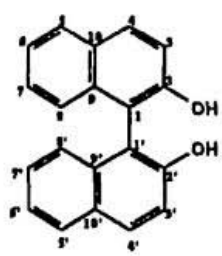
$C_{16}H_{16}O_4$: 274.1204.



83

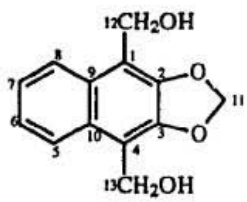
Cyclic ether **83** was obtained in 52% yield: mp 178-179 °C; IR (nujol, cm^{-1}): 1204 (s), 1225 (s, $-OCH_2O-$); ^1H NMR ($CDCl_3$): 5.67 (s, 2H, H-11), 7.26 (m, 2H, H-7, H-7'), 7.40 (m, 2H, H-6, H-6'), 7.45 (d, J=8.7, 2H, H-3, H-3'), 7.51 (d, 2H, H-4, H-4'), 7.90 (d, J=8.1, 2H, H-8, H-8'), 7.94 (d, J=8.7, 2H, H-5, H-5'); ^{13}C NMR ($CDCl_3$): 103.1 (C-11), 120.9, 124.9, 126.0, 126.8, 128.3, 130.3 (C-3-C-8, C-3'-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 $C_{21}H_{14}O$: 298.0993.

*(±)-1,1'-Bis-2-naphthol (**82**).*



1,1'-*Bis*-2-naphthol was prepared according to a literature procedure [85a] in 61.3% yield as almost colourless crystals: lit. mp 218 °C, mp 216-217 °C; ^{1}H NMR ($CDCl_3$): 5.05 (s, 2H, exchangeable with D_2O, 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').

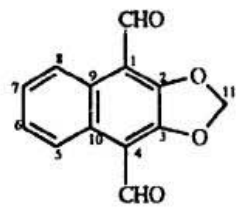
*1,4-bis-(hydroxymethyl)-2,3-methylenedioxynaphthalene (**84**).*



Bis-(bromomethyl)-2,3-methylenedioxynaphthalene (**59**) (100 mg, 0.28 mmol) was dissolved in aqueous 50% *p*-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); ^{1}H 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),

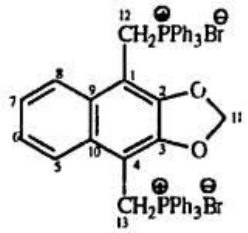
201 (28), 185 (42), 173 (29), 156 (22), 145 (8), 128 (31), 115 (29).

*1,4-Diformyl-2,3-methylenedioxynaphthalene (**85**).*



To a vigorously-stirred suspention 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-d_7) at 100 °C: 6.57 (s, 2H, H-11), 7.58 (m, H-6, H-7), 9.00 (m, H-5, H-8), 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 $C_{13}H_8O_4$: 228.0422.

1,4-Bis-phosphonium salt ***86.***

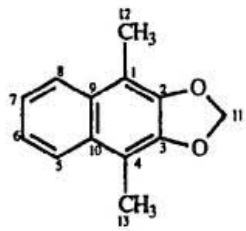


To a solution of **59** (200 mg, 0.56 mmol) in dry DMF (2 mL) was added triphenyl phosphine (Ph_3P) (323 mg, 1.23 mmol). The reaction mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture was cooled to 0 °C 30 min. A white precipitate formed, which was filtered and washed 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; ^{1}H NMR (DMSO-d_6): 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).

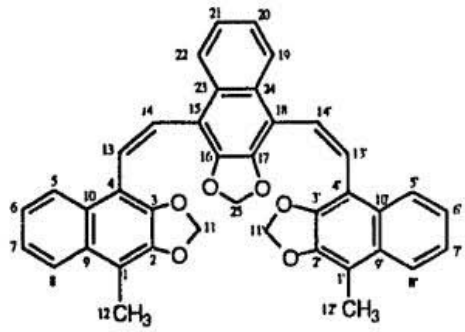
Wittig reaction of ***85*** *and* ***86.***

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 $MgSO_4$, 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.



87



88

Compound **87** was obtained as colourless needles: mp 87-89 °C; ^{1}H NMR ($CDCl_3$): 2.48 (s, 6H, H-12, H-13), 6.01 (s, 2H, H-11), 7.39 (m, 2H, H-6, H-7), 7.82 (m, H-5, H-8); ^{13}C NMR ($CDCl_3$): 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; ^{1}H NMR ($CDCl_3$): 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 $CHCl_3$), 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 $C_{39}H_{28}O_6$: 592.1884.

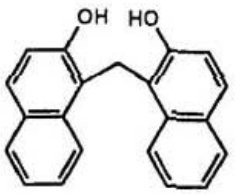
Chapter 6.

Other Calixnaphthalenes, Functionalized Calixresorcinarenes, and Calixspherands

6.1. Attempted Synthesis of Other Calixnaphthalenes.

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 biding 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**), [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.

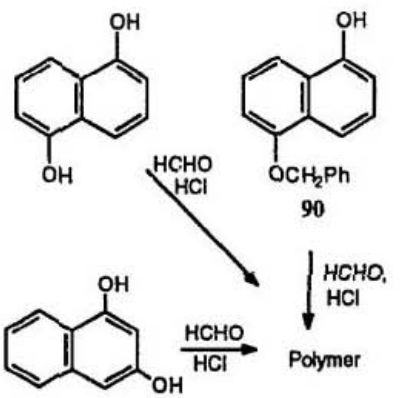


89

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).

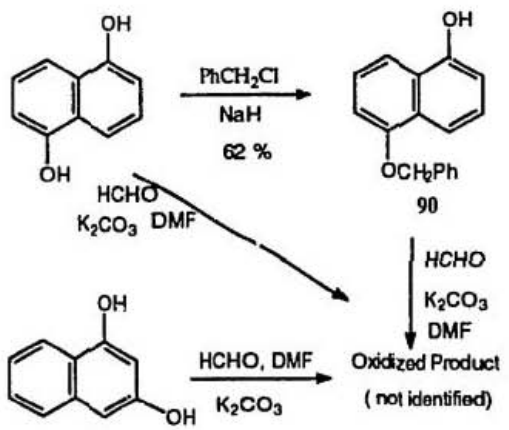
Scheme 6.1.



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.



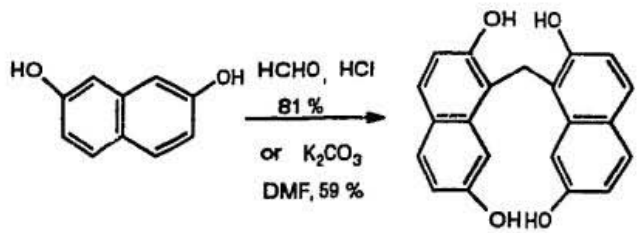
Both 1,5- and 1,3-dihydroxynaphthalene are electron-rich aromatic compounds. Therefore, they are highly reactive towards electrophiles, with the result that their condensation with formaldehyde under acidic conditions produces polymeric products. Under basic conditions, they are very labile to oxidation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



91

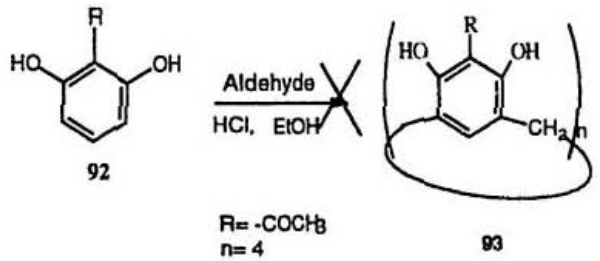
6.2. Attempted Synthesis of Functionalised Calixresorcinarenes.

As previously indicated, calixresorcinarenes are another major class of calixarenes. Compared with calixarenes derived from phenols, few derivatized calixresorcinarenes have been reported. The condensation of aldehydes with 2,6-dihydroxyacetophenone (**92**) was investigated to try to form the corresponding calixresorcinarene **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 ^{1}H 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.

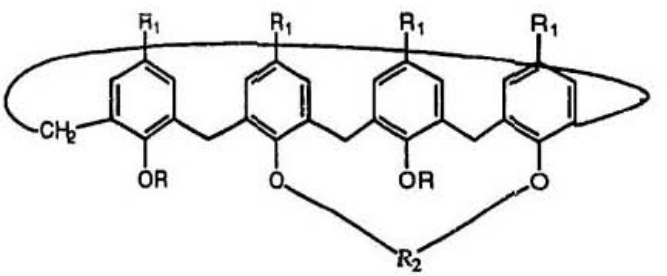


Examination of Dreiding models suggested strong steric repulsion between the aceto groups, which could limit formation of any cyclic oligomer. Another factor could be that strong hydrogen bonding between the aceto and hydroxy groups could be formed, which could diminish any intramolecular hydrogen bonding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



R= H

$R_1 = t\text{-}C_4H_9$

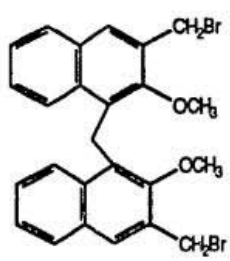
R_2 = Ar

94

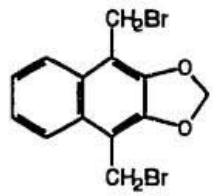
Since the naphthalene ring is larger than benzene, a calixspherand having naphthalene tethers might be more rigid, and, therefore, its complexes with alkaline cations would be more stable.

6.3.1. Synthesis of Calixspherands.

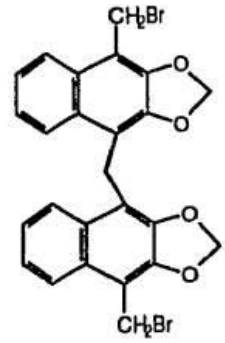
Calixspherands made from *p-tert*-butylcalix[4]arene (**1**) and naphthalene tethers derived from **49**, **59**, and **60** were studied. Calixarene **1** was prepared according to Gustche's procedure.[106] The preparation of **49** was described in Chapter 4, and those of **59**, and **60** were described Chapter 5. The major synthetic task was to effect the coupling of **1** with **49**, **59**, or **60**.



49



59

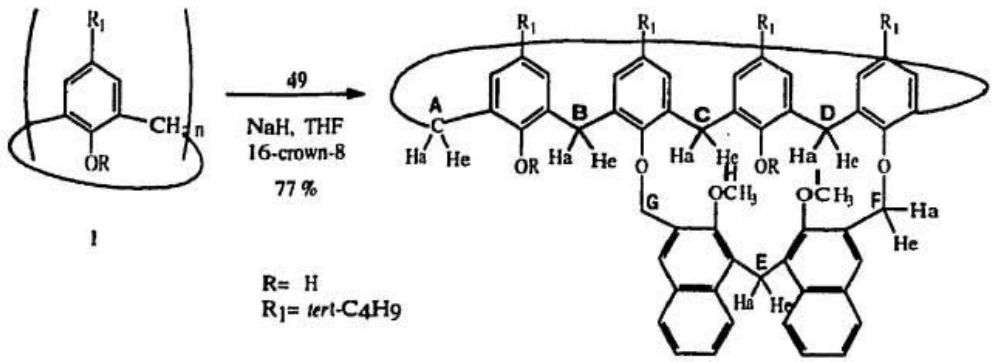


60

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

Scheme 6.5.



1

95

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.[30]

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 $CDCl_3$.

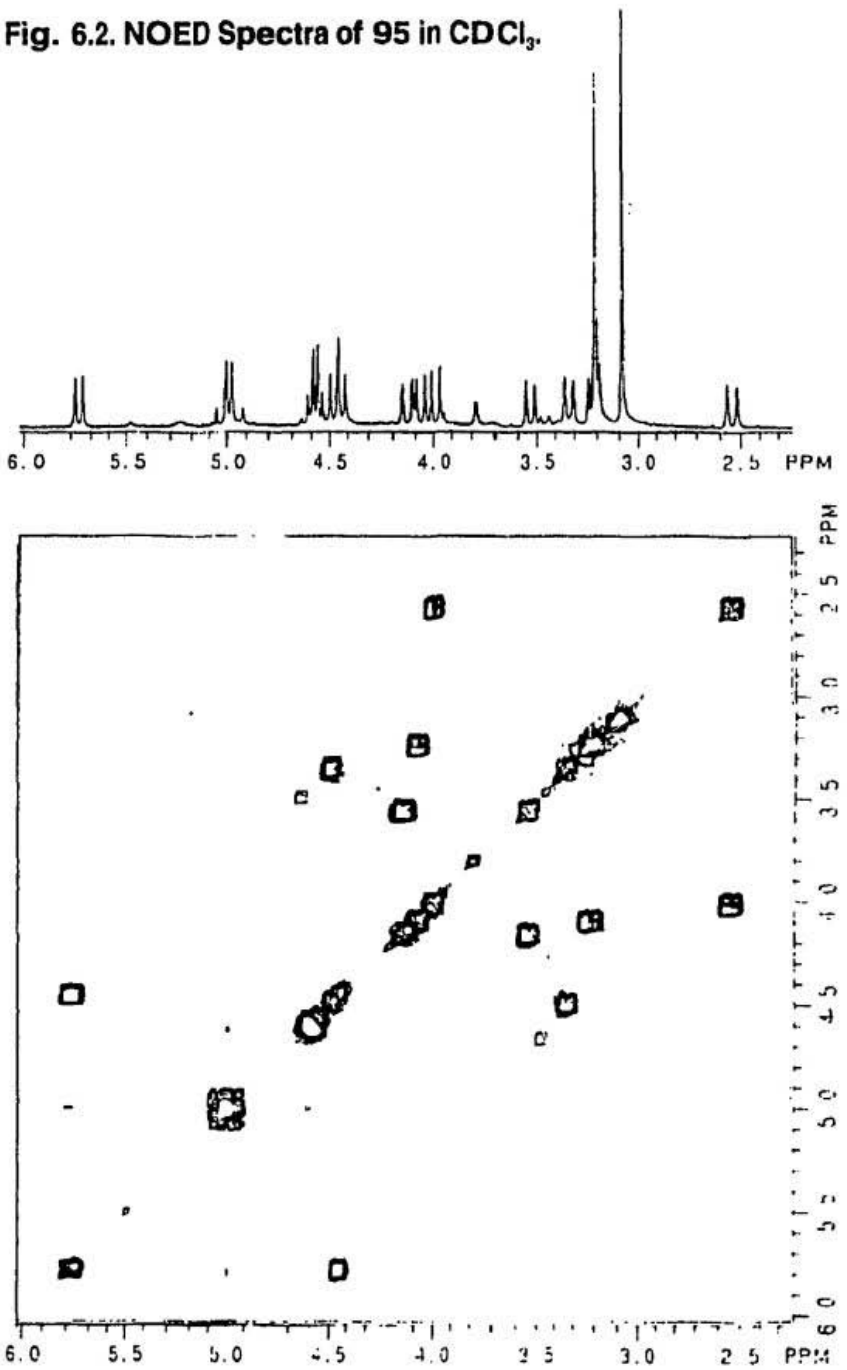
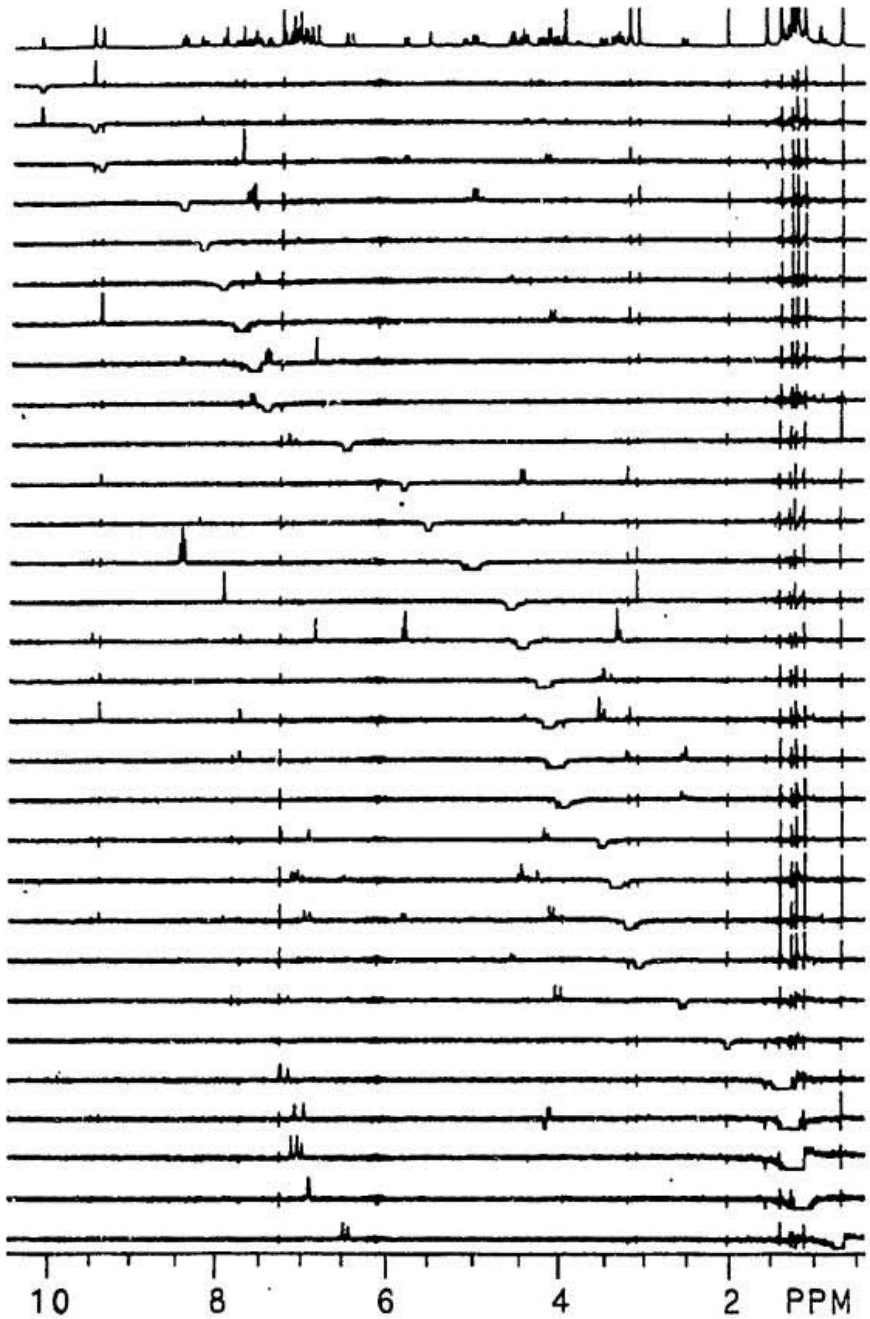


Fig. 6.1. HH COSY Spectrum of 95 in $CDCl_3$.



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* axial proton (H_a); the other which we call the *pseudo* equatorial proton (H_e) 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 *bis*naphthalene 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.

tert-butyl	^{1}H	0.696(s)	1.12 (s)	1.27 (s)	1.39 (s)
	^{13}C	31.3(q)	31.7(q)	32.0 (q)	
Ph-CH_2-Ph		H_a (**A**)	H_e (**A**)	H_a (**B**)	H_e (**B**)
	^{1}H	2.54 (d, J=14.1)	3.99 (d, J=14.1)	3.20 (d, J=13.8)	4.08 (d, J=13.8)
	^{13}C	28.74 (t)		32.14 (t)	
		H_a (**C**)	H_e (**C**)	H_a (**D**)	H_e (**D**)
	^{1}H	3.33 (d, J=12.6)	4.48 (d, J=12.6)	3.54 (d, J=13.6)	4.14 (d, J=13.6)
	^{13}C	32.3 (t)		34.7 (t)	
Naph-CH_2-Naph		H_a (**E**)		H_e(**E**)	
	^{1}H	4.99 (q, 16.6)			
	^{13}C	24.96 (t)			
OCH_2		H_a (**F**)	H_e (**F**)	H_a (**G**)	H_e (**G**)
	^{1}H	4.44 (d, J=11.7)	5.76 (d, J=11.7)	4.59 (q, J=8.4)	
	^{13}C	75.7 (t)		74.5 (t)	
OCH_3		(**H**)		(**I**)	
	^{1}H	3.21 (s)		3.09 (s)	
	^{13}C	63.4 (q)		62.5 (q)	

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**.

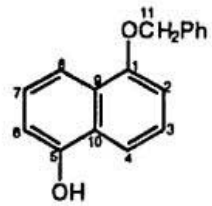
Condensation of 2,6-dihydroxyacetophenone with aldehydes such as acetaldehyde and benzaldehyde under acidic conditions gave polymers, but did not give cyclic the anticipated calixresorcinarene.

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**).*



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 (CD_3COCD_3): 5.30 (s, 2H, H-11), 6.95 (q, $J_{6,7}$=7.5, $J_{6,8}$=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.

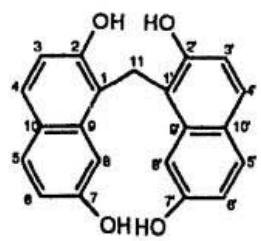
When the reaction of 1-hydroxy-5-naphthyl benzyl ether (**90**) or 1,3-dihydroxynaphthalene with formaldehyde was carried out under the same conditions as described above, similar polymeric products were obtained, and were not further characterized.

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% K_2CO_3 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 N_2 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 (CD_3COCD_3): 4.67 (s, 2H, H-11), 6.82 (q, $J_{6,5}$=8.7, $J_{6,8}$=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'); ^{13}C NMR (CD_3COCD_3) 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 (28), 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 N_2. 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.[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.

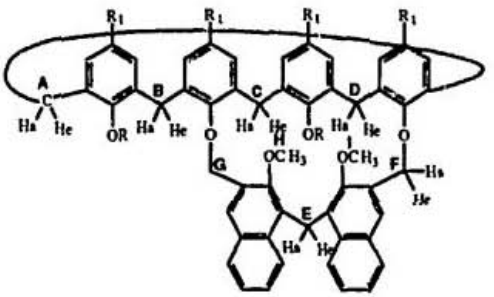
To a solution of purified **92** (0.79 g, 5 mmol) in 95% ethanol (10 mL) was added aqueous 10% acetaldehyde solution (2.2 mL). During refluxing for 12 h, a white precipitate formed. After cooling to room temperature, the precipitate was filtered, washed with water until the washings were neutral to pH paper, and dried under vacuum to afford a crude product (1.45 g). The ^{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 ^{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-tert-Butylcalixarene (**1**).*

p-tert-Butylcalixarene was prepared according to Gutsche's procedure[107] in 42% yield. MP >300 °C (with decomposition); IR (Nujol, cm^{-1}): 3135 (s, br, OH), 1665 (w), 1600 (w), 1550 (w); ^1H NMR ($CDCl_3$): δ 1.21 (s, 36H, $C(CH_3)_3$), 3.52 (d, 4H, $(CH_2)_a$), 4.28 (d, 4H, $(CH_2)_e$), 7.05 (s, 8H, aromatic), 10.3 (s, 4H, OH); ^{13}C NMR ($CDCl_3$): 31.4 (CH_3), 32.6 (CH_2), 34.0 ($\mathbf{C}(CH_3)_3$), 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 *bis*bromomethyl 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

1. Diederich, F., *Cyclophanes*, p v, Monographs in Supramolecular Chemistry, Stoddard, J. F. (Ed.), Royal Society of Chemistry, Cambridge, **1989**, Vol.2.
2. Breslow, R., *Acc. Chem. Res.*, **1991**, *24*, 317.
3. Anderson, H. L. and Sanders, J. K. M., *J. Chem. Soc., Chem. Commun.*, **1989**, 1714.
4. Cram, D.J., *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 1009.
5. Peterson, C. J., *J. Am. Chem. Soc.*, **1967**, *89*, 2495.
6. Cram, D. J., *Acc. Chem. Res.* **1984**, *98*, 1041.
7. Lehn, J.-M., *Angew. Chem., Int. Ed. Engl.*, **1988**, *27*, 89.
8. (a). Rebek, J., *Science* (Washington D.C.), **1987**, *235*, 1478.
   (b). Wilcox, C. S. and Lynch, V., *J. Am. Chem. Soc.*, **1987**, *109*, 1885.
9. Murakami, Y., *Top. Curr. Chem.*, **1983**, *115*, 107.
10. Taushi, I., *Pure Appl. Chem.*, **1986**, *58*, 1529.
11. Breslow, R., *Acc. Chem. Res.*, **1980**, *13*, 120.
12. Gutsche, C. D., *Calixarenes*, Monographs in Supramolecular Chemistry, Stoddard, J. F. (Ed.), Royal Society of Chemistry, Cambridge, **1989**, Vol. 1. (and references therein): (a) p 107; (b) pp 58-59; (c) pp 167-172;

(d) p 190; and (e) pp197-200.

13. Högberg, A. G. S., *J. Am. Chem. Soc.*, **1980,** *102*, 6046.

14. Cram, D. J. and Cram, J. M., *Container Molecules and their Guests*, pp 131-147, Monographs in Supramolecular Chemistry, Stoddard, J. F. (Ed.), Royal Society of Chemistry, Cambridge, **1994**, Vol. 4. (and references therein).

15. Baeyer, A., *Ber. Dtsch. Chem. Ges.*, **1872,** *5*, 25.

16. Baekeland, L. H., *U. S. Patent 942,669*, October **1908**.

17. Zinke, A., Kretz, R., Leggewie, E., Hössinger, K., Hoffman, G. and Weber, P., *Monatsh.*, **1952**, *83*, 1213.

18. Vicens, J. and Böhmer, V. (Eds.), *Calixarenes: A Versatile Class of Macrocyclic Compounds*, Topics in Inclusion Science, Kluwer Academic Publishers, Dordrecht, **1991**, Vol. 3. (and references therein): (a) pp 39-42; (b) pp 42-44; (c) pp 249-251; and (d) pp 237-238.

19. Chasar, D.W., *J. Org. Chem.*, **1985**, *50*, 545.

20. Winberg, H.E., Fawcett, F. S. and Theobald, C. W., *J. Am. Chem. Soc.*, **1960,** *82*, 1428.

21. Burri, K. and Jenny, W., *Helv. Chim. Acta.*, **1967**, *50*, 1978.

22. Thulin, B., Wennerström, O. and Högberg, H., *Acta Chem. Scand.*, **1975,** *B29*, 138.

23. Staab, H. A. and Schwendemann, M., *Liebigs Ann. Chem.*, **1979**, 1258.

24. Bockmann, K. and Vögtle, F., *Chem. Ber.*, **1981**, *114*, 1048.

25. Mitchell, R. H., Otsubo,T. and Boekelheide, V., *Tetrahedron Lett.*, **1975**, 219.

26. Mitchell, R. H. and Boekelheide, V., *J. Am. Chem. Soc.*, **1974**, *96*, 1546.

27. Takahashi, S. and Mori, N., *J. Chem. Soc., Perkin Trans 1*, **1991**, 2029.

28. Bates, R.B., Gangwar, S., Kane, V. V., Suvannachut, K. and Taylor, S. R., *J. Org. Chem.*, **1991**, *56*, 1696.

29. Reinhoudt, D. and van Loon, J.-D., in *Calixarenes: A Versatile Class of Macrocyclic Compounds*, pp 54-61, Vicens, J. and Böhmer, V. (Eds.), Kluwer, Dordrecht, **1991**.

30. Bakker, W. I. I., Haas, M., Khoo-Beattie, C., Ostaszewski, R., Franken, S.M., den Hertog, J., Verboom, W., de Zeeuw, D., Harkema, S. and Reinhoudt, D. N., *J. Am. Chem. Soc.*, **1994**, *116*, 123.

31. Shinkai, S., Arimura, T., Satoh, H. and Manabe, O., *J. Chem. Soc., Chem. Commun.*, **1987**, 1495.

32. Shinkai, S., Araki, K., Arimura, T. and Manabe, O., *J. Chem. Soc., Perkin Trans.1*, **1987**, 2297.

33. Goldmann, H., Vogt, W., Paulus, E. and Böhmer, V., *J. Am. Chem. Soc.*, **1988**, *110*, 6811.

34. Cram, D. J., Tanner, M. E. and Knobler, C.B., *J. Am. Chem. Soc.*, **1991**, *113*, 7717.

35. Andreetti, G. D. and Pochini, A., J. *Chem. Soc., Chem. Commun.*, **1979**, 1005.

36. Gutsche, C. D. and Bauer, L. J., *J. Am. Chem. Soc.*, **1985**, *107*, 6052.

37. Arduini, A., Fabbi, M., Mantovani, M., Mirone, L., Pochini, A., Secchi, A. and Ungaro, R., *J. Org. Chem.*, **1995**, *60*, 1454.

38. Rizzoli, C., Andreetti, G. D. and Pochini, A., *J. Mol. Struct.*, **1982**, *82*, 133.

39. McKervey, M. A., Seward, E.M., Ferguson, G. and Ruhl, B. L., *J. Org. Chem.*, **1986**, *51*, 3581.

40. Iwamoto, K. and Shinkai, S., *J. Org. Chem.*, **1992**, *57*, 7066.

41. Verboom, W., Datta, S., Asfari, Z., Hakema, S. and Reinhoudt, D. N., *J. Org. Chem.*, **1992**, *57*, 5394.

42. Papplardo, S., Ferguson, G. and Gallagher, J. F., *J. Org. Chem.* **1992**, *57*, 7102.

43. Egberink, R. J. M., Cobben, P. L. H., Verboom, W., Harkema, S. and Reinhoudt, D. N., *J. Incl. Phenom.*, **1992**, *12*,151.

44. Sakaki, T., *J. Incl. Phenom.*, **1992**, *14*, 285.

45. Ungaro, R., Pochini, A. and Andreetti, D., *J. Incl. Phenom.*, **1984**, *2*, 199.

46. Beer, P., *J. Chem. Soc., Chem. Commun.*, **1993**, 229.

47. Atwood, J. L., Hamada, F., Robinson, D., Orr, G. W. and Vincent, R. L., *Nature* (London), **1991**, *349*, 683.

48. Shinkai, S. in *Calixarenes: A Versatile class of Macrocyclic Compounds*, pp 173-198, Vicens, J. and Böhmer, V. (Eds.); Kluwer, Dordrecht, **1991**.

49. (a) Cram, D. J. and Tanner, M. E., *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1024. (b) Robbins, T. A. and Cram, D. J., *J. Am. Chem. Soc.*, **1993**, *115*, 12199. (c) Kurdistani, S. K., Helgeson, R. C. and Cram, D. J., *J. Am. Chem. Soc.*, **1995**, *117*, 1659.

50. Izatt, S. R., Hawkins, R. T., Christensen, J. J. and Izatt, R. M., *J. Am. Chem. Soc.*, **1985**, *107*, 63.

51. Groenen, L. C., Brunink, J. A. J., Bakker, W. I., Harkema, S., Wijmenga, S. S. and Reinhoudt, D. N., *J. Chem. Soc., Perkin Trans. 2*, **1992**, 1899.

52. (a). Behr, J.P. and Lehn, J.-M., *J. Am. Chem. Soc.*, **1985**, 107, 241. (b).Cobben, P. L. H. M. and Egberink, R. J. M., Böhmer, J. G., Bergveld, P., Verboom, W. and Reinhoudt, D. N., *J. Am. Chem. Soc.*, **1992**, *114*, 10573.

53. Perrin, R. and Harris, S., in *Calixarenes: A Versatile Class of Macrocyclic Compounds*; pp 235-257, Vicens, J. and Böhmer, V. (Eds.);

Kluwer, Dordrecht, **1991.**

54. Gutsche, C. D. and Alam, I., *Tetrahedron*, **1988**, *44*, 4689.

55. Atwood, J., *Nature*, **1994**, *368*, 229.

56. Suzuli, T., Nakashimas, K. and Shinkai, S., *Chem. Lett.*, **1994**, 699.

57. Kurihara, K. Ohto, K., Tanaka, Y., Aoyama, Y. and Kunitake, T., *J. Am. Chem. Soc.*, **1991**, *113*, 444.

58. King, A. M., Moore, C. P., Sandnayake, K. R. A. S. and Sutherland, I. O., *J. Chem. Soc., Chem. Commun.*, **1992,** 582.

59. Deng, G., Sakaki, T., Kawahara, Y. and Sinkai, S., *Tetrahedron Lett.*, **1992**, *33*, 2136.

60. Diamond, D., in *Calixarenes: 50th Anniversary*, pp149-166, Vicens, J., Zouhair, A. and Harrowfield, J. M. (Eds.), Kluwer, **1994**,

61. Xu, B. and Swager, T. M., *J. Am. Chem. Soc.*, **1993**, *115*, 1159.

62. Kelderman, E., Derhaeg, L., Heeesink, G. J. T., Verboom, W., Engbersen, J. F. J., van Hulst, N. F., Persoons, A. and Reinhoudt, D. N., *Angew. Chem., Int. Ed. Engl.*, **1992**, *31*, 1107.

63. Brake, M., Böhmer, V., Kram, P., Vogt, W. and Wortmann, R., *Supramol. Chem.*, **1993**, *2*, 65.

64. Conner, M., Janout, V. and Regan, S. L., *J. Am. Chem. Soc.*, **1993**, *115*, 1178.

65. Arimura,T., Nagasaki, T., Shinkai, S. and Matsuda, S., *J. Org. Chem.*, **1989**, *54*, 3766.

66. Poh, B.-L., Lim, C. S., Khoo, K. S., *Tetrahedron Lett.*, **1989**, *30*, 1005.

67. Georghiou, P. E. and Ho, C. K., *Can. J. Chem.*, **1989**, *67*, 871.

68. Donaldson, N., *The Chemistry and Technology of Naphthalene Compounds*, Edward Arnold, London, **1958**.

69. Walker, J. F., *Formaldehyde*, American Chemical Society Monograph Series, No. 159, Reinhold, New York, **1964**.

70. Breslauer, J. and Pictet, A., *Ber. Dtsch. Chem. Ges.*, **1907**, *40*, 3785.

71. Abel, J., *Ber.* Dtsch. Chem. Ges., **1892**, *27*, 2409.

72. Patai, S. (Ed.), *The Chemistry of the Hydroxyl Group, Part 1*, pp 505-592, Wiley, London, **1971**.

73. Georghiou, P., Ashram, M., Li, Z.-P. and Chaulk, S. *J. Org. Chem.*, **1995**, *60*, 7284.

74. Georghiou, P., Ashram, M., *J. Org. Chem.*, **1995**, *60*, 2909.

75. Chaulk, S., *B.Sc (Hons) Thesis*, Memorial University of Newfoundland, **1995**.

75a. Andreetti, G. D., Böhmer, V., Jordon, G., Tabatabai, M., Ugozzoli, F., Vogt, W. and Wolff, A., J. Org. Chem., **1993**, *58*, 4023.

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

Chemistry, pp 1-37, VCH, Weinheim, **1985**.

77. Alchemy III. 3D Molecular Modeling Software, Tripos Associates Inc., St. Louis, Missouri, **1992**.

77a. Still, W. C., Kahn, M. and Mitra, A., *J. Org. Chem.*, **1978**, *43*, 2923.

78. Brady, P. and Levy, E., *Chem. Ind.*, **1995**, 18.

79. Arduini, A., Pochini, A., Reverberi, S. and Ungaro, R., *J. Chem. Soc., Chem. Commun.*, **1984**, 981.

80. Shinkai, S., *Pure and Appl. Chem.*, **1986**, *58*, 1523.

81. Patai, S. (Ed.), *The Chemistry of Sulphonic Acid, Esters, and Their Derivatives*, pp 789-878, Wiley, Toronto, **1991**.

82. Mustafa, A., Asker, W., Hishmat, O. H., Shalably, A. F. A. and Kamei, M., *J. Am. Chem. Soc.*, **1954**, *76*, 5447.

83. (a) Diederich, F., Dick, K. and Griebel, D. J., *J. Am. Chem. Soc.*, **1986**, *108*, 2273. (b) Poh, B.-L., Koay, L.-S., *Tetrahedron Lett.*, **1990**, 1911.

84. Schetly, G., *Helv. Chim. Acta*, **1948**, *31*, 1229.

85. Keehn, P. M. and Rosenfeld, S. M. (Eds.), *Cyclophanes*, Vol. II, pp 443-484, Academic Press, New York, 1983.

86. Smith, W. T. and Campanaro, L., *J. Am. Chem. Soc.*, **1952**, *74*, 1107.

87. *Chemical Abstracts*, **1964**, *61*, 5580f.

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

J. Incl. Phenom., **1993**, *15*, 247.

88. Bashall, A. P. and Collins, J. F., *Tetrahedron Lett.*, **1975**, 3489.

89. Clark, J. H. and Holand, J. F.,*Tetrahedron Lett.*, **1976**, 3361.

90. Greene, T. W. and Wuts, P. G. M., *Protecting Groups in Organic Synthesis*, Wiley, New York, **1990**.

90a. Pedersen, C. J., *J. Am. Chem. Soc.*, **1967**, 85, 1080.

91. Vogel, A. I., *Vogel's Text Book of Practical Organic Chemistry*, 5th ed., pp 838-839, Longman Scientific and Technical, **1989**.

92. Noyori, R., *Tetraherdron*, **1994**, *50*, 4259.

93. Vögtle, F., in *Cyclophane*, pp 1-86, Boschke, F. L. (Ed.) Springer-Verlag, Berlin, **1983**.

94. Bodwell, G., Houghton, T., Koury, H. E. and Yarlagadda, B., *Synlett*, **1995**, 751.

95. Snieckus, V., *Chem. Rev.*, **1990**, *90*, 879.

96. Shirley, D. A. and Cheng, C. F., *J. Organometal. Chem.*, **1969**, *20*, 251.

97. Crowther, G. P., Sundberg, R. J. and Sarpeshkar, A. M., *J. Org. Chem.*, **1984**, *49*, 4657.

98. Eustache, J., Bernardon, J.-M. and Shroot, B., *Tetrahedron Lett.*, **1987**, *28*, 4681.

99. McMurry, J. E. and Erion, M. D., *J. Am. Chem. Soc.*, **1985**, *107*, 2712.

100. Shih, T. L., Wyvratt, M. J. and Mrozik, H., *J. Org. Chem.*, **1987**, *52*, 2029.

101. Bell, F. and Buck, K. R., *J. Chem. Soc.*, **1963**, 4626.

102. *Dictionary of Organic Compounds*, Vol. 4, p 4144, 5*th*, Chapman & Hall, **1982**.

103. Fieser, L.F. and Jones, J. E., *Org. Syn., Collective Vol .III*, p 590,**1955**.

104. Manasses, O., *Ber. Dtsch. Chem. Ges.*, **1894,** *27*, 2409.

105. Hosaeus, H., *Ber. Dtsch. Chem. Ges.*, **1892,** *25*, 3213.

106. Gutsche, C. D. and Iqbal, M., *Org. Synth.*, **1989,** *68*, 243.

107. Russell, A. and Frye, J. R., *Org. Syn, Collective Vol. III*, p 281, **1955**.

Appendix I

Data of X-ray Crystallography of Compound ***46.***

EXPERIMENTAL

DATA COLLECTION

A colourless irregular crystal of $C_{50}H_{44}O_4$ having approximate dimensions of 0.400 X 0.200 X 0.400 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Mo Kα radiation and a 2KW sealed tube generator.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 19 carefully centered reflections in the range $37.54 < 2\theta < 45.79°$ corresponded to a triclinic cell with dimensions:

a =	10.343 (3)Å	α =	96.15 (4)°
b =	11.240 (6)Å	β =	110.13 (3)°
c =	8.992 (4)Å	γ =	104.46 (3)°
V =	928.7 (7)Å^3		

For $Z = 1$ and F.W. = 708.90, the calculated density is 1.267 g/cm^3. Based on packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be:

P$\bar{1}$ (#2)

The data were collected at a temperature of 26 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 50.2°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.32° with a take off angle of 6.0°. Scans of (1.73 + 0.35 tan θ)° were made at a speed of 4.0°/min (in omega). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 2 rescans) and the counts were accumulated to assure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm and the crystal to detector distance was 400.0 mm.

DATA REDUCTION

Of the 3501 reflections which were collected, 3304 were unique (R_{int} = .021). The intensities of three representative reflections which were measured after every 150 reflections remained constant throughout data collection indicating crystal and electronic stability (no decay correction was applied).

The linear absorption coefficient for Mo Kα is 0.7 cm^{-1}. An empirical absorption correction, based on azimuthal scans of several reflections, was applied which resulted in transmission factors ranging from 0.91 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 0.35228E-05).

STRUCTURE SOLUTION AND REFINEMENT

The structure was solved by direct methods[3]. The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement[4] was based on 2392 observed reflections ($I > 2.00\sigma(I)$) and 259 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \Sigma \, ||Fo| - |Fc|| \, / \, \Sigma \, |Fo| = 0.042$$

$$R_w = [(\Sigma \, w \, (|Fo| - |Fc|)^2 \, / \, \Sigma \, w \, Fo^2)]^{1/2} = 0.038$$

The standard deviation of an observation of unit weight[5] was 2.54. The weighting scheme was based on counting statistics and included a factor (p = 0.01) to downweight the intense reflections. Plots of $\Sigma \, w \, (|Fo| - |Fc|)^2$ versus |Fo|, reflection order in data collection, $\sin\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and -0.14 e$^-$/Å^3, respectively.

Neutral atom scattering factors were taken from Cromer and Waber[6]. Anomalous dispersion effects were included in Fcalc[7]; the values for Δf' and Δf" were those of Cromer[8]. All calculations were performed using the TEXSAN[9] crystallographic software package of Molecular Structure Corporation.

References

(1) PLUTO:
Motherwell,S. & Clegg,W.; PLUTO. Program for plotting molecular and crystal structures. Univ. of Cambridge, England (1978).

(2) ORTEP:
Johnson,C.K.; ORTEPII. Report ORNL-5138. Oak Ridge National Laboratory, Oak Ridge, Tennessee (1976).

(3) Structure Solution Methods:
MITHRIL
Gilmore,C.J.; MITHRIL - an integrated direct methods computer program. J. Appl. Cryst. 17, 42-46, Univ. of Glasgow, Scotland, (1984).
DIRDIF
Beurskens,P.T.; DIRDIF: Direct Methods for Difference Structures - an automatic procedure for phase extension and refinement of difference structure factors. Technical Report 1984/1 Crystallography Laboratory, Toernooiveld, 6525 Ed Nijmegen, Netherlands.

(4) Least-Squares:
Function minimized: $\Sigma w (|Fo| - |Fc|)^2$
where: $w = 4Fo^2/\sigma^2(Fo^2)$
$\sigma^2(Fo^2) = [S^2(C+R^2B) + (pFo^2)^2]/Lp^2$
S = Scan rate
C = Total Integrated Peak Count
R = Ratio of Scan Time to background counting time.
B = Total Background Count
Lp = Lorentz-polarization factor
p = p-factor

(5) Standard deviation of an observation of unit weight:
$$[\Sigma w(|Fo| - |Fc|)^2/(No - Nv)]^{1/2}$$
where: No = number of observations
Nv = number of variables

(6) Cromer,D.T. & Waber,J.T.; "International Tables for X-ray Crystallography", Vol. IV, The Kynoch Press, Birmingham, England, Table 2.2 A (1974).

(7) Ibers,J.A. & Hamilton,W.C.; Acta Crystallogr., 17, 781 (1964).

(8) D.T. Cromer, "International Tables for X-ray Crystallography", Vol/ IV, The Kynoch Press, Birmingham, England, Table 2.3.1 (1974).

(9) TEXSAN - TEXRAY Structure Analysis Package, Molecular Structure Corporation (1985).

EXPERIMENTAL DETAILS

A. Crystal Data

Empirical Formula	$C_{50}H_{44}O_4$
Formula Weight	708.90
Crystal Color, Habit	colourless, irregular
Crystal Dimensions (mm)	0.400 X 0.200 X 0.400
Crystal System	triclinic
No. Reflections Used for Unit Cell Determination (2θ range)	19 (37.5 - 45.8°)
Omega Scan Peak Width at Half-height	0.32
Lattice Parameters:	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 (3)° V = 928.7 (7)Å^3
Space Group	$P\bar{1}$ (#2)
z value	1
D_{calc}	1.267 g/cm^3
F_{000}	376
μ(MoKα)	0.73 cm^{-1}

B. Intensity Measurements

Diffractometer	Rigaku AFC6S
Radiation	MoKα (λ = 0.71069 Å)
Temperature	25°C
Take-off Angle	6.0°

Detector Aperture	4.5 mm horizontal 3.0 mm vertical
Crystal to Detector Distance	40 cm
Scan Type	ω–2θ
Scan Rate	4.0°/min (in omega) (2 rescans)
Scan Width	(1.73 + 0.35 tanθ)°
$2\theta_{max}$	50.2°
No. of Reflections Measured	Total: 3501 Unique: 3304 (R_{int} = .021)
Corrections	Lorentz-polarization Absorption (trans. factors: 0.91 - 1.00) Secondary Extinction (coefficient: 0.35228E-05)

C. Structure Solution and Refinement

Structure Solution	Direct Methods
Refinement	Full-matrix least-squares
Function Minimized	$\Sigma w (\|Fo\| - \|Fc\|)^2$
Least-squares Weights	$4Fo^2/\sigma^2(Fo^2)$
p-factor	0.01
Anomalous Dispersion	All non-hydrogen atoms
No. Observations (I>2.00σ(I))	2392
No. Variables	259
Reflection/Parameter Ratio	9.24
Residuals: R; R_w	0.042; 0.038
Goodness of Fit Indicator	2.54
Max Shift/Error in Final Cycle	0.00
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

atom	atom	atom	angle	atom	atom	atom	angle
C(45)	O(3)	C(49)	113.3(2)	C(15)	C(14)	C(45)	118.4(2)
C(46)	O(4)	C(50)	115.6(2)	C(14)	C(15)	C(16)	124.4(2)
C(4)	C(3)	C(23)	114.2(2)	C(14)	C(15)	C(20)	118.5(2)
C(3)	C(4)	C(5)	119.4(2)	C(16)	C(15)	C(20)	117.0(2)
C(3)	C(4)	C(46)	123.0(2)	C(15)	C(16)	C(17)	121.5(2)
C(5)	C(4)	C(46)	117.5(2)	C(16)	C(17)	C(18)	120.9(2)
C(4)	C(5)	C(6)	121.7(2)	C(17)	C(18)	C(19)	119.6(2)
C(5)	C(6)	C(7)	120.1(2)	C(18)	C(19)	C(20)	121.1(2)
C(5)	C(6)	C(11)	119.7(2)	C(15)	C(20)	C(19)	119.7(2)
C(7)	C(6)	C(11)	120.1(2)	C(15)	C(20)	C(21)	119.7(2)
C(6)	C(7)	C(8)	120.2(2)	C(19)	C(20)	C(21)	120.5(2)
C(7)	C(8)	C(9)	120.2(2)	C(20)	C(21)	C(22)	122.1(2)
C(8)	C(9)	C(10)	121.5(3)	C(21)	C(22)	C(23)	122.5(2)
C(9)	C(10)	C(11)	120.3(2)	C(21)	C(22)	C(45)	117.2(2)
C(6)	C(11)	C(10)	117.7(2)	C(23)	C(22)	C(45)	120.2(2)
C(6)	C(11)	C(12)	118.8(2)	C(3)	C(23)	C(22)	117.2(2)
C(10)	C(11)	C(12)	123.5(2)	O(3)	C(45)	C(14)	118.2(1)
C(11)	C(12)	C(13)	122.4(2)	O(3)	C(45)	C(22)	118.0(2)
C(11)	C(12)	C(46)	118.1(2)	C(14)	C(45)	C(22)	123.6(2)
C(13)	C(12)	C(46)	119.5(2)	O(4)	C(46)	C(4)	120.3(2)
C(12)	C(13)	C(14)	116.1(2)	O(4)	C(46)	C(12)	115.9(2)
C(13)	C(14)	C(15)	121.5(2)	C(4)	C(46)	C(12)	123.6(2)
C(13)	C(14)	C(45)	120.1(2)				

Angles are in degrees. Estimated standard deviations in the least significant figure are given in parentheses.

Intramolecular Distances Involving the Nonhydrogen Atoms

atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(3)	C(45)	1.397(3)	1	C(12)	C(13)	1.513(3)	1
O(3)	C(49)	1.441(3)	1	C(12)	C(46)	1.382(4)	1
O(4)	C(46)	1.391(3)	1	C(13)	C(14)	1.521(3)	1
O(4)	C(50)	1.431(4)	1	C(14)	C(15)	1.437(3)	1
C(3)	C(4)	1.524(4)	1	C(14)	C(45)	1.374(3)	1
C(3)	C(23)	1.539(3)	56602	C(15)	C(16)	1.421(3)	1
C(4)	C(5)	1.371(3)	1	C(15)	C(20)	1.414(2)	1
C(4)	C(46)	1.406(3)	1	C(16)	C(17)	1.369(4)	1
C(5)	C(6)	1.417(4)	1	C(17)	C(18)	1.392(3)	1
C(6)	C(7)	1.421(3)	1	C(18)	C(19)	1.359(4)	1
C(6)	C(11)	1.417(3)	1	C(19)	C(20)	1.423(3)	1
C(7)	C(8)	1.363(4)	1	C(20)	C(21)	1.414(3)	1
C(8)	C(9)	1.392(4)	1	C(21)	C(22)	1.367(3)	1
C(9)	C(10)	1.371(4)	1	C(22)	C(23)	1.518(3)	1
C(10)	C(11)	1.427(4)	1	C(22)	C(45)	1.416(2)	1
C(11)	C(12)	1.436(3)	1				

Intermolecular Distances Involving the Nonhydrogen Atoms

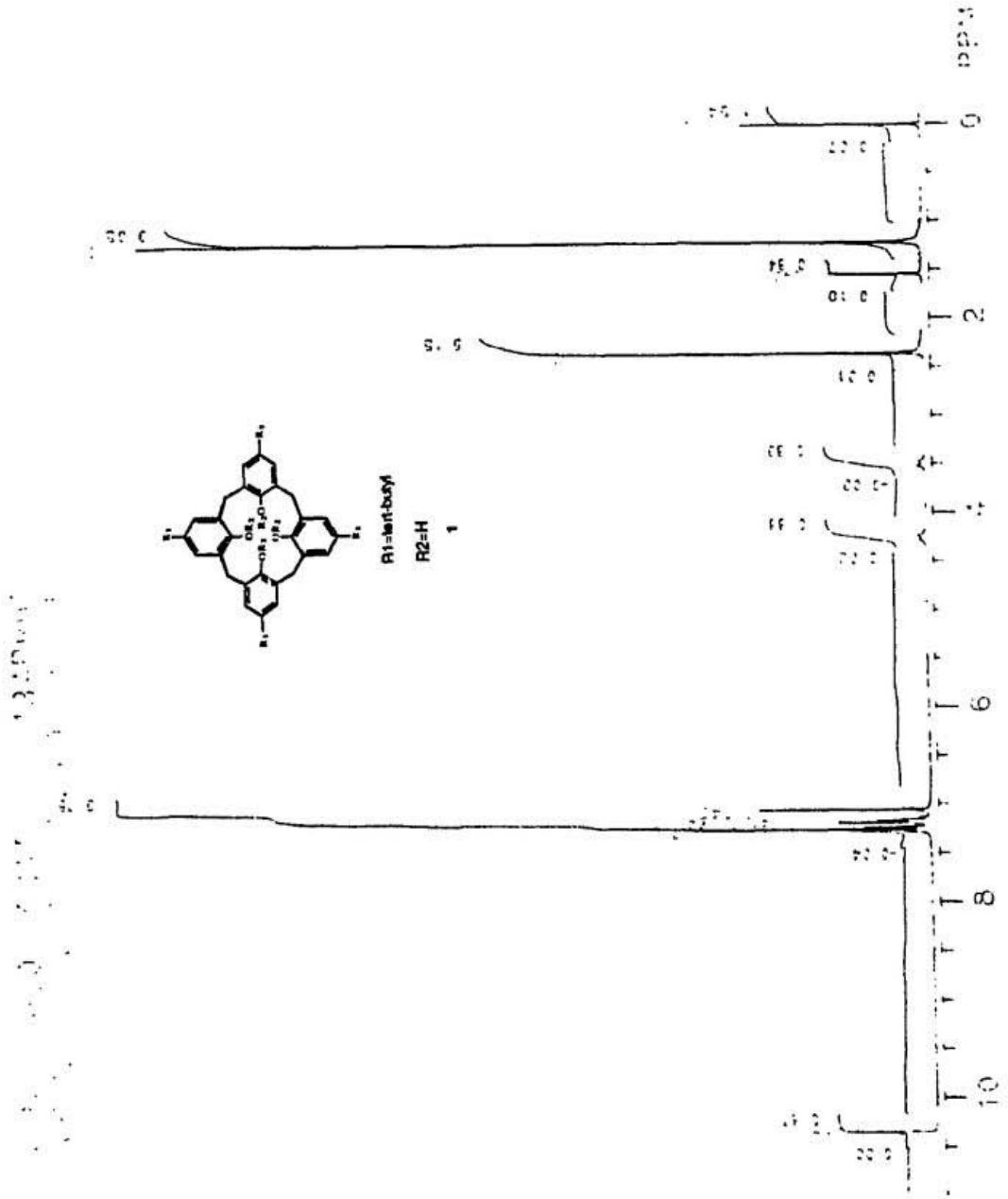
atom	atom	distance	ADC(*)	atom	atom	distance	ADC(*)
O(3)	C(50)	3.356(4)	55401	C(19)	C(21)	3.544(4)	55602
C(18)	C(21)	3.596(4)	55602	C(49)	C(50)	3.528(5)	55401
C(19)	C(19)	3.426(5)	55602				

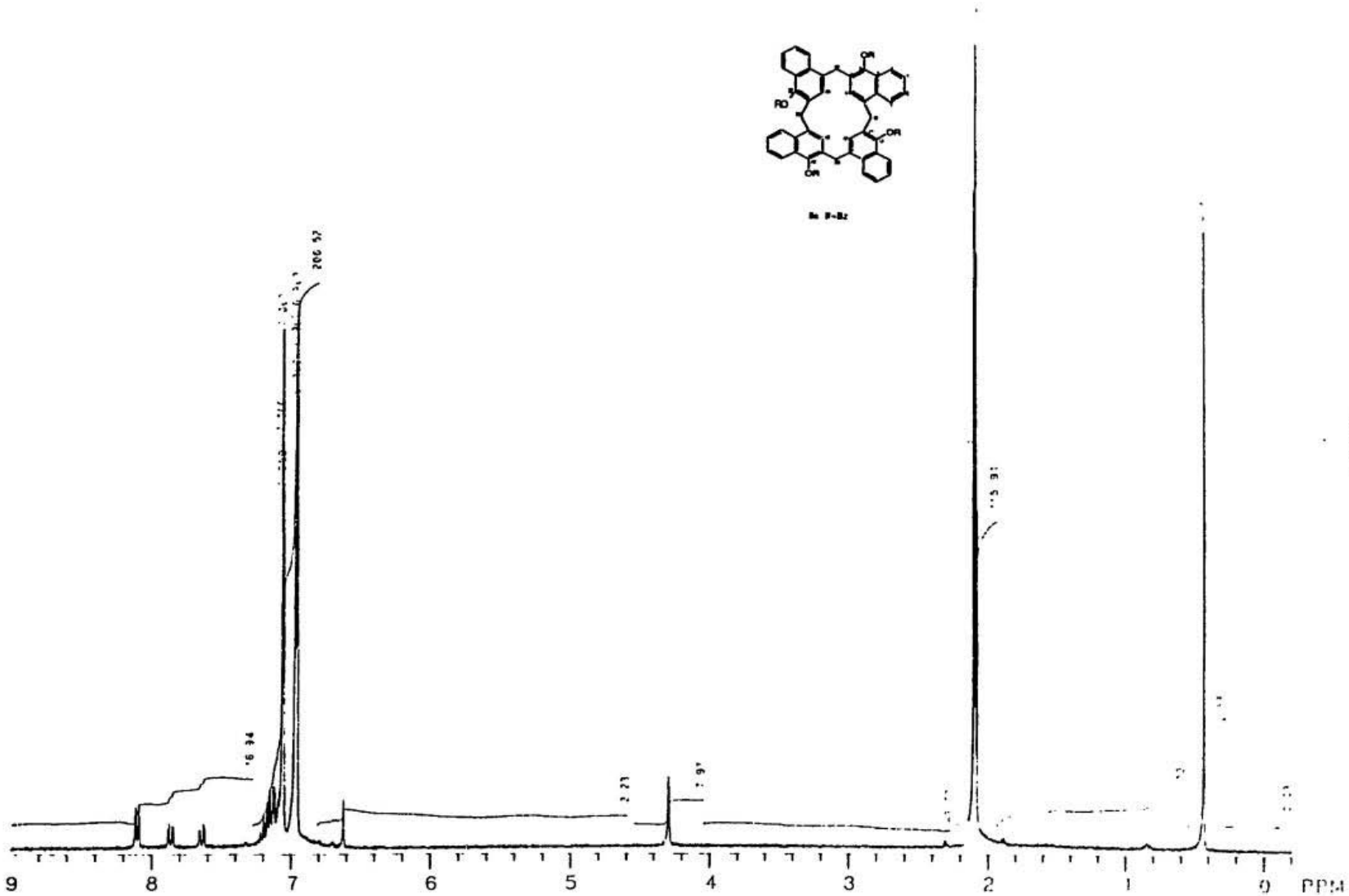
Distances are in angstroms. Estimated standard deviations i
the least significant figure are given in parentheses.

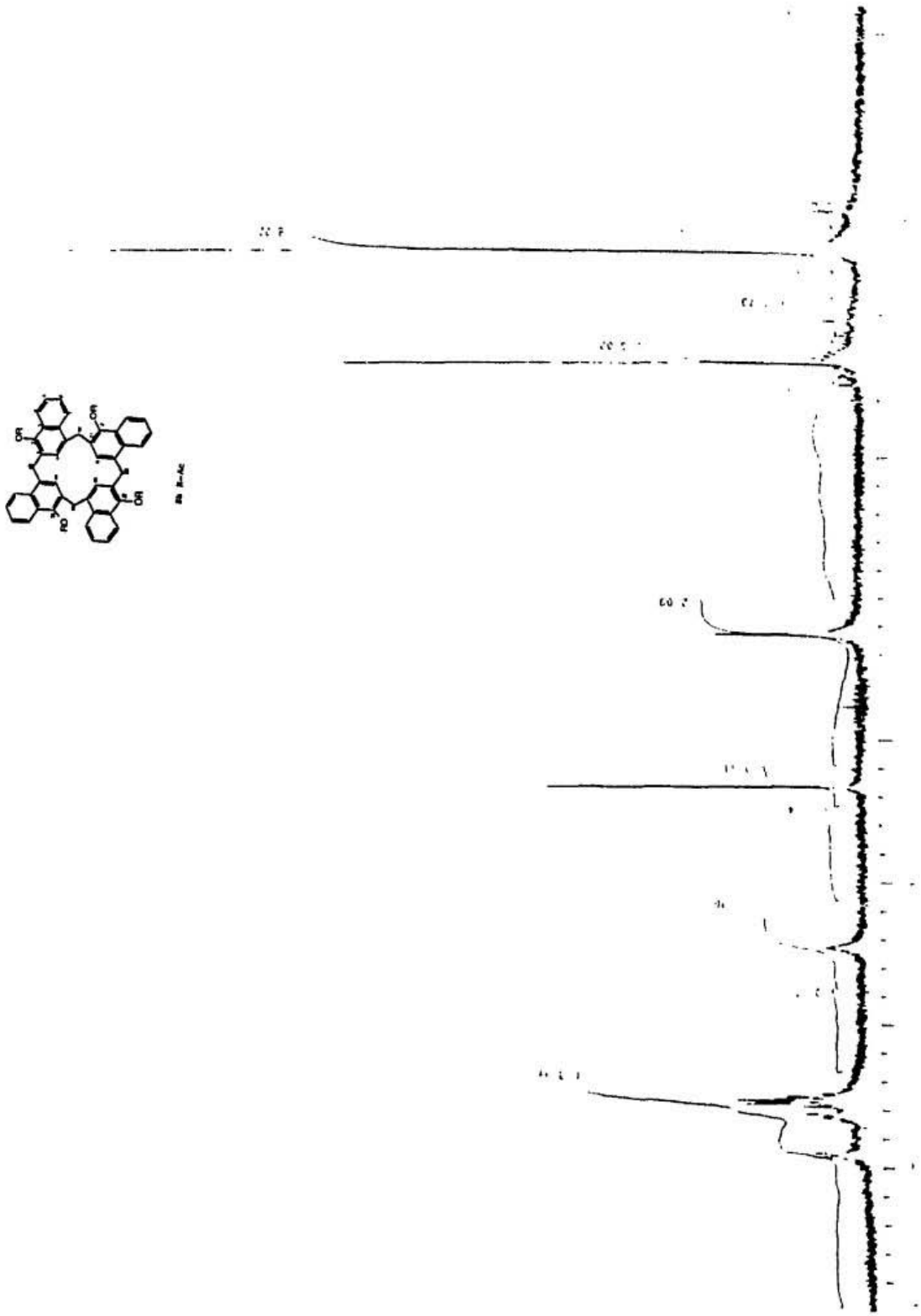
Appendix II

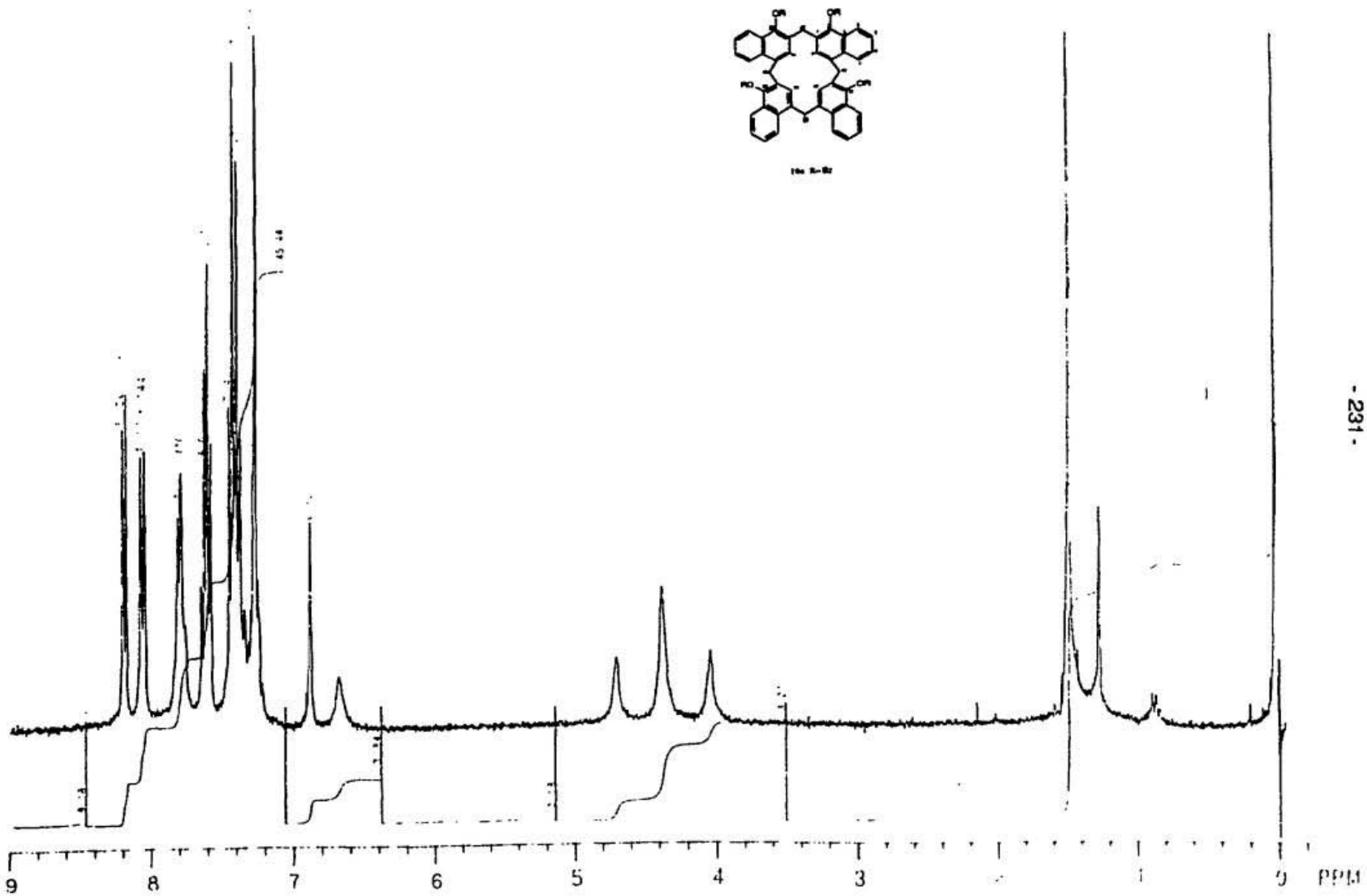
^1H NMR Spectra of Compounds.

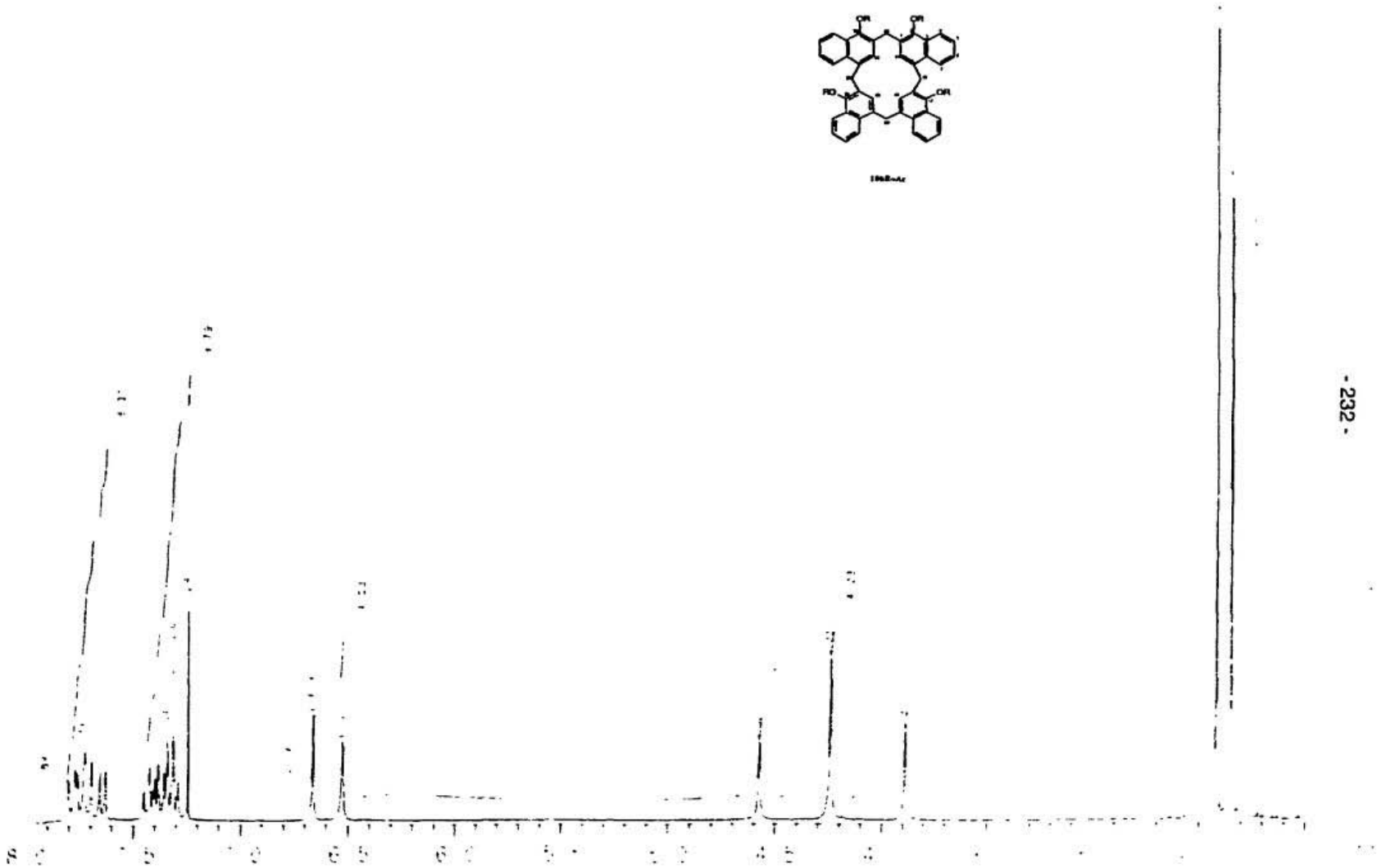
(In Order of Compound Number)

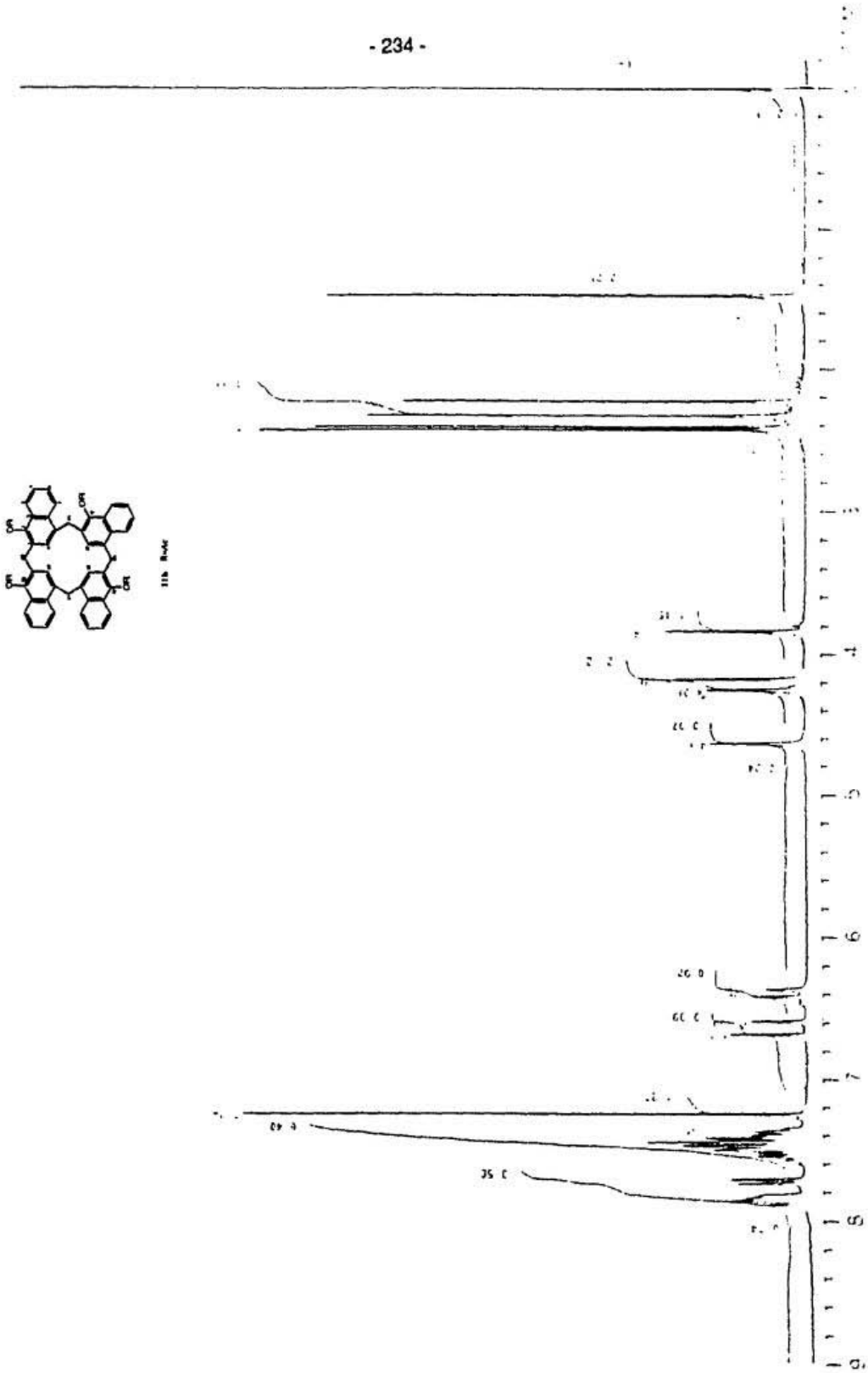

R1=tert-butyl
R2=H
1
0
2
4
6
8
10

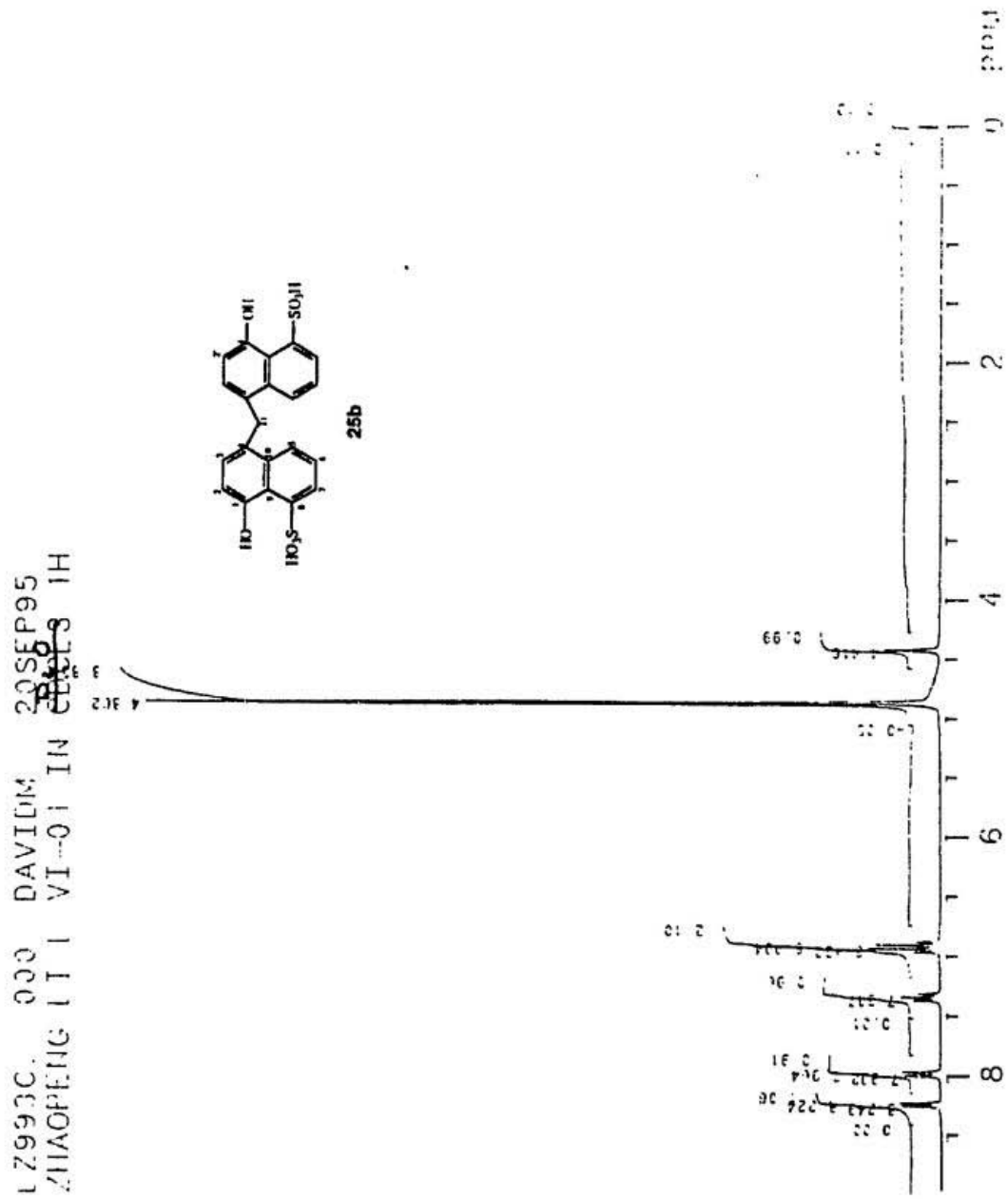

9
8
7
6
5
4
3
2
1
0
PPM



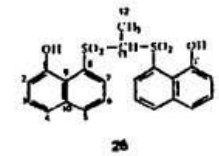

9
8
7
6
5
4
3
1
0
PPM



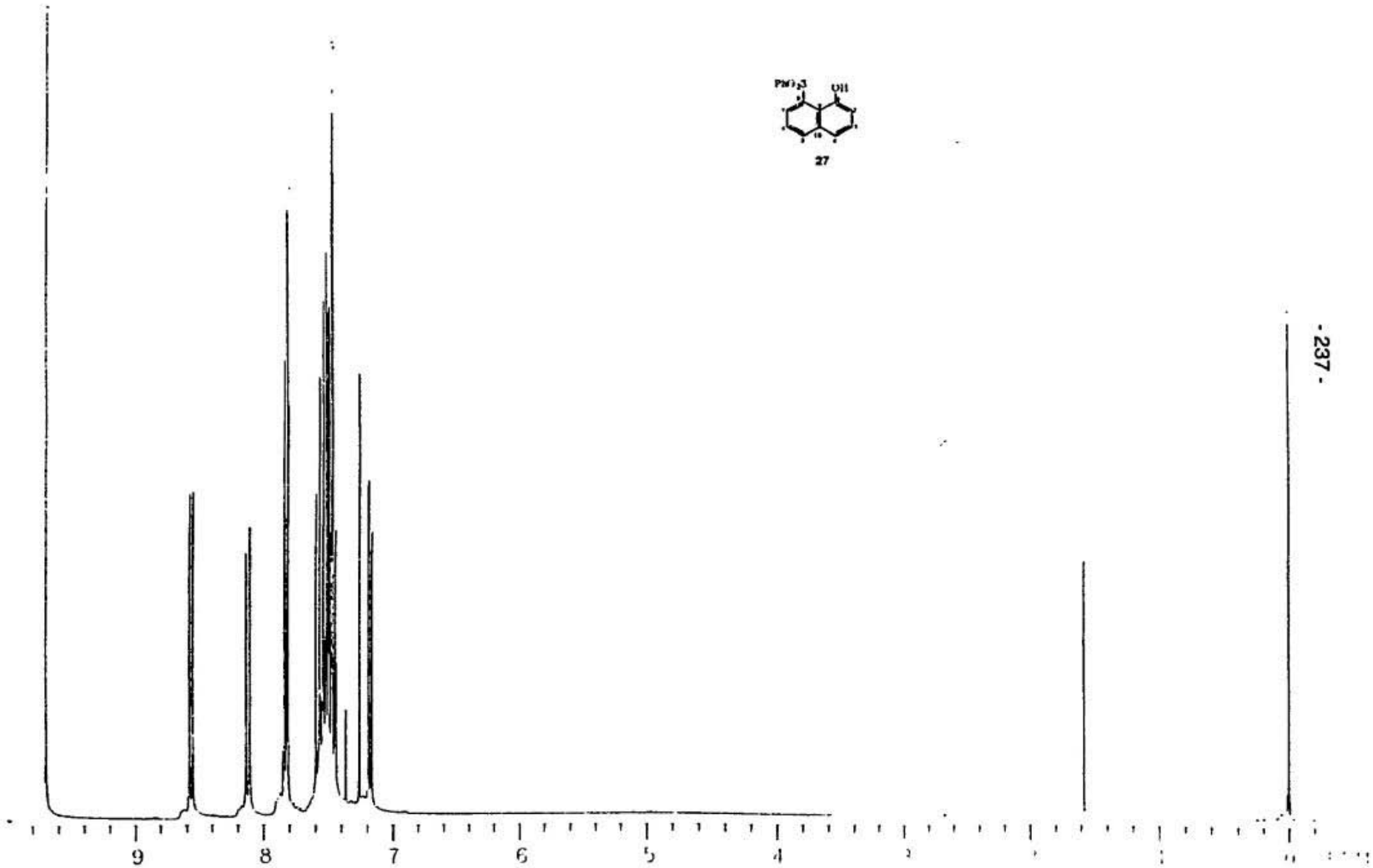



LZ9930. 000 DAVIDM 20SEP95
ZHAOPENG III VI-01 IN CDCL3 1H
25b
PPM

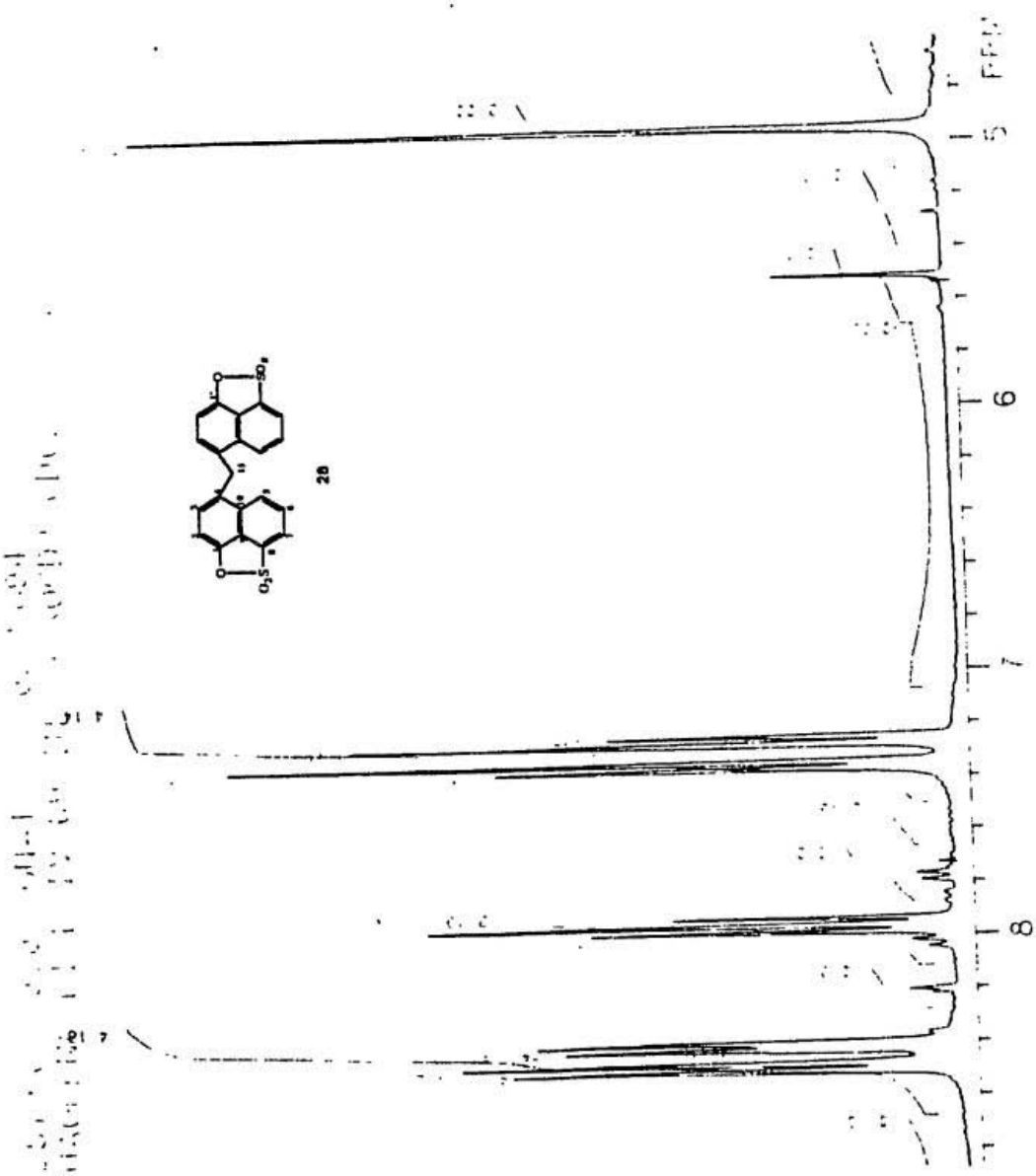
LZ032B 000 GNAT 01FEB92
ZHAOPENG LI L II 30 IN CD3COCD3 1H

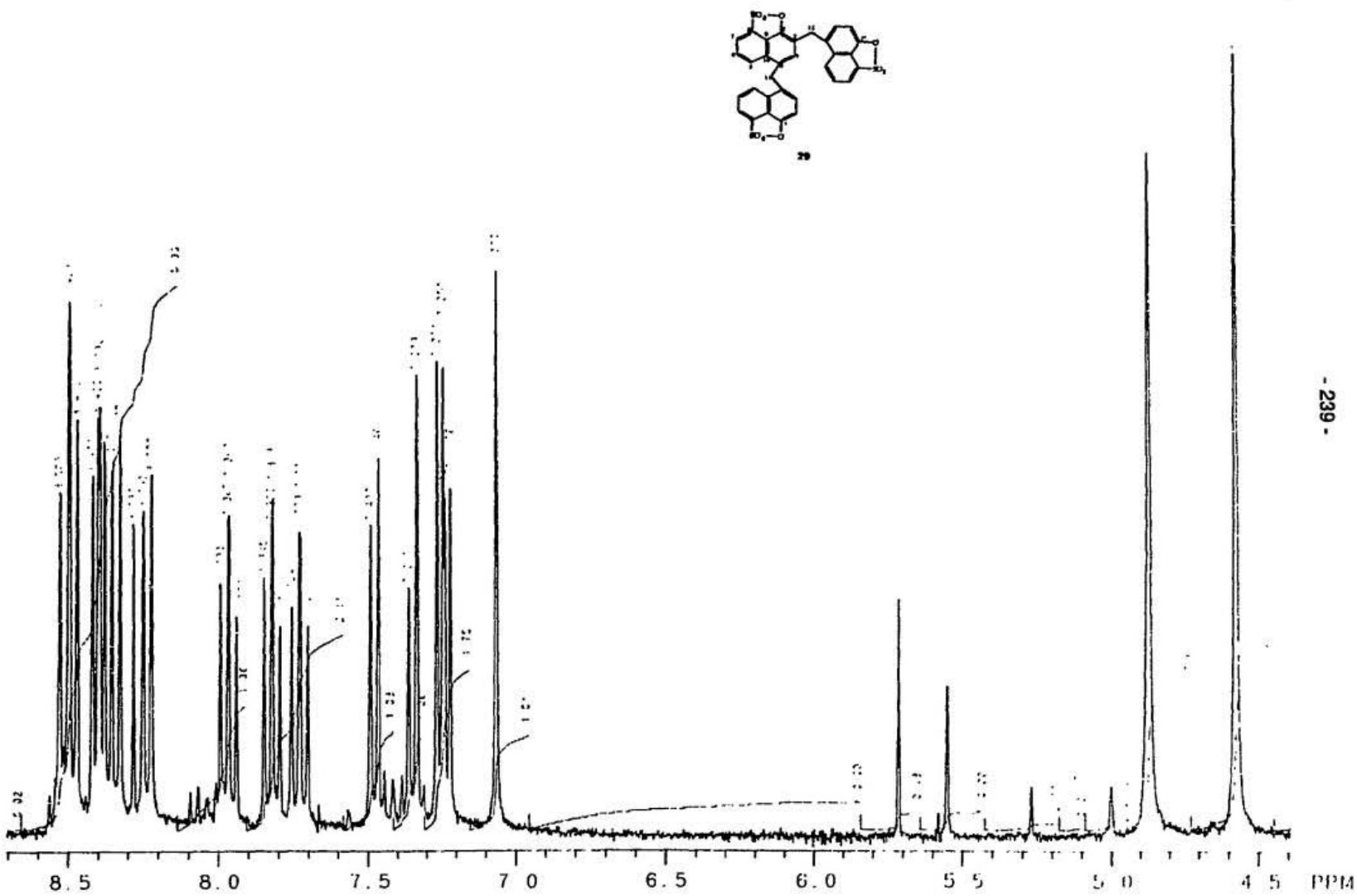


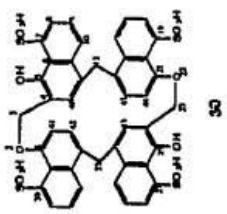
26



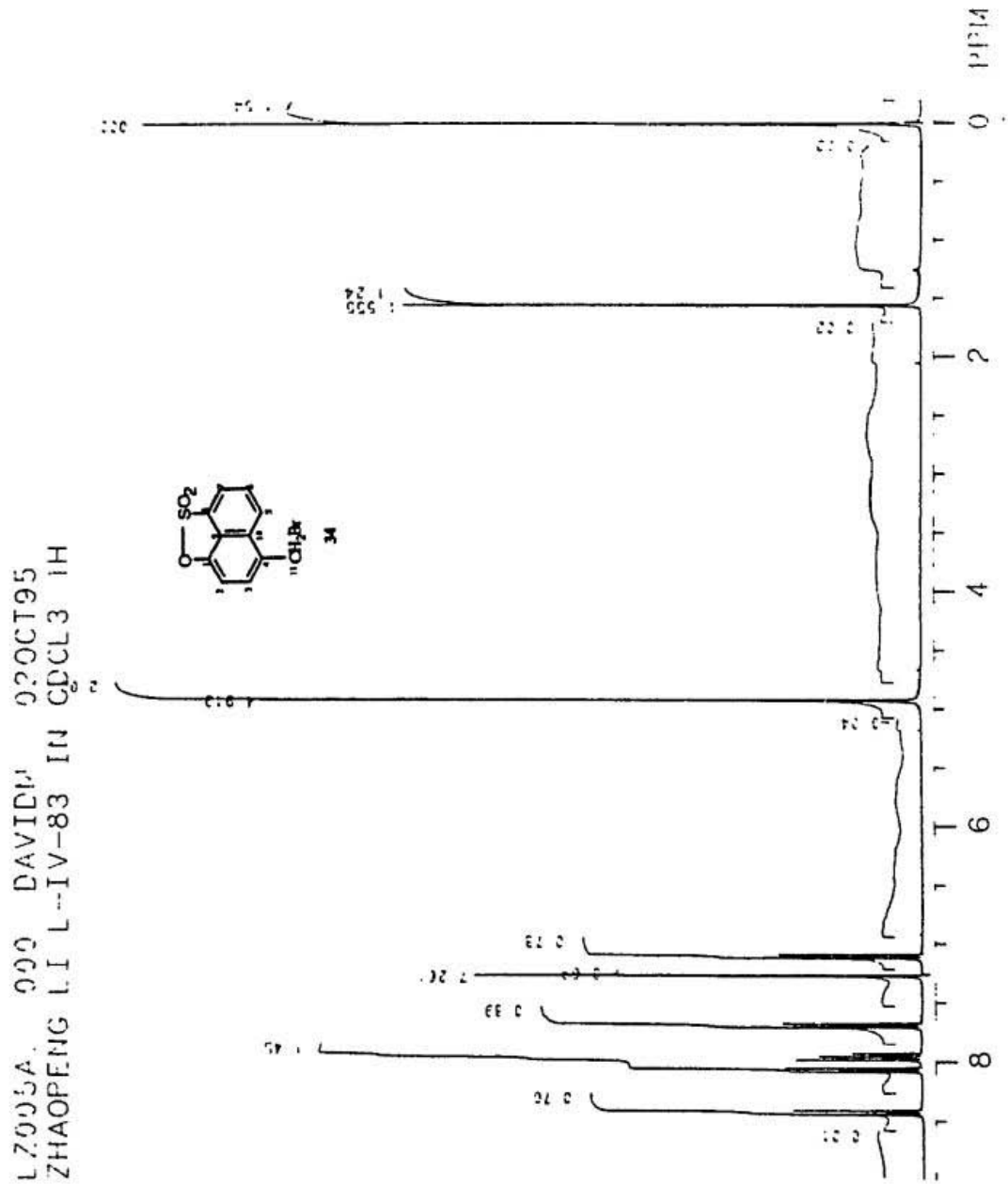
27

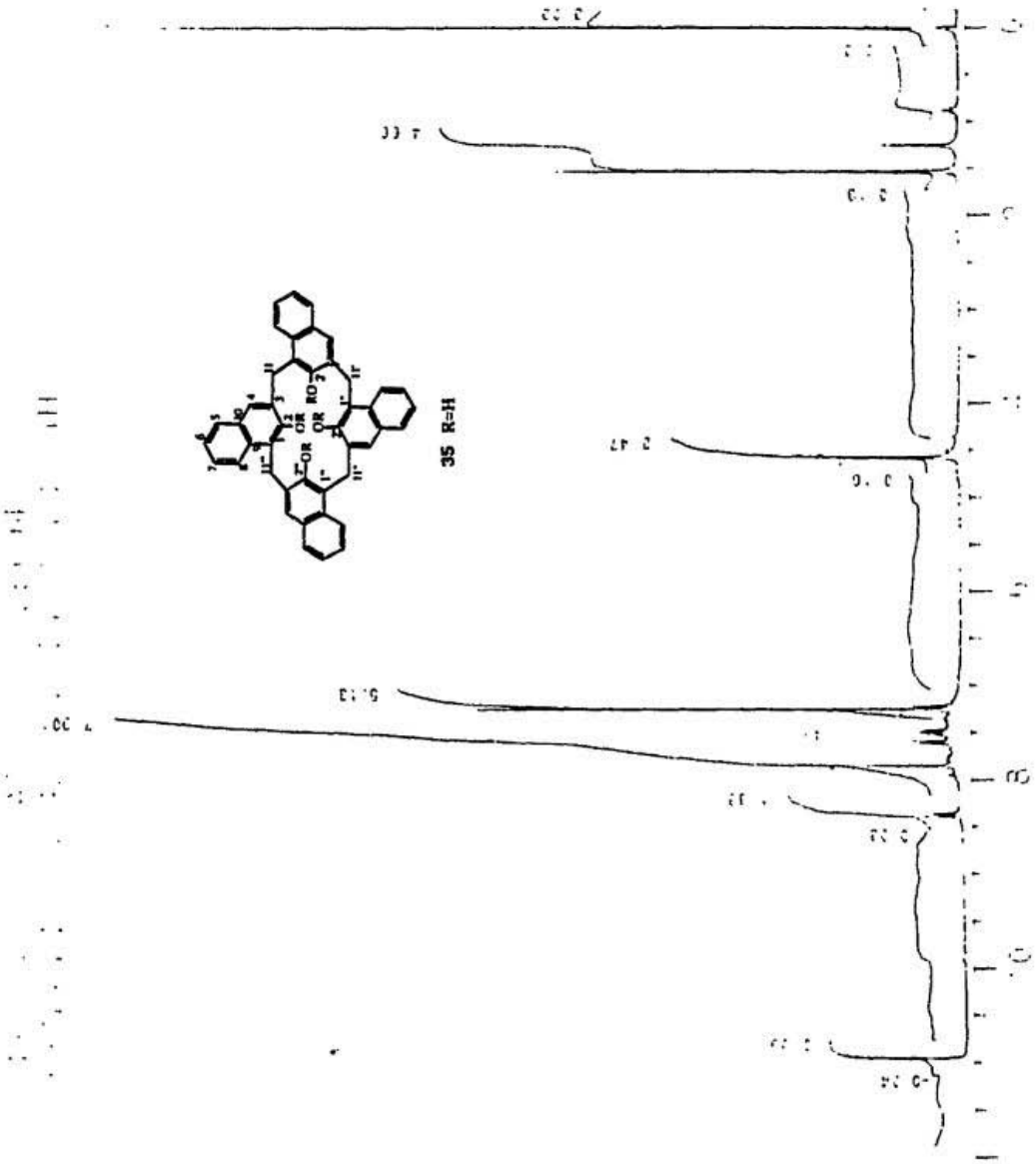

5
6
7
8
PPM

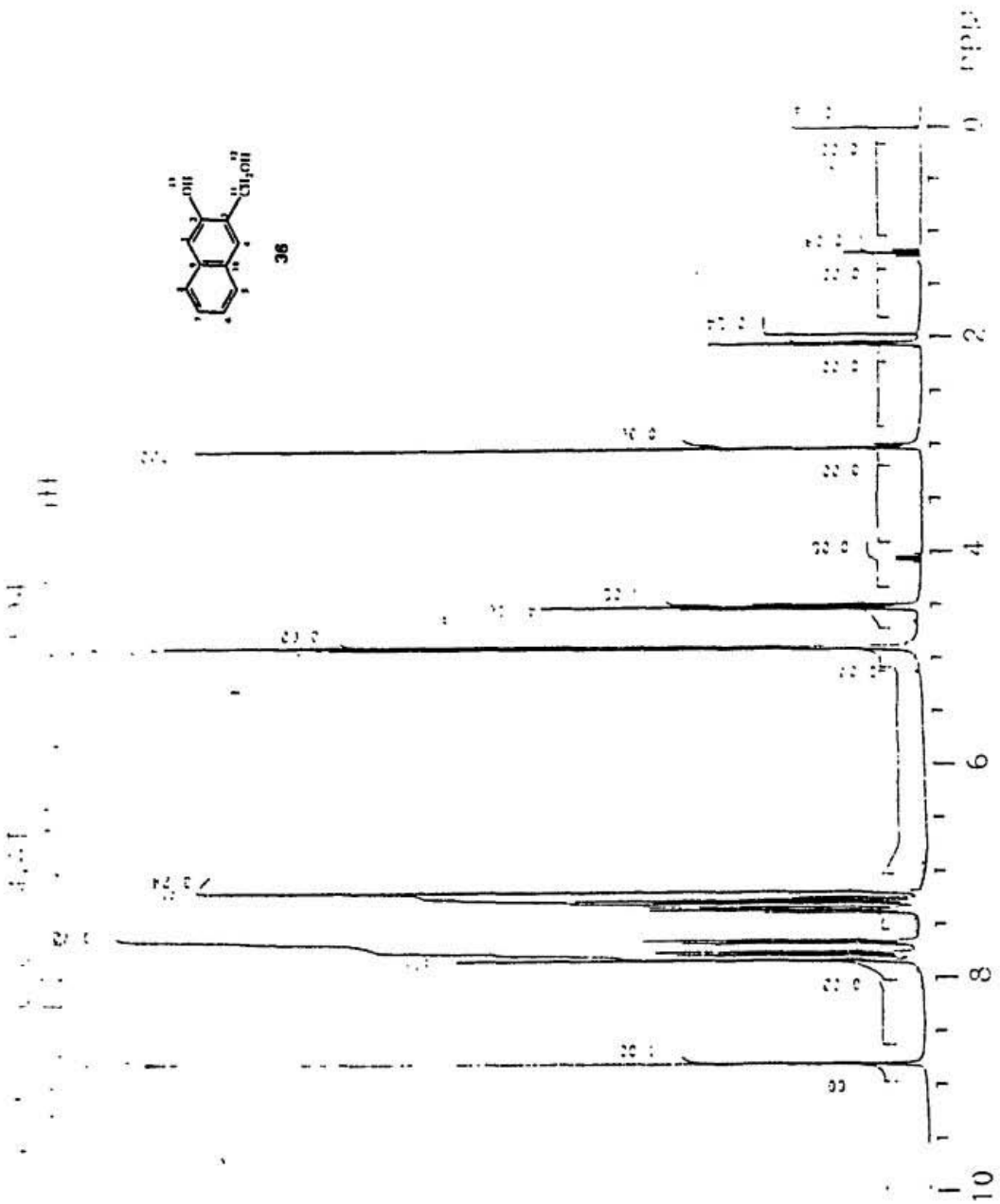

8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
PPM

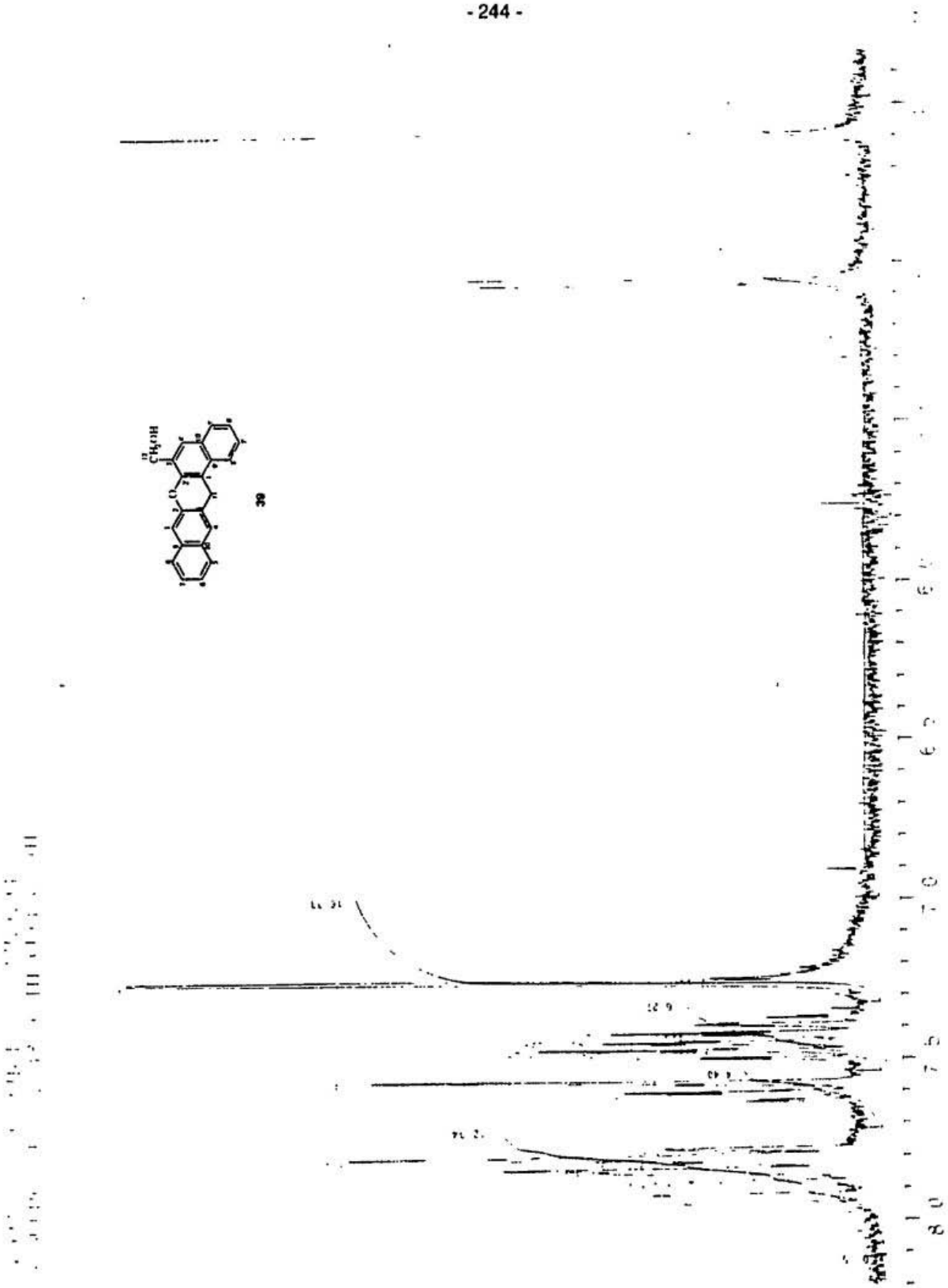


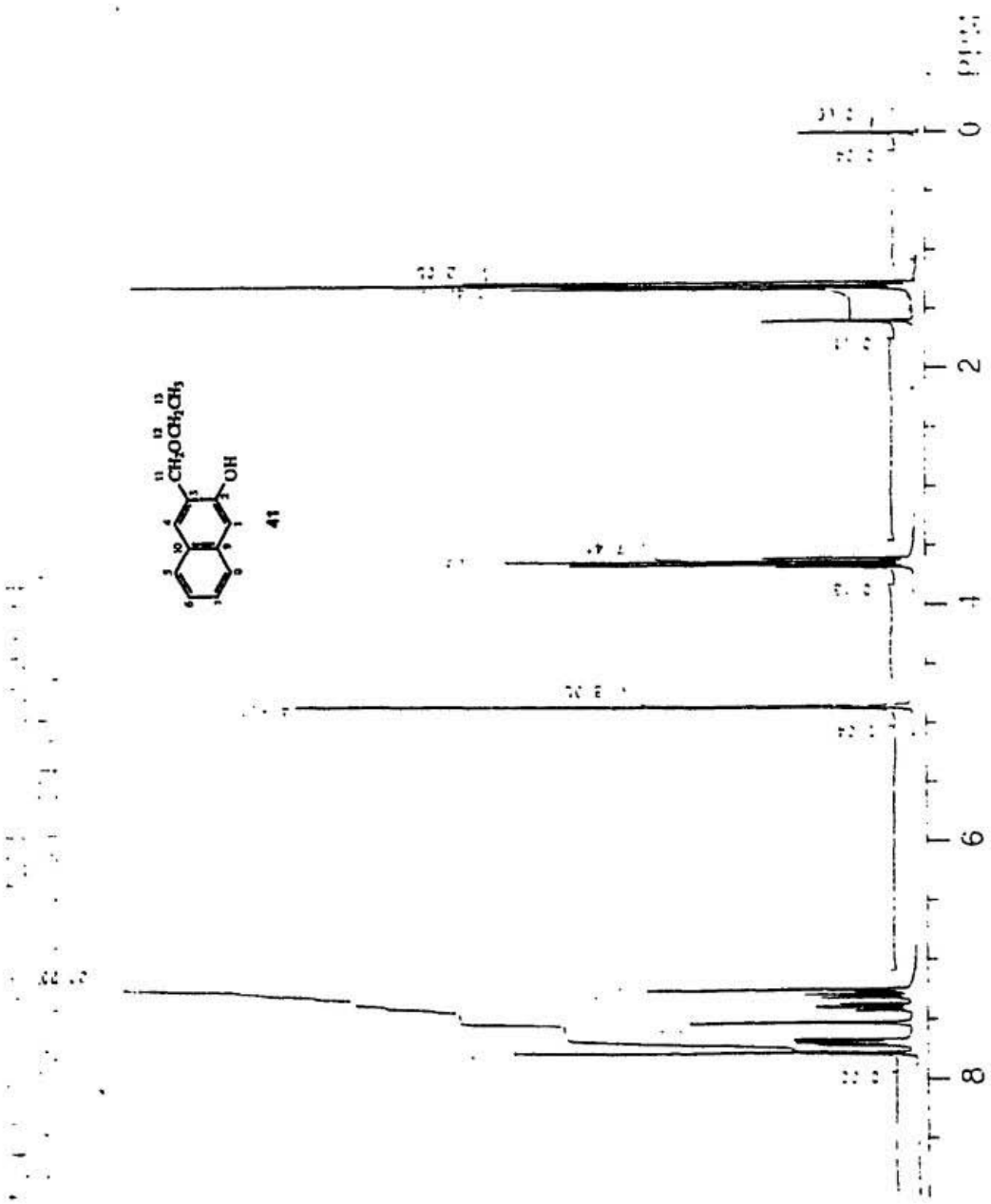
55

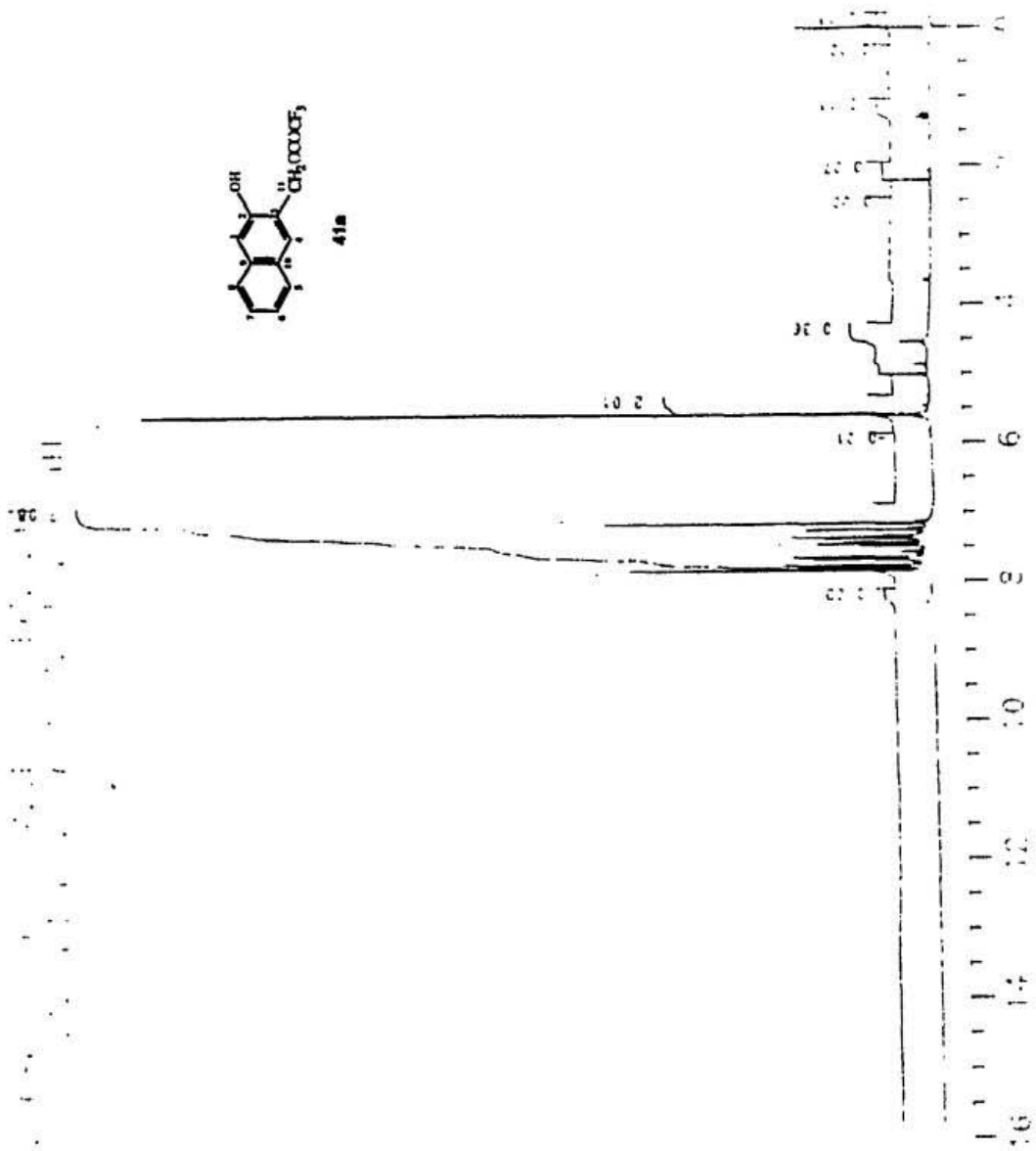

LZ0054 DAVIDI 02OCT95
ZHAOPENG LI L--IV-83 IN CDCL3 1H
PPM

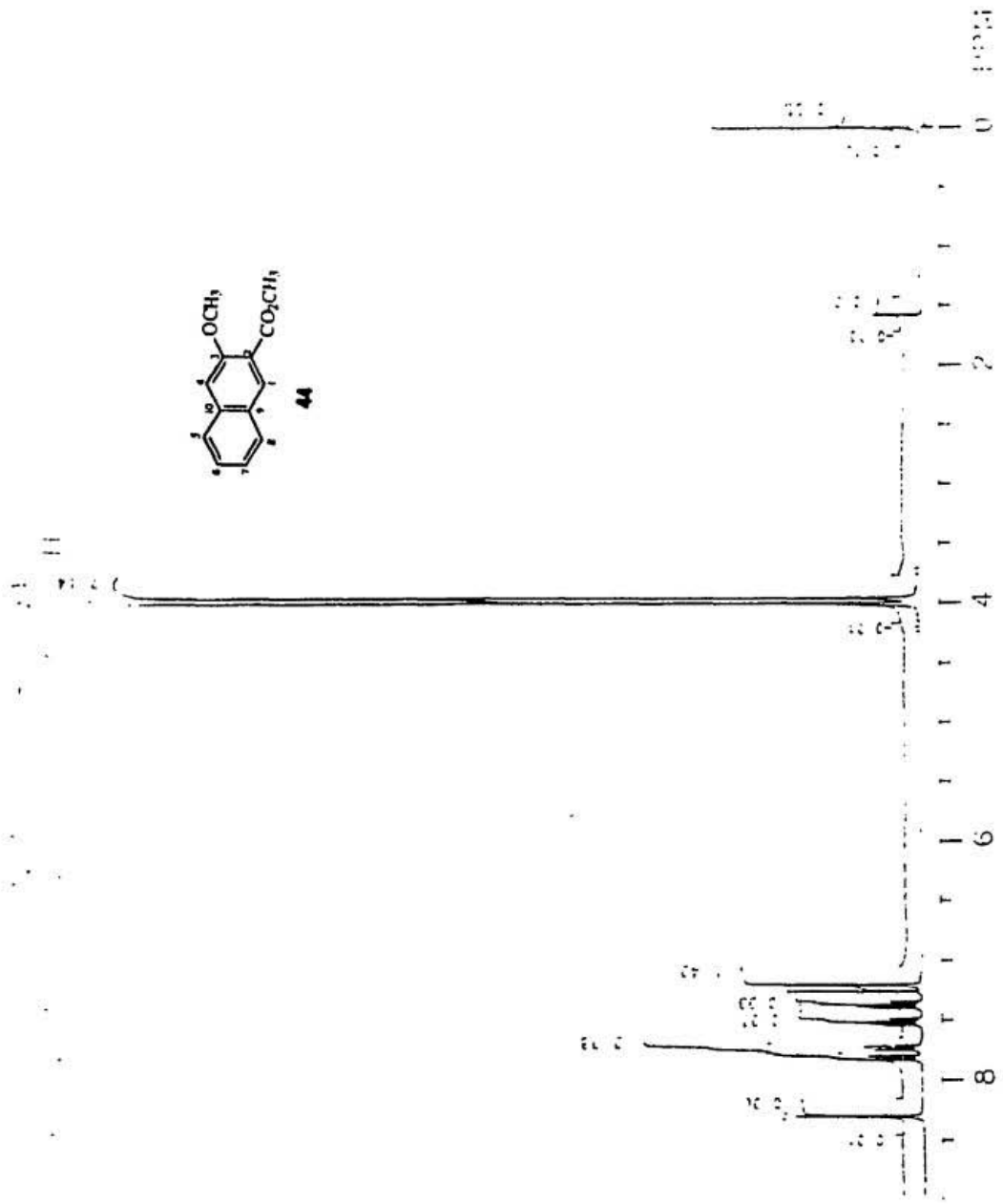

35 R=H

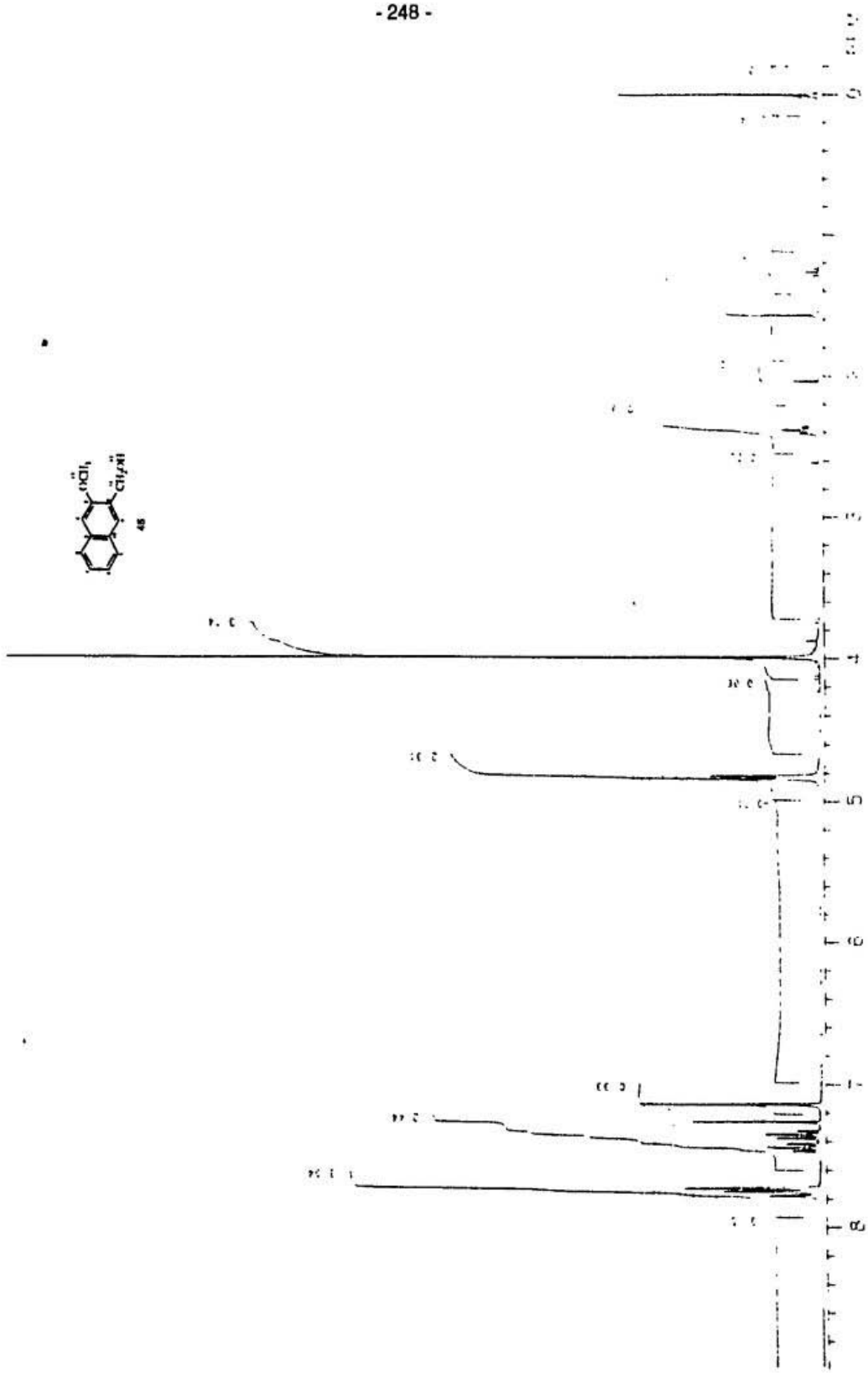

36
ppm
0
2
4
6
8
10

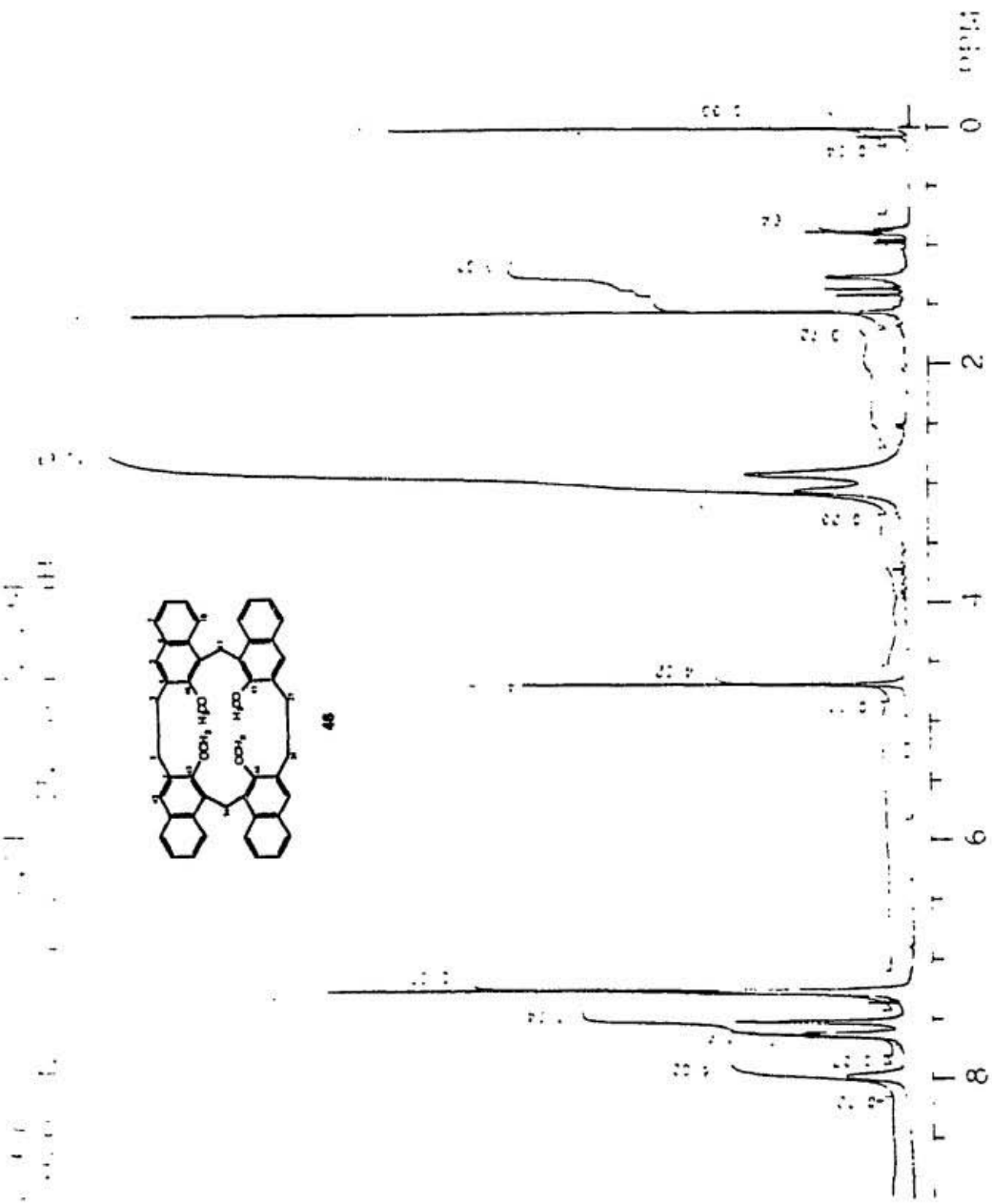



CH2OCH2CH3
OH
41
8
6
2
0
ppm

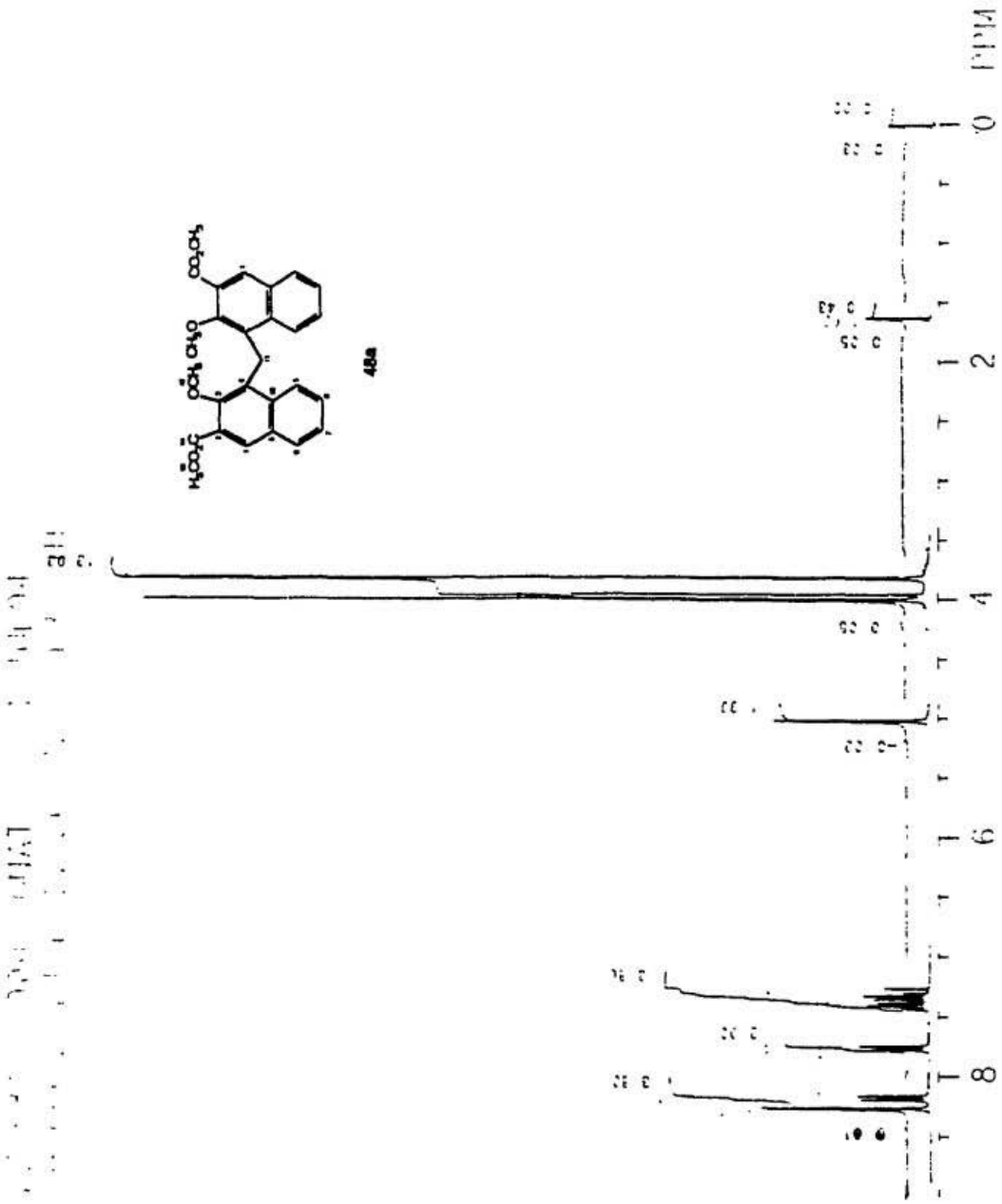

41a

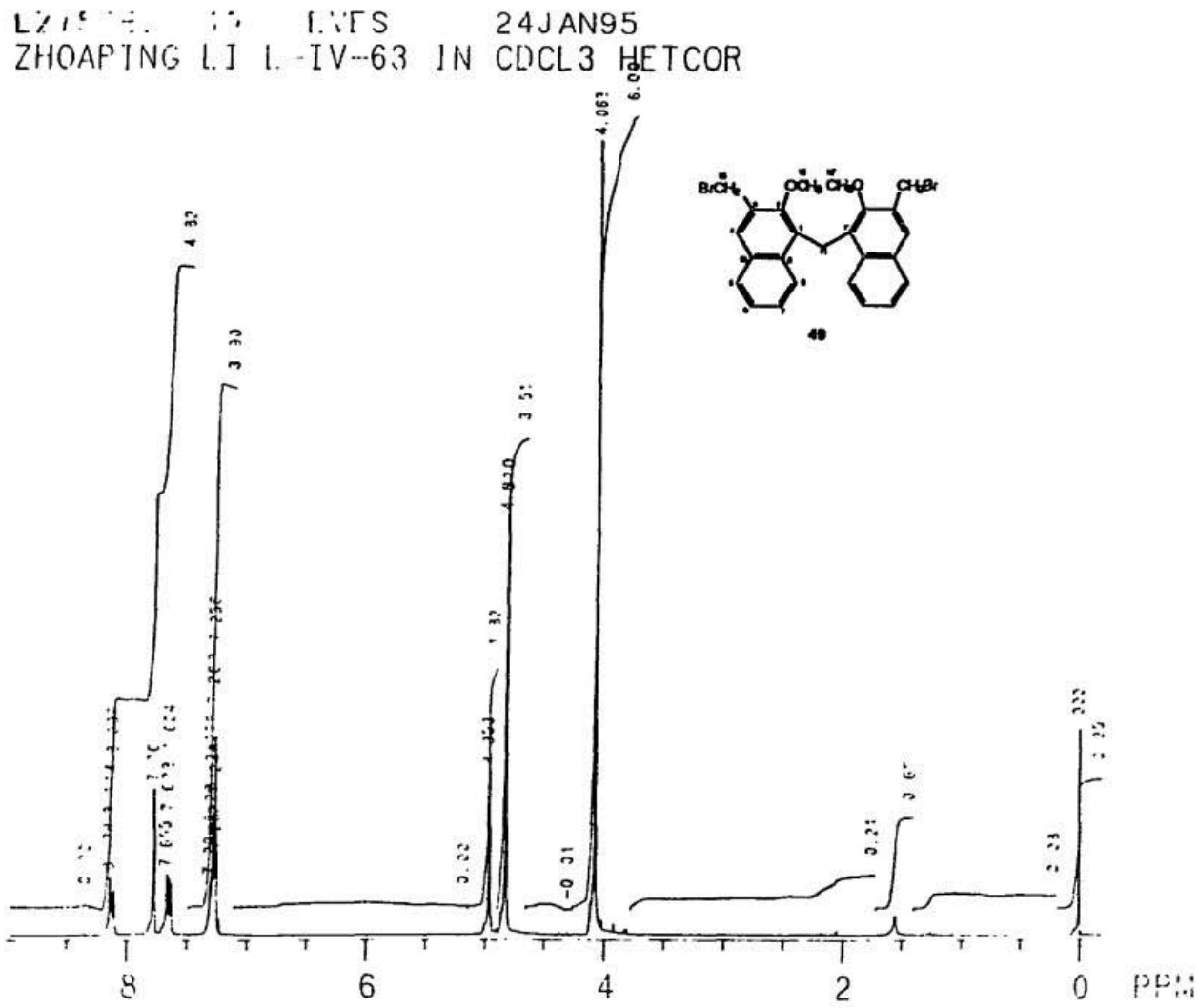

OCH3
CO2CH3
44

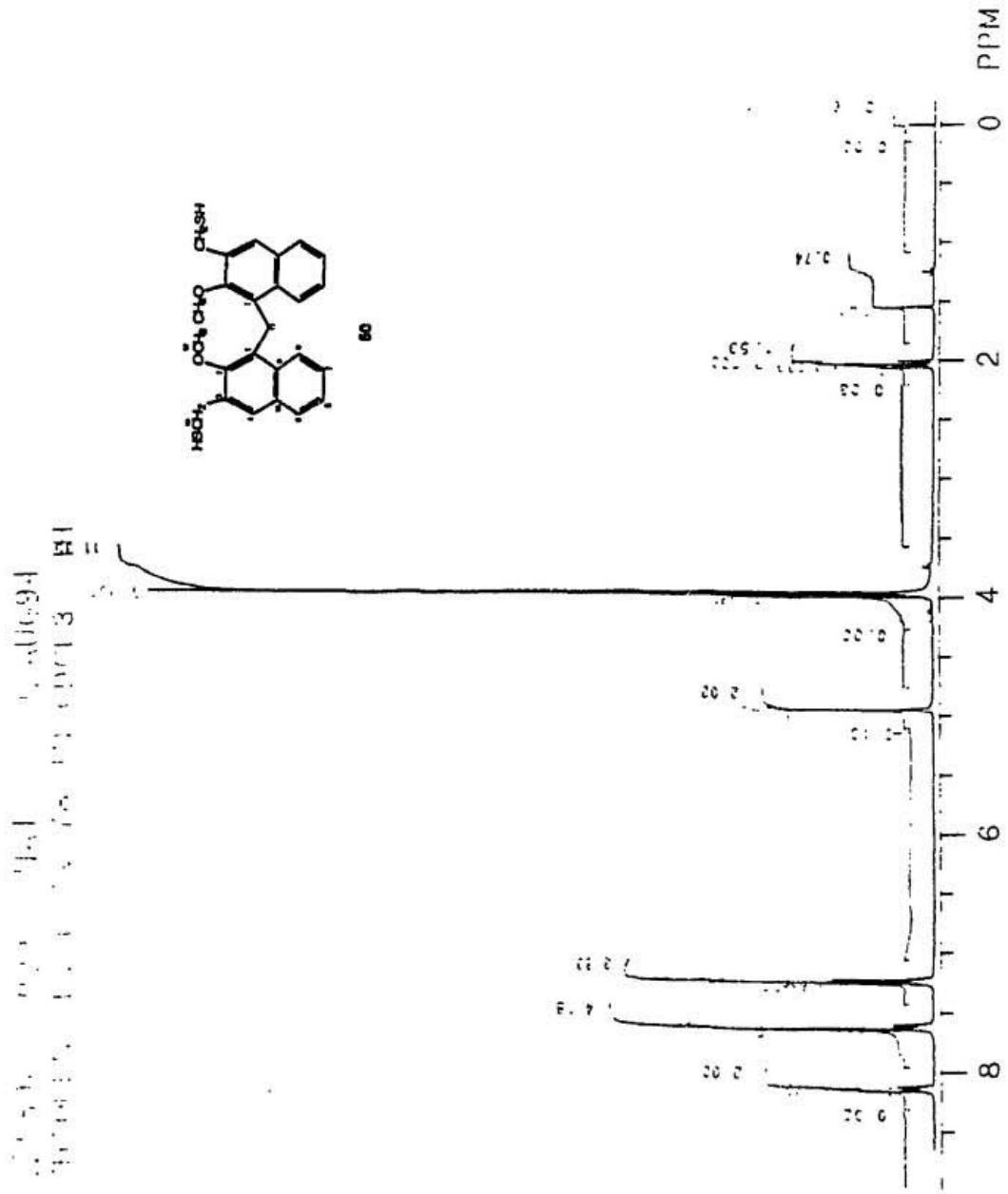


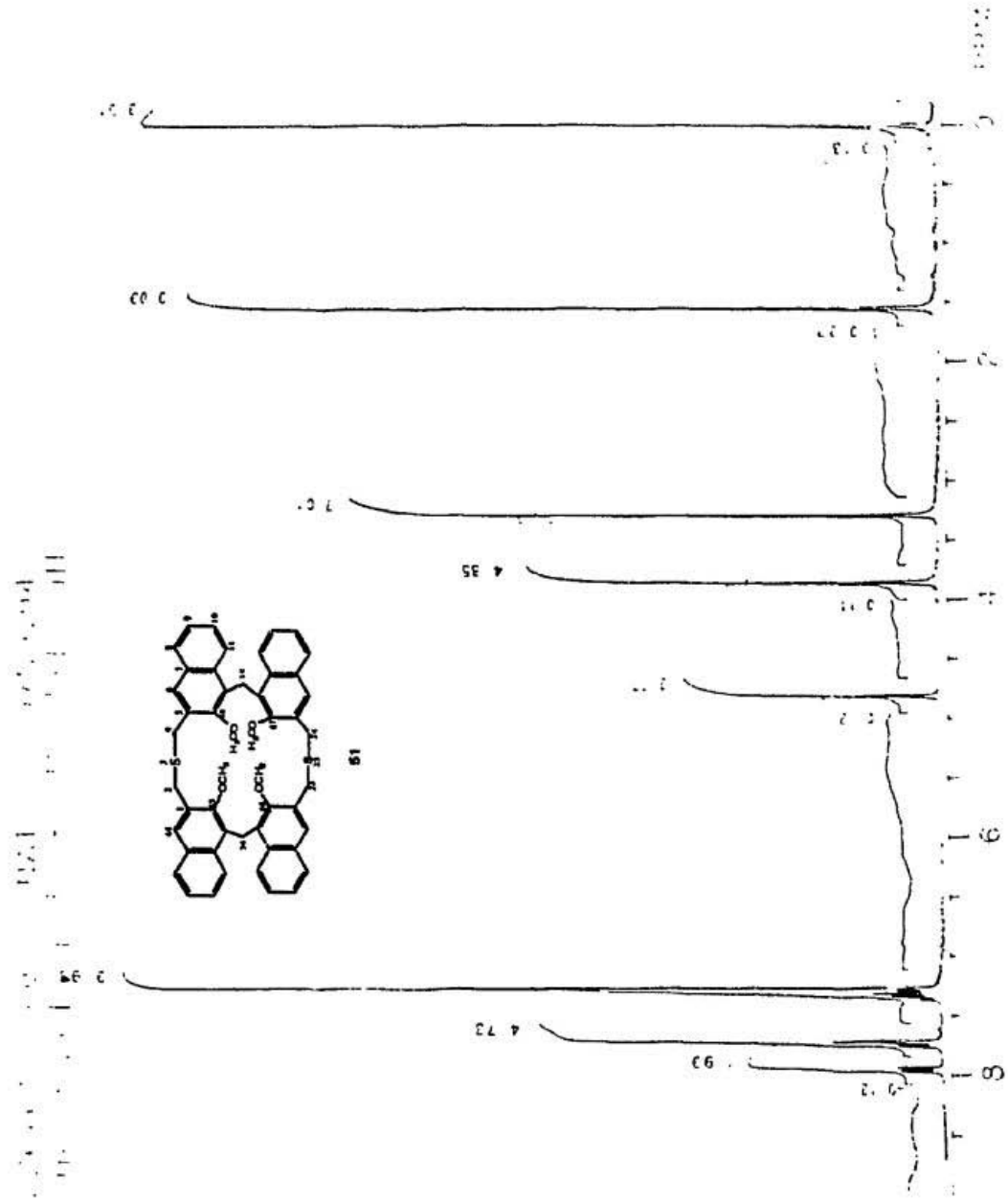


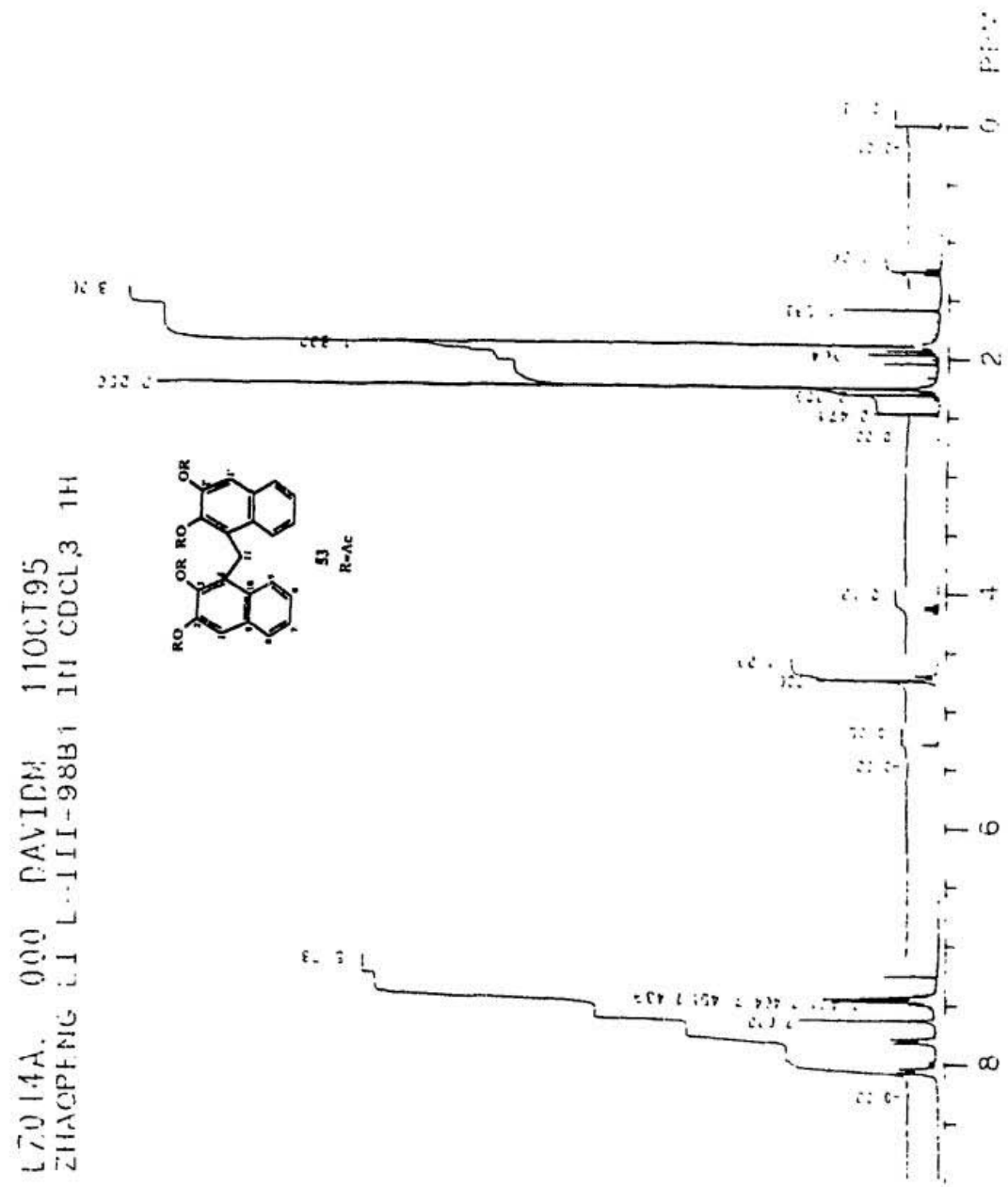
45

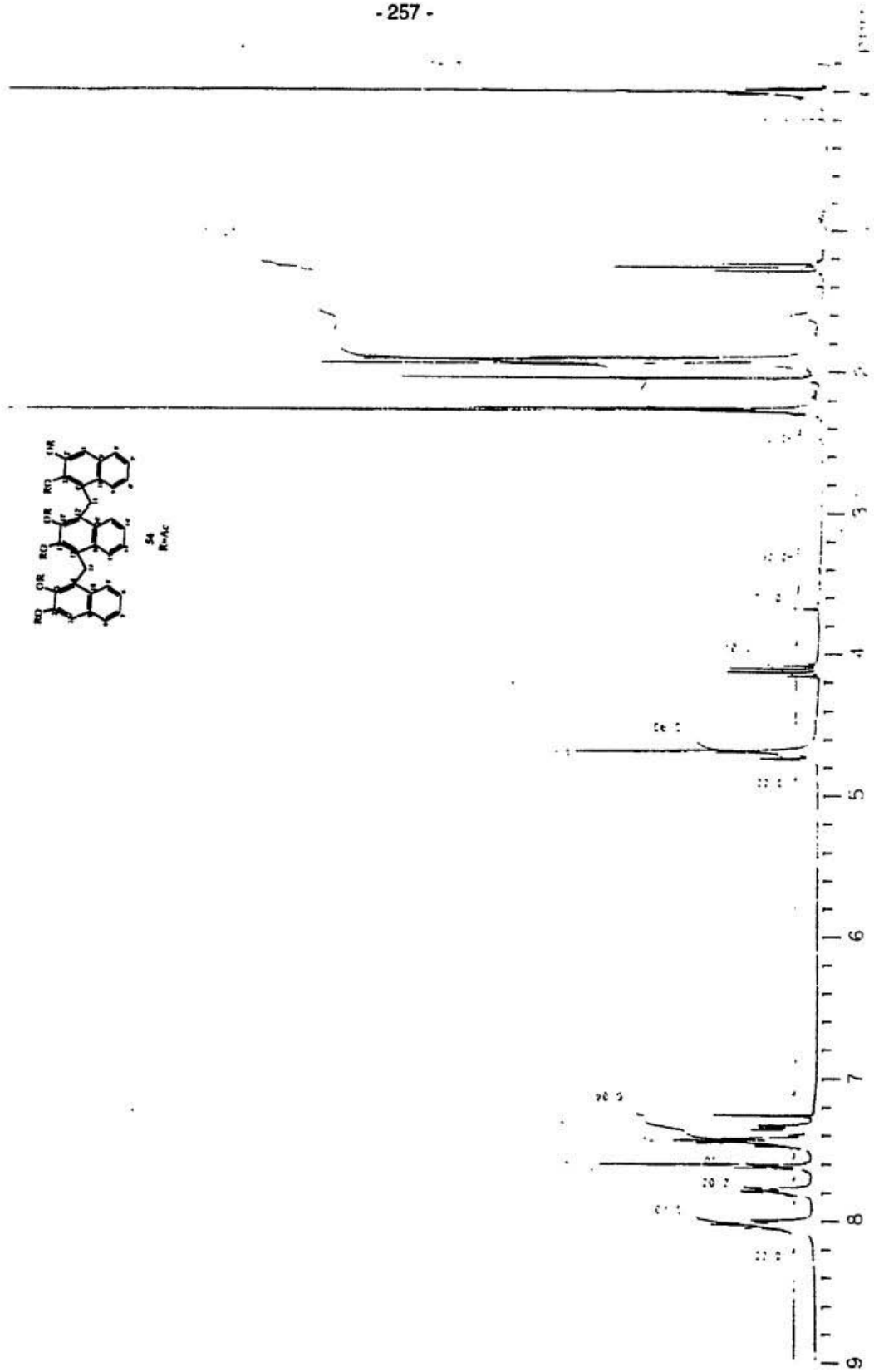

48a
PPM
0
2
4
6
8

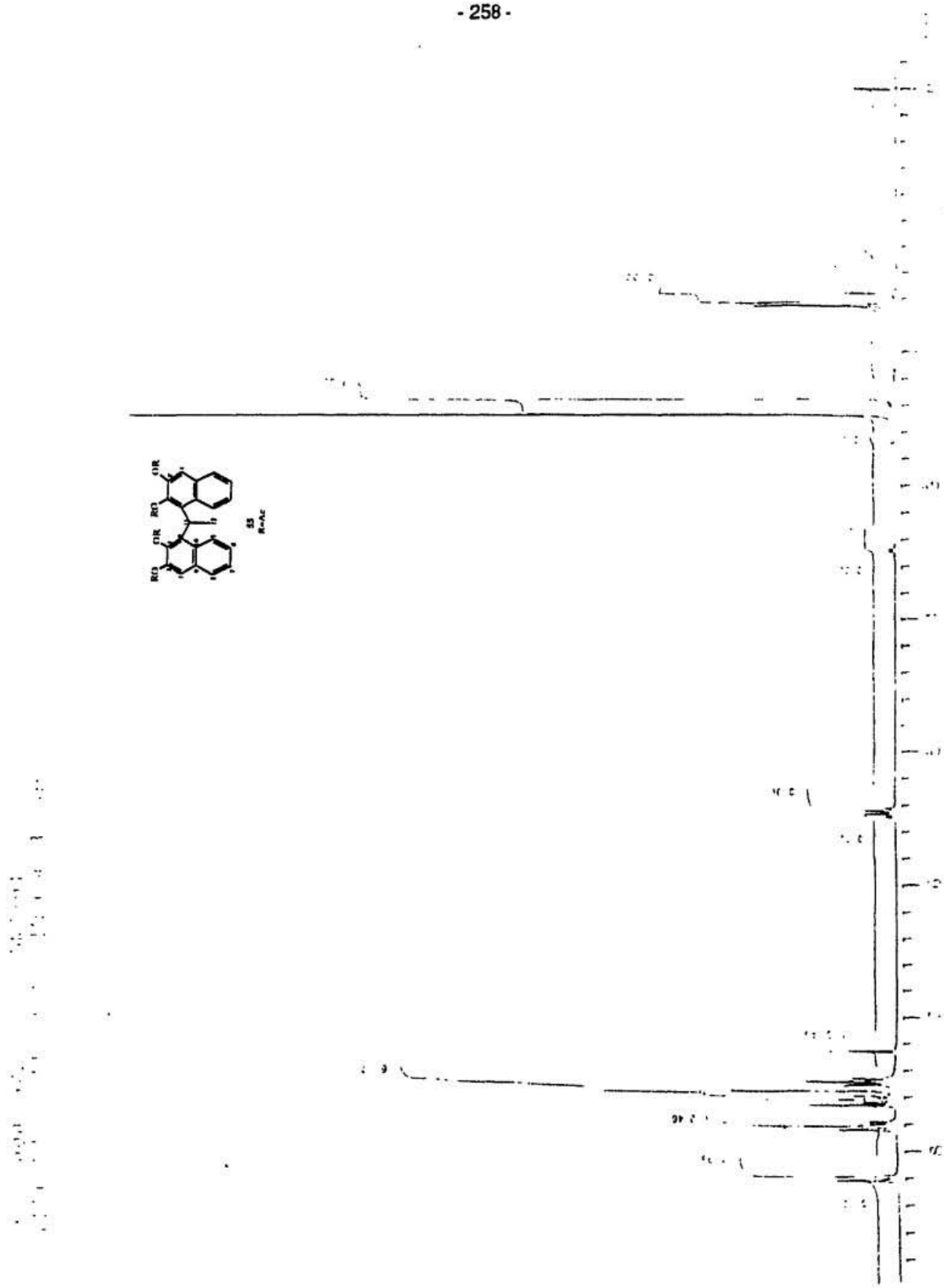

24JAN95
ZHOAPING LI L-IV-63 IN CDCL3 HETCOR
4.063
6.000
4.32
3.30
8
6
4
2
0
PPM

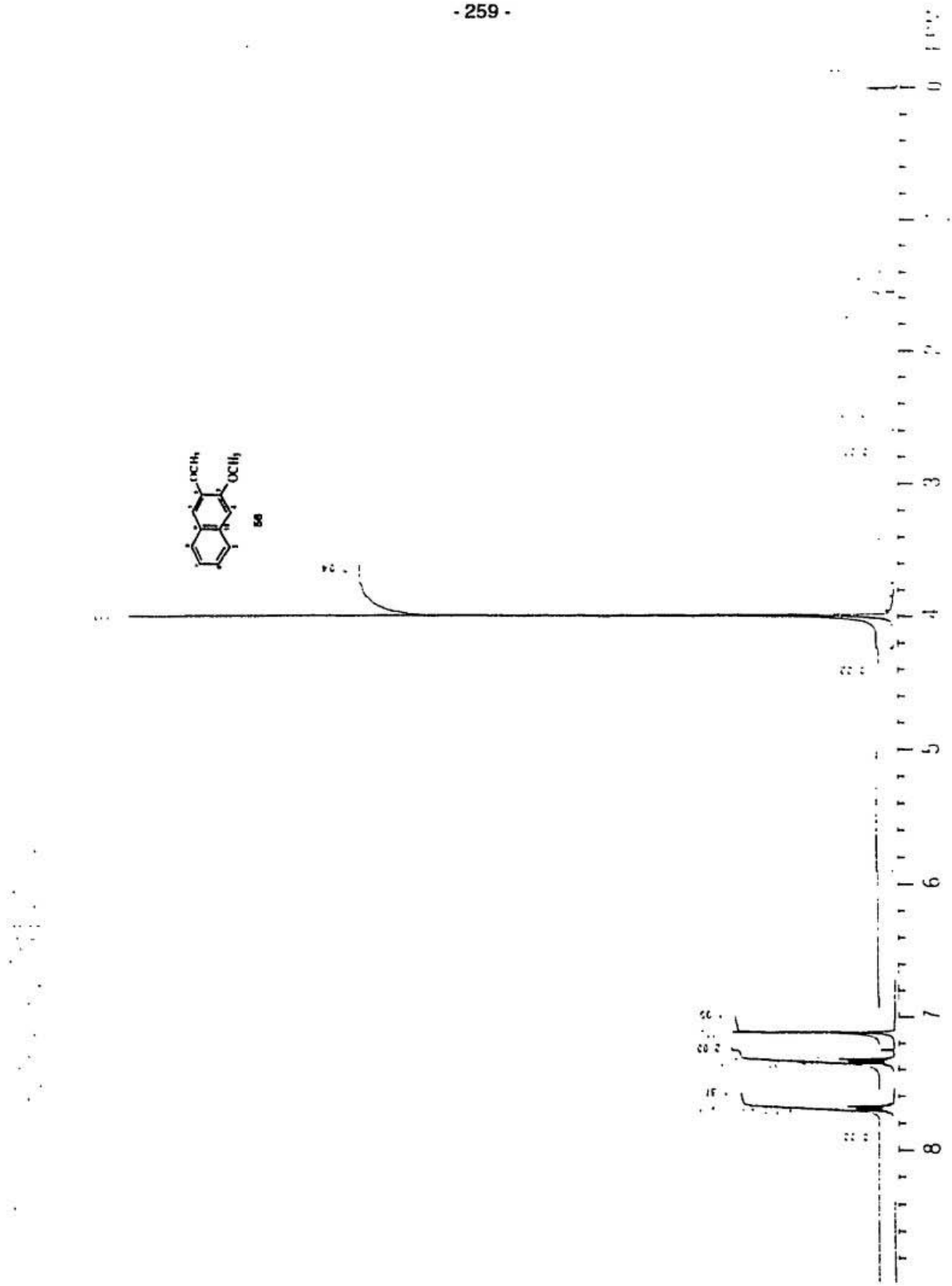

PPM
0
2
4
6
8
0.74
2.02
4.78
50

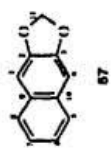


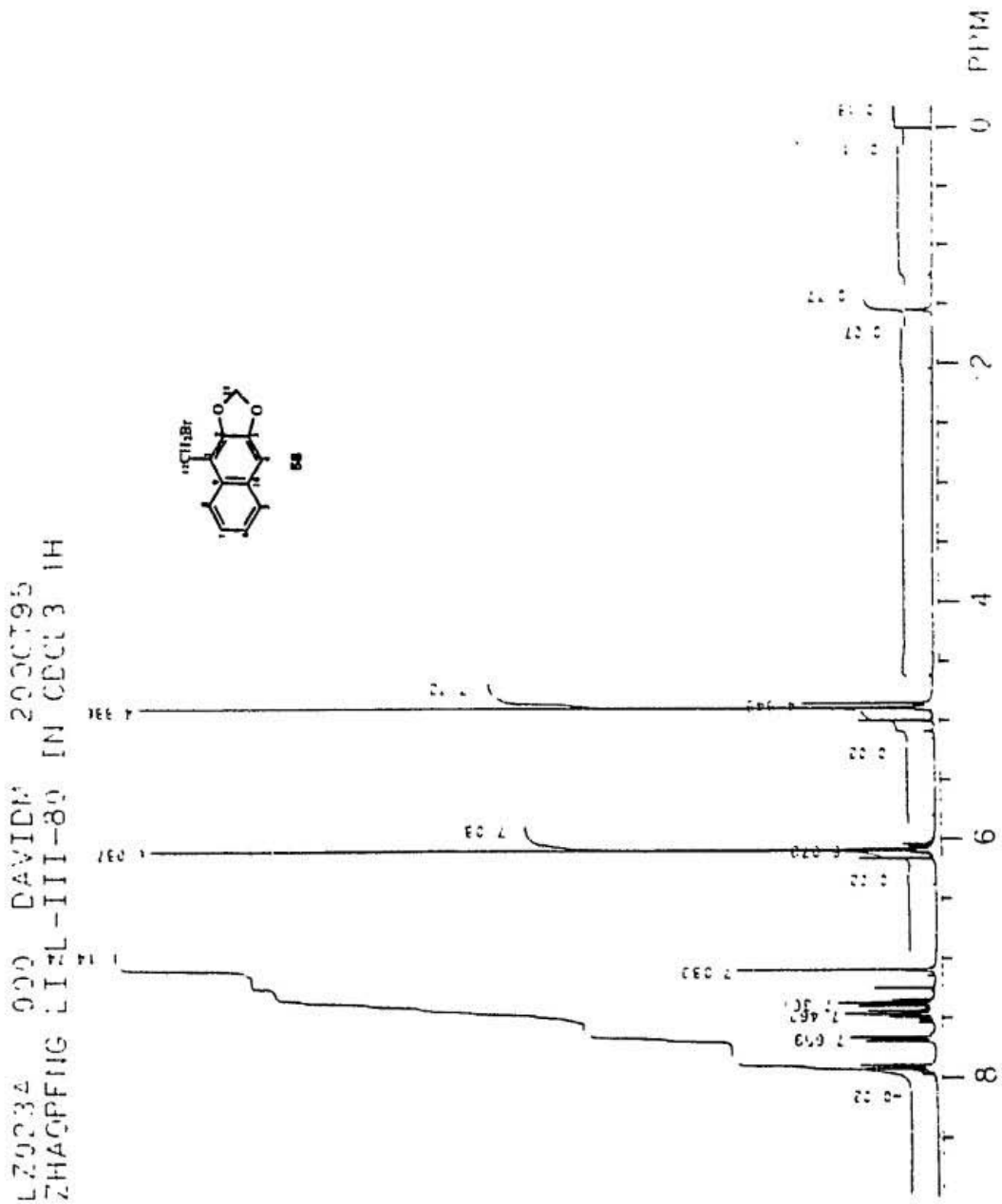

L70144. 000 DAVIDM 11OCT95
ZHAOPENG LI L-III-98B1 1H CDCL3 1H
OR
RO
OR
RO
53
R=Ac
PPM

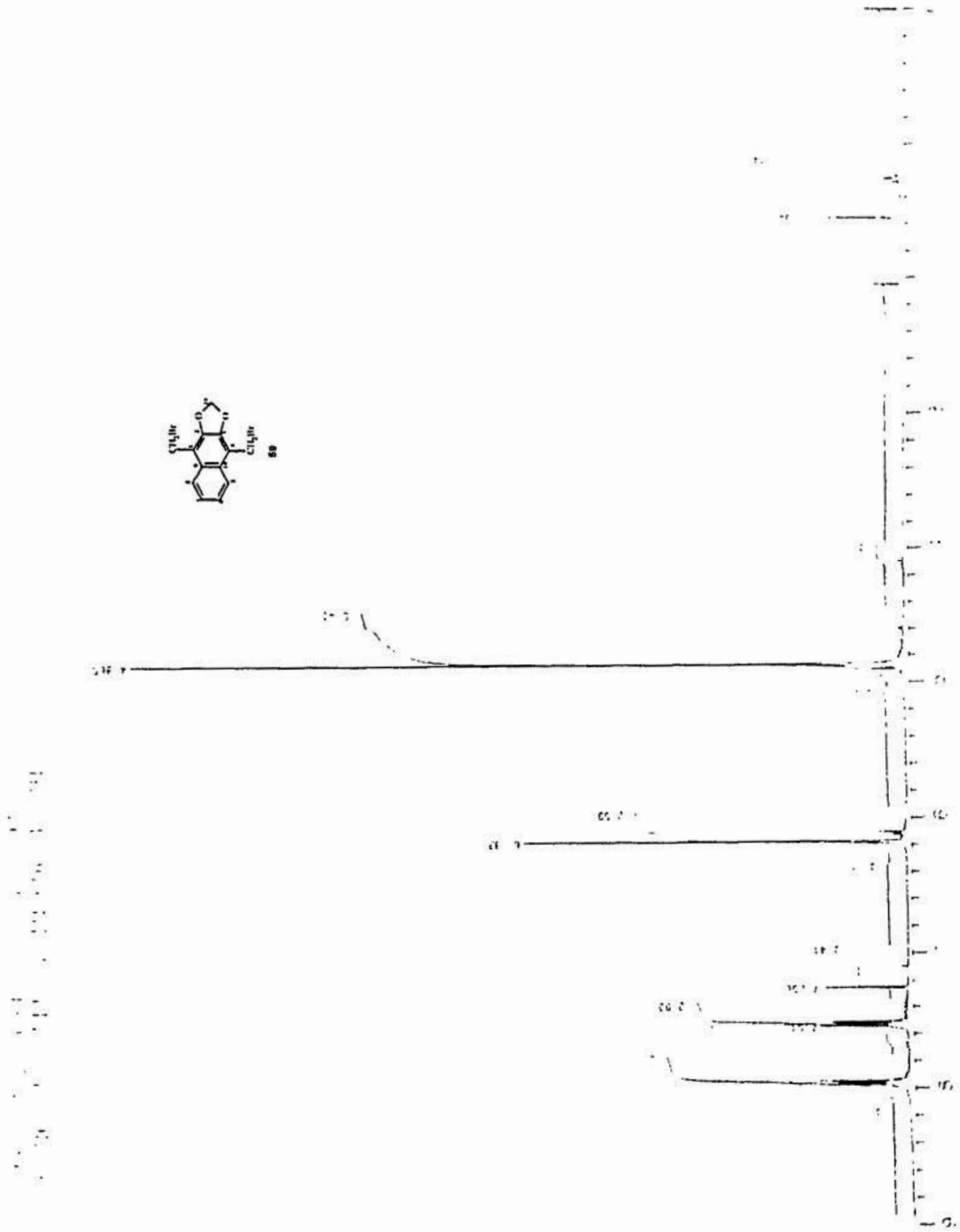


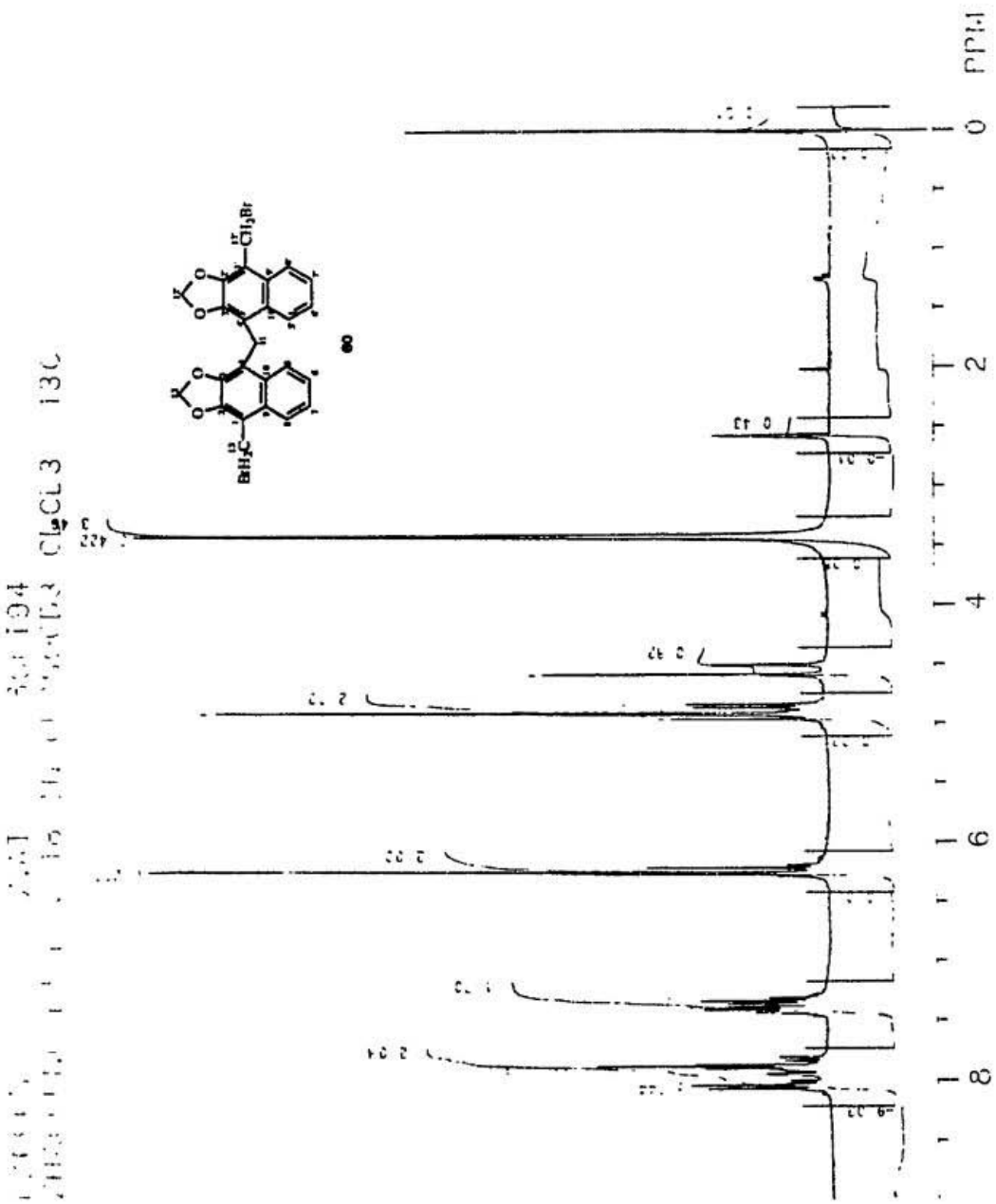


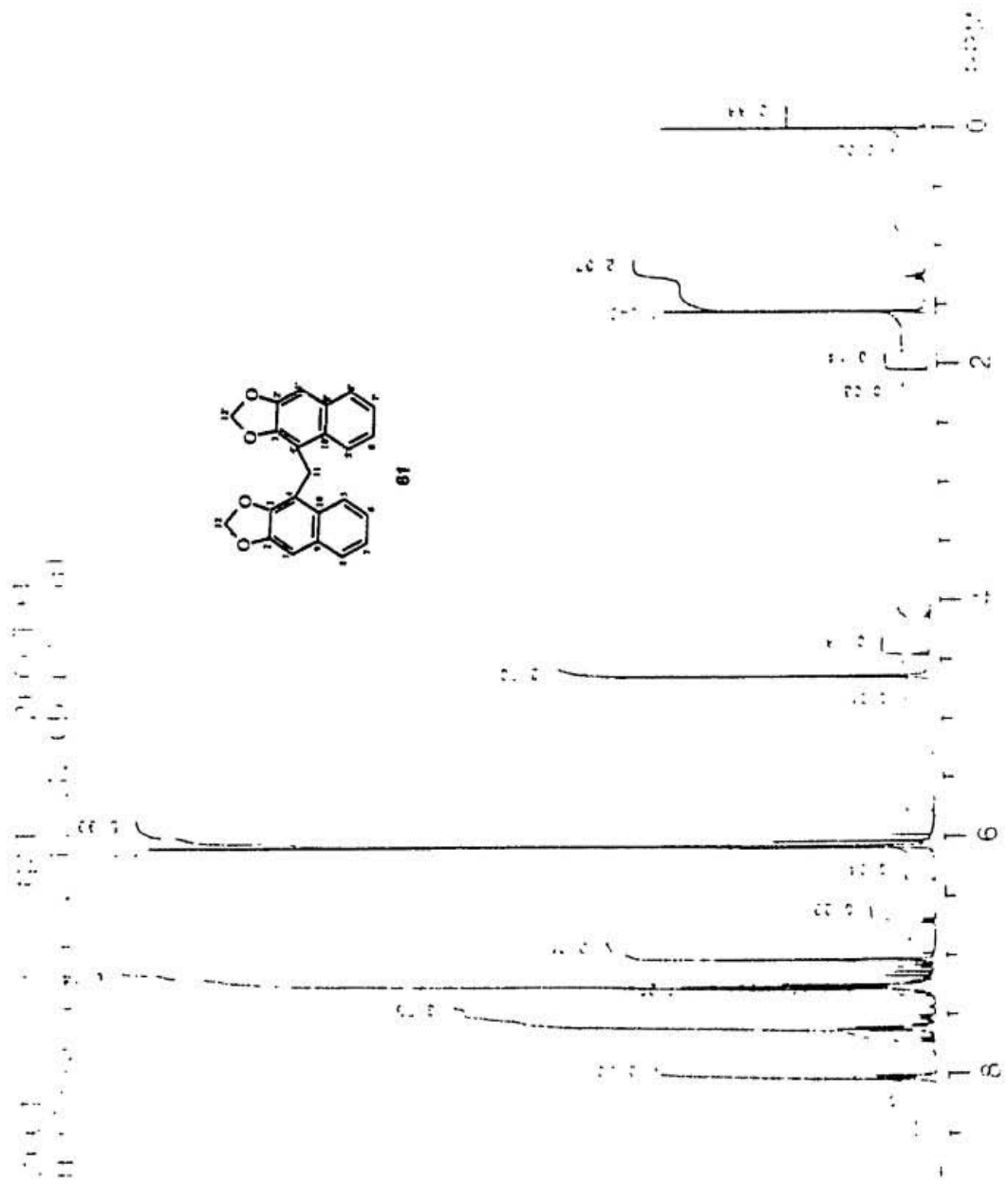


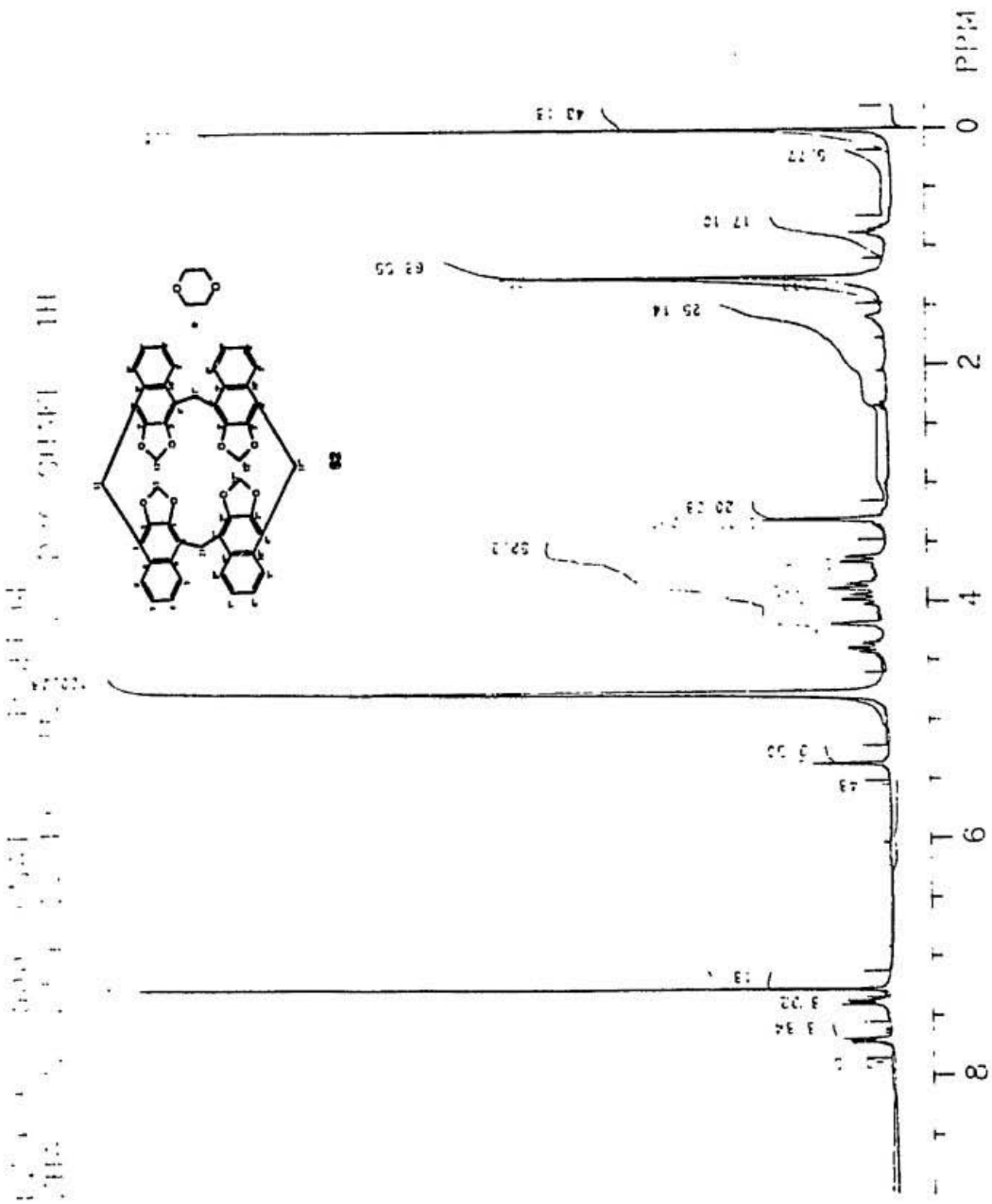


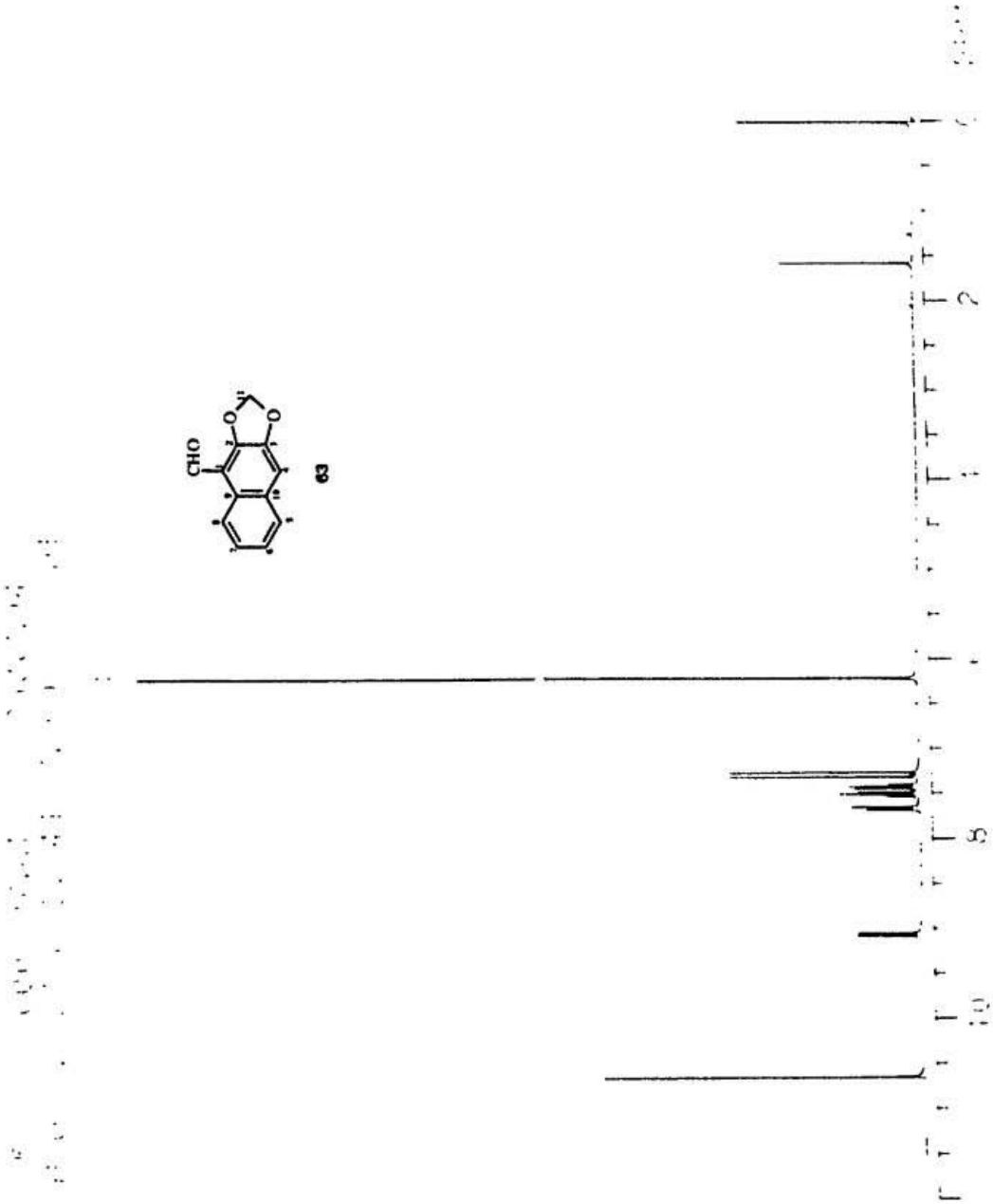

LZ02234 900 DAVIDP 20000795
ZHAOPING LIU-III-80 IN CDCl3 1H
PPM

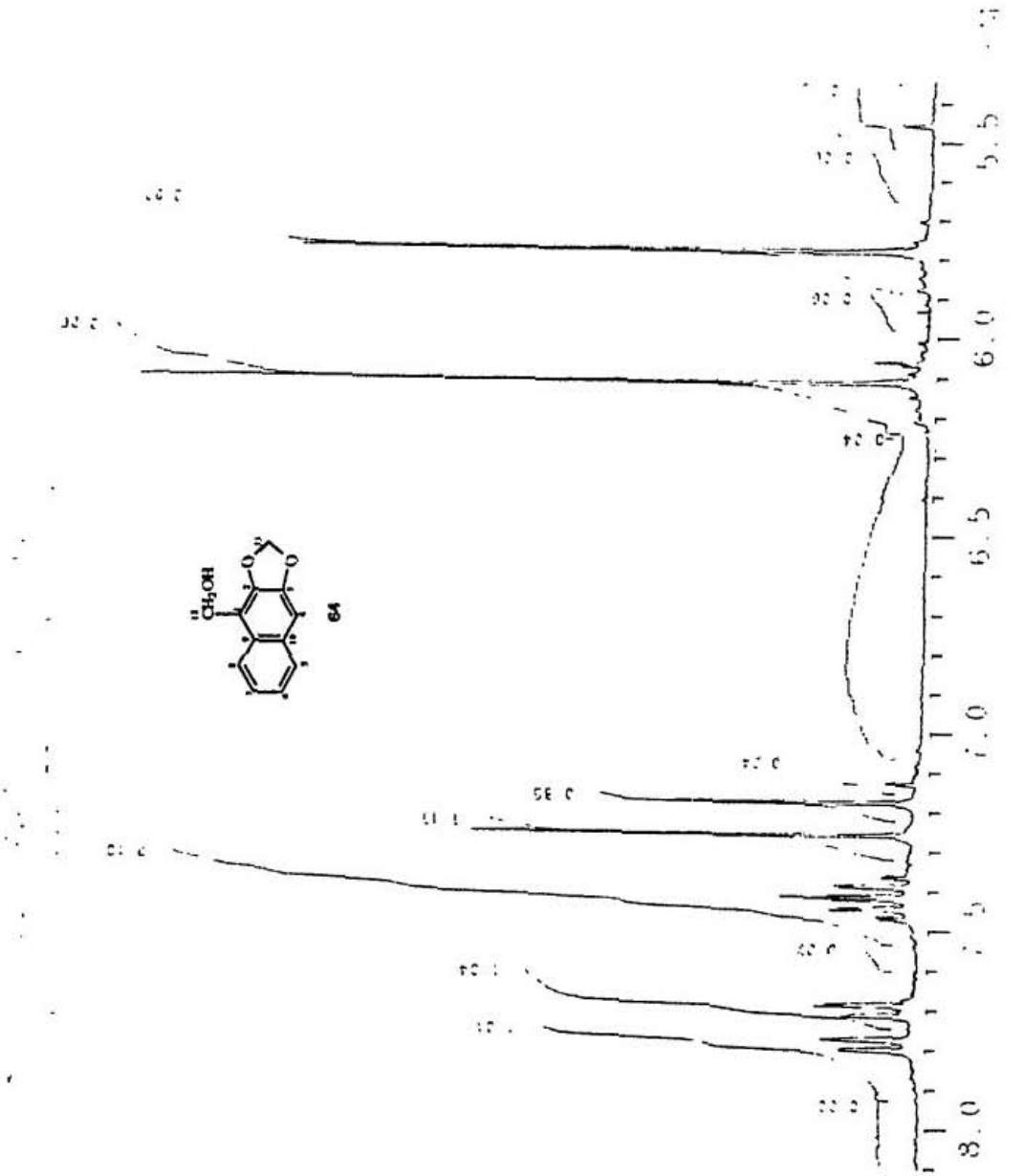


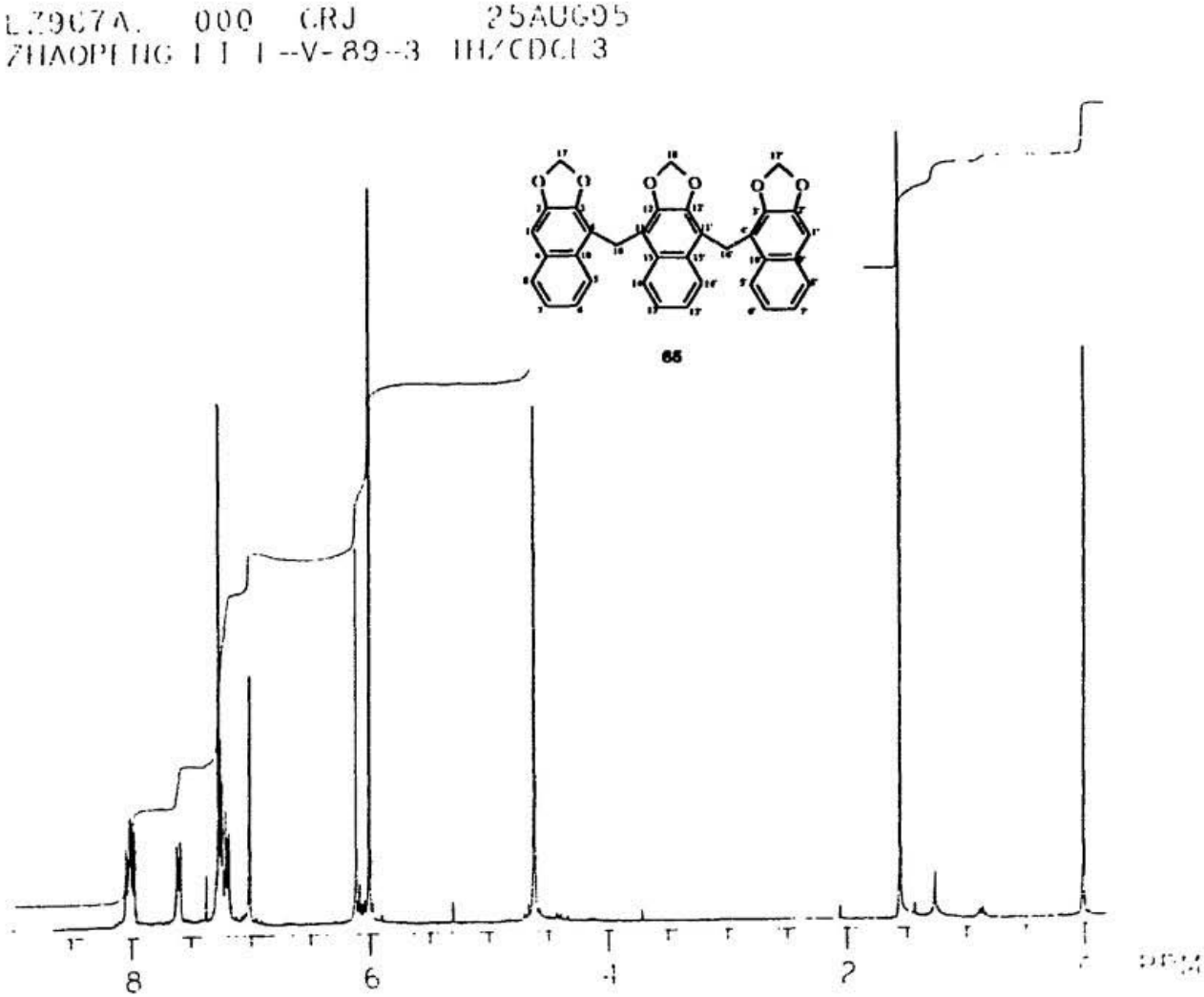

CDCL3
PPM
8

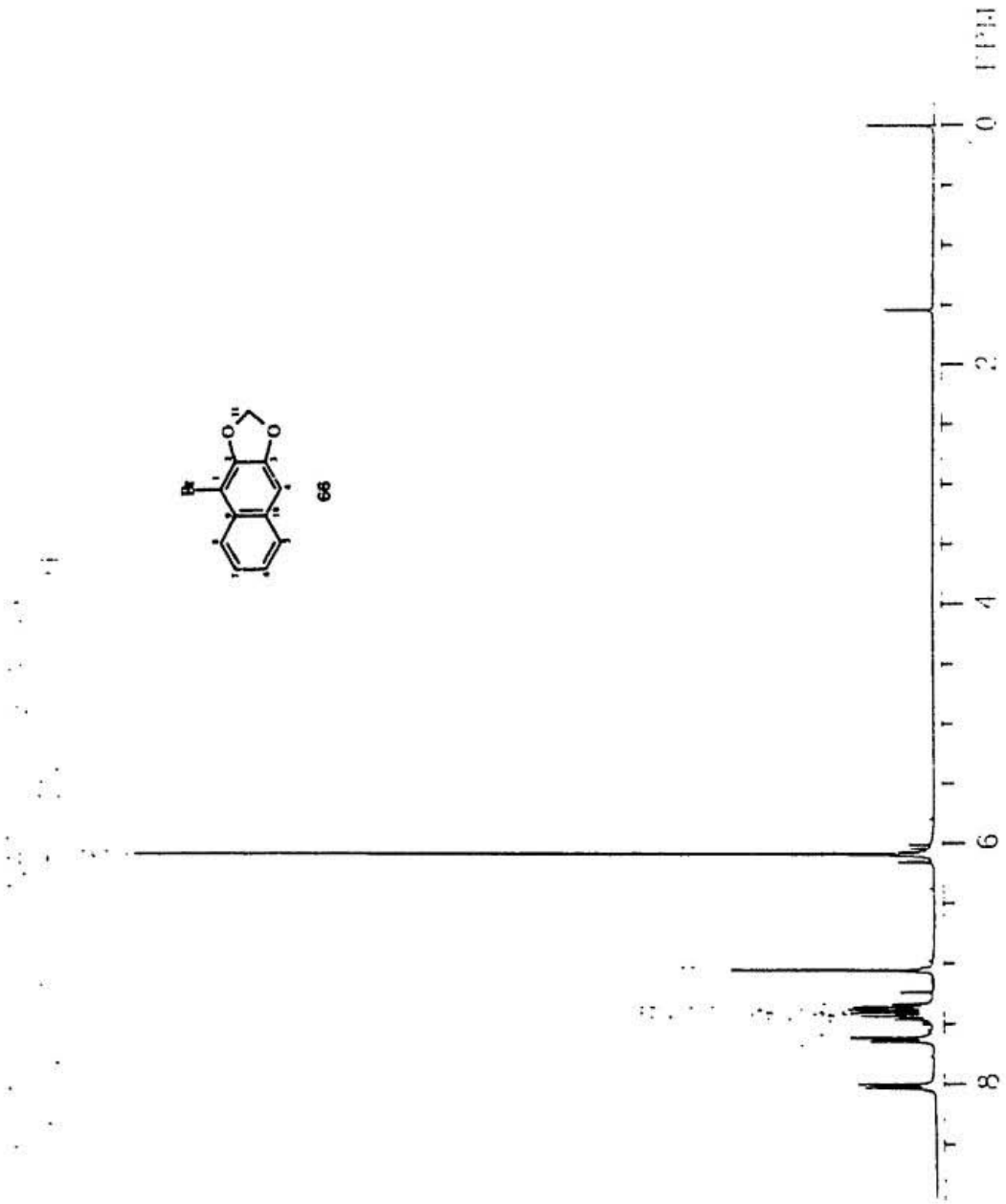


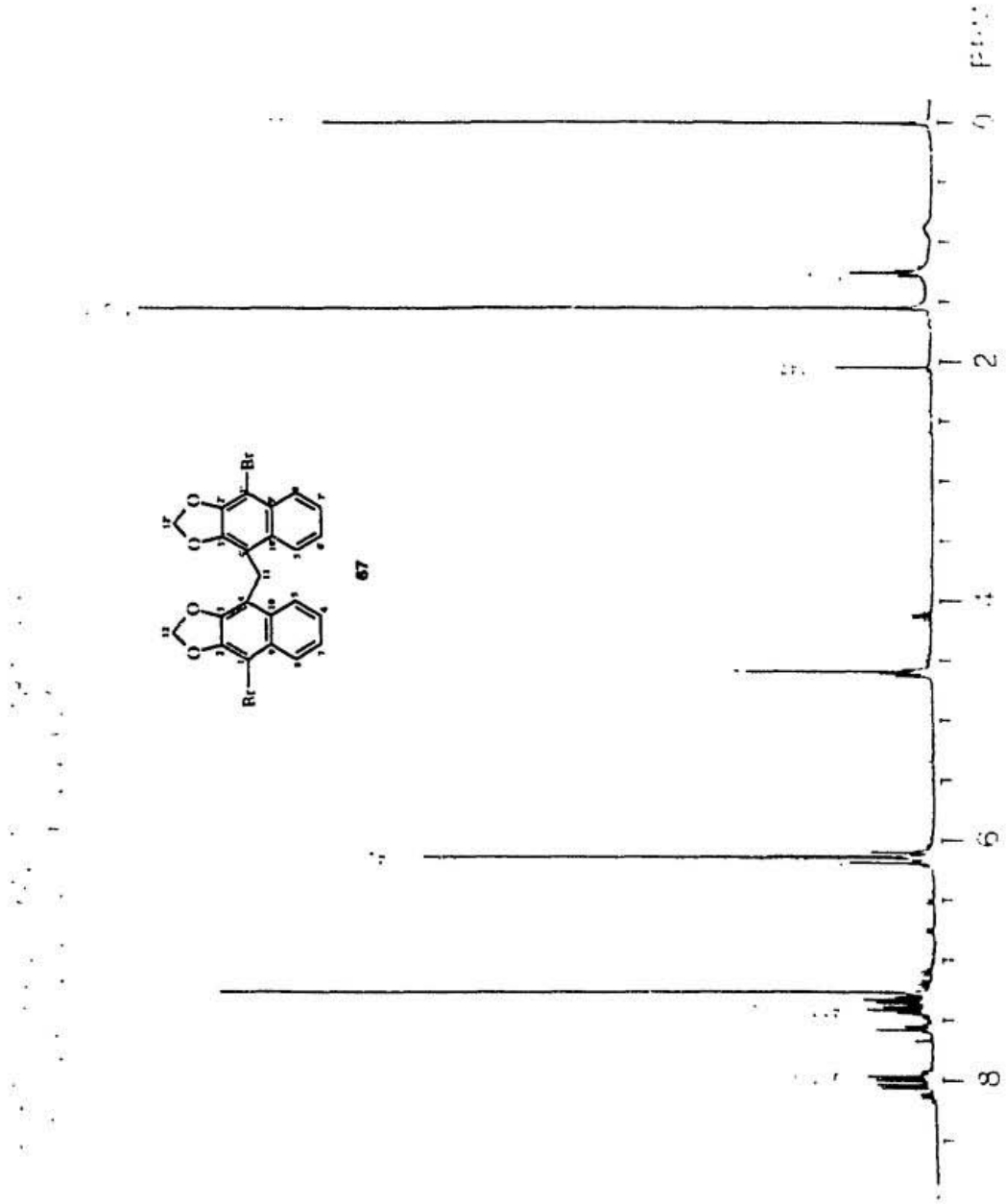

PPM
0
2
4
6
8

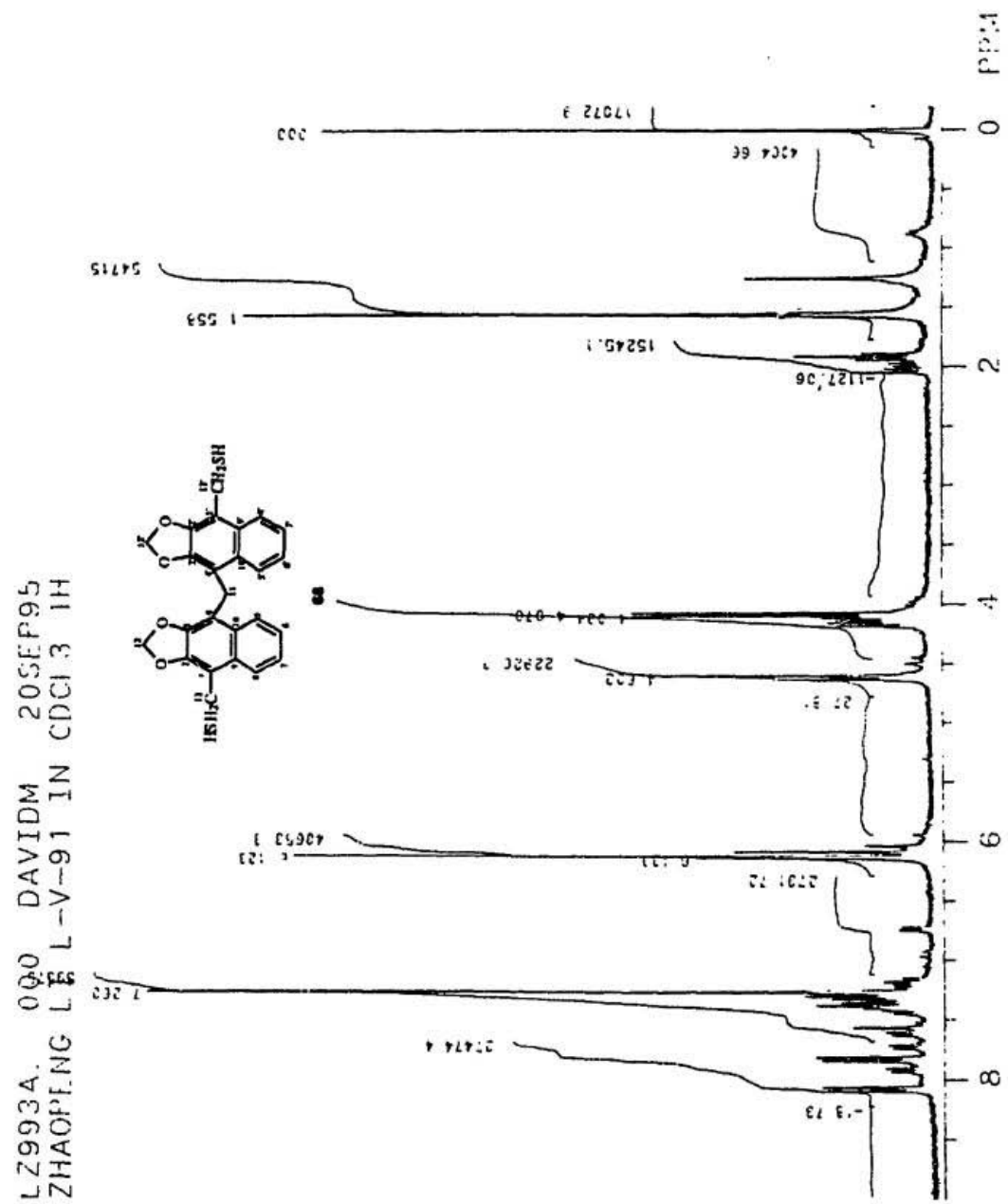

CHO
63

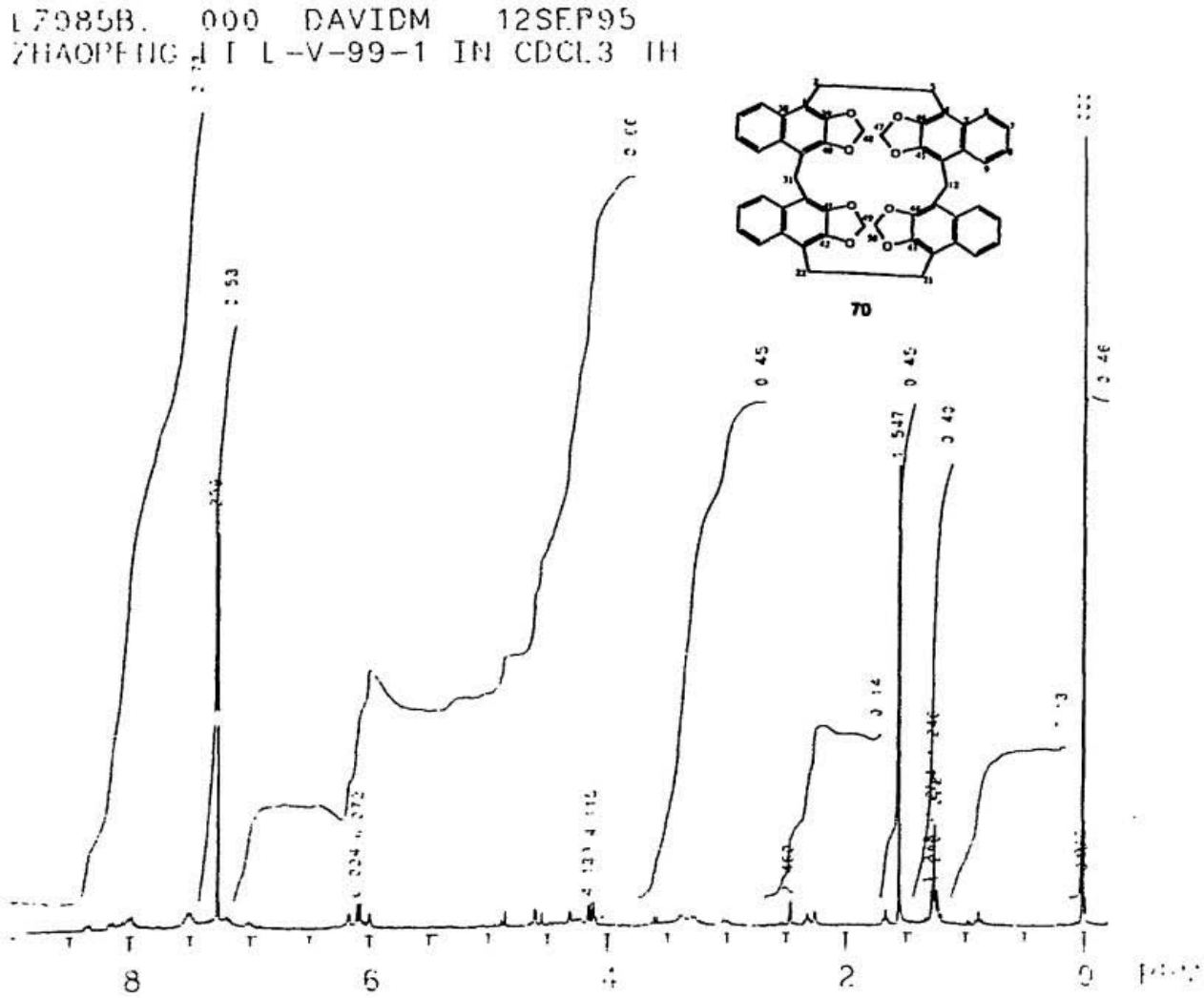

CH2OH
64
8.0
7.5
7.0
6.5
6.0
5.5

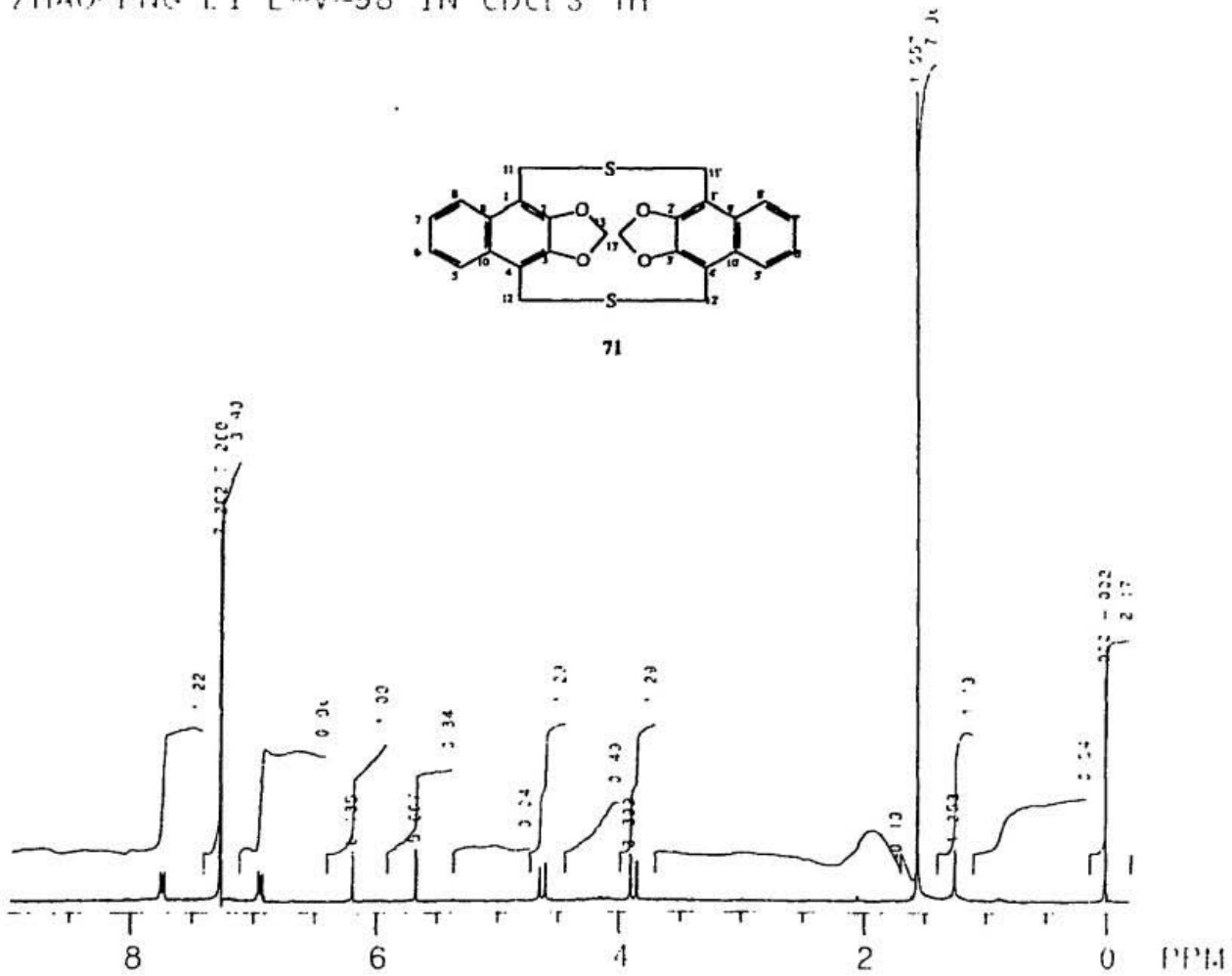

L29C7A. 000 CRJ 25AUG95
ZHAOPING I I I --V-89--3 IH/CDCL3
65
8
6
4
2

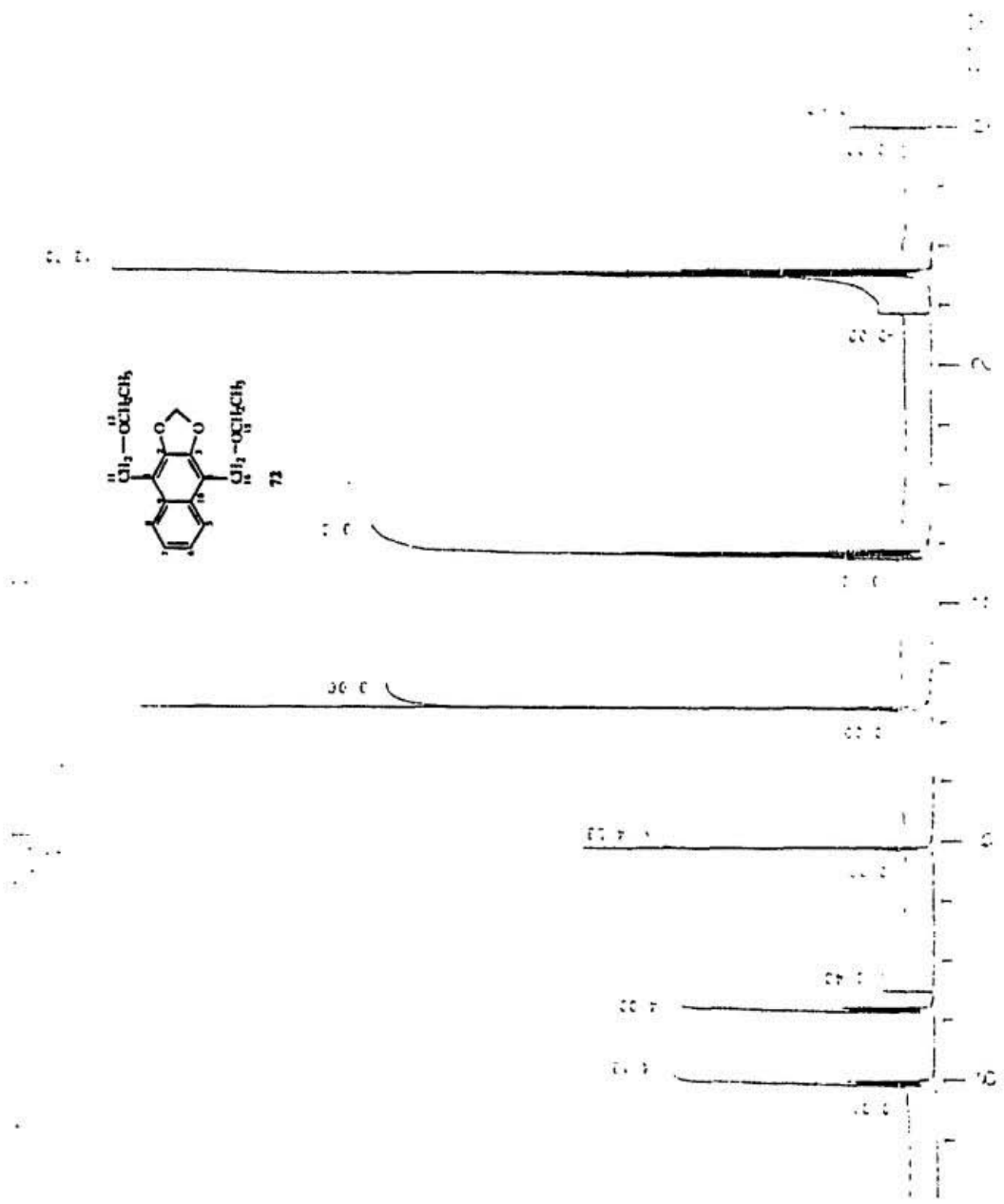

Br
O
O
66
PPM
0
2
4
6
8

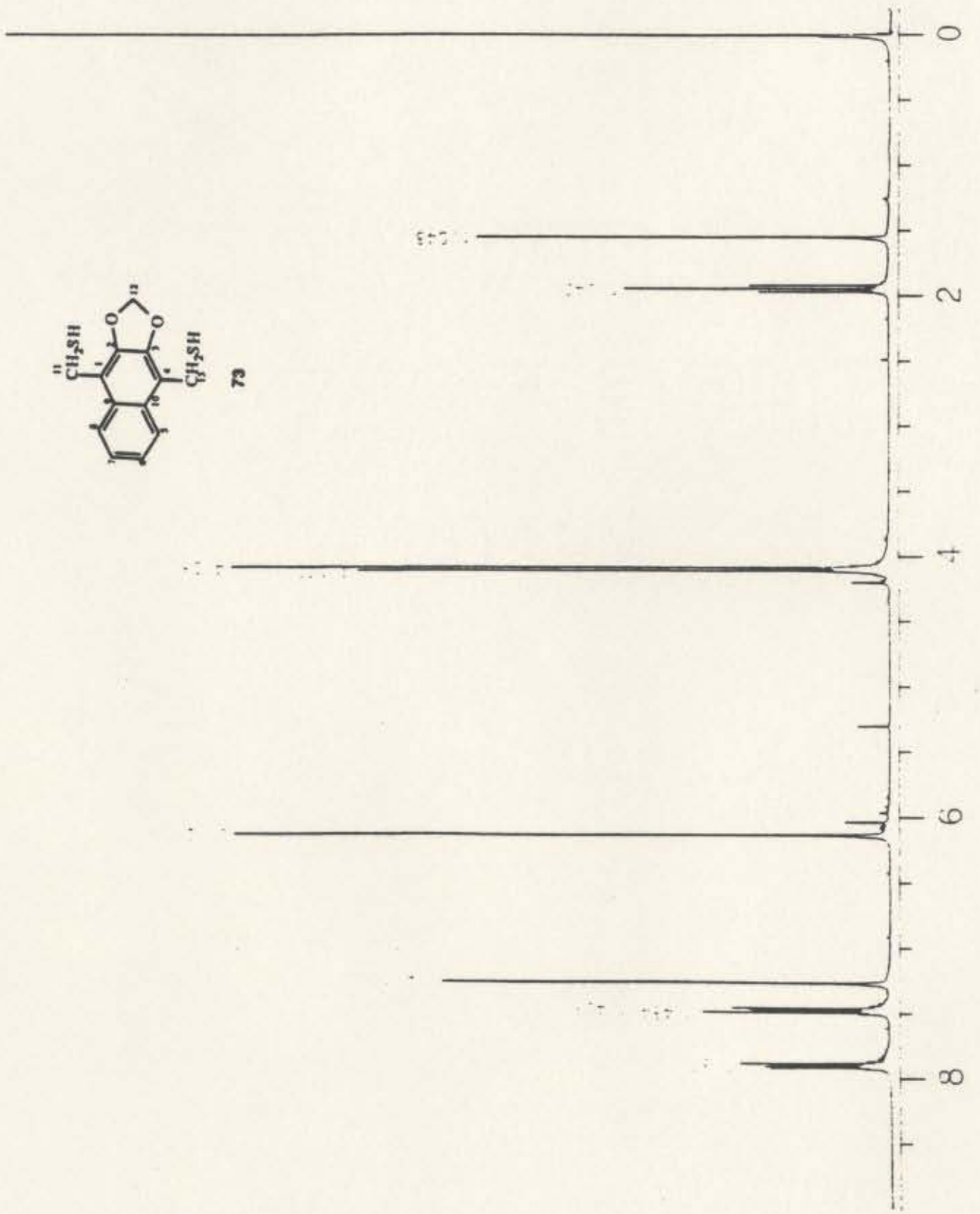

Br
Br
67
8
6
4
2
0


LZ9934. 000 DAVIDM 20SEP95
ZHAOPENG LEE L-V-91 IN CDCL3 1H
PPM
0
2
4
6
8
CH3SH
H3C

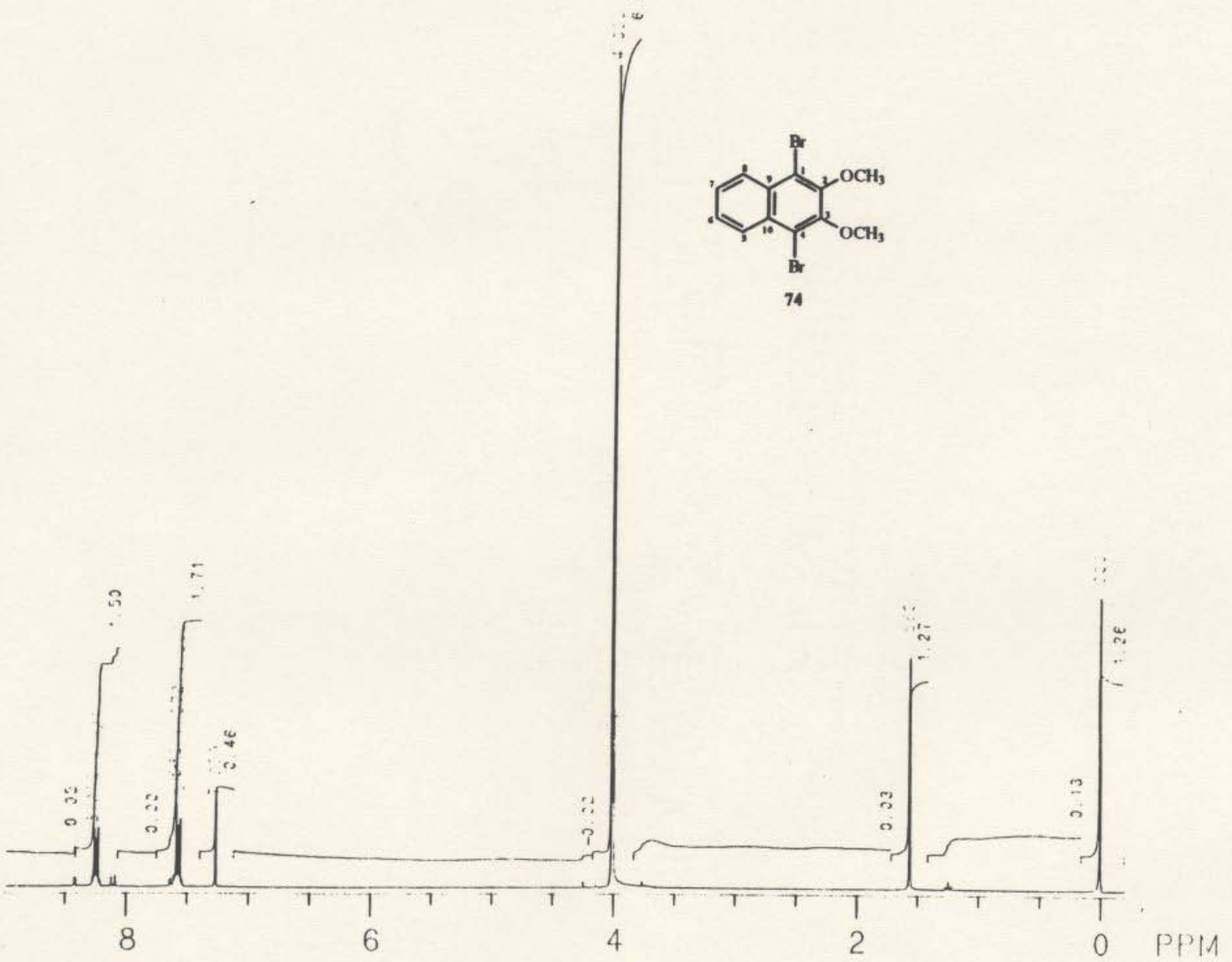

L7985B. 000 DAVIDM 12SEP95
ZHAOPENG J T L-V-99-1 IN CDCL3 1H
8
6
4
2
0

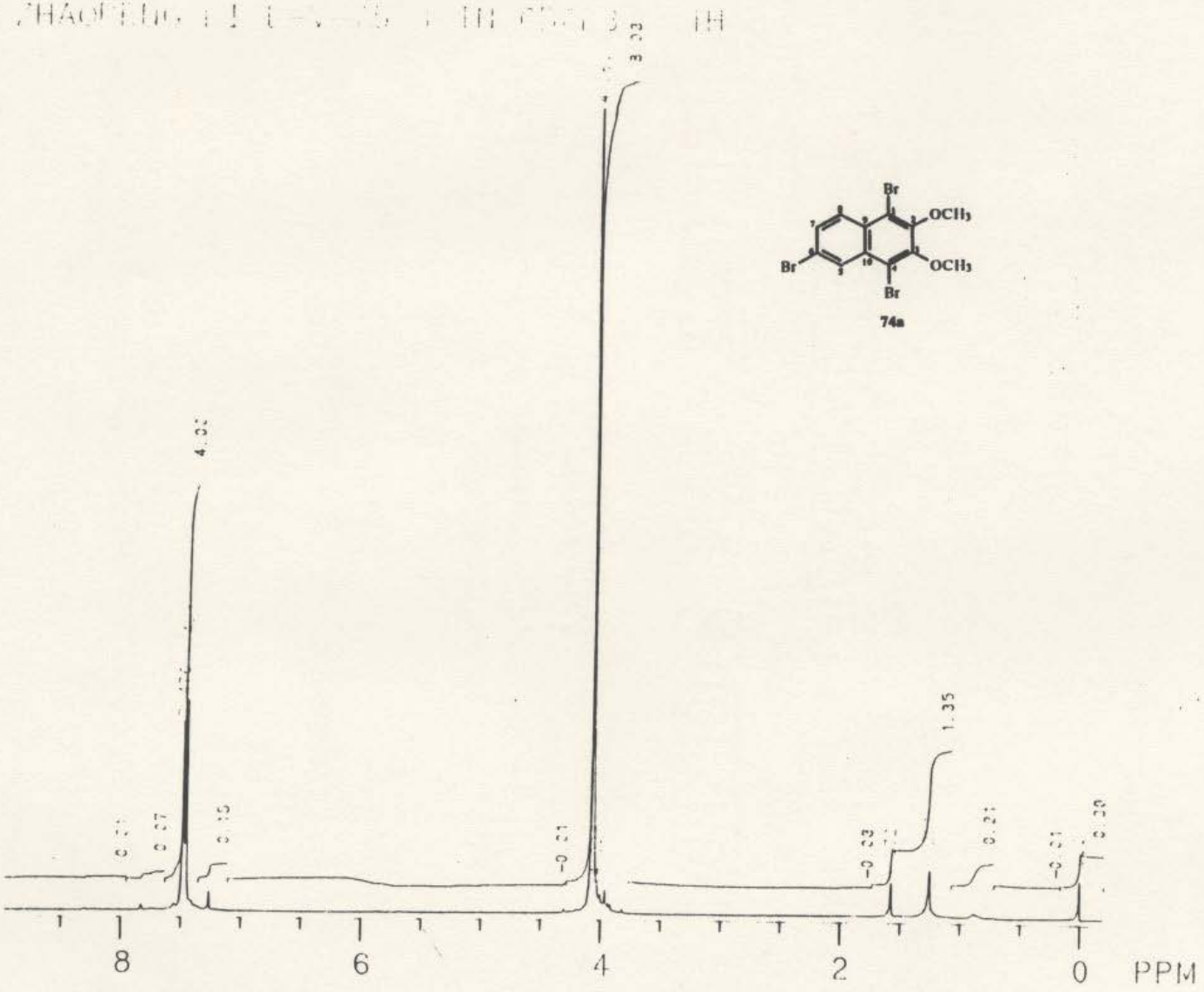

7999B. 000 DAVIDM 26SEP95
ZHAOPENG LI L-V-98 IN CDCL3 1H
S
S
O
O
O
O
71
8
6
4
2
0
PPM

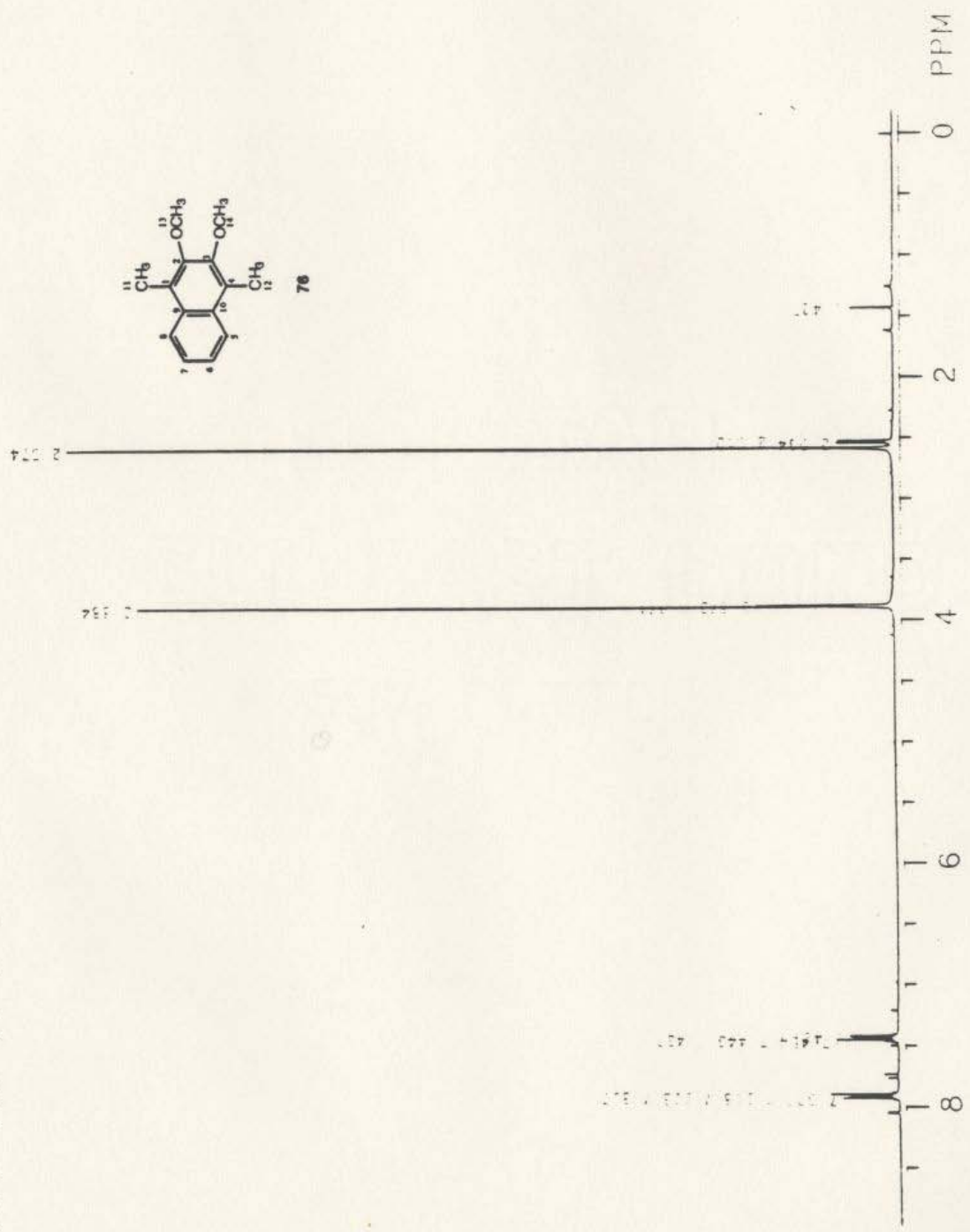


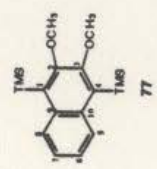


73

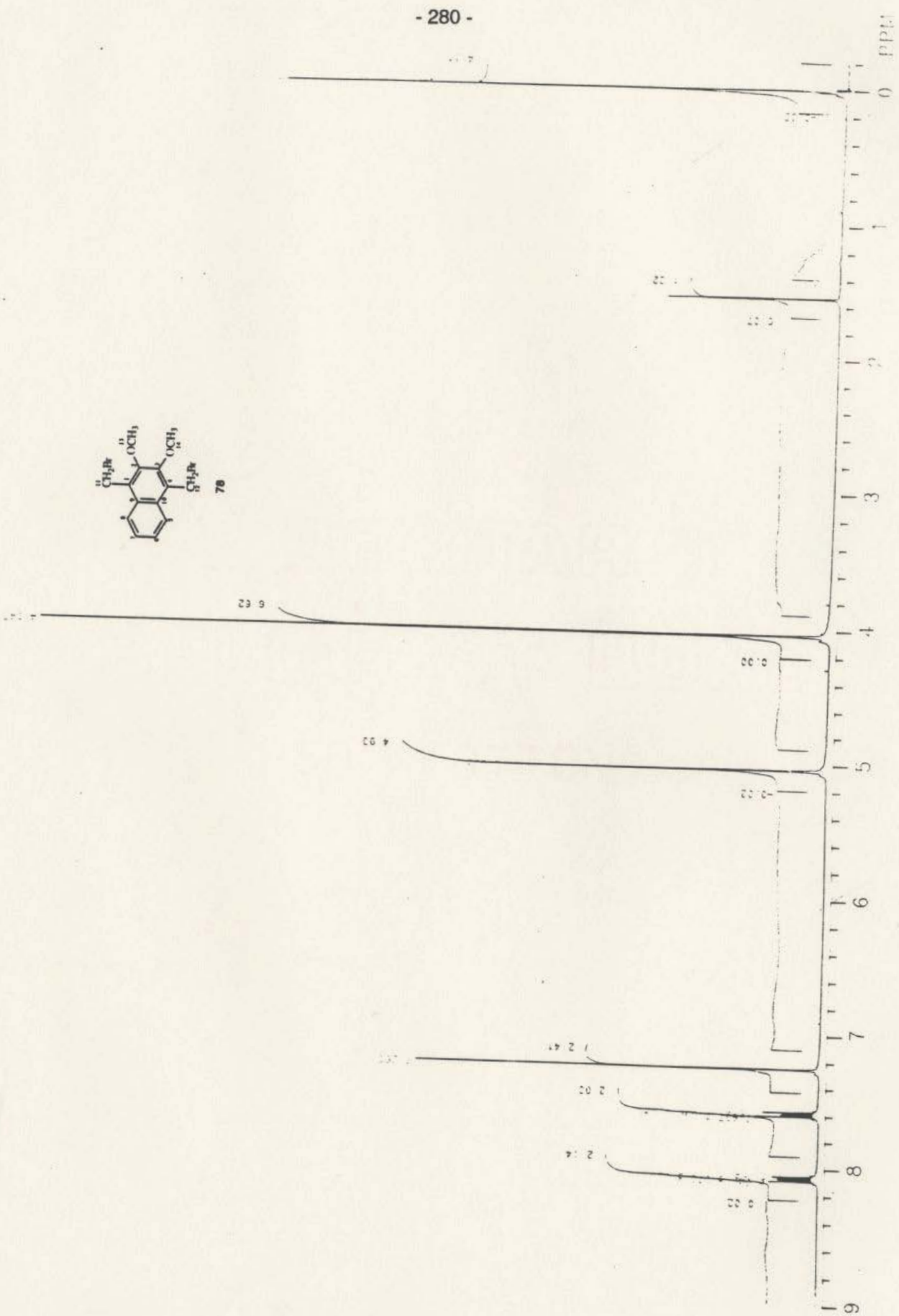

Br
OCH3
OCH3
Br
74
8
6
4
2
0
PPM

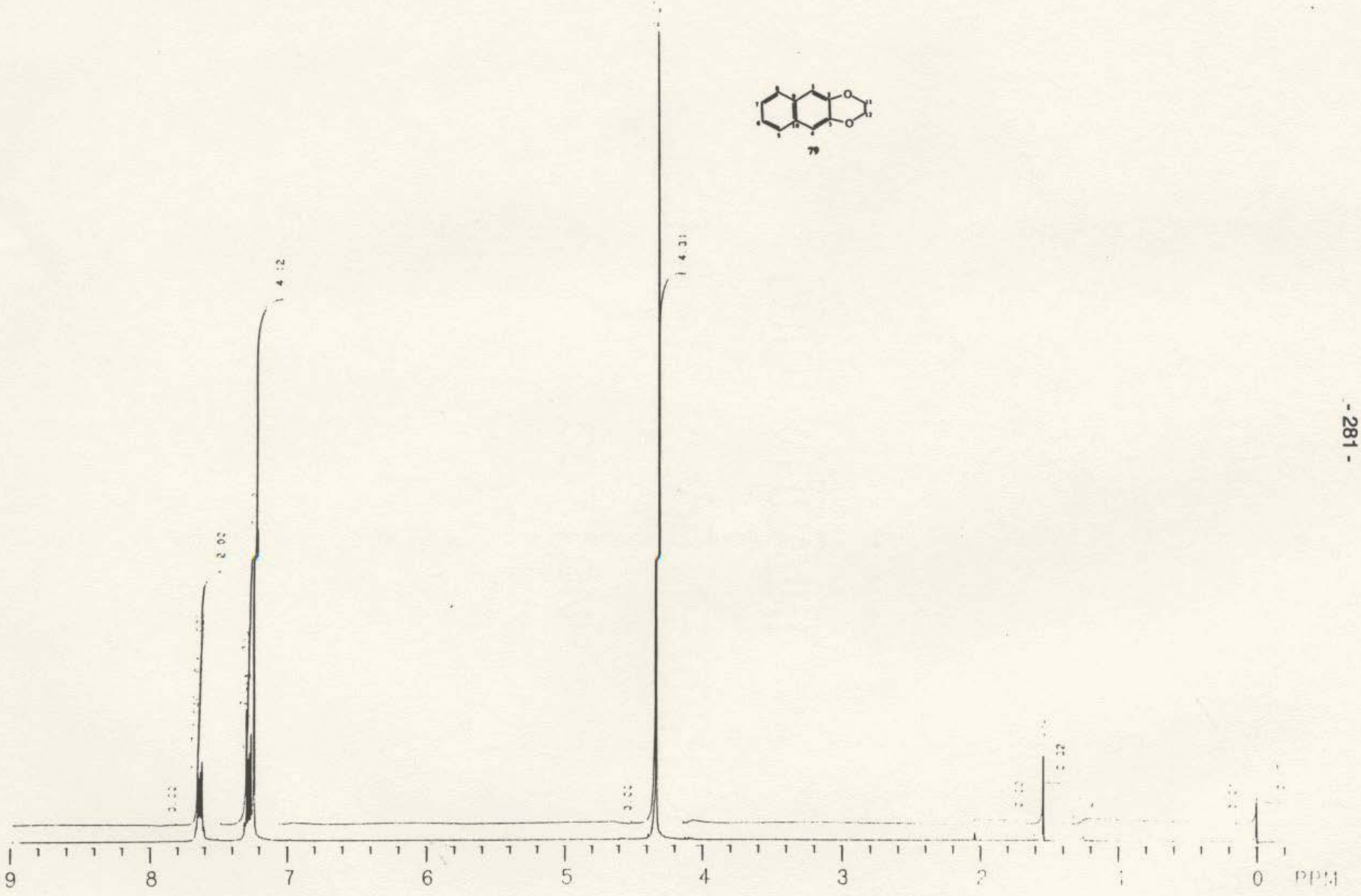

Br
OCH3
OCH3
Br
Br
74a
8
6
4
2
0
PPM


PPM
0
2
4
6
8

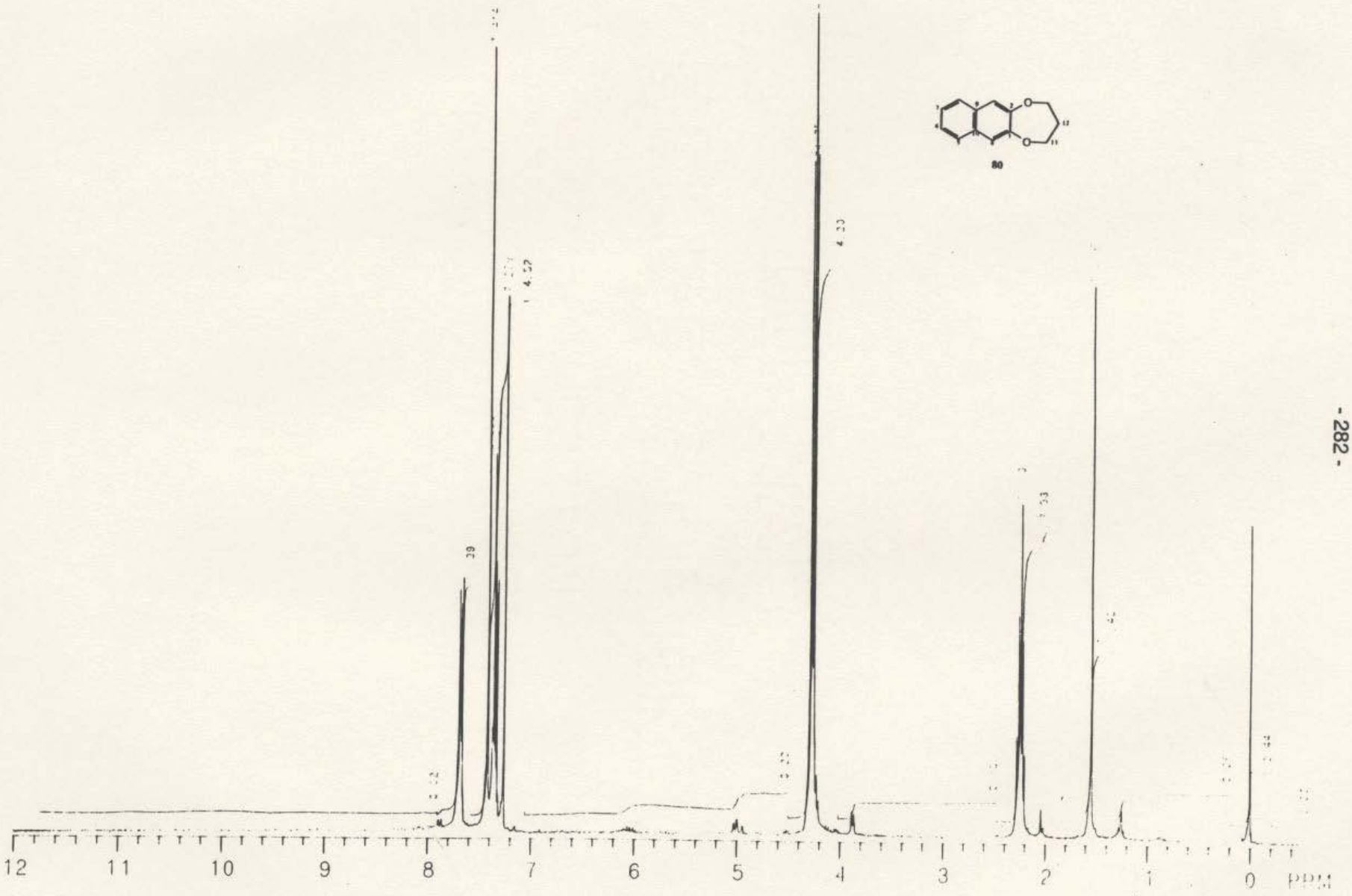


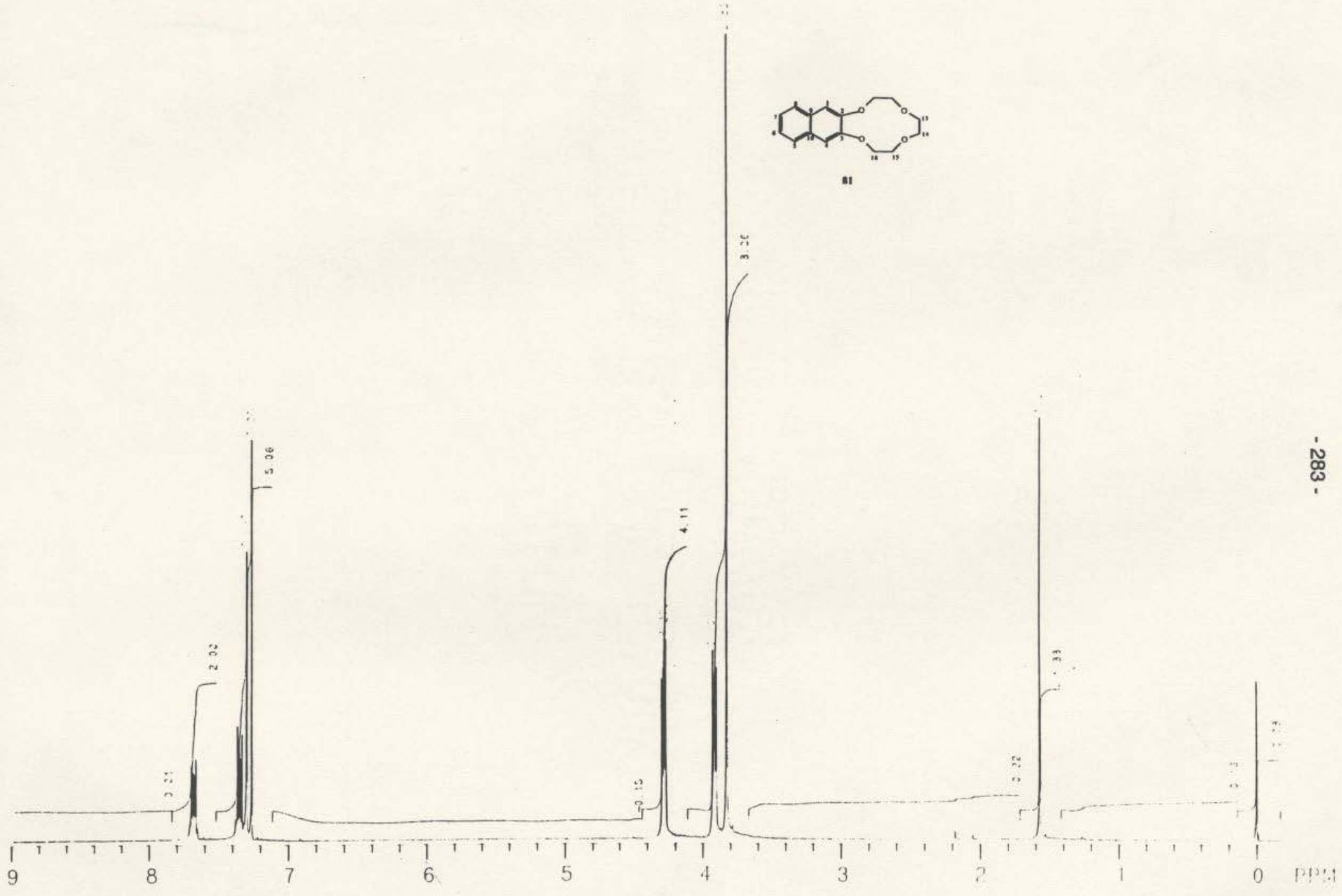
77

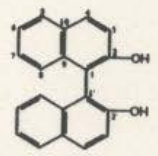

78
6.62
4.02
2.47
2.02
2.14
0.22
PPM


14.12
3.05
14.31
3.00
3.00
3.00
3.00
9
8
7
6
5
4
3
2
1
0
PPM

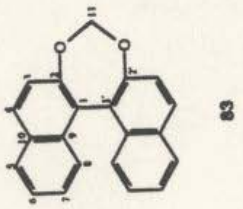
mp 120 120°C



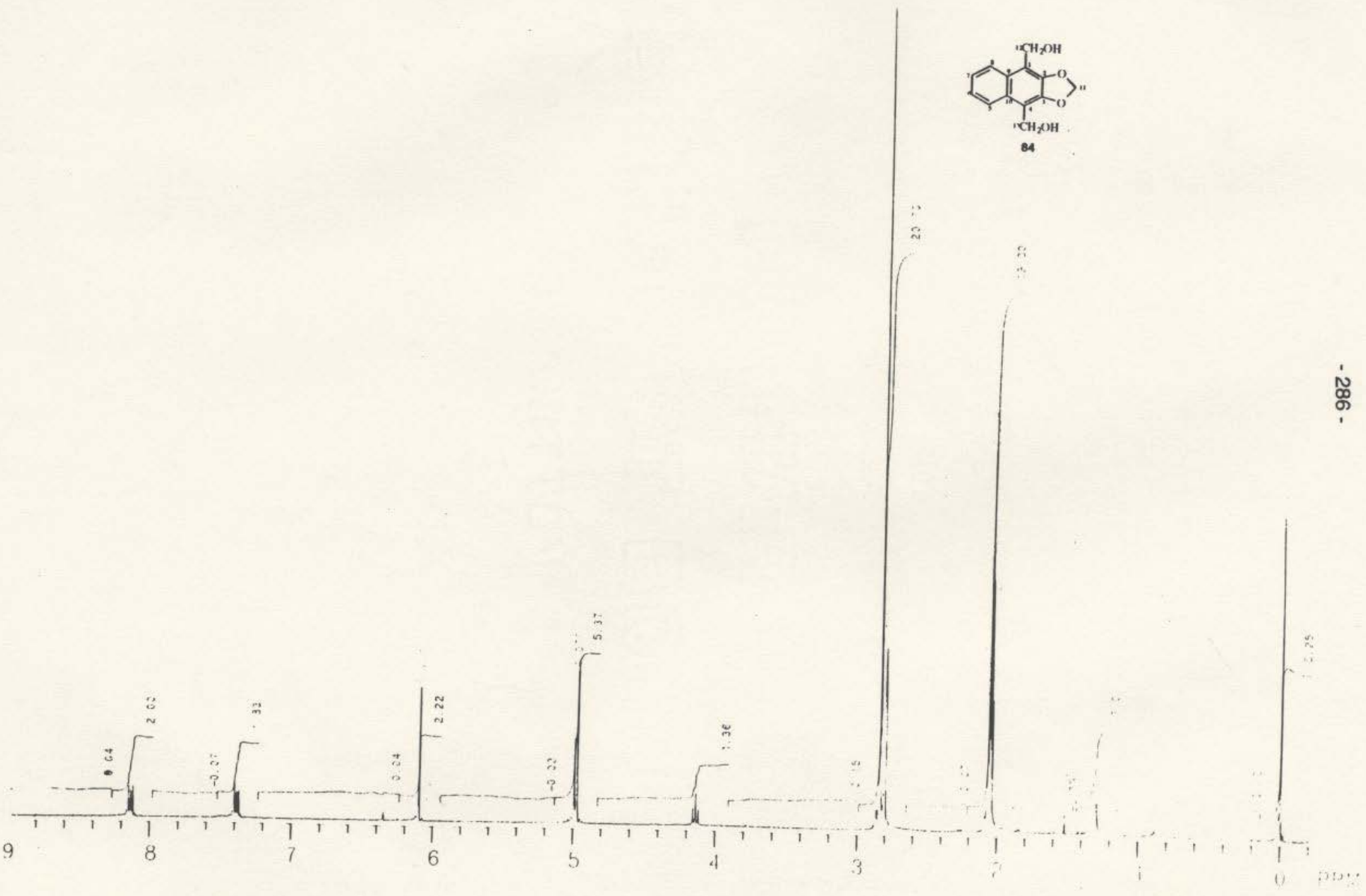

81
9
8
7
6
5
4
3
2
1
0
PPM

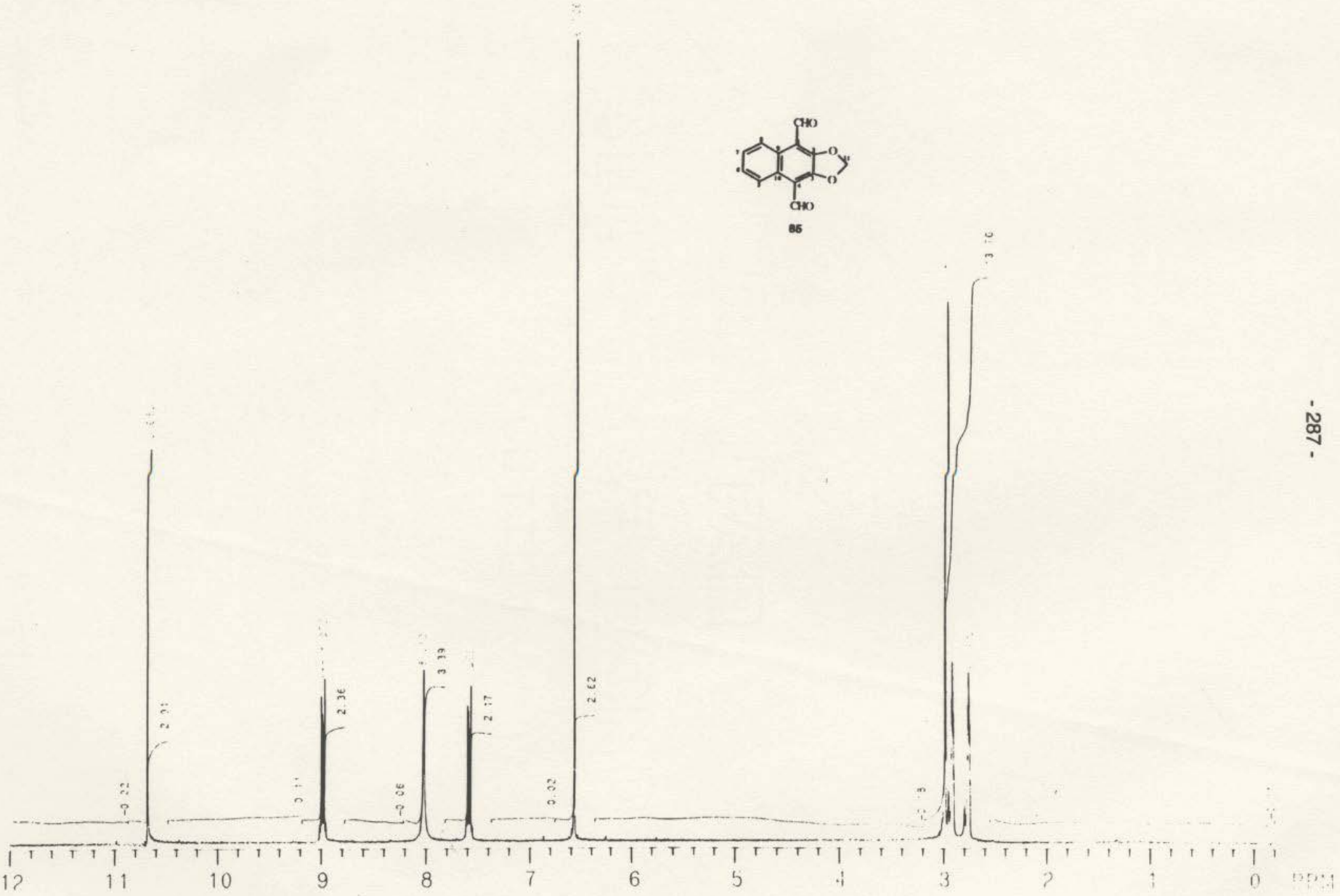


82

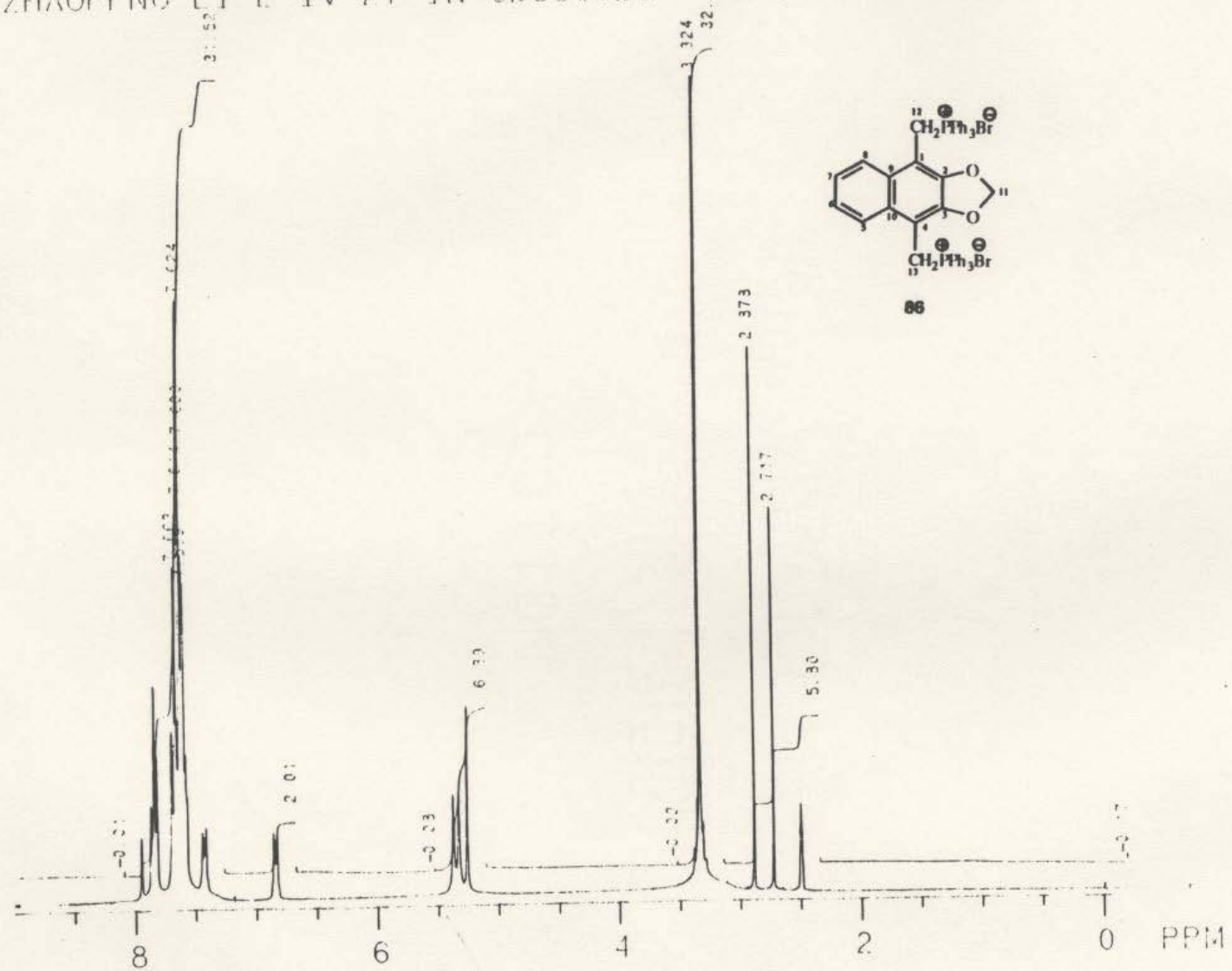


83

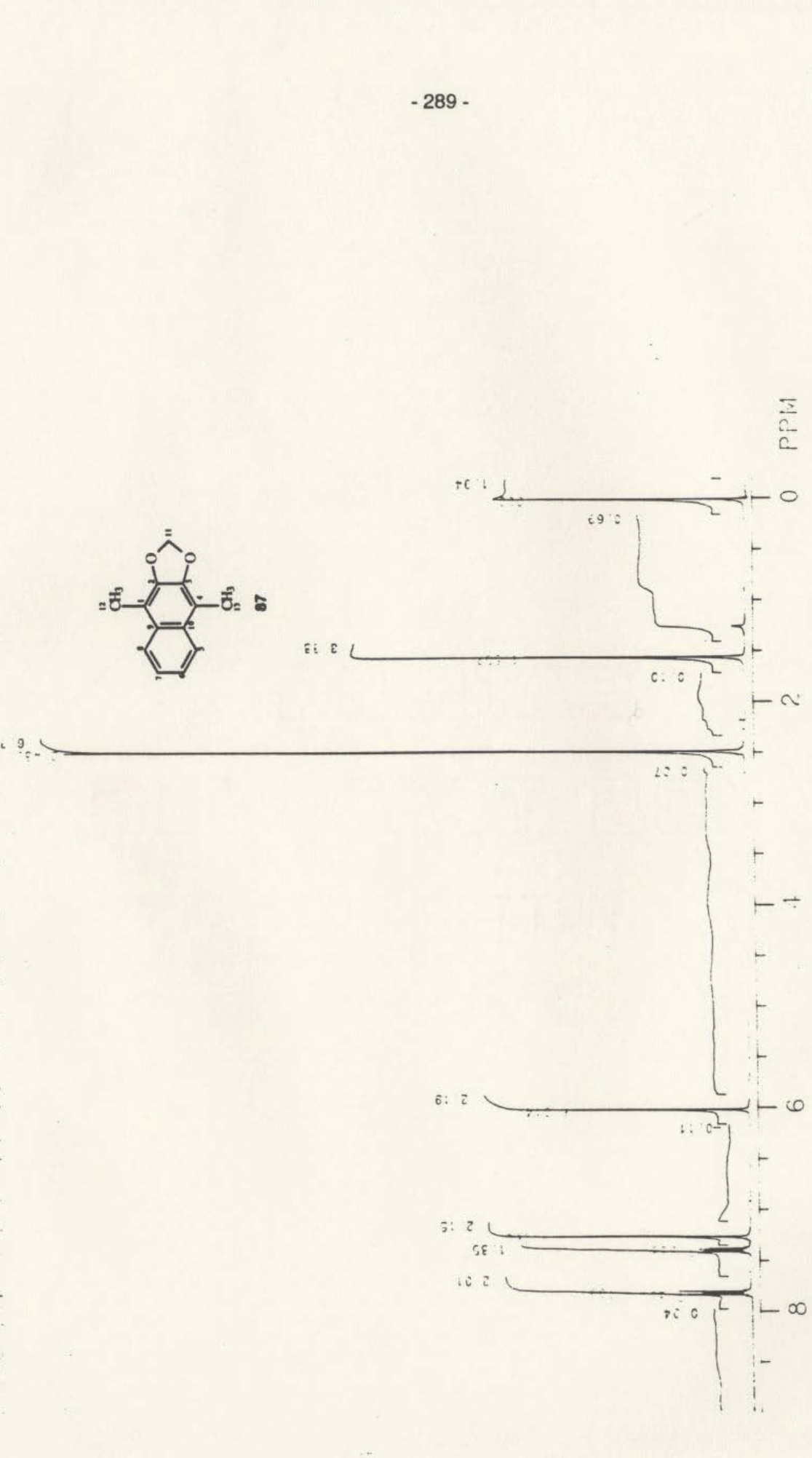

84
9
8
7
6
5
4
3
2
1
0
PPM

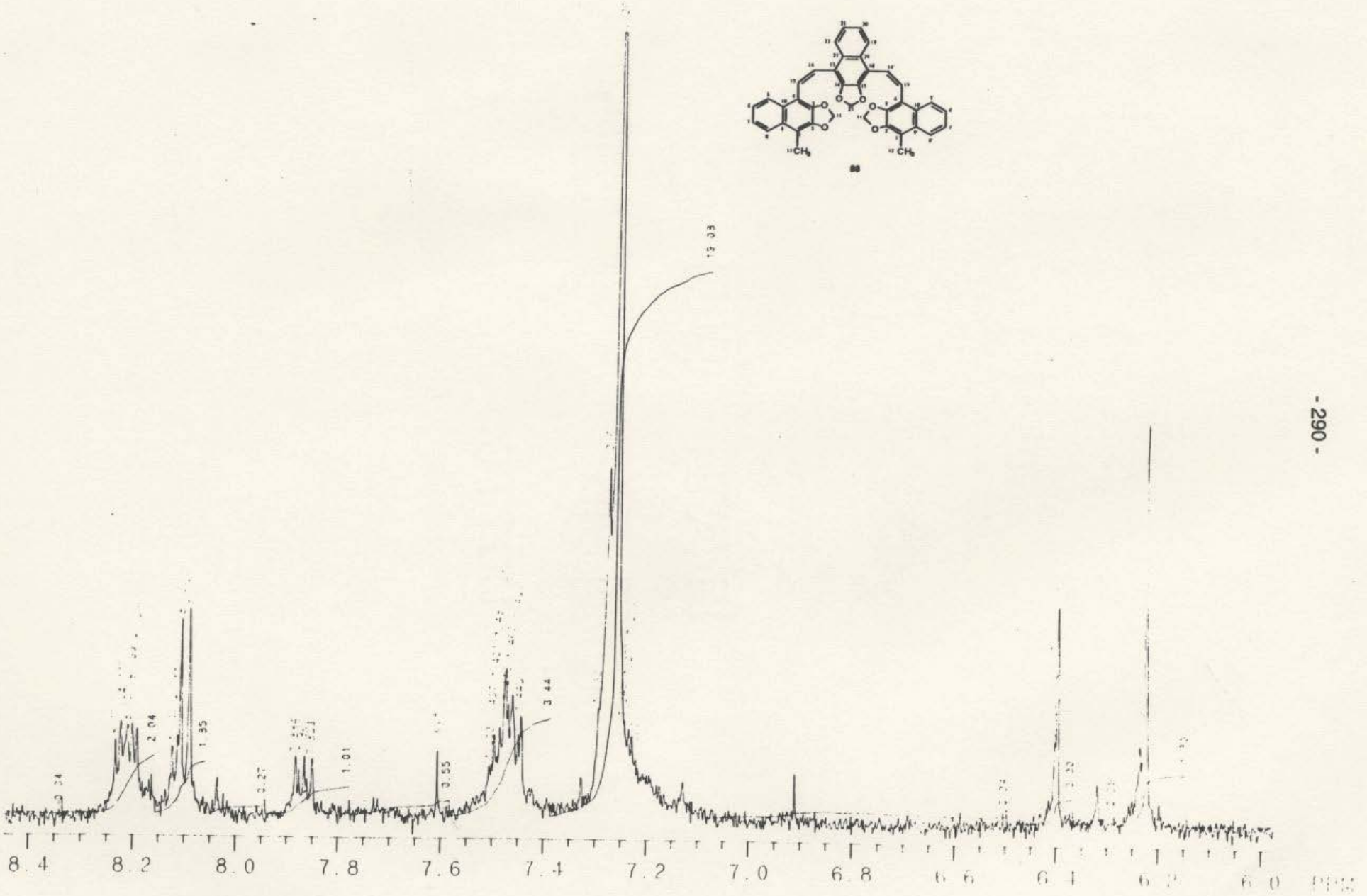

CHO
CHO
85
2.01
2.36
3.19
2.17
2.62
3.10
12
11
10
9
8
7
6
5
4
3
2
1
0
PPM

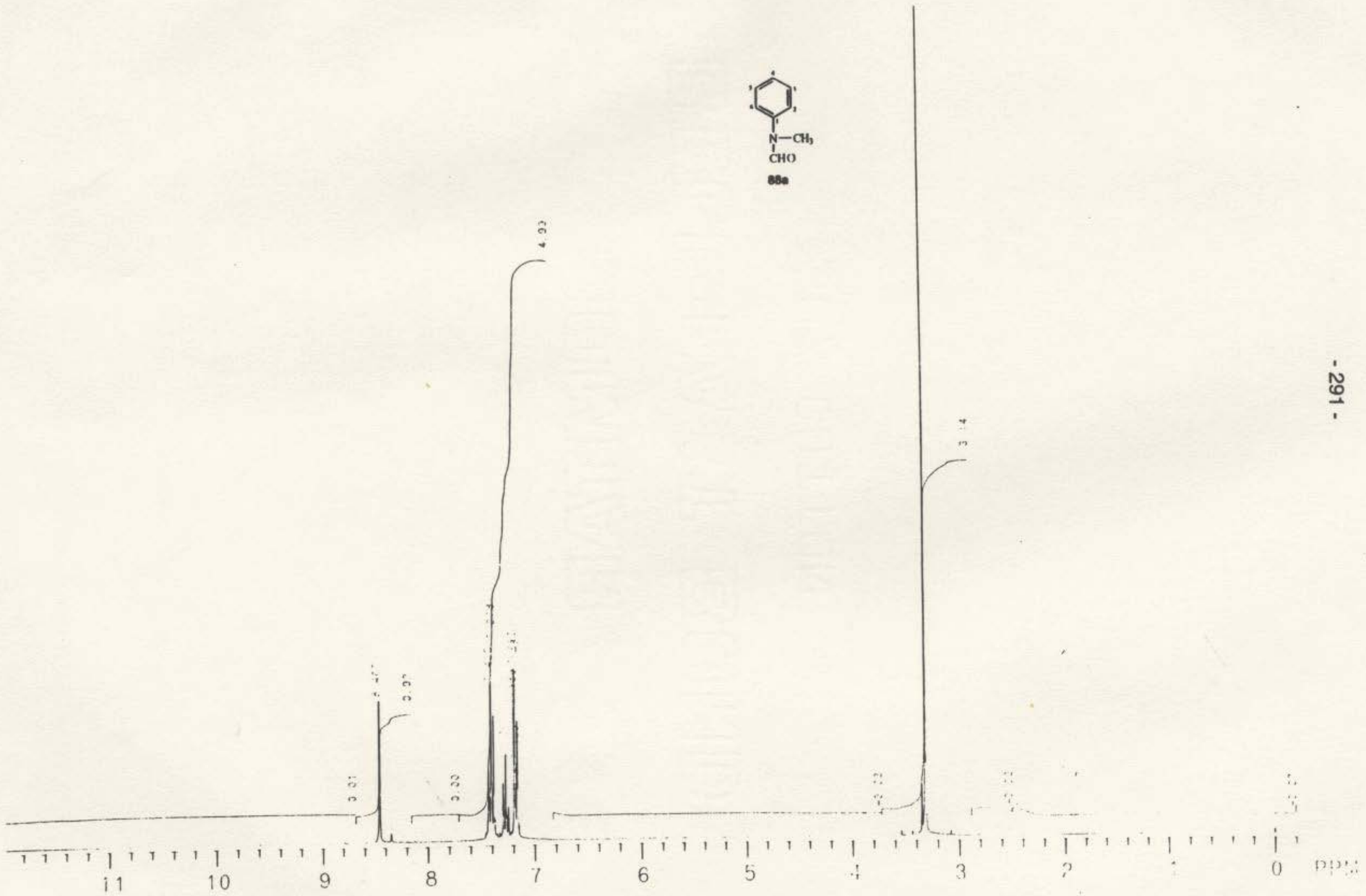
L7522A. 000 GNAT 06JUN94
ZHAOPING LI L-IV-27 IN CD3SOCD3 1H

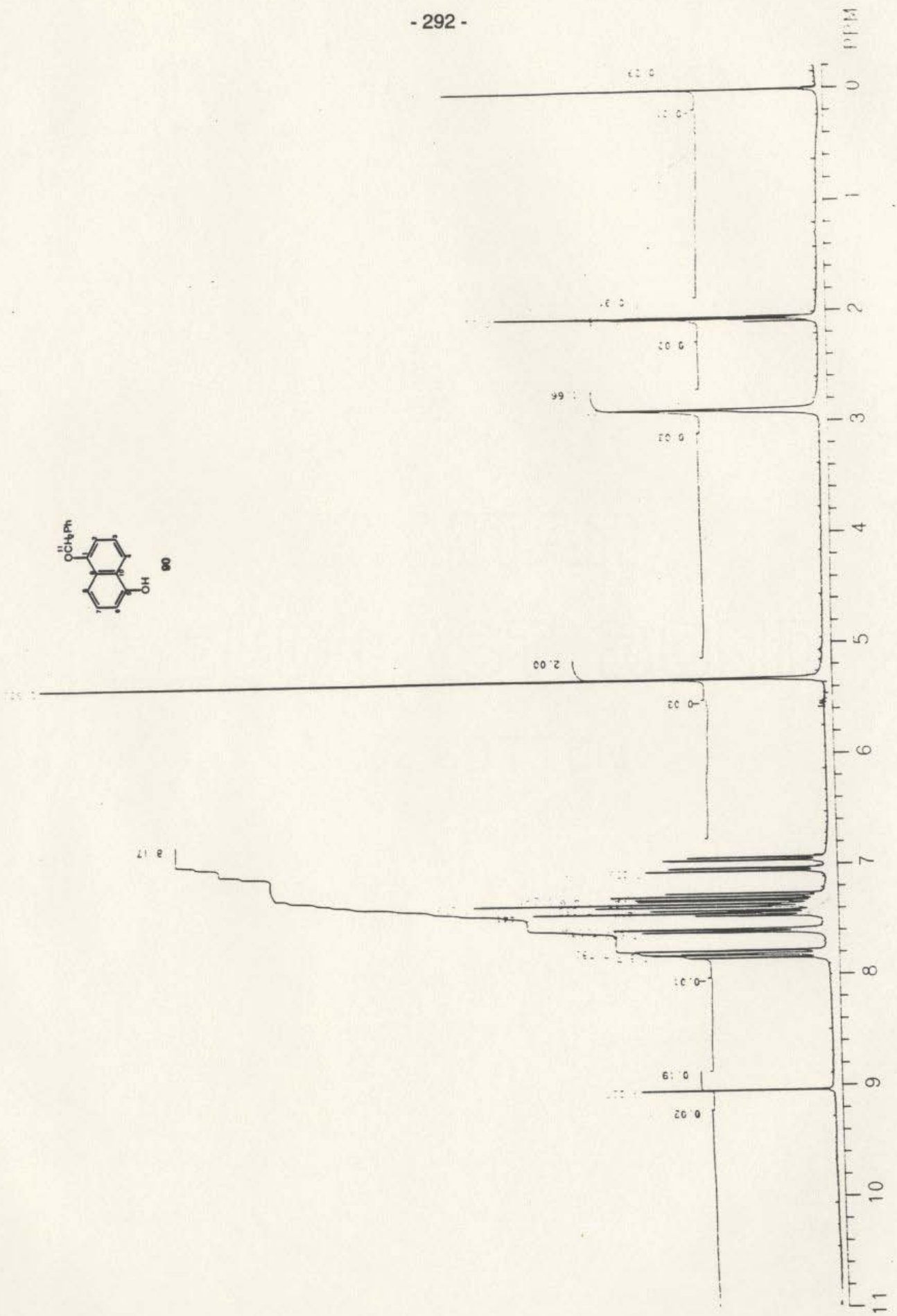


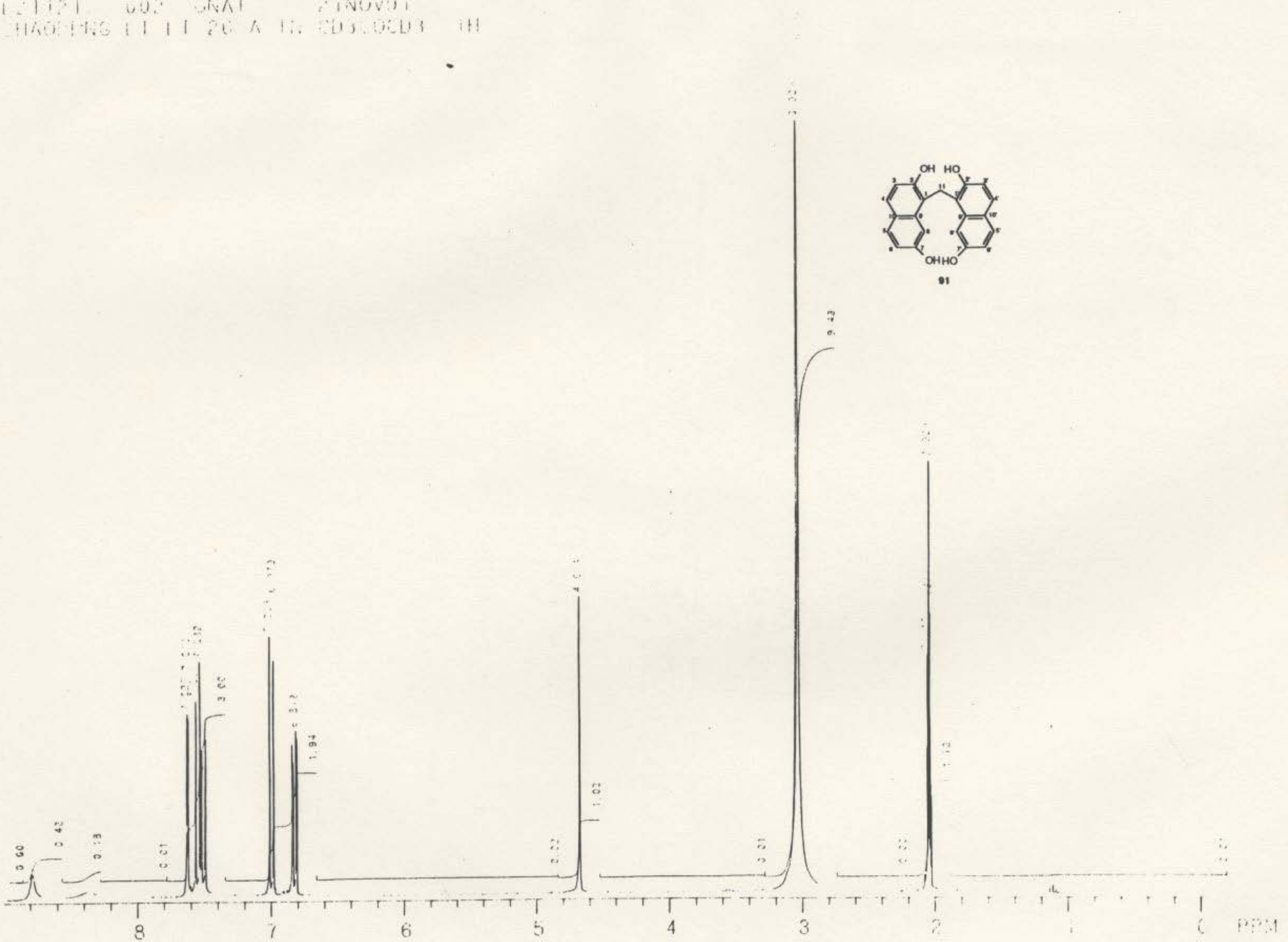
86


87
PPM
0
2
4
6
8
1.04
0.69
3.13
0.13
6.12
0.27
2.19
0.11
2.15
1.35
2.01
0.24


2.04
1.35
1.01
0.55
3.44
19.33
8.4
8.2
8.0
7.8
7.6
7.4
7.2
7.0
6.8
6.6
6.4
6.2
6.0
PPM


N—CH3
CHO
88a
4.93
3.14
11
10
9
8
7
6
5
4
3
2
1
0
PPM


OCH2Ph
OH
8a
PPM


OH HO
OH HO
91
8
7
6
5
4
3
2
1
0
PPM

LZ980B. 000 DAVIDM 07SEP95
ZHAOPENG LI L--V-71-2 IN CDCL3 1H