SYNTHESIS AND CHEMISTRY OF HIGHLY DISTORTED POLYCYCLIC AROMATIC HYDROCARBONS

MICHAEL R. MANNION

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Synthesis and Chemistry of Highly Distorted Polycyclic Aromatic Hydrocarbons

by

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St. John's, Newfoundland, 1994

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Abstract

A significant feature of smaller cyclophanes and buckminsterfullerenes is the presence of nonplanar aromatic rings. Such compounds are of considerable interest due to both the synthetic challenge they pose and to their unusual conformational, spectroscopic, and chemical behavior. A great deal of work has focussed on determining the extent to which an aromatic ring can be distorted from planarity while remaining isolable under ambient conditions. Although this question has been examined in detail for isolated benzene rings (for example, through investigations of [n]paracyclophanes), analogous studies of polycyclic aromatic hydrocarbon (PAH) frameworks have never been pursued.

Here the first systematic examination of the distortion from planarity of a PAH moiety is reported. The synthesis of a number of [n](2,7)pyrenophanes from [3.3]dithiacyclophane precursors is described. Some physical, spectroscopic, and chemical properties of these molecules are also described, and a number of X-ray structures of markedly nonplanar aromatic moieties are reported. From this data, it is concluded that the end-to-end bend of the most strained pyrenophane prepared is greater than the average end-to-end bend of the pyrene moiety. However, POAV analysis of the pyramidalization of pyrenophane sp^2 carbon atoms reveals markedly lower pyramidalizations than are observed in D_{5h} C_{70}. Attempts at the functionalization of [n](2,7)pyrenophanes in the hope of using them as precursors for larger nonplanar PAHs were made. However, suitable conditions for functionalization of pyrenophanes were not found. A synthetic approach to a C_2-chiral 1,6-[n]pyrenophane is also described.

An attempted synthesis of a derivative of the buckybowl pinakene using a tandem Bergman cycloaromatization/free radical conjugate addition is presented.

The experimental work is preceded by reviews of the literature concerning the concept of aromaticity, nonplanar aromatic molecules (especially [n]paracyclophanes) and fullerene fragments.

Acknowledgements

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χ_m	Molar Magnetic Susceptibility
α	"Alpha" band (in aromatic UV Spectrum)
α	Bend angle (in [n]paracyclophanes)
β	"Beta" band (in aromatic UV Spectrum)
β	Bend angle (in [n]paracyclophanes)
Δ	Heat
δ	(in NMR) Chemical Shift
ε	Extinction Coefficient
Λ	Magnetic Susceptibility Exaltation
λ	Wavelength
ϕ	Pyramidalization angle
Å	Angstroms
A	Amperes
Ac	Acetyl, $CH_3C(O)$-
Add.	Addition
AO	Atomic Orbital
ARE	Adiabatic Resonance Energy
Av	Average
BAC	Bond Alternation Coefficient
BB	Broad Band (in NMR)
BE	Bond Energy Coefficient
bp	Boiling Point
Cat.	Catalyst
CE	Conjugation Energy
CHD	Cyclohexadiene
CV	Cyclic Voltammetry
d	Deuterium (in NMR solvents, e.g. THF-d_8
DABCO	1,4-Diazabicyclo[2.2.2]octane

DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DDQ	1,2-Dichloro-5,6-dicyanobenzoquinone
DMDHP	15,16-Dimethyl-15,16-Dihydropyrene
DMSO	Dimethylsulfoxide
DMF	Dimethylformamide
DRE	Dewar Resonance Energy
E	Electrophilic group
EI-MS	Electron Impact Mass Spectrum
EN	Energetic Index
ENDOR	Electron-Nuclear Double Resonance
Eq.	Equivalents
ESR	Electron Spin Resonance Spectroscopy
Et	Ethyl, C_2H_5-
Fig.	Figure
FVP	Flash Vacuum Pyrolysis
FVT	Flash Vacuum Thermolysis
GEO	Geometric Index
HETCORR	Heteronuclear Correlation
HMPA	Hexamethylphosphoramide
HOMA	Harmonic Oscillator Model of Aromaticity
HOMO	Highest Occupied Molecular Orbital
HOSE	Harmonic Oscillator Stabilization Energy
HSE	Homodesmic Stabilization Energy
HSRE	Hess-Schaad Resonance Energy

h	Hour
HPLC	High Pressure Liquid Chromatography
hν	Light
IPR	Isolated Pentagon Rule
IR	Infrared
ISE	Isodesmic Stabilization Energy
^{n}J	(in NMR) Coupling Constant (Hz)
K	Kelvin
kJ	Kilojoule
KDE	Kekulé Deformation Energy
LiHMDS	Lithium Hexamethyldisilazide
lit.	Literature
LUMO	Lowest Unoccupied Molecular Orbital
COSY	Correlation Spectroscopy
m-CPBA	*meta*-chloroperoxybenzoic acid
M^{+}	Mass peak
Max.	Maximum
Me	Methyl, CH_3-
min	Minute -or- minimum
MM	Molecular Mechanics
MO	Molecular Orbital
mp	Melting Point
NICS	Nucleus Independent Chemical Shift
NMR	Nuclear Magnetic Resonance
NOED	Nuclear Overhauser Effect Difference
[O]	Oxidation
p	"Para" band (in aromatic UV Spectrum)
P_a	Anodic Peak Potential
PAH	Polycyclic Aromatic Hydrocarbon
P_c	Cathodic Peak Potential
PCA	Principal Component Analysis

Ph	Phenyl, C_6H_5-
PPP	Pariser-Parr-Pople
POAV	π-Orbital Axis Vector
ppm	Parts per Million
PTAD	*N*-Phenyl-1,3,4-triazoline-2,5-dione
pyr.	Pyridine, C_5H_5N
RA	Relative Aromaticity
RBF	Round Bottom Flask
RBFA	Relative Bond-Fixing Ability
RE	Resonance Energy
REPE	Resonance Energy Per Electron
rgt.	Reagent
RT	Room Temperature
SCE	Saturated Calomel Electrode
SCF	Self-Consistent Field
SSCE	Saturated Sodium Chloride/Calomel
STO	Slater-Type Orbital
TBAI	Tetrabutylammonium iodide
^{t}Bu	*tert*-Butyl, $(CH_3)_3C$-
^{t}BuOK	Potassium *tert*-butoxide, $(CH_3)_3COK$
TCNE	Tetracyanoethylene
Tf	Trifluoromethanesulfonyl, CF_3SO_2-
THF	Tetrahydrofuran
tlc	Thin Layer Chromatography
TMEDA	Tetramethylethylenediamine
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
Vis	Visible (light)
V	Volts
VRE	Vertical Resonance Energy
VT	Variable Temperature

Introduction

Since the discovery of benzene by Michael Faraday in 1825, the study of benzene and its properties has played a central role in the development of modern chemistry. Such concepts as valence, resonance, and molecular orbital theory arose, at least in part, as attempts to explain the unusual stability and spectroscopic properties associated with benzene's "aromatic sextet." Indeed, accounting for these unusual properties, usually referred to collectively as "aromaticity," has become one of the most fascinating and frustrating problems to face theoretical and experimental chemists during the 20th century, and, as this thesis will demonstrate, it seems unlikely that any simple resolution to this issue will be presented in the near future.

Among the many questions posed about benzene, one concerns the effect that bending the (normally flat) six-membered ring out of planarity would have on its "aromatic" properties. During the second half of the twentieth century, this problem was investigated extensively by the preparation and study of [n]meta- and [n]paracyclophanes, molecules whose benzene rings are forced to bend by a short tether attached to two ends of the "aromatic" moiety. As computational chemistry became more sophisticated and reliable in the 1980s and 1990s, a great number of theoretical studies of these compounds was conducted as well.

The discovery of buckminsterfullerenes ("fullerenes") in the mid-1980s added new significance to the earlier, curiosity-driven research into the effects of nonplanarity on aromaticity. Many practical applications were postulated for fullerenes and related compounds, including their potential uses as molecular wires and high temperature superconductors. This made a detailed understanding of electron delocalization and 'aromaticity' in fullerenes very important, and considerable work has been and is currently being conducted to investigate this problem.

The work described in this thesis spans all these topics. At the outset of our research into the properties of pyrenophanes, no systematic investigation into the effects of bending a polycyclic aromatic hydrocarbon (PAH) out of planarity had ever been pursued. Many questions could be answered by such studies: How does significant nonplanarity affect the "aromatic" properties of polycyclic aromatic hydrocarbons – the delocalization, the diatropic ring current, the stability? How far can the aromatic moiety

be bent before the compounds fail to form or become too unstable to be isolable under ambient conditions? What sort of reactivity patterns do these compounds display? How do these properties compare with the known properties of buckminsterfullerenes?

It is hard to know if the answers to these questions will have any practical applications or profound influence on the topics described above. However, to appreciate the significance they do have, a detailed understanding of aromaticity and cyclophane chemistry is essential. This work will therefore begin with an overview of these topics. It will then describe our research into curved PAHs, and discuss the significance of this work in the contexts of aromaticity, cyclophane chemistry, and fullerene chemistry.

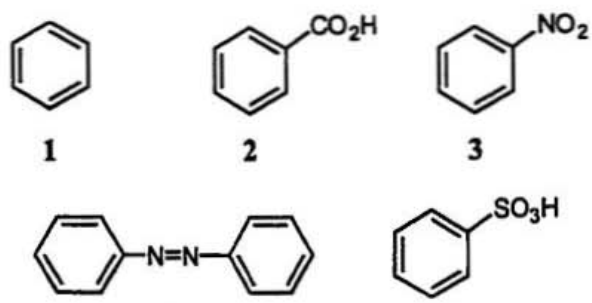
Chapter 1 - Benzene and Aromaticity

1.1 Benzene and its Properties

1.1.1 – Early History

On June 16, 1825, Michael Faraday presented a paper to the Royal Society in London entitled "On New Compounds of Carbon and Hydrogen, and on Certain Other Products Obtained During the Decomposition of Oil by Heat."[1] At the time, Faraday was working as a laboratory assistant to Prof. Humphry Davy at the Royal Institution, and much of their work involved the isolation and condensation of gases. In this case, Faraday had been given several cylinders of compressed illuminating gas, which was manufactured by the "Portable Gas Company"[2] by decomposing whale oil at red heat. Faraday collected the condensed liquid from these cylinders and from it, using fractional crystallization, he isolated a compound we now know as benzene, **1**. Faraday determined the density and melting point of this new compound, and demonstrated that it burned with a smoky yellow flame. Due to the uncertain atomic weight values at the time, Faraday determined the empirical formula of this new compound to be C_2H, and he therefore named it "Bicarburet of Hydrogen."

A decade later, by dry-distilling the acid isolated from benzoin resin (benzoic acid, **2**) with lime, Eilhard Mitscherlich obtained a volatile liquid which he called "Benzin."[3] He recognized that this liquid was identical with that described earlier by Faraday. He conducted the first chemical studies of benzene, synthesizing nitrobenzene,



1 **2** **3** **4** **5**

[1] a) Faraday, M. *Phil. Trans. Royal Soc.* **1825**, *115*, 440-451. b) Hafner, K. *Angew Chem., Int. Ed. Engl.* **1979**, *18*, 641-651.
[2] Findlay, A. *A Hundred Years of Chemistry* Duckworth & Co., London: **1937**, p. 131.

3, azobenzene, **4**, and benzenesulfonic acid, **5**, experiments that laid the groundwork for the development of the dyestuffs industry later in the century.

Justus von Liebig considered the name "Benzin" to imply a relationship with strychnine and quinine, so he renamed this compound benzol (the suffix -öl refers to "oil" in German). Ironically, this early attempt at systematic nomenclature resulted in confusion in England and France due to its similarity to the systematic names of alcohols, so in these countries the compound was finally renamed "benzene."[4] Auguste Laurent,[5] the French chemist who proposed this –ene ending, also recommended changing the compound's name entirely to "phene" (etymologically related to the Greek φαιυω, "to shine") to indicate the compound's original discovery from illuminating gas. Although this nomenclature never replaced the term benzene itself, the benzene ring as a substituent is still referred to as "phenyl."[6]

By the 1860s, the chemical formula of benzene had been conclusively determined to be C_6H_6. The structure, or arrangement of these atoms in space, was unknown. However, in 1858, Friederich August Kekulé[7] and Archibald Couper[8] had independently proposed a theory on the structure of organic compounds, known as the valence theory, that suggested that carbon atoms always attach themselves to four other groups – in modern terms, carbon is tetravalent. Although obvious to modern chemists, at the time this proposal was (at risk of using an unintentional pun) a radical[9] one. Most chemists had resigned themselves to the belief that the arrangement of carbons and hydrogens in

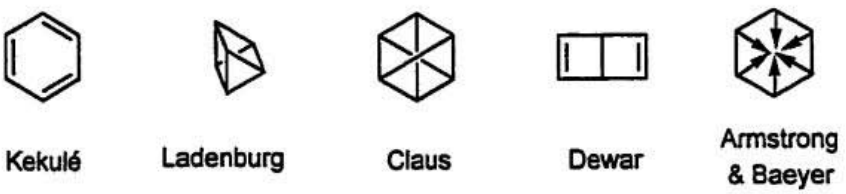


Figure 1-1: Proposed Structures of Benzene

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[3] Winderlich, R. *J. Chem. Ed.* **1949**, *26*, 358-361.
[4] Badger, G.M. *Aromatic Character and Aromaticity* Cambridge University Press, **1969**, p. 1.
[5] de Milt, C. *J. Chem. Ed.* **1951**, *28*, 198-204.
[6] Thorpe, T.E. *Essays in Historical Chemistry* Books for Libraries Press, **1894** (1972 reprint).
[7] a) Kekulé, F.A., Speech at Berlin City Hall, 1890. Translated by O.T. Benfey, in *J. Chem. Ed.* **1958**, *35*, 21-23. b) Kauffman, G.B. *J. Chem. Ed.* **1972**, *49*, 813-817.
[8] Benfey, O.T. *J. Chem. Ed.* **1959**, *36*, 319-320.

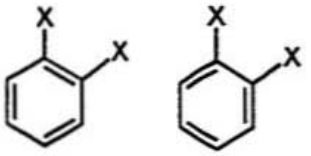
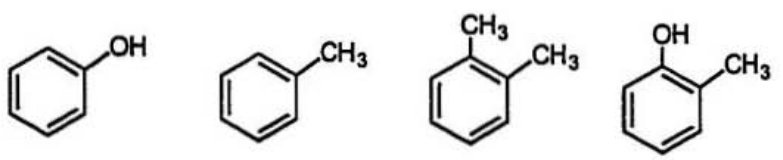


Figure 1-2: Ladenburg's Objection to Kekulé's Structure. Two possible *o*-isomers

organic compounds was too complex to determine, and such compounds could only be characterized and classified by, for instance, the number of carbons they contained. Kekulé applied his controversial theory to benzene in 1865, proposing the now familiar cyclohexatriene or 'hexagon' structure (Fig. 1-1). Whether there is any truth to the legend that Kekulé conceived this idea after a dream in which he saw a snake eating its own tail is debatable. Some historians suggest that this imaginative story was promoted by Kekulé himself to discourage rumors that he had stolen his idea from someone else, perhaps Couper. In any event, his proposal immediately afforded a simple explanation to hitherto intractable problems concerning isomeric derivatives of benzene – for instance, why there was only one isomer of phenol, **6**, and toluene, **7**, but three isomers of xylene and cresol, of which the respective *o*-isomers (**8** & **9**) are shown. [10]

Some objections were raised to Kekulé's theory. Ladenburg, for instance, demonstrated how, if a static structure were postulated, there should be *four*, not three, isomers of disubstituted benzenes, such as xylene (Fig. 1-2).[11] Kekulé, rather vaguely, proposed a "mechanical motion" or oscillation of the double bonds around the ring, thereby rendering the two 1,2-disubstituted structures equivalent. This was considered by many a rather desperate device to save his hexagon theory, and other proposals for the structure of benzene were subsequently advanced (Fig. 1-1). However, the idea that



6 **7** **8** **9**

[9] In the 19th Century, the term "radical" referred to organic groups, often of uncertain structure, which could be carried through reactions without changing their composition, e.g. methyl radical, benzoyl radical.
[10] Brock, W.H. *Fontana History of Chemistry* Fontana Press, London, 1992, p. 267.

organic structures were inherently unknowable was rapidly discarded. By the 1870s, effectively all organic chemists were structuralists,[12] dedicated to exploring a substance's properties by determining its chemical structure. Kekulé's proposed structure of benzene, which initiated this revolution in thinking, was appropriately described in 1898 as "the most brilliant piece of scientific production in the whole of organic chemistry."[13]

The discovery of the electron in 1897 by J. J. Thompson, and his subsequent interpretation of bonding as electron transfer – the polar theory of valence - once again allowed benzene to play a role in the development of structural chemistry. While the polar theory worked excellently with polar molecules such as HCl, invoking a polar bond between two carbon atoms or a carbon and a hydrogen atom seemed less likely. In 1916, Gilbert Lewis proposed the concept of the 'shared pair'.[14] Electrons were not transferred from one atom to another, but were shared between them. Carbon, for instance, would arrange itself such that it was sharing eight electrons with other atoms. This 'octet rule' was accepted due to its utility in explaining regioselectivity in the substitution of benzene and its derivatives. The distortion of the octets of the benzene ring carbons by electron withdrawing or electron donating substituents, and their resultant respective *meta-* or *ortho, para-* directing behaviour, could be explained by the octet rule, but not by the earlier polar theory of valence.[15] Once again, benzene had been central in the development of a fundamental theory of modern chemistry.

In this section, a brief historical overview of the important role benzene has played in the evolution of modern chemistry has been presented. However, the most puzzling property of benzene, and the one most relevant to the work that this thesis will ultimately describe, has not yet been considered. It is this property – commonly known as aromaticity – that will now be examined in detail.

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[11] Garratt, P.J. *Aromaticity* Wiley and Sons, New York, 1986.
[12] Ref. 10, p. 268.
[13] Ref. 10, p. 269.
[14] Lewis, G.N. *J. Am. Chem. Soc.* 1916, *38*, 762.
[15] Saltzman, M.D. *J. Chem. Ed.* 1974, *51*, 498-502.

1.1.2 - The Paradox of Benzene

Lloyd[16] has suggested that chemists have become "desensitized" to just how unusual the chemistry of benzene is, when compared to that of other unsaturated compounds. He goes on to describe the following thought experiment (Fig. 1-3): Consider a chemist who has been taught only the chemistry of aliphatic compounds, saturated and unsaturated. When presented with the structural formula of benzene and asked to predict its properties, such an individual would almost certainly suggest that benzene would:

-undergo addition of bromine to yield a vicinal dibromide;

-decolorize an aqueous permanganate solution, to afford oxidized products;

-react rapidly with hydrogen and a catalyst to yield cyclohexane.

Many more items could be added to this list, but the point is already clear. "Normal" unsaturated compounds, such as cyclohexene, **10**, will undergo addition reactions like those illustrated below. The misinformed chemist would no doubt be puzzled to learn that all these predictions are wrong. Benzene does not react with bromine without a catalyst, and when it does, it undergoes a substitution rather than an addition, regenerating the unsaturated system. Nor does it decolorize permanganate, nor add hydrogen, except under extremely forcing conditions. This pair of apparently contradictory properties – unsaturated, yet inert – is what P. J. Garratt referred to as the "Paradox of Benzene."[11]

Next, suppose the chemist was presented with the structure of cyclobutadiene, **11**. If observant, he or she might have concluded that there was something special about

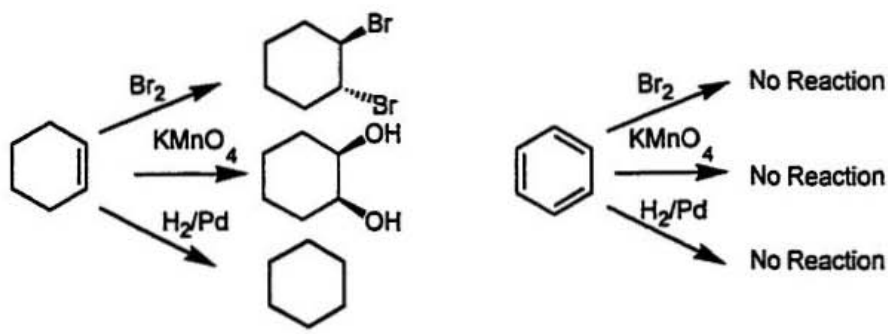

Figure 1-3: The Paradox of Benzene: Unsaturated, yet Inert.

[16] Lloyd, D. *The Chemistry of Conjugated Cyclic Compounds – To Be or Not To Be Like Benzene* John Wiley & Sons, Chichester, 1989.

cyclic conjugated systems like benzene. Not wishing to appear ignorant twice, he or she may predict that this compound would be inert to the previously mentioned conditions, or react with electrophiles such as bromine to afford substitution products. Of course, he or she would be, once again, totally incorrect. Not only does cyclobutadiene not display

10

11

unusual stability, it is in fact so unstable that it cannot be isolated or even observed except under special conditions at exceedingly low temperatures, or when stabilized by incarceration in a carceplex.[16,17]

Some other examples of atypical behavior of cyclic, conjugated compounds should be mentioned at this point. Instead of displaying alternating double and single bonds and a D_{3h} symmetry (as suggested by the Kekulé structure), all experimental data suggest that benzene has a bond-equalized structure with six C-C bonds of equal length. In the NMR, benzene's protons resonate much further downfield than those of conjugated polyenes, while hydrogens held above or below the plane of the benzene ring are shifted upfield. Finally, as will be discussed later, benzene's behavior when placed in strong magnetic fields is decidedly different from that expected of a 'normal' polyene.

This bizarre and complex behavior of cyclic conjugated systems is one of the most thoroughly investigated phenomena in chemistry, and yet simple, universally accepted explanations and classifications remain elusive.[18] Such behavior is generally denoted by the term "aromaticity," but, as will be seen, this term has become almost as confusing and intractable as the phenomenon (or phenomena? – *vide infra*) that it describes.

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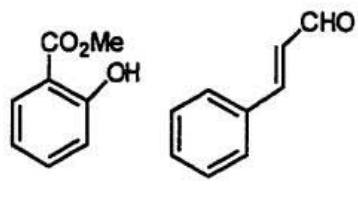
[17] Cram, D.J.; Tanner, M.E.; Thomas, R. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1024-1027.

[18] For General References see: a) Agranat, I. in Bergmann E.D.; Pullman, B. (Eds.) *Aromaticity, Pseudo-Aromaticity, Antiaromaticity, Vol. 3*, Israel Acad. Of Sciences and Humanities, Jerusalem, 1971. b) Pozharskii, A.F. *Chem. Heterocyc. Comp.* **1986**, *21*, 717-749. c) Cook, M.J.; Katritzky, A.R.; Lindon, P. *Adv. Heterocyc. Chem.* **1974**, *17*, 255-356. d) Minkin, V.I.; Glukhovtsev, M.N.; Simkin, B.Y. *Aromaticity and Antiaromaticity* John Wiley & Sons, New York, **1994**. See also Refs. 4,11,16, and 30.

1.2 – Aromaticity

1.2.1 – Aromaticity – Early Developments

As early as the 1820's, hydrocarbons with distinctive, generally pleasant odors and a high C:H ratio (compared to other, "aliphatic" organic compounds) were denoted by the term "aromatic hydrocarbons."[19] Among these were oil of wintergreen (methyl salicylate, **12**) and oil of cinnamon (cinnamaldehyde, **13**), as well as certain compounds such as camphor, **14**, and limonene, **15**, that would not be considered "aromatic" now.[20]



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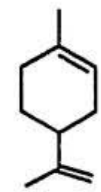

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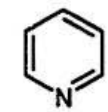

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17

The term was gradually limited to substances that displayed the abnormal chemical reactivity described earlier. Many of these substances, it was noted, contained a benzene ring moiety, but others, such as pyridine, **16**, and furan, **17**, did not. In 1890, Bamberger suggested that all aromatics bore a hexacentric system of "potential valences," but this proposal did not become popular.[21] With the advent of the electronic theory of valence, it was suggested that, for some reason, the arrangement of the π-electrons in benzene led to enhanced stability. This theory of the "aromatic sextet," proposed in 1925 by Armit and Robinson,[22] was completely empirical and offered no theoretical rationale. However, it was one of the first serious attempts to define aromatic compounds: a compound is aromatic if it contains a cyclic, conjugated system of 6 π–electrons. In 1931, Hückel[23] proposed a far more elaborate model, based on quantum theory, that demonstrated that any compound with a cyclic, conjugated π–system containing 4n+2 electrons, where n is any integer, will display enhanced stability (like benzene), while any compound with a

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[19] Ref. 10, p. 263.
[20] Sinclair, J.P. (Ed.). *Organic Chemistry Monographs – Nonbenzenoid Aromatics* Academic Press, New York, 1969.
[21] Kolb, D. *J. Chem. Ed.* **1979**, *56*, 334-337.
[22] Armit, J.W.; Robinson, R. *J. Chem. Soc.* **1925**, *127*, 1604-1618.
[23] a) Hückel, E. *Z. Physik* **1931**, *70*, 201. b) Hückel, E. *Z. Physik* **1932**, *76*, 628. c) Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry* McGraw-Hill, New York, 1969, pp. 92-100.

cyclic, conjugated π–system containing 4n electrons will display reduced stability (like cyclobutadiene). This system, known as Hückel's rule, is familiar to most chemists, and is still frequently invoked by nonspecialists as the definition of aromaticity.

Hückel's rule, however, suffers from some shortcomings. One is that it is not quantifiable. According to Hückel's rule, a molecule is either aromatic or it is not, and there is no way to determine, for example, how aromatic pyridine is relative to benzene. Secondly, Hückel's rule is based on an extremely simplified view of quantum theory, and is theoretically deeply flawed. Finally, Hückel's rule does not account for the behavior of large annulenes or polycyclic aromatic hydrocarbons.

For six decades, theoreticians and experimentalists have struggled to come up with a simple, reliable method to determine *quantitatively* the aromaticity of any molecule of interest. The body of relevant literature is vast, confusing, and encompasses diverse areas such as quantum physics, computational chemistry, various forms of molecular spectroscopy, crystallography, and statistics. A comprehensive review of this topic is well outside the scope of this thesis.[24] However, a detailed exposition of some of the approaches to this problem will now be presented.

1.2.2 - Aromaticity – Reactivity Criteria

The phenomenon that most people intuitively associate with aromatic molecules is their relative unreactivity, and their tendency to undergo substitution instead of addition reactions. This tendency to "retain the type," as described by Armit and Robinson, has been termed "menedeism,"[25] and a numerical quantification of this tendency (e.g. by measuring the rate of a Diels-Alder reaction of the aromatic moiety of a molecule) has been proposed as a suitable criterion for the measurement of aromaticity.[26] Other suggestions include examining a compound's thermal stability or its reactivity towards nucleophiles or electrophiles.[18b] These reactivity definitions of aromaticity amount to stating that aromaticity involves "having a chemistry like that of benzene."

One problem with proposals involving the measurement of reaction rates, besides such practical difficulties as compensating for differences in solvation and other factors

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[24] The most recent major examination of this topic is that of Minkin *et al.*; ref. 17d
[25] Lloyd, D.; Marshall, D.R. *Angew. Chem., Int. Ed. Engl.* **1972**, *11*, 404-408.

unrelated to aromaticity, is that aromaticity is generally considered to be a ground state property. Reactivity (at least kinetic reactivity), on the other hand, is determined by the difference in energy between the ground state and the transition state of whatever reaction is being considered. So reactivity is not *directly* related to the ground state, and kinetic measurements of reactivity do not provide unambiguous information about the ground state energy of a molecule.[27] Perhaps a better definition than "having a chemistry like benzene," one that does not involve excited (or transition) states, is "having a low ground state enthalpy." A low ground state enthalpy of, for example, an aromatic sextet of electrons, would disfavor addition reactions and favor substitutions. So, by measuring the thermodynamic equilibrium between an aromatic compound and its addition reaction product, a measure of the compound's aromaticity could be obtained. The objection to this proposal can be illustrated by the consideration of 'aromatic' molecules like the cyclopentadienide anion **18**, or a strained molecule like [5]paracyclophane, **19**, substances which have pronounced tendencies to undergo addition reactions, and therefore most emphatically do not "have a chemistry like benzene." However, as will be discussed in more detail later, their ground state energies are well below those predicted for 'nonaromatic' molecules. Consider, for example, the reduced basicity of cyclopentadienide **18** when compared to that of a linear polyene-anion such as pentadienide, **20**, and **18** and **19** display other properties normally associated with "aromaticity," such as a diatropic ring current. It was to account for the properties of compounds like **18** and **19** that the reactivity definition of aromaticity was discarded, in favor of energetic criteria, which will now be discussed.

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[26] Dixon, W.T. *J. Chem. Soc. B.* **1970**, 612-616.
[27] Peters, D. *J. Chem. Soc.* **1960**, 1274-1279.

1.2.3 - Aromaticity – Energetic Criteria

1.2.3.1 - A Miscellany of Resonance Energies

Undergraduate textbooks usually state that the enthalpy of hydrogenation of benzene is 36 kcal/mol less than three times the enthalpy of hydrogenation of cyclohexene, and this value is therefore quoted as the resonance energy of benzene.[28] This extremely naïve experiment, which neglects such fundamental factors as changes in bond lengths, hybridization, and nonbonded repulsion, is an attempt to demonstrate quantitatively the energetic stabilization obtained by the cyclic delocalization of π–electrons in benzene. The magnitude of this stabilization, called the resonance energy[29], can be defined formally as the difference in energy between real, delocalized benzene and an hypothetical, localized cyclohexatriene. Because the latter does not exist, the energy of this reference molecule cannot be determined experimentally. The energy must be calculated, either by adding up empirical bond energies, or by using sophisticated computational techniques. In simple terms, the resonance energy (RE) of benzene can be expressed by the equation:

$$RE_{(benzene)} = \Delta H_{a\ (benzene)} - 6E(C\text{-}H) - 3E(C\text{-}C) - 3E(C{=}C) \quad (1)$$

where $\Delta H_{a\ (benzene)}$ is the enthalpy of atomization of benzene, and E represents the bond energies of C-H, C-C (single) and C=C (double) bonds, respectively. The energy of the real molecule, $\Delta H_{a\ (benzene)}$, can be determined experimentally or computationally. Although apparently simple, the values determined for the resonance energy of benzene range from 5 to 64 kcal/mol.[30,31] This astonishingly wide range is the result of a lack of agreement on what the exact structure of "cyclohexatriene" really is, and how the bond enthalpies used in equation 1 should be calculated.[32]

Although many papers and textbooks refer confidently to the "resonance energy" (or stabilization energy, or delocalization energy) of benzene and other aromatic compounds, most authors appear unaware, or at least fail to mention, that there are

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[28] For example: a) Streitweiser, A.; Heathcock, C.; Kosower, E.M. *Introduction to Organic Chemistry* MacMillan Publishing, New York, 1992; pp. 608-610. b) Carey, F.A.; Sundberg, R.J. *Advanced Organic Chemistry, Part A, 2nd Ed.* Plenum Press, New York, 1984, p. 458.

[29] In the literature, the terms "resonance energy," "delocalization energy," "stabilization energy" and (in older papers) "mesomeric energy" are used interchangeably.

[30] Lewis, D.; Peters, D. *Facts and Theories of Aromaticity* McMillan Press, London, 1975, p. 19.

[31] Janoschek, R. *J. Mol. Struc. (Theochem)* 1991, *229*, 197-203.

several different types of resonance energy.[33] The types differ in the geometric and energetic assumptions made in calculating the energy of the reference molecule.

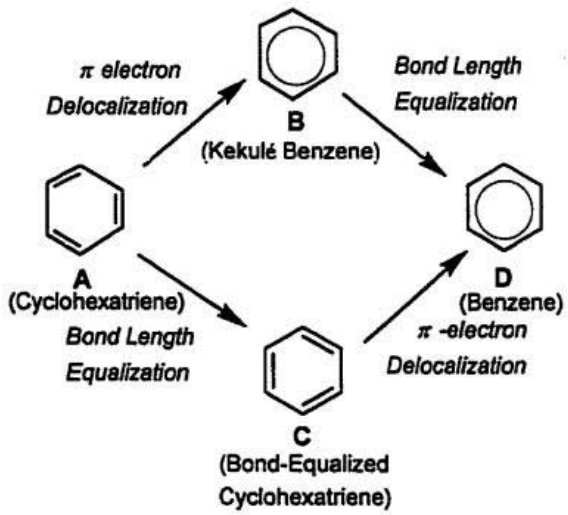

Figure 1-4: Conversion of Cyclohexatriene to Benzene

To simplify this discussion, consider the thermochemical cycle in Fig. 1-4.[34] It shows the conversion of the model compound, cyclohexatriene (**A**) to benzene (**D**). The exact geometry (bond lengths) of cyclohexatriene **A** varies according to the assumptions made (*vide infra*), but it is always assumed to be 'bond localized' – displaying D_{3h} symmetry with alternating long and short single and double bonds. The π electrons in **A** are also assumed to be completely localized, in other words, non-interacting. Benzene (**D**), as described before, is both bond-equalized and π electron delocalized.

Now let us consider the changes required to transform **A** into **D**. There are two ways of doing this. First, one can allow the electrons of **A** to delocalize fully, while maintaining the geometry of **A** constant. This gives **B**, a structure we shall call "Kekulé Benzene." The energy for the delocalization step **A** → **B** shall be called $E_{A \rightarrow B}$. Kekulé benzene is simply benzene whose bonds have been stretched and compressed, as in a molecular vibration. The molecule can now relax to the lowest energy D_{6h} geometry

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[32] George, P.; Bock, C.W.; Trachtman, M. *J. Chem. Ed.* **1984**, *61*, 225-227.
[33] Glukhovtsev, M. *J. Chem. Ed.* **1997**, *74*, 132-136.
[34] a) Mulliken, R.S.; Parr, R.G. *J. Chem. Phys.* **1951**, *19*, 1271-1278. b) Coulson, C.A.; Altmann, S.L. *Trans. Faraday Soc.* **1952**, *48*, 293-302. c) Coulson, C.A. in *Chemical Society Symposia: Special Publication 12* Chemical Society, London, **1958**. p. 95.

of benzene, **D**. The energy for the bond length equalization step, **B** → **D**, shall be termed $E_{B \rightarrow D}$. The other way to convert cyclohexatriene to benzene simply involves reversing the order of the operations. Cyclohexatriene **A** can first be distorted to a bond equalized but π-electron-localized structure **C**, that can be called "Bond-equalized Cyclohexatriene," whose geometry is the same as that of benzene. The energy for **A** → **C** is $E_{A \rightarrow C}$. Finally, the electrons in structure **C** can be allowed to be fully delocalized, transforming **C** into benzene, **D**, with an energy $E_{C \rightarrow D}$. The total energy of the cycle, $E_{A \rightarrow D}$, will be equal to ($E_{A \rightarrow B} + E_{B \rightarrow D}$) or ($E_{A \rightarrow C} + E_{C \rightarrow D}$). Depending on the context, $E_{A \rightarrow D}$, $E_{B \rightarrow D}$, and $E_{C \rightarrow D}$ have *all* been termed the "resonance energy" of benzene. Now the terminology referring to these various changes in energy shall be considered.

The ***isodesmic stabilization energy (ISE)*** measures the energy gained by delocalization of electrons relative to a reference structure with *completely isolated* (noninteracting) double bonds ($E_{A \rightarrow D}$). Thus, the bond energies and geometries used in calculating the energy of the reference structure **A** would be determined from ethylene (C=C), ethane (C-C), and methane (C-H). Examples of ISE include the Hückel resonance energy (as originally proposed), and empirical resonance energy methods[35] sometimes applied to heterocycles. It should be noted that even nonaromatic, conjugated molecules will display considerable ISE. For example, the ISE for butadiene (relative to 2 moles of ethylene) has been estimated at 6-8 kcal/mol.[36] The 64 kcal/mol value for the resonance of benzene is an ISE value, corresponding to the energy calculated for the reaction (*vide infra* for more on this):

$$\text{Benzene} + 6\ CH_4 \rightarrow 3\ CH_3CH_3 + 3\ CH_2CH_2 \qquad (2)^{32}$$

Aromatic compounds are assumed to display stabilization energy *in excess* of that already found in acyclic, conjugated polyenes such as butadiene. The ***homodesmic stabilization energy (HSE)*** measures only the energy gained by the *cyclic* delocalization of electrons (also $E_{A \rightarrow D}$). The difference from the ISE is that the reference structure is calculated using the bond lengths and energies of an *acyclic polyene*, not those of isolated single and double bonds as in ethylene and ethane, so that it lacks only cyclic delocalization. The HSE is therefore lower than the corresponding ISE in aromatic

[35] Cook *et al.*; ref. 17c.

compounds. Since the bond energies of an acyclic, conjugated polyene can be calculated very accurately, the HSE is frequently more reliable than the ISE. The Dewar Resonance Energy (DRE)[37] and the Hess-Schaad Resonance Energy (HSRE)[38] are examples of HSEs. HSEs like the DRE are useful tools for obtaining numerical estimates of aromatic stabilization. If positive, the molecule is considered to be aromatic (DRE of benzene = 21.5 kcal/mol).[34b] If close to zero (+/- 2 kcal/mol) the molecule is taken to be nonaromatic, and if negative, the molecule is considered antiaromatic. Therefore, the sign and magnitude of HSEs can be used to describe quantitatively aromaticity in molecules. Frequently, the HSE is divided by the number of electrons in the aromatic system to afford a Resonance Energy Per Electron (REPE)[39] value, which allows the comparison of, for example, polycyclic aromatic hydrocarbons with benzene. The REPE is therefore, in theory, a universally applicable, quantitative measure of aromaticity.

The ISEs and HSEs both involve comparing a real molecule (benzene) with a hypothetical molecule *in its optimized geometry* (**A** → **D**). Thus the bond lengths and energies of imaginary cyclohexatriene **A** are equal to those of ethane/ethylene (in the case of ISE) or those of an acyclic polyene (in the case of HSE). The point is that the geometry of the real molecule is *different* from that of the reference molecule, and a change in geometry accompanies the delocalization of the electrons. The stabilization energies thus determined are called ***adiabatic resonance energies (AREs)***. However, computational techniques allow the comparison of a real molecule (benzene) with an 'olefinic', nondelocalized reference molecule (Bond-equalized Cyclohexatriene, **C**) *in the same geometry as benzene*. In such calculations, the atoms are held in the same positions, and interactions between certain orbitals can be turned off by 'fictitious walls' that electrons cannot penetrate.[40] Such methods, where the geometry of the two structures being compared is identical, determine the ***vertical resonance energies (VREs)***[41] as in $E_{A\rightarrow B}$ and $E_{C\rightarrow D}$.[42] An example of VRE is the Jug resonance energy.[28]

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[36] Ref. 34c, p. 107.
[37] a) Dewar, M.J.S. *The Molecular Orbital Theory of Organic Chemistry*. McGraw-Hill Book Co., New York: 1969. b) Baird, N.C. *Can. J. Chem.* **1969**, *47*, 3535-3538.
[38] Hess, B.A.; Schaad, L.J. *J. Am. Chem. Soc.* **1971**, *93*, 305-310.
[39] Hess, B.A.; Schaad, L.J. *J. Org. Chem.* **1971**, *36*, 3418-3423.
[40] Behrens, S.; Köster, A.M.; Jug, K. *J. Org. Chem.* **1994**, *59*, 2546-2551.
[41] The term 'vertical' is used in the sense implied by the Franck – Condon principle. The change in electronic structure occurs without a change in internuclear distances.

The significance of the VRE is that it describes the aromatic stabilization attributable to the delocalization of the π-system *only*, because the geometry (and hence the energy) of the σ system does not change. The ARE, on the other hand, consists of changes in both the π and σ energy components. The graph in Fig. 1-5 demonstrates qualitatively the changes in energy (at the PPP-SCF-MO level of calculation) that occur as 'cyclohexatriene' and benzene are distorted from their optimal geometries (**A** and **D**, respectively). Note that electron delocalization stabilizes benzene at all geometries, but most of all in the bond-equalized D_{6h} geometry.[41]

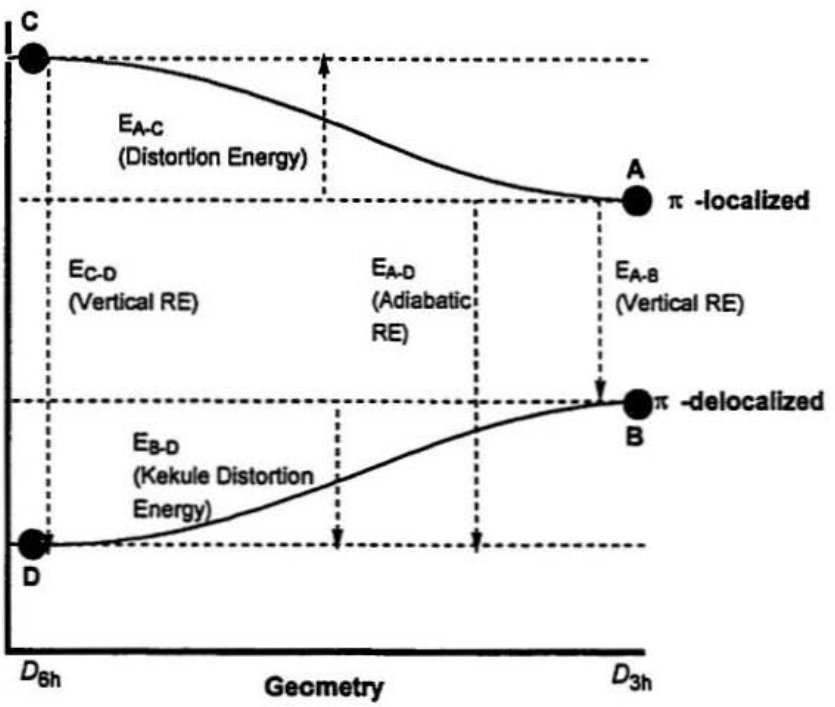

Figure 1-5: Delocalization Energy Scheme for Benzene.

[42] Aihara, J.-I. *Bull. Chem. Soc. Japan.* **1990**, *63*, 1956-1960.

1.2.3.2 - σ vs. π Energetics in Benzene

The issue of the energy of the π and σ frameworks on going from a localized to a delocalized structure requires a brief digression. It was always assumed that the properties of benzene resulted from a stabilization of the π-system. It was also always assumed that the equalization of bond lengths observed in benzene was a product of π-delocalization as well – in other words, the π-system prefers the D_{6h} geometry to the localized D_{3h}. However, in 1985 Shaik and Hiberty released the first of a series of papers[43] that questioned this 'conventional wisdom'. Their conclusions were surprising: the σ system, not the π, was responsible for bond equalization in benzene. The π-system prefers to be bond-alternant, but the presence of the σ-system forces the π-system to assume an otherwise unstable, bond-equalized conformation. The basis for this rather heretical assertion was their (computational) demonstration of the tendency of atoms that form strong bonds, with low triplet excitation energies, to prefer a localized rather than a delocalized state. Since C-C π-bonds are relatively strong, the π-system should prefer to be geometrically localized into a D_{3h} geometry. Although some of their conclusions have been called into question,[44] their conclusion that the π-system in benzene is distortive at D_{6h} geometry (i.e., would prefer to relax to a D_{3h} geometry) has been confirmed by other groups' computational[45] and experimental[46] evidence. Their work, and the work of others, has allowed a detailed partitioning of energy of the π and σ electrons in both real, "aromatic" benzene and olefinic cyclohexatriene at both alternating and nonalternating geometries. This is illustated in Fig. 1-6.

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[43] a) Hiberty, P.C.; Shaik, S.S.; Lefour, J.-M.; Ohanessian, G. *J. Org. Chem.* **1985**, *50*, 4657-4659. b) Shaik, S.S.; Hiberty, P.C. *J. Am. Chem. Soc.* **1985**; *107*, 3089-3095. c) Hiberty, P.C.; Shaik, S.S.; Ohanessian, G.; Lefour, J.-M. *J. Org. Chem.* **1986**, *51*, 3908-3909. d) Hiberty, P.C.; Shaik, S.S.; Ohanessian, G.; Lefour, J.-M. *J. Am. Chem. Soc.* **1987**, *109*, 363-374. e) Hiberty, P.C.; Shaik, S.S.; Ohanessian, G.; Lefour, J.-M. *J. Phys. Chem.* **1988**, *92*, 5086-5094. f) Hiberty, P.C.; Danovich, D.; Shurki, A.; Shaik, S.S. *J. Am. Chem. Soc.* **1995**, *117*, 7760-7768.

[44] a) Baird, N.C. *J. Org. Chem.* **1986**, *51*, 3907-3908. b) Glendening, E.D.; Faust, R.; Streitwieser, A.; Vollhardt, K.P.C.; Weinhold, F. *J. Am. Chem. Soc.* **1993**, *115*, 10952-10957.

[45] a) Jug, K.; Koster, A.M *J. Am. Chem. Soc.* **1990**, *112*, 6772-6777. b) Gobbi, A.; Yamaguchi,Y.; Frenking, G.; Schaefer, H.F. *Chem. Phys. Lett.* **1995**, *244*, 27-31.

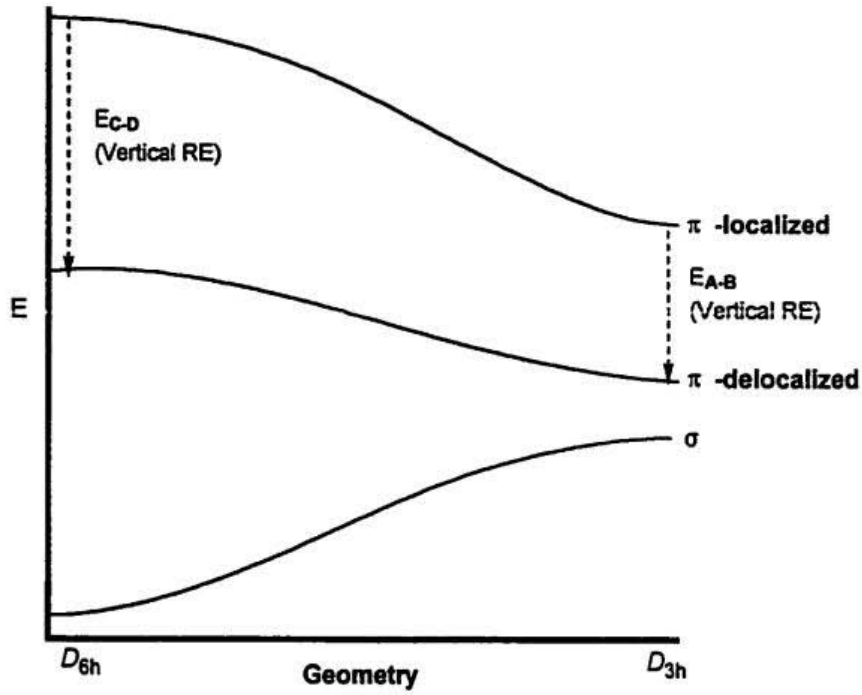

Figure 1-6 : Partitioning of π- and σ- Energies in Benzene.

Several conclusions can be deduced from this partition scheme:

- Benzene (with delocalized electrons) is stabilized relative to an olefinic, π-localized reference at all geometries, but the greatest VRE is obtained at the D_{6h} geometry.
- The σ-framework is most stable at the D_{6h} geometry.
- The π-framework, whether localized or delocalized, prefers the D_{3h} geometry. Without the σ-framework's tendency to prefer the D_{6h} geometry, benzene would have a structure with alternating single and double bonds, like acyclic polyolefins.

So what is the significance of these studies? Besides demonstrating that the "aromatic" properties of benzene are extremely complex, it calls into question most of the work that implicitly assumed that aromaticity and aromatic stabilization were solely an effect of the π-system. By demonstrating the role of the σ-frame in aromatic

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[46] a) Haas, Y.; Zilberg, S. *J. Am. Chem. Soc.* **1995**, *117*, 5387-5388. b) Shaik, S.S.; Zilberg, S.; Haas, Y. *Acc. Chem. Res.* **1996**, *29*, 211-218. c) Shaik, S.S.; Shurki, A.; Danovich, D.; Hiberty, P.C. *J. Am. Chem.*

stabilization, a new variable is added to the confused concept of 'resonance energy'. One must now consider the vertical resonance energy, which involves the π-system alone, and adiabatic resonance energy, which results from energy changes of both the σ- and π-systems.

1.2.3.3 - Other Energetic Criteria

Not all methods of determining the stabilization energy of benzene require comparison to an imaginary structure. The enthalpy of reactions, such as:

$$C_6H_6 + 6\ CH_4 \rightarrow 3\ CH_3CH_3 + 3\ CH_2CH_2 \qquad (2)$$

and

$$C_6H_6 + 3\ H_2CCH_2 \rightarrow 3\ H_2CCHCHCH_2 \qquad (3)$$

can be calculated using computational techniques. The advantage is that no imaginary, ill-defined structure needs to be invoked. However, depending on the basis sets and other variables used, the energy calculated for these reactions can still vary. Reaction **2**, already mentioned in the section describing isodesmic stabilization energies, produces a ΔH° of 64.2 kcal/mol,[31] possibly the highest value ever proposed for the RE of benzene. Reaction **2** is an *isodesmic* reaction, in which there are equal numbers of formal single and double bonds between C atoms in the reactants and products. Reaction **3**, on the other hand, is a *homodesmotic* reaction, in which the reactants and products have the same number and type of C-C *and* C-H bonds. This has been evaluated using a number of computational methods, with results ranging from 20.6 (AM1) to 28 (SCF-3-21G*) kcal/mol.[18d,30] Because the product of this reaction (butadiene) contains conjugated double bonds, the results of this calculation refer to homodesmic stabilization energies (HSEs).

Another method of avoiding the problematic imaginary reference molecule is to consider benzene alone. For instance, consider the energy required to distort benzene from its preferred D_{6h} geometry to an olefinic, D_{3h} geometry ($E_{D\rightarrow B}$). This energy has been called the "compression energy," however this name is misleading, as bonds are

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Soc. 1996, *118*, 666-671. d) Shurki, A.; Shaik, S.S. *Angew. Chem., Int. Ed. Engl.* 1997, *36*, 2205-2207.

stretched as well as compressed. We shall therefore refer to it as the Kekulé Distortion Energy (KDE). The energies determined for the KDE using quantum mechanical calculations ranges from 4.2 to 6.0 kcal/mol.[30,47] Using a harmonic oscillator model, a value of 12.3 kcal/mol was obtained (*vide infra*).[48] However, simply distorting benzene to a bond-alternant, olefinic geometry does not remove the stabilization due to the π-electronic delocalization, and it is the latter quantity that is generally understood to be associated with the aromaticity of benzene. Given the recent findings concerning π and σ energetics in aromatic compounds, it is debatable whether the KDE is necessarily proportional to adiabatic resonance energies or any other value normally associated with aromaticity. A more recent approach along these lines will be considered later.

1.2.3.4 - Conclusion – Energetics

The preceding paragraphs have described a number of different methods of determining the 'stabilization energy' that differ on the basis of the characteristics of the reference molecule, or the lack of one. Although the examples of the methods described here all involved benzene, most of these methods can also be applied to heterocycles and PAHs. Is it therefore applicable to a quantitative, universal measurement of aromaticity? In theory, the answer is yes. The stabilization energy, as long as it is specifically and rigorously defined, should be determinable for any molecule, and the value could be compared to that of benzene, which is generally accepted as the "paradigm" of aromaticity.[43f] Practical problems remain, however. Even for benzene, the recently computed *ab initio* resonance energies range from 23.4 (6-31G*)[49] to 36 (MP3/6-31G*)[50] kcal/mol, values which differ by about 50%. Nor is it always clear whether an adiabatic or a vertical resonance energy is being described by such calculations, adding to the confusion. Systems such as heterocycles and PAHs are more complex, and pose a greater challenge for the accurate calculation of resonance energies. With the constant improvement of *ab initio* techniques, a reliable, consistent method for the accurate determination of resonance energies might be developed in the future. Until then, the

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[47] Janoschek, R. *Angew. Chem., Int. Ed. Engl.* **1987**, *26*, 1298.
[48] Krygowski, T.M.; Anulewicz, R.; Kruszewski, J. *Acta Cryst.* **1983**, *B39*, 732-739.
[49] Hess, B.A.J.; Schaad, L. *J. Am. Chem. Soc.* **1983**, *105*, 7500-7505.
[50] Wiberg, K.B.; Nakaji, D.; Breneman, C.M. *J. Am. Chem. Soc.* **1989**, *111*, 4178-4190.

energetic criterion will be of limited use as a universal, quantitative measure of aromaticity.

1.2.4 – Aromaticity – Magnetic Criteria

1.2.4.1 - Magnetochemistry – A Brief Introduction[51]

The unusual magnetochemical behavior of benzene and other aromatic compounds was known by the early 20th century. However, it was not until the 1960s that a wide array of obscure experimental techniques was used in an attempt to analyze this behavior, and perhaps to use it as a quantitative measurement of aromaticity. This section will describe some of the theory and the methods used in magnetic studies of aromatic compounds.

When any matter is placed in a magnetic field, H, the electrons in that matter will circulate and generate a magnetic field, I, opposing the applied field. So the net magnetic field in the matter, B, is different from the magnetic field in the surrounding space, H. The ratio of the magnetic field in the matter to the applied field is μ.

$$\mu = B/H \qquad (4)$$

B can be related to the induced magnetic field in the substance, I:

$$B = H + 4\pi I \quad (5)$$

The ***magnetic susceptibility*** of the matter per unit volume, κ, can be calculated:

$$\kappa = I/H \qquad (6)$$

This can be converted to the ***susceptibility per gram***, χ:

$$\chi = \kappa / \text{density} \quad (7)$$

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[51] Mulay, L.N.; Boudreaux, A. *Theory and Applications of Molecular Diamagnetism* John Wiley and Sons, New York, 1976, pp. 2-7. See also Pozharskii, A.F. Ref. 18b.

In turn, χ can be converted into the ***molar magnetic susceptibility***, χ_m:

$$\chi_m = \chi \cdot \text{Molar Mass} \quad (8)$$

The magnetic susceptibility of a compound is generally reported as χ_m. If μ is less than 1, the induced magnetic field will be opposed to the applied field B, and the susceptibilities κ, χ, and χ_m will be negative. Substances with negative susceptibilities, in a nonhomogenous magnetic field, tend to move to the region of the lowest field possible – in other words, they are repelled from the magnetic field. Such substances are called ***diamagnetic***. Compounds with unpaired electrons usually generate an induced magnetic field aligned with the external field, so they are attracted to the magnetic field and display positive magnetic susceptibilities. Such substances are called ***paramagnetic.***

1.2.4.2 - Magnetic Susceptibility and Aromaticity

For most organic compounds, it was found that molecular magnetic susceptibilities are additive – they correlate well with values predicted by adding the known susceptibilities of the constituent atoms of the molecule. So, χ_m could be calculated by adding empirically determined atomic susceptibilities, such as those of Pascal or Haberdietzl.[52] However, some substances deviate from this additivity scheme. For double and triple bonds, for instance, small corrections had to be made. But aromatic compounds, like benzene and pyridine, show far more negative values of χ_m than the additivity schemes suggests. For example, the calculated susceptibility, χ_m', for pyridine is -30.9 x 10^{-6} cm^3/mol. The experimental value, χ_m, for pyridine is -49.2 x10^{-6} cm^3/mol.[53] The difference between the calculated and the experimental value is therefore:

$$\Lambda_{pyridine} = \chi_m' - \chi_m = -18.3 \times 10^{-6}\ cm^3/mol \quad (9)$$

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[52] Ref. 51, p. 73.
[53] Described in Pozharskii, A. F. ref. 18b.

This increase in the magnitude of the magnetic susceptibility of an aromatic compound from its empirically predicted value, denoted by the symbol Λ, is called the ***magnetic susceptibility exaltation***. For an aromatic compound, Λ will be large and negative. It will be close to zero (+/- 2 cm^3/mol) for nonaromatic compounds, and large and positive for antiaromatic molecules. The magnetic susceptibility exaltation of a compound can either be determined experimentally (using magnetic balance or NMR techniques) or it can be obtained through computational techniques.

The magnetic properties of benzene and aromatic molecules in general are the result of a phenomenon known as ***magnetic susceptibility anisotropy***. This refers to magnetic susceptibility of a molecule varying as the orientation of the molecule with respect to the magnetic field varies. The χ_m of benzene has a much larger negative value when the magnetic field is normal (perpendicular) to the plane of the ring than when the magnetic field is parallel to the plane of the ring, and the difference is sometimes written as $\Delta\chi$. This property can be demonstrated experimentally using a large crystal, whose orientation in the magnetic field can be controlled. The magnetic susceptibility exaltation of benzene is really a result of this anisotropy. In a bulk liquid sample, some of the molecular planes will always be normal to the applied magnetic field, which results in an increased bulk susceptibility.

In 1936, Linus Pauling explained the magnetic anisotropy phenomenon as resulting from the π-electrons' ability to circulate freely around the cyclic π-system under the influence of a magnetic field.[54] The magnetic susceptibility of a substance is proportional to the radius travelled by its electrons. For electrons in atoms, or in localized bonds, such radii are small. However, in aromatic π-systems, the electrons are free to move throughout the π-system of the ring, which has a much larger radius than localized bonds have. So the magnetic susceptibilities for such compounds are much greater, and are also proportional to the size of the ring. Pauling's "ring current" theory is still used to explain the physical behavior of aromatic rings in external magnetic fields, although the existence of such a ring current has been questioned on theoretical

[54] Pauling, L. *J. Chem. Phys.* **1936**, *4*, 673-677.

grounds.[55] It has also been shown that the total anisotropy $\Delta\chi$ results from both delocalized (ring current) and localized contributions.[56] In other words, the magnitude of $\Delta\chi$ is not solely a function of the magnitude of the ring current.

Since the ring current and the magnetic susceptibility exaltation should be proportional to the magnetic anisotropy, and since the magnetic anisotropy appears to be (partially) an effect of the electron delocalization, it was proposed that measuring any one of the magnetic properties of a molecule would allow a quantitative determination of its aromaticity. With this brief introduction to magnetic chemistry and its relationship to aromaticity, we can now consider some of the experimental techniques that have been applied to the measurement of the magnetic properties, and hence aromaticity, in molecules.

1.2.4.3 - Diamagnetic Susceptibility Exaltation

The best way to determine the magnetic anisotropy, $\Delta\chi$, of an aromatic molecule is to measure it directly with magnetic experiments on large crystals. Unfortunately, this method is very cumbersome and not applicable to most aromatic molecules of interest. The bulk magnetic susceptibility exaltation, Λ, is much easier to determine, and was suggested as an appropriate quantitative measurement of aromaticity.[57] Λ is clearly very useful at distinguishing aromatic compounds (benzene, Λ = -17.9[58]) from nonaromatic compounds (cyclohexane Λ = 0.0). As early as 1948, the absence of a large negative Λ led workers to conclude that cyclooctatetraene was neither aromatic nor antiaromatic.[59] Unfortunately, Λ does not appear to be sensitive enough to differentiate between two similar compounds (for example, benzene Λ = -17.9, pyridine Λ = - 18.3). Heteroatoms are magnetically anisotropic themselves, and will inevitably contribute to the bulk susceptibility along with the ring current. Also, because of the change in the radius of the delocalized π-system, Λ is totally unsuitable to compare systems with differing ring sizes

[55] Musher, J.I. *J. Chem. Phys.* **1965**, *43*, 4081-4083. See also a critique in: Gaidis, J.M.; West, R. *J. Chem. Phys.* **1967**, *46*, 1218-1219; and a rebuttal in: Musher, J.I. *J. Chem. Phys.* **1967**, *46*, 1219-1221.
[56] Kutzelnigg, W.; Fleisher, U.; Lazzeretti, P.; Muhlenkamp, V. *J. Am. Chem. Soc.* **1994**, *116*, 5298-5306
[57] a) Dauben, H.J.; Wilson, J.D.; Laity, J.L. *J. Am. Chem. Soc.* **1968**, *90*, 811-813. b) Dauben, H.J.; Wilson, J.D.; Laity, J.L. *J. Am. Chem. Soc.* **1969**, *91*, 1991-1998. See also Dailey, B.P. ref. 63 c).
[58] In this discussion, all Λ values are expressed in units of 10^{-6} cm^3/mol.
[59] Pink, R.C.; Ubbelohde, A.R. *Trans. Faraday Soc.* **1948**, *44*, 708-716.

or number of π-electrons. Attempts to scale Λ with respect to ring size have been made,[17c] where the ring-size adjusted aromaticity index ρ is given by:

$$\rho = K(n\Lambda/S^2) \quad (10)$$

Where ρ = aromaticity Index

K = scaling factor

n = number of delocalized electrons

Λ = bulk magnetic susceptibility

S = ring size.

Unfortunately, this index still cannot compensate for local and heteroatomic contributions to Λ, and has therefore not been widely used.

1.2.4.4 - NMR Methods

In the late 1950's, Pople[60] suggested that the downfield shift of benzene's protons relative to those of ethylene could be explained by the induced magnetic field resulting from the ring current (sometimes called the Pauling-Pople current) when benzene is placed in an external magnetic field. This induced magnetic field would enhance the applied magnetic field outside the circulating ring of electrons, resulting in a deshielding and a consequent downfield movement of their chemical shift. On the other hand, atoms held above or below (or inside) the ring would encounter a reduced magnetic field relative to the applied field, and therefore be shielded, demonstrating an upfield change in their chemical shift. It therefore seemed plausible that the chemical shift of aromatic molecules, relative to some nonaromatic model, might be an effective means of quantifying aromaticity.

[60] Pople, J.A. *J. Chem. Phys.* **1956**, *24*, 1111.

1.2.4.4.1 -Chemical Shifts

In 1961, Elvidge and Jackman first defined aromaticity explicitly as "a compound that will sustain an induced diatropic ring current."[61] They then proposed a method to measure aromaticity based on the chemical shifts of protons or methyls attached to aromatic rings, compared to the shifts of groups attached to nonaromatic, model compounds. For example, the chemical shift of the methyl protons of toluene is $\delta = 2.34$ ppm. That of a methyl attached to a carotenoid (an acyclic polyene) is $\delta = 1.94$ ppm. So the difference due to ring current deshielding, $\Delta\delta$, is 0.40 ppm. By comparing this difference to the difference in other sets of compounds, a relative aromaticity scale can be produced. For instance, 2-pyridone showed a difference from an acyclic model of $\Delta\delta =$ 0.14 ppm. So, they concluded 2-pyridone has 35 % of the aromaticity of benzene.

The obvious Achilles heel of this method is the need to come up with a suitable acyclic, nonaromatic model compound. There was some confusion over what constituted a suitable model compound, and because of this the results of different authors varied widely.[62] The relationship between the magnitude of the ring current and the empirically determined resonance energy was also questioned.[63] In any event, it was soon shown that the changes in chemical shift on going from an acyclic to a cyclic structure were not all attributable to the ring current.[64] Locally induced currents, the magnetic anisotropy of heteroatoms, and changes in total charge on the C atoms all contributed to the observed changes in chemical shift. Only in some structurally very similar molecules can $\Delta\delta$ be used quantitatively. Otherwise, it is only useful as a qualitative index of aromaticity.

1.2.4.4.2 - Coupling Constants

Another NMR-related method for the determination of aromaticity proposed using the magnitude of the $^3J_{H\text{-}H}$ coupling constant (the one between vicinal H's). It involves the observation that aromatic $^3J_{H\text{-}H}$ values are consistently smaller than olefinic $^3J_{H\text{-}H}$

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[61] Elvidge, J.A.; Jackman, L.M. *J. Chem. Soc.* **1961**, 859-866.
[62] a) Abraham, R.J.; Sheppard, R.C.; Thomas, W.A.; Turner, S. *J. Chem. Soc., Chem. Comm.* **1965**, 43-44. b) Elvidge, J.A. *J. Chem. Soc., Chem. Commun.* **1965**, 160-161.
[63] Abraham, R.J.; Thomas, W.A. *J. Chem. Soc. B.* **1966**, 127-131.
[64] a) Pople, J.A. *J. Chem. Phys.* **1964**, *41*, 2559-2560. b) Pople, J.A. *J. Chem. Phys.* **1965**, *43*, 1560-1563. c) Dailey, B.P. *J. Chem. Phys.* **1964**, *41*, 2304-2310.

values.[65] However, since the ^3J is proportional to the bond order,[66] and hence the bond length, this method does not actually measure the ring current or any other magnetic property of the molecule. In fact, it is just an indirect method of measuring the bond length (see Section 1.2.5 for further discussion of geometric criteria of aromaticity). Furthermore, the value will depend on the dihedral angle between the C-H bonds being compared, so rings of different sizes, and rings undergoing nonplanar distortions (which will change the dihedral angle between the protons) are not comparable by this method. It is therefore far simpler just to determine the geometry using crystallographic or other methods.

1.2.4.4.3 - Solvent Shift Methods

The magnetic field generated by the ring current in aromatic molecules reinforces the applied magnetic field at the periphery of the molecule, while opposing the field above and below the ring. Dipolar solvent molecules will tend to be attracted to electron-rich areas (the shielding region) above and below the ring, and will therefore receive a net shielding. By measuring the chemical shift of the solvent in the presence of and in the absence of the aromatic molecule, the magnitude of the ring current can be determined.[67] Similarly, in what is called the "dilution shift" method, the difference between the chemical shift of aromatic protons in the pure liquid state and at infinite dilution in a nonpolar solvent can be used to estimate the ring current.[68] For example, the difference in the chemical shifts of the protons of acetonitrile and cyclohexane in neat cyclohexane is $\Delta\sigma_{cyclohexane}$. In another solvent, X, the difference is $\Delta\sigma_x$. Then, the solvent shift parameter S is:

$$S = \Delta\sigma_x - \Delta\sigma_{cyclohexane} \qquad (11)$$

S for most nonaromatic solvents is 0, while for benzene, S is 1.00 ppm. Solids can be studied as well, by dissolving them in a nonaromatic solvent. The values obtained by this

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[65] Laszlo, P.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1965**, *85*, 2017-2018.
[66] Jonathan, N.; Gordon, S.; Dailey, B.P. *J. Chem. Phys.* **1962**, *36*, 2443-2448.
[67] Anet, F.A.L.; Schenk, G.E. *J. Am. Chem. Soc.* **1971**, *93*, 556-557.
[68] Bertelli, D.J.; Golino, C. *J. Org. Chem.* **1965**, *30*, 368-372.

method seem to correlate well with other (e.g. energetic) measurements of aromaticity, although basicity and association are believed to affect the results somewhat.

1.2.4.5 - Nucleus-Independent Chemical Shifts

Schleyer and co-workers recently proposed a computational method for the determination of the magnitude of the ring current called the Nucleus-Independent Chemical Shift method, or NICS.[69] As originally proposed, it involved placing a "ghost atom" at the center of the aromatic ring current and measuring the absolute magnetic shielding encountered by that atom. It was later shown that NICS values at the centers of many compounds are reduced due to the local paramagnetic contributions of σ-bonds. This is avoided by either measuring the shielding at a position 0.5 Å above the ring, or by calculating specifically the π-contribution to the shielding.[70] NICS has been used extensively to probe the aromaticity of a wide range of carbocyclic and heterocyclic molecules, and, unlike most magnetic measurements of aromaticity, NICS can be applied to individual rings in a polycyclic system and requires no imaginary reference molecule or incremental system.[69-71]

NICS seems to correlate well with other measurements of aromaticity when ring systems of the same size are being measured, but despite Schleyer's statement that "Unlike Λ, NICS values for [n]annulenes show only a modest dependence on ring size" NICS is still clearly not suitable for the direct comparison of the aromaticity of, for instance, 5-membered rings with 6-membered rings. At the 6-31G* level, benzene has NICS = -11.5 ppm, while pyrrole is -17.3 ppm, which would imply that the latter compound is more aromatic than benzene. The direct comparison of rings of different sizes would therefore require the application of rather arbitrary constants. Incidentally,

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[69] Schleyer, P.v.R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N.J.R. v. E. *J. Am. Chem. Soc.* **1996**, *118*, 6317-6318. See also Kutzelnigg, W.; Fleisher, U.; Lazzeretti, P.; Muhlenkamp, V. *J. Am. Chem. Soc.* **1994**, *116*, 5298-5306.

[70] Schleyer, P.v.R.; Jiao, H.; Hommes, N.J.R. v. E.; Malkin, V.G.; Malkina, O.L. *J. Am. Chem. Soc.* **1997**, *119*, 12669-12670.

[71] a) Schulman, J.M.; Disch, R.L. *J. Phys. Chem. A* **1997**, *101*, 9176-9179. b) Jiao, H.; Schleyer, P.v.R.; Beno, B.R.; Houk, K.N.; Warmuth, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2761-2764. c) West, R.; Buffy, J.J.; Haaf, M.; Muller, T.; Gehrhus, B.; Lappert, M.F.; Apeloig, Y. *J. Am. Chem. Soc.* **1998**, *120*, 1639-1640. d) Zywietz, T.K.; Jiao, H.; Schleyer, P.v.R.; de Meijere, A. *J. Org. Chem.* **1998**, *63*, 3417-3422. e) Gogonea, V.; Schleyer, P.v.R.; Schreiner, P.R. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1945-1948. f) Schulman, J.M.; Disch, R.L.; Jiao, H.; Schleyer, P.v.R. *J. Phys. Chem. A* **1998**, *102*, 8051-8055.

the NICS for Kekulé benzene (structure **B**, *vide supra*) is -9.7 ppm, only 0.8 ppm less than that of benzene itself.[69] This implies that even the marked distortion of benzene to a D_{3h} geometry has little effect on its electronic delocalization and ring current.

1.2.4.6 - Magnetic Anisotropy – Assorted Spectroscopic Methods

In addition to NMR, a number of less common spectroscopic methods have been applied to the determination of magnetic anisotropy and aromaticity. These will be briefly discussed here.

1.2.4.6.1 - Magneto-optical Methods: The Faraday and Cotton – Mouton Effects

In 1845, Faraday (the discoverer of benzene) demonstrated that, in a magnetic field, all matter becomes optically active. Plane-polarized light shone through a transparent substance in a magnetic field will therefore be rotated.[72] The magnitude of this rotation is additive and can be calculated from known individual bond rotations. However, some substances (such as aromatic molecules) display a magnetic rotation exaltation, E_{Ar}, an increase over that predicted by calculations. When the light passing through the substance is parallel to the magnetic field, the rotation is called the Faraday Effect. When it is perpendicular to the magnetic field, the rotation is called the Cotton-Mouton Effect.[73] Measurement of either of these effects, along with the knowledge of the electrical polarizability and the magnetic susceptibility of the substance, allows the calculation of its magnetic anisotropy.[74] This calculated magnetic anisotropy was used as a measurement of the aromaticity of substances.[75,76] Unfortunately, in addition to requiring specialized equipment, assumptions that had to be made about the variation of

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[72] Klessinger, M.; Michl, J. *Excited States and Photochemistry of Organic Molecules* VCH, New York, 1995, p. 154.

[73] Partington, J.R. *An Advanced Treatise of Physical Chemistry, Vol. 4* Longmans, Green & Co., London, 1953, p. 285.

[74] Buckingham. A.D.; Prichard, W.H.; Whiffin, D.H. *Trans. Faraday Soc.* 1967, *63*, 1057-1064.

[75] a) LeFevre, R.J.W.; Williams, P.H.; Eckert, J.M. *Aust. J. Chem.* 1965, *18*, 1133-1152. b) Battaglia, M.R.; Ritchie, G.D. *J. Chem. Soc., Faraday Trans. II* 1977, 209-221. c) Battaglia, M.R.; Ritchie, G.D. *J. Chem. Soc., Perkin Trans. 2* 1977, 897-900. d) Battaglia, M.R.; Ritchie, G.D. *J. Chem. Soc., Perkin Trans 2* 1977, 901-904. e) Calderbank, K.E.; Calvert, R.L.; Lukins, P.B.; Ritchie, G.L.D. *Aust. J. Chem.* 1981, *34*, 1835-1844.

[76] Labarre, J.F.; Gallais, F. in E.D. Bergmann, B. Pullman (Eds.) *Aromaticity, Pseudo-Aromaticity, Antiaromaticity, Vol. 3,* Israel Acad. Of Sciences and Humanities, Jerusalem, 1971, p. 48.

the electric polarizability in the magnetic field led to errors of up to 20 % by this method, making it not very useful for quantitative work.

1.2.4.6.2 - Molecular Zeeman Effect

Another technique unfamiliar to most organic chemists involves the use of gas-phase microwave rotational spectroscopy in a strong magnetic field to evaluate the magnetic anisotropy of molecules. When a magnetically anisotropic molecule such as benzene is placed in a magnetic field, the induced magnetic field generates torque on the molecule, as the molecule attempts to align its magnetic dipole with that of the external field. This perturbs the rotation of the molecule, and this perturbation can be seen as a splitting in the rotational microwave spectrum. This splitting is called the Zeeman Effect.[77] The magnitude of the Zeeman Effect, combined with bulk susceptibility data, allows the calculation of the magnetic susceptibility anisotropy $\Delta\chi$ of the molecule. The Zeeman Effect was therefore proposed as a method for the measurement of aromaticity, and was applied to some carbocyclic and heterocyclic molecules.[78] This method is (often) more accurate than the magneto-optical methods described earlier, and is the best experimental method known for the direct determination of $\Delta\chi$. Unfortunately, it involves a gas-phase measurement and is only applicable to molecules with reasonable vapor pressures and a permanent electronic dipole. A great many molecules of interest are therefore not suited to this method of analysis, including benzene itself. Furthermore, uncertainties as to the local atom anisotropies of some heteroatoms lead to large uncertainties in the $\Delta\chi$ values for heterocycles. For example, the $\Delta\chi$ of oxazole is given as –18.4 +/- 8.5, an uncertainty of +/- 46 %![78b]

1.2.4.6.3 - High Field Deuterium NMR

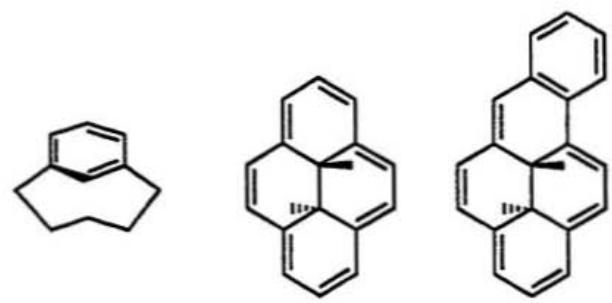
As described in the previous section on the Molecular Zeeman Effect, magnetically anisotropic molecules in a strong magnetic field tend to align themselves with the field. This alignment may reveal interactions between anisotropic (quadrupolar) nuclei and the anisotropic electric field. These interactions can be measured by the

[77] Sutter, D.H.; Flygare, W.H. *Topics in Current Chemistry* **1976**, *63*, 91-196.

splitting of a quadrupolar nucleus in the NMR, and this splitting can be related to the magnetic susceptibility anisotropy by means of Boltzmann statistics.[79] It has been found that deuterium is the best nucleus with which to observe this phenomenon: its quadrupole moment is large enough to generate detectable splitting, but small enough to prevent excessive line broadening.[80] Unlike the Zeeman splitting experiment, this method can be applied to any molecule as long as it can be deuterated. It was used by Bickelhaupt and co-workers to evaluate the aromaticity of [5]metacyclophane, **21**.[81] They concluded that, at least magnetically, [5]metacyclophane was just as aromatic as benzene.

1.2.4.6.4 - Mitchell's DMDHP "Localization Probe"

One other method that will be mentioned in this section (principally because it involves NMR) is Mitchell's use of *trans*-15,16-dimethyl-15,16-dihydropyrene (DMDHP), **22**, fused to aromatic rings to probe the latter's aromaticity. DMDHP is a molecule in which the two methyls are rigidly held in the center of an [14]annulene system, and are therefore shielded by the ring current. The chemical shift of these methyls has been shown to vary depending on the extent of delocalization of the [14]annulene, ranging from δ = -4.25 ppm in the parent system, to δ=+ 0.97 ppm in a fully localized (quinonoid) analogue.[82] By fusing aromatic rings to these systems, each



21 **22** **23**

[78] a) Schmalz, T.G.; Norris, C.L.; Flygare, W.H. *J. Am. Chem. Soc.* **1973**, *95*, 7961-7968. b) Davidson, J.R.; Burnham, A.K.; Siegel, B.; Beak, P.; Flygare, W.H. *J. Am. Chem. Soc.* **1974**, *96*, 7394-7396.
[79] van Zijl, P.C.M.; MacLean, C.; Bothner-By, A.A. *J. Chem. Phys.* **1973**, *83*, 4410-4417.
[80] a) Lohman, J.A.B.; Maclean, C. *Chem. Phys.* **1978**, *35*, 269-274. b) Lohman, J.A.B.; Maclean, C. *Chem. Phys. Lett.* **1978**, *58*, 483-486.
[81] van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1986**, *108*, 1415-1418.
[82] a) Mitchell, R.H.; Carruthers, R.J.; Mazuch, L.; Dingle, T.W. *J. Am. Chem. Soc.* **1982**, *104*, 2544-2551. b) Mitchell, R.H.; Williams, R.V.; Mahadevan, R.; Lai, Y-H.; Dingle, T.W. *J. Am. Chem. Soc.* **1982**, *104*, 2571-2578.

ring partially localizes the other, and the "bond fixing ability" of the fused aromatic ring can be determined by the change in the chemical shift of the DMDHP methyls. The DMDHP thereby becomes a "localization probe," which measures the ability of the fused aromatic moiety to localize the DMDHP annulene – the more "aromatic" the fused ring is, the more the DMDHP will be localized, and the lower field the methyl proton chemical shifts will be. This method has been applied to numerous aromatic rings.[83] Annelation of benzene (to the [a] position, **23**) reduces the ring current shielding of the methyls to $\delta = -1.62$, while naphthalene reduces it to $\delta = -0.44$. The "relative bond fixing ability" (RBFA) of the aromatic ring reflects its "bond localization energy," and is therefore a measure of the "Relative Aromaticity" (RA) of that ring. Among Mitchell's more interesting results is the observation that metal-arene complexes such as those of Ru or $Cr(CO)_3$ have a greater RBFA, and hence a greater RA, than benzene. In other words, by this criterion, they are more aromatic than benzene. The advantage of Mitchell's method is that no imaginary or model compound needs to be proposed, no empirical additivity schemes are required. The method is completely empirical. It also allows the comparison of different sized rings, and heterocycles should not pose any problems either, although few syntheses of such compounds appear to have been attempted. The question becomes where does Mitchell's RA quantity belong in the energetic vs. geometric vs. magnetic criteria framework? Although it relies on NMR, it is not the 'ring current' of the fused ring that is being measured, rather the *reduction* in the ring current of the [14]annulene generated by the fused ring. Nor can this method be directly linked to any geometric index - it is linearly related to the *bond order of the [14]annulene*, but it is meaningless to suggest that a molecule could be *geometrically* more aromatic than benzene, since such geometric criteria measure the degree of bond alternation and benzene has none. Since both RA and the Dewar Resonance Energy DRE measure the energy change on going from a π-delocalized aromatic ring to a π-localized one, it would make sense for the RA to reflect the DRE, and such a linear relationship has been demonstrated.[83c] Of course, this method gives no *numerical* data on the resonance

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[83] a) Mitchell, R.H.; Zhou, P.; Venugopalan, S.; Dingle, T.W. *J. Am. Chem. Soc.* **1990**, *112*, 7812-7813. b) Mitchell, R.H.; Khalifa, N.A.; Dingle, T.W. *J. Am. Chem. Soc.* **1991**, *113*, 6696-6697. c) Mitchell, R.H.; Iyer, V.S.; Khalifa, N.A.; Mahadevan, R.; Venugopalan, S.; Weerawarna, S.A.; Zhou, P. *J. Am. Chem. Soc.*

energy, only a value relative to that of benzene. Still, this method seems very promising as a method for determining a universal scale of aromaticity.

1.2.4.7 - Magnetic Criteria – Conclusion

As has been shown, a wide array of experimental and computational techiques have been advanced to determine the extent of the magnetic anisotropy (or a related property) in molecules. Although it is simple to tell an obviously aromatic compound from a totally nonaromatic one, the application of magnetic methods to the quantitative measurement of aromaticity seems less useful. The difficulty of separating empirically determined magnetic properties from other effects, such as anisotropy due to localized bonds or heteroatoms, is considerable, and the values thus obtained are difficult to compare to other, structurally different molecules. As *ab initio* calculations of properties like ring currents become more reliable, this method of determining aromaticity might become quantitatively useful. Experimentally, however, only qualitative data can be determined with any degree of confidence.

1.2.5 - Aromaticity – Geometric Criteria

It has already been described that benzene (and other 'aromatic' molecules) display bond length equalization, or nonalternation. Thus, instead of alternating single (1.51 Å)[84] and double (1.34 Å) bonds, benzene's carbon-carbon bonds are all of equal length, 1.397 Å. In the 1950's it was suggested that the lack of bond length alternation might be an effective criterion to determine whether a molecule is aromatic. It was suggested that if a compound's C-C bond lengths were between 1.36 and 1.43 Å, then that compound could be considered aromatic.[85] Of course, this distinction was rather arbitrary, and since then, a number of mathematical methods to evaluate the aromaticity of a molecule from its geometry (i.e., bond lengths) have been proposed.

1995, *117*, 1514-1522. d) Mitchell, R.H.; Chen, Y.; Khalifa, N.A.; Zhou, P. *J. Am. Chem. Soc.* 1998, *120*, 1785-1794.

[84] The length of an unconjugated C_{sp2}-C_{sp2} bond has been estimated to be about 1.51Å, not the 1.54 Å value sometimes used. See ref. 33 c).

1.2.5.1 - Julg's Index A_1

The first geometric index[86] was that of Julg and François.[87] They proposed that a quantitative measure of aromaticity could be obtained by considering the degree of equalization of bond lengths, using the following equation:

$$A_1 = 1-(225/n)\,\Sigma_{rs}\,(1-d_{rs}/d_m)^2 \qquad (12)$$

In which: n = the number of peripheral bonds (rs)

d_{rs} = length of bond rs (in Å)

d_m = mean length of peripheral bonds.

The number 225 is an arbitrary value, chosen so that value of A_1 for the fully bond-alternant Kekulé structure, with bond lengths 1.33 and 1.52 Å, is zero. Given adequate structural data, Julg's aromaticity index is simple to apply. Unfortunately, since bond lengths to heteroatoms differ from C-C bond lengths, it is not applicable to heterocycles, and gives some unusual results for hydrocarbons. Azulene, for instance, has a value of 1.00 (the same as benzene), while anthracene's value (and hence aromaticity) is 0.95, higher than that of phenanthrene, 0.91.[88] This may result from the consideration of peripheral bonds only. Julg later proposed a correction term to his index which would account for the resistance to the cyclic circulation of the π-electrons due to charge differences on neighboring atoms, thereby allowing the application of his index to heterocycles.[89] Unfortunately, this correction factor is hard to calculate for many heterocyclic molecules.[41] As a quantitative measure of aromaticity, therefore, Julg's index is only moderately useful.

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[85] Albert, A. *Heterocyclic Chemistry* Athlone Press, London, 1959, p. 201.

[86] An "index," in this sense, is simply a number, derived by a mathematical analysis of some geometric property of a molecule, that indicates the relative aromaticity of that molecule. Usually, indices are normalized so that an acyclic polyene = 0, while benzene = 1.

[87] Julg, A.; François, P. *Theor. Chim. Acta (Berl.)* 1967, *7*, 249-259.

[88] These numbers are quoted by Kruszewski and Krygowski[96] in their HOMA work, but they do *not* correspond to the values in Julg's original paper. There, phenanthrene=0.93, while anthracene = 0.89, values which make more intuitive sense, due to the greater reactivity of anthracene. The reason for this discrepancy is unclear.

[89] Julg, A. in: E.D. Bergmann, B. Pullman (Eds.) *Aromaticity, Pseudo-Aromaticity, Antiaromaticity, Vol. 3*, Israel Acad. Of Sciences and Humanities, Jerusalem, 1971, p. 383.

1.2.5.2 - Pozharskii's Index $\Delta\bar{N}$

To compare the aromaticity of a series of five-membered heterocycles, Fringuelli[90] proposed an index based, not on the variation of bond lengths, but on the sum of the differences of bond orders, $\Sigma\Delta N$, where N = absolute value of differences in bond orders of C-C bonds. Bond orders indicate the number of electron pairs shared by two atoms in a molecule, and can be determined either computationally or from experimental bond length data using the Gordy equation: [91]

$$N = a/R^2 - b \quad (13)$$

where: N = bond order

R = bond length

a, b = constants depending on atoms involved, e.g. for C-C a = 6.80, b = 1.71.

The disadvantage of this simple 'index' is that it does not permit comparison of heterocycles of different sizes, such as five- and six-membered rings. A slightly more elaborate index, $\Delta\bar{N}$ that takes into account all bonds, not just C-C bonds, was proposed by Pozharskii.[18b] It involved compiling a table of the differences between bond orders in the molecule, adding them up, and dividing by the total number of differences. This system could compare differently sized rings and also examine individual rings in condensed, polycyclic systems. However, it was unsuitable for antiaromatic heterocycles, and it becomes extremely complicated for larger, asymmetric molecules.

1.2.5.3 - Bird's Index I_A

To allow the application of a geometric index of aromaticity to heterocyclic compounds, Bird, like Pozharskii, proposed a completely general method based on the statistical degree of uniformity of the peripheral bond orders.[92] Unlike Pozharskii's index, Bird's method was, and continues to be, applied and refined. The coefficient of variation of the bond orders can be determined by the expression:

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[90] Fringuelli, F.; Marino, G.; Tuticchi, A. *J. Chem. Soc., Perkin Trans. 2* **1974**, 332-337.
[91] Gordy, W. *J. Chem. Phys.* **1947**, *15*, 305-310.

$$V = 100/\bar{N}\ [\Sigma\ (N - \bar{N})^2 / n]^{1/2} \qquad (14)$$

where V = coefficient of variation

N = bond orders

$\bar{N}$ = arithmetic mean of bond orders

n = number of bonds.

A fully delocalized molecule will have V=0, while, for a fully localized Kekulé form with alternating single and double bonds, V_k will depend on the size of the ring: 35 for five-membered rings or [5,6]-fused ring systems, and 33.3 for 6-membered rings. To transform this value into a more convenient scale, the aromaticity index is defined as:

$$I_n = 100(1-V/V_k) \qquad (15)$$

where I_n = Aromaticity Index for a ring of size n

V = coefficient of variation

V_k = Coefficient of variation for a fully localized Kekulé structure.

On this scale, a fully aromatic molecule like benzene will have a $I_6 = 100$, while a fully bond-localized molecule will have $I_6 = 0$. Bird's index allows bond order data of carbocyclic or heterocyclic molecules, either determined by computational techniques or from experimental geometrical data, to be transformed into an index of aromaticity. Although, as described here, the index only allows ring systems of the same size (e.g. five membered rings) to be compared directly, he later introduced a unified index, I_A, based on the Hückel MO energies of various ring systems.[93] I_A allows the direct comparison of any two aromatic compounds, whether of the same ring size or not. Bird has applied his index to a large number of heterocyclic aromatic compounds.[94]

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[92] Bird, C.W. *Tetrahedron* **1985**, *41*, 1409-1414.
[93] Bird, C.W. *Tetrahedron* **1992**, *48*, 335-340.
[94] a) Bird, C.W. *Tetrahedron*, **1986**, *42*, 89-92. b) Bird, C.W. *Tetrahedron*, **1990**, *46*, 5697-5702. c) Bird, C.W. *Tetrahedron*, **1992**, *48*, 1675-1682. d) Bird, C.W. *Tetrahedron*, **1993**, *49*, 8441-8448.

The I_A values obtained by Bird qualitatively agree with the known chemical behavior of the compounds analyzed, and there is a "reasonable parallel" between the I_A and empirically determined resonance energies. However, the resonance energies quoted in Bird's first paper[92] vary over such a wide range (e.g. furan, 34-96 kJ/mol; isoxazole 4-46 kJ/mol) that quantitative comparisons would be meaningless. Bird's Aromaticity Index does appear to be a quantitative, simple and widely applicable geometrical measurement of aromaticity.

1.2.5.4 - Jursic's Index, D

Recently, an index of aromaticity remarkably similar to Bird's was proposed by Jursic.[95] It computes the average bond order deviation by the expression:

$$D = \Sigma | (1.5 - N_j) | / n \qquad (16)$$

where D = index of aromaticity

N_j = bond order of bond j

n = number of atoms (or bonds) in ring

This index correlates reasonably well with Julg's parameters. indeed the only difference between D and Bird's I appear to be that while the former uses a summation of the absolute value of the individual bond order deviations, the latter involves the summation of a squared variation function. The paper makes no reference to Bird's or Pozharskii's work at all, leading one to wonder whether the author is aware of (or is deliberately ignoring) their work in this area. In any event, Jursic's D index certainly does not appear to be superior to the other indices being described in this section.

1.2.5.5 - Krygowski's HOMA, EN, GEO, and Related Indices

In an effort to improve upon Julg's index, Kruszewski and Krygowski first introduced their Harmonic Oscillator Model of Aromaticity, or HOMA, in 1972.[96] The

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[95] Jursic, B.S. *J. Heterocyclic Chem.* **1997**, *34*, 1387-1389

[96] Kruszewski, J.; Krygowski, T.M. *Tetrahedron Lett.* **1972**, *36*, 3839-3842.

harmonic oscillator model calculates the excess energy resulting from the distortion of bond lengths from their optimal values,[97] assuming an (empirically determined) harmonic potential energy of deformation. So HOMA is in a sense an energetic parameter, except that the energetic data are obtained from geometric data. The relevant equation is:

$$HOMA = 1 - \alpha/n \Sigma (R_{opt} - R_i)^2 \qquad (17)$$

where HOMA = Harmonic Oscillator Model of Aromaticity index

α = empirical constant

n = number of bonds being summated

R_{opt} = optimal bond length

R_i = experimental bond length.

The empirical constant α was chosen so that, for the Kekulé structure (fully localized to double and single bonds) of the molecule in question, HOMA = 0, while for a fully bond-equalized structure (all $R_i = R_{opt}$) HOMA = 1. The optimal bond length was determined by minimizing the deformation energy due to the extension and compression of double and single bonds, respectively. Like Bird's index, the HOMA index could be applied to either computationally or experimentally determined bond lengths, and was found to correlate reasonably well with empirically determined resonance energies.[96]

After its formulation in 1972, the HOMA index appears to have been little used until resurrected in the 1990s with the new knowledge about the role of the σ and π-frameworks in aromaticity. It was then shown that HOMA can be used to estimate the aromaticity of whole molecules, and also of fragments of aromatic systems, whether carbocyclic or heterocyclic.[98]

Related to the HOMA is the HOSE (Harmonic Oscillator Stabilization Energy), which is defined as the negative value of the energy necessary to deform the molecule into its Kekulé structure, as determined using the harmonic oscillator method.[43] This method is therefore an attempt to calculate the KDE, as described earlier. Although the

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[97] The optimal value of the bond length in benzene was calculated using bond length data from butadiene, resulting a optimal bond length of 1.388 Å.

deformation energies calculated by this method (12 kcal/mol for benzene) are much greater than the KDE valuse obtained by quantum chemical calculations, they seem to correlate reasonably with the Dewar Resonance Energy.[99]

Because HOMA is calculated using bond energy data, it is actually a complex index, based on both geometric and energetic parameters. Recently, it was shown that the HOMA index could be divided into two 'sub-indices'– an energetic and a geometric one.[100]

$$HOMA = 1 - [\alpha(R_{opt} - R_{av})^2 + \alpha/n \Sigma (R_{av} - R_i)^2$$

$$= 1 - (EN + GEO) \qquad (18)$$

So:

$$EN = \alpha(R_{opt} - R_{av})^2 \qquad (19)$$

$$GEO = \alpha/n \Sigma (R_{av} - R_i)^2 \qquad (20)$$

where HOMA = Harmonic Oscillator Model of Aromaticity index

EN = Energetic index EN

GEO = Geometric Index GEO

α = empirical constant

n = number of bonds being summated

R_{opt} = optimal bond length

R_{av} = average experimental bond length

R_i = experimental bond length.

The energetic index EN depends on the mean experimental bond lengths, compared to the optimal bond lengths. It has been shown that the C=C bond energy is proportional to the

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[98] Krygowski, T.M. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 70-78.
[99] Krygowski, T.M.; Anulewicz, R.; Kruszewski, J. *Acta. Cryst.* **1983**, *B39*, 732-739.

bond length, so by measuring the variation of the average bond length R_{av} from the optimal bond length R_{opt}, the loss of "stabilization energy" due to aromaticity can be estimated. The closer EN is to zero, the more "energetically" aromatic the molecule is. For example in benzene, EN = 0.021, while for the central ring in anthracene, E = 0.174. This is certainly consistent with our qualitative knowledge of the reactivity of these systems.

The GEO term, reminiscent of Julg's index, is related to the variance of bond lengths of the ring in question. It determines the extent to which the bond lengths deviate from uniformity, so a lower GEO indicates a more "geometrically" aromatic molecule. For benzene GEO = 0 while for the central ring of phenanthrene GEO = 0.419.

To illustrate the application of EN and GEO, consider benzene in its preferred geometry and in two distorted geometries (Fig. 1-7). Benzene, with an equilibrium bond length of 1.397 Å, is completely aromatic geometrically (GEO = 0) but it varies slightly

1a	**1b**	**1c**
GEO = 0	GEO = 0	GEO = 1.00
EN = 0.021	EN = 1.00	EN = 0
HOMA = 0.979	HOMA =0	HOMA =0

Figure 1-7: GEO, EN and HOMA Analyses of Benzene in Selected Conformations

from the calculated optimal bond length, and therefore displays a small reduction in 'energetic' aromaticity (EN = 0.021).[101] The HOMA value for this compound is 0.979, indicating very high aromaticity. Now consider "stretched" benzene, in which each bond has been expanded to 1.45 Å. Because the bond lengths are all equal, the GEO term remains zero – geometrically, the molecule is still aromatic. However, the marked distortion of the bond lengths from their optimal value of 1.388 Å results in an EN term

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[100] Krygowski, T.M.; Cyranski, M. *Tetrahedron* **1996**, *52*, 1713-1722.

[101] That benzene's bond lengths do *not* correspond to the optimal "aromatic" bond length is curious. Some earlier papers (Kruszewski, J.; Krygowski, T.M. *Can. J. Chem.* **1975**, *53*, 945-951), using ethane and ethylene deformation energies as references, report 1.397 Å to be the calculated "optimal" aromatic bond length. Why this is not used is unknown.

of 1.00, and consequently a HOMA of 0. By the HOMA measurement, therefore, distortion of benzene to this geometry has totally destroyed its aromaticity. Finally, consider Kekulé benzene, with alternating bond lengths of 1.32 and 1.45 Å. The bonds in this structure are stretched and compressed equally from the optimal, so that the overall EN term is 0. However, the large variation in bond lengths has driven the GEO term to 1.00, so again the HOMA value is 0. Again, this distortion has destroyed the overall aromaticity of the molecule, as measured by the HOMA index.

The application of the EN and GEO indices to known crystal structures has produced some intriguing results. Consider the data in Table 1-1:

Table 1-1: HOMA Data of Selected Molecules

Molecule (Ring)	HOMA	EN	GEO
Benzene	0.979	0.021	0.00
Phenanthrene (central)	0.400	0.181	0.419
Phenanthrene (terminal)	0.898	0.021	0.081

The HOMA values are as expected. Benzene's HOMA value is very close to unity, the terminal rings of phenanthrene are lower but still very high, while the central (and most chemically reactive) ring of phenanthrene is much lower. The EN and GEO terms, however, are peculiar. According to the HOMA, the central ring of phenanthrene is about "40% aromatic," so 60% of its aromaticity has been lost. While 18 % of the aromaticity is lost due to the change in energy as determined by a change in average bond length (EN), 42% results from the increase in the variance of the bond lengths (GEO). For the terminal ring ("90 % aromatic"), 2% of the aromaticity is lost due to the energetic term, while the other 8 % is lost due to the geometric index. As for benzene itself, its small deviation from full aromaticity stems solely from the deviation of its bond lengths from their optimal length, the EN term. Geometrically (GEO = 0) benzene is fully aromatic.

The important point is that there appears to be *no correlation* between aromaticity measured by the EN term, and aromaticity measured by the GEO term. It was always assumed that aromaticity was a single phenomenon, and if one aspect of it (for example,

the geometric term) could be measured, all the other aspects (energetic, magnetic) would be proportional to it. The GEO and EN results listed above, barring some drastic mistake in the theoretical background of the indices, seem to imply that the geometric and energetic measurements of aromaticity are *not proportional to one another*. So, like benzene above, a molecule can be fully aromatic geometrically, but only partially aromatic energetically. For another example, consider the data on the "Kekulé benzene" presented earlier in this section (Fig. 1-7). It was shown how this compound had an EN term of 0 (no energetic loss of aromaticity) but a GEO term of 1.0 (complete loss of aromaticity), resulting in an overall HOMA value of 0, implying that this molecule is not aromatic. Contrast this assertion with Schleyer's NICS work,[69a] mentioned earlier, which demonstrated that Kekulé benzene displays as NICS only slightly less than benzene itself – so magnetically, Kekulé benzene appears to be almost fully aromatic. This "multidimensionality of aromaticity" concept is very controversial, and will be discussed fully later.

Before leaving Krygowski's work, it should be mentioned that he and his co-workers have proposed other indices of aromaticity to compare to GEO and EN: BAC, the Bond Alternation Coefficient, which is very similar to GEO, and BE, the Bond Energy coefficient, closely related to EN. These indices will not be discussed further, and the interested reader is referred to the original literature. [96,98-100]

1.2.5.6 - Bird's CE Index

The final 'geometrical' index of aromaticity that will be discussed is a recent proposal by Bird. It is based on Krygowski's HOSE (Harmonic Oscillator Stabilization Energy) approach, using the deformation energy of bonds to calculate the energy necessary to deform the molecule from its real, experimental geometry to its Kekulé or resonance structure.[102] The energy to deform one bond in benzene is given by:

$$E_B = 85.94(R_s \text{ or } R_d - R)^2(44.39 - 26.02R) \text{ kcal/mol.} \qquad (21)$$

[102] a) Bird, C. W. *Tetrahedron* **1997**, *53*, 13111-13118. b) Bird, C.W. *Tetrahedron* **1997**, *53*, 17195-17200. c) Bird, C. W. *Tetrahedron* **1998**, *54*, 4641-4646.

Where E_B = energy required to distort bond to length of ethane or ethylene

R_s = bond length of C-C bond in ethane.

R_d = bond length of C=C bond in ethylene.

R = experimental length of bond.

Summation of the E_B values gives the conjugation energy, CE.

In effect, CE is a method of determining the Kekulé Deformation Energy from experimentally determined molecular geometry. Because it uses ethane and ethylene bond lengths for the 'reference structure', CE can be considered a sort of isodesmic KDE. The value Bird obtains in his calculation is 38.4 kcal/mol for the deformation of benzene to a D_{3h} geometry, which is almost an order of magnitude higher than some of the quantum chemical values for KDE cited earlier, although he is stretching the single bonds to 1.54 rather than 1.46 Å. Bird then uses a scaling factor to convert CE into an empirically determined ISE of benzene. This CE index is new, so it is hard to tell whether the concept will be useful, or whether it will just render the Kekulé Deformation Energy concept as confused as the "resonance energy" concept. In any event, the work of Krygowski, mentioned earlier, has suggested that the energetic and geometric terms of aromaticity are not proportional to one another. If true, this seems to undermine the key assumption of Bird's CE index: that the 'resonance energy' is proportional to, and can be determined from, the molecular geometry. The controversy surrounding the "multidimensionality of aromaticity" must now be considered.

1.2.6 - Multidimensionality of Aromaticity?

In our discussion of the various criteria for aromaticity, we occasionally touched on instances where a compound displayed reduced magnetic aromaticity (ring current, negative Λ) relative to benzene without displaying increased bond alternation, or *vice versa*. Such observations provoked an unsettling question. It was always assumed that aromaticity was a single phenomenon, which gave rise to a number of experimentally measurable properties, such as resonance energy, bond equalization, and magnetic anisotropy. If aromaticity were a single phenomenon, these properties should be

proportional to one another in all aromatic molecules. Recent work, however, has demonstrated that this assumption is, quite possibly, invalid.

The seminal paper on this topic was published in 1989 by Katritzky and co-workers.[103] They analyzed a large array of magnetic, energetic, and geometric indices of aromaticity by an elaborate statistical method called Principal Component Analysis, or PCA. PCA demonstrated that there are two "orthogonal" (not correlated) forms of aromaticity: "Classical" aromaticity, which is composed of geometric and energetic terms, and "magnetic" aromaticity, which obviously refers to the magnetic behavior of aromatic compounds. Thus, a compound could show one form of aromaticity, or the other, or both, and no conclusion about the degree of "classical" aromaticity in a compound could be made from "magnetic" data such as Λ or NICS.

This work was challenged by Schleyer *et al.*, and by Bird. Schleyer[104] used a set of C_4H_4X heterocycles to demonstrate that Julg's parameter A (geometric), the magnetic susceptibility Λ (magnetic), and the aromatic stabilization energy (energetic, determined by a homodesmotic reaction method) are linearly related. In a similar vein, Bird[105] demonstrated how his (geometric) index I_A, (isodesmic) resonance energy RE (energetic), and magnetic susceptibility exaltation Λ were all linearly related across a wide range of monocyclic and polycyclic compounds, both carbocyclic and heterocyclic.

Bird's conclusions were questioned in a paper by Cyranski, Krygowski, and Bird,[106] an unusual case of an author apparently contributing to a refutation of his own work. This paper studied a number of cyclophanes, and demonstrated that while HOMA correlated very well with *ab initio* (RHF/6-31G*) calculated energies, I_6 did not. As demonstrated earlier, HOMA is an index which includes both energetic and geometric terms, while I_6 is purely geometric. Thus, a purely geometric index of aromaticity I_6 does not correlate with a purely energetic one (the calculated energies), and so the geometric and energetic criteria of aromaticity can also be thought of as being 'orthogonal'. This may seem confusing at first, as all the same data were used to determine HOMA and I_6,

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[103] Katritzky, A.R.; Barczynski, P.; Musumarra, G.; Pisano, D.; Szafran, M. *J. Am. Chem. Soc.* **1989**, *111*, 7-15.
[104] Schleyer, P. v. R.; Freeman, P.K.; Jiao, H.; Goldfuss, B. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 337-340.
[105] Bird, C.W. *Tetrahedron* **1996**, *52*, 9945-9952.
[106] Cyranski, M.; Krygowski, T.M.; Bird, C.W. *Tetrahedron* **1998**, *54*, 9711-9720.

namely the experimental geometries of the molecules. However, "geometric" criteria of aromaticity, such as GEO and I_6, are based solely on the degree of alternation of the bond lengths. In addition to its geometric term GEO, HOMA contains an energetic term EN, estimated from the degree of compression or elongation of the bonds in the molecule. As displayed in the comparison of benzene and phenanthrene (*vide supra*) these geometric and energetic parameters are not correlated.

The most recent contribution to this debate, by Katritzky, Krygowski, and co-workers,[107] effectively refutes Schleyer's and Bird's demonstrations of a linear relationship between magnetic, geometric, and energetic terms. It shows that, within "restricted classes of compounds" such as Hückel annulenes or the five-membered heterocycles that Schleyer considered, assumptions of the linearity of magnetic, geometric, and energetic contributions to aromaticity may be valid. But, over wider classes of compounds, when the size of the ring, the number of heteroatoms, or the number and arrangement of fused rings are varied, there exists no correlation between Λ and the ASE determined by homodesmotic reactions. They also re-analyzed Bird's data and concluded that his apparent correlation of I_A and Λ is an artifact of plotting compounds with increasing numbers of rings on the same graph. When compounds with the same number of rings are compared alone, little correlation between I_A and Λ is observed. Research into the phenomenon of multidimensionality is ongoing, and it is uncertain whether the controversy will be resolved in the near future.

1.2.7 - Aromaticity – Other Criteria

Lengthy as it has been, this exposition of criteria of aromaticity is not exhaustive. Many other definitions have been and continue to be proposed, such as Binsch and Heilbronner's "first and second order double bond fixation" proposal,[108] *ab initio* C-H charge fluxes and experimental C-H stretching and out-of-plane deformation frequencies,[109] electron density distributions,[110] a "Stability Index" (a complex set of

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[107] Katritzky, A.R.; Karelson, M.; Sild, S.; Krygowski, T.M.; Jug, K. *J. Org. Chem.* **1998**, *63*, 5228-5231.
[108] Binsch, G.; Heilbronner, E.; Murrell, J.N. *Mol. Phys.* **1966**, *11*, 305-320.
[109] Ramos, M.N.; da Costa, N.B.; Neto, B.B. *J. Mol. Struc.* **1993**, *294*, 29-32.
[110] Ogorodnikova, N.A. *J. Mol. Struc. (Theochem)* **1993**, *279*, 71-78.

parameters based on REPE, π-electron densities, and other properties),[111] an "Aromaticity Constant" (related to each atom's tendency to release or attract π-electrons in the delocalized π cloud),[112] and the ability of the ring to transmit inductive effects.[113] However, to prevent this chapter from becoming even more extensive than it already is, these proposals will not be discussed further and the interested reader is referred to the original literature.

1.2.8 - Aromaticity – Conclusion

This chapter has described benzene, and the phenomenon of aromaticity for which benzene is the archetypal representative. Most of the chapter has focussed on attempts to answer the questions "What is aromaticity?" and "How can aromaticity be quantified?" Consider the following definitions of aromaticity:

> "An unsaturated cyclic or polycyclic molecule or ion may be classified as aromatic if all the annular atoms participate in a conjugated system such that, in the ground state, all the π electrons (which are derived from atomic orbitals having axial orientation to the ring) are accommodated in bonding molecular orbitals in a closed (annular) shell." (Badger, 1969).[114]

> "The defining characteristic of an aromatic species is the ability to sustain a diatropic ring current. Cyclic electron delocalization results in enhanced special chemical, geometrical, and magnetic properties." (Schleyer, de Meijere *et al.*, 1998).[71d]

> "Aromaticity is a label applied to a group of molecules which seem to have something in common ... an inexact concept for which it is probably impossible to find a rigorous definition." (Lewis & Peters, 1975).[115]

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[111] Zahradnik, R.; Michl, J.; Pancir, J. *Tetrahedron* **1966**, *22*, 1355-1366.
[112] Balaban, A.T.; Simon, Z. *Tetrahedron* **1962**, *18*, 315-321.
[113] Described in Cook, M.J. *et al.*, ref. 18c.
[114] Ref. 4, p. 37.

Comparing these three definitions[116] reveals not a difference due to the facts being considered, but a difference in the underlying assumptions as to the nature of scientific definitions and theories. Badger's definition, effectively a verbose restatement of Hückel's 4n+2 rule, is purely theoretical. Simply looking at the molecular structure of a molecule will suffice to determine whether it is aromatic. No experimental data is required. It is, however, extremely difficult to quantify. Schleyer's definition is far more empirical, relying on experimental or computational data to determine whether the compound is aromatic. The numerical data obtained in such a determination can easily be used to quantify the aromaticity of the molecules in question, at least in theory. Unfortunately, such a "magnetic fundamentalist" definition ignores the recent work which questions whether such properties as bond equalization and stabilization are related in any quantitative way to the magnetic properties of an aromatic molecule. The word "aromaticity" has always implied all these properties. Reducing the definition of aromaticity to a magnetic (or any other) property strips it of much of the information the term has always carried. The third "definition" by Lewis and Peters freely admits that the term aromaticity refers to an ill-defined group of characteristics that may not be related. This definition, by its nature, encompasses any experimental or theoretical data one wishes to associate with aromaticity. However, it is so diffuse that whether a compound is aromatic or not is determined mostly by intuition. Such a vague concept is, of course, impossible to quantify in any meaningful way. Some suggest that there is a sort of uncertainty principle in effect here.[117] A definition can account for all the data only if it is extremely broad and vague, while it can only be precise and quantifiable by ignoring some (or most) of the facts. This is perhaps true of all scientific theories, but is especially visible in the concept of aromaticity.

The difficulty in proposing any meaningful and all-encompassing definition for the term aromaticity has led some scientists to suggest that the term should be done away

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[115] Ref. 30, p. 1.

[116] It has been suggested that the statement by Lewis and Peters is not a "definition." It is perhaps more of an "anti-definition" – an assertion that that term "aromaticity" can not be defined.

[117] a) Labarre, J.F. in E.D. Bergmann, B. Pullman (Eds.) *Aromaticity, Pseudo-Aromaticity, Antiaromaticity, Vol. 3,* Israel Acad. Of Sciences and Humanities, Jerusalem, 1971, p. 55-56. b) Binsch, G. *Naturwissenschaften*, 1973, *60*, 369-374. c) Balaban, A.T. *Pure Appl. Chem.* 1980, *52*, 1409-1429. d) Heilbronner, E. in E.D. Bergmann, B. Pullman (Eds.) *Aromaticity, Pseudo-Aromaticity, Antiaromaticity, Vol. 3,* Israel Acad. Of Sciences and Humanities, Jerusalem, 1971, p. 21-22.

with completely and replaced with more meaningful, precise terminology.[25,117] For instance, the tendency to 'retain the type', to undergo substitution rather than addition, has been termed "menedeism."[25] Compounds with 4n+2 electrons in their periphery could be called "Hückelian." The ring-current-related properties of aromatic molecules have been referred to as "strobilism."[117a] Terms such as "bond-equalized" and "resonance stabilized" are self-explanatory and have already been used in this discussion. So instead of saying that "Benzene is aromatic," one would say "Benzene is Hückelian, menedeic, strobilic, bond-equalized and resonance stabilized." In doing this, a relatively simple term, although admittedly imprecise, is being replaced by an inelegant and cumbersome array of jargon.

Ultimately, the debate over the best way to define aromaticity depends on personal taste. Those who prefer simple, broad definitions and concepts, even if difficult or impossible to quantify and 'fuzzy' in borderline cases, will embrace statements like that of Lewis and Peters. Others, who feel that there is no place in science for an unquantifiable concept based principally on intuition, will continue to propose elaborate, multidimensional definitions of aromaticity, or attempt to introduce a whole new terminology. In the end, the definition of aromaticity rests not so much on chemistry as on an individual's personal interpretation of the philosophy of science.

Chapter 2 – Nonplanar Aromatic Molecules

The previous chapter described the concept of aromaticity and the many methods proposed to define and quantify it. Now, attention will be turned to the question of what happens to an aromatic molecule when its π-system is bent out of planarity. Such a distortion obviously involves an increase in strain, so a brief discussion of the phenomenon of strain in organic chemistry, and the ways in which strain manifests itself in nonplanar aromatics, will be presented. Then, the chemistry of molecules containing non-planar benzene moieties will be presented. This will lead up to the discussion of non-planar polycylic aromatic hydrocarbons in the next chapter.

2.1 Introduction to Strain in Organic Chemistry

In 1874, Van't Hoff and LeBel independently suggested that a tetracoordinate carbon atom has a tetrahedral geometry, with bond angles of 109.5°.[1] A decade later, Adolf von Baeyer used this proposal as the basis for his 'ring strain theory', which explained the scarcity of three and four-membered rings (relative to five- and six-membered rings) in nature. This theory stated that when bond angles vary from their optimal, tetrahedral geometry (as they must in small rings) the molecule becomes more strained, and therefore less stable.[2] Although far more complex than von Baeyer originally imagined, strain remains an important concept in organic chemistry: the distortion of atoms in molecules from their optimal geometries results in an increase in the molecule's energy content.

Joel Liebman pointed out that aromaticity and strain are, in a very simplistic sense, opposites – aromaticity means a species is more stable than a reference state suggests, while strain results in the species being less stable.[3] Like aromaticity, the quantitative determination of strain energy requires the definition of some "strain-free"

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[1] Hanack, M. *Conformation Theory* Academic Press, New York, 1965, pp. 2-6.
[2] Wiberg, K.B. *Angew. Chem., Int. Ed. Engl.* 1986, *25*, 312-322.
[3] Liebman, J.F. in Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, Vol. 1* Academic Press, New York, 1983, p. 24.

reference molecule, which can be almost as problematic as defining a reference structure for aromaticity, as discussed in the previous chapter.[4]

Wiberg[2] partitions strain into five distinct contributions:

1. Bond length distortions
2. Bond angle distortions
3. Torsional strain
4. Nonbonded interactions
5. Energy changes due to rehybridization.

Bond length distortions are usually small, due to the large amount of energy required to stretch or compress a bond. Bond angle distortions (Fig. 2-1) are common and quite familiar to most chemists. The C-C bond angles in cyclopropane **2** (60°) and cyclobutane[5] (90°) are perhaps the archetypal examples of "in plane" bond angle distortions from the optimal value of 109.5°, as seen in methane, **1**. Less well known, or

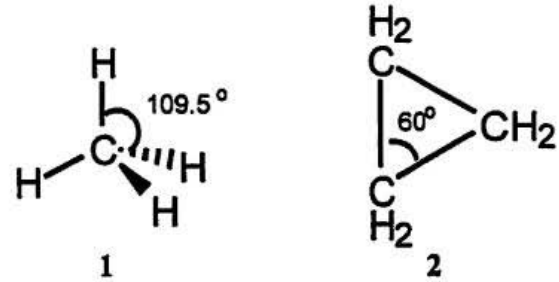

Figure 2-1: Bond Angle Strain, Cyclopropane vs. Methane

well studied, are out-of-plane bond angle distortions, where normally planar groups are forced into non-planar conformations. This is the type of distortion observed in non-planar aromatic molecules, and will be discussed in detail below. Torsional strain (Fig. 2-2) simply refers to the energetic preference molecules (such as *n*-butane) have for staggered (e.g. gauche or anti), rather than eclipsed, conformations. Nonbonded interactions, usually simply termed "sterics," describe the tendency of large ("sterically

[4] Greenberg, A.; Liebman, J.F. *Strained Organic Molecules* Academic Press, New York, 1978. pp. 1-7.

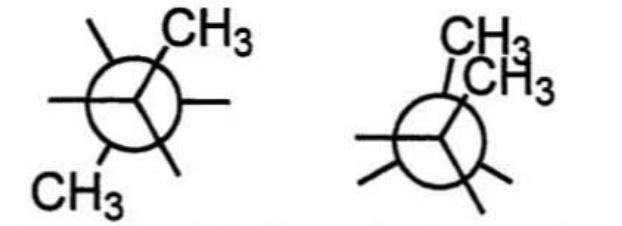

Figure 2-2: Torsional Strain in *n*-Butane

demanding") groups to avoid occupying the same position in space. When such groups are forced into proximity, as in *cis*-di-*tert*-butylethylene, **3b**, strain results (Fig. 2-3). The final contribution, energy changes due to rehybridization, refers to the tendency of a

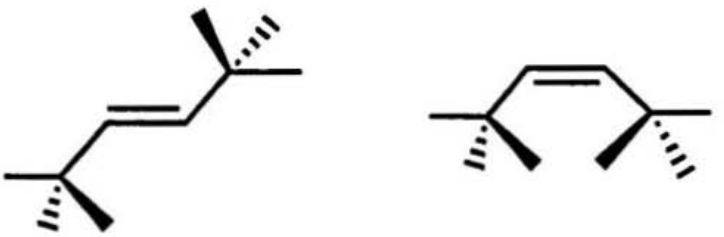

Figure 2-3: Non-bonded Strain in 1,2-Di-*tert*-butylethylene

strained atom in a molecule to maximize its bonding overlap with its neighbors by changing its hybridization state. As with all hybridization of atomic orbitals, this rehybridization requires energy (relative to the unstrained system), but ultimately results in a more favorable bonding arrangement than would otherwise occur. This rehybridization occurs in the out-of-plane distortion of alkenes, which will now be discussed.

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[5] For an older, but excellent summary of strain in cyclobutane, see: Wilson, A.; Goldhamer, D. *J. Chem. Ed.* **1963**, *40*, 504-511.

2.2 - Carbon Pyramidalization

2.2.1 – Definition of Pyramidalization

A 'normal' alkene such as ethylene is ideally planar, with all bond angles equal to approximately 120°. The carbon atomic orbitals (AOs) that form the bonds of the σ-framework are sp^2 hybridized, while the carbon AOs that form the π-bond are pure p-orbitals. Now consider what happens when ethylene is distorted.[6] The distortion most often studied is a torsional distortion, in which one CH_2 group rotates about the C-C bond to yield a C_2 symmetric structure. Another distortion, which is more relevant to this discussion, is termed pyramidalization. It occurs when the two hydrogens (or other substituents) move out of the plane of the double bond to yield a non-planar,

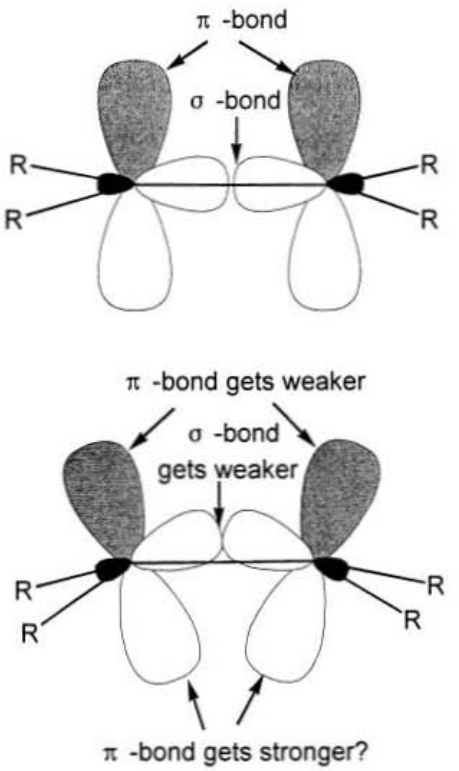

Figure 2-4 : Effect of Pyramidalization Without Rehybridization

[6] Volland, W.V.; Davidson, E.R.; Border, W.T. *J. Am. Chem. Soc.* **1979**, *101*, 533-537.

pyramidalized carbon. This is termed the C_s distortion, as the resulting molecule has C_s symmetry.[7]

If we assume that the hybridization of the C atom in a C_s distortion remains constant, two major changes can be observed on pyramidalization (Fig. 2-4). The C-C σ-bond will be weakened due to the reduced alignment of the two sp^2 orbitals with respect to each other. The effect on the π-bond is harder to ascertain, as pyramidalization will result in a decrease in p-p overlap on the "convex" side of the carbon, but an increase on the "concave" side. It seems reasonable to assume that the π-bond will be weakened somewhat.[8] This weakening of the σ and π bonds produces a drastic increase in energy

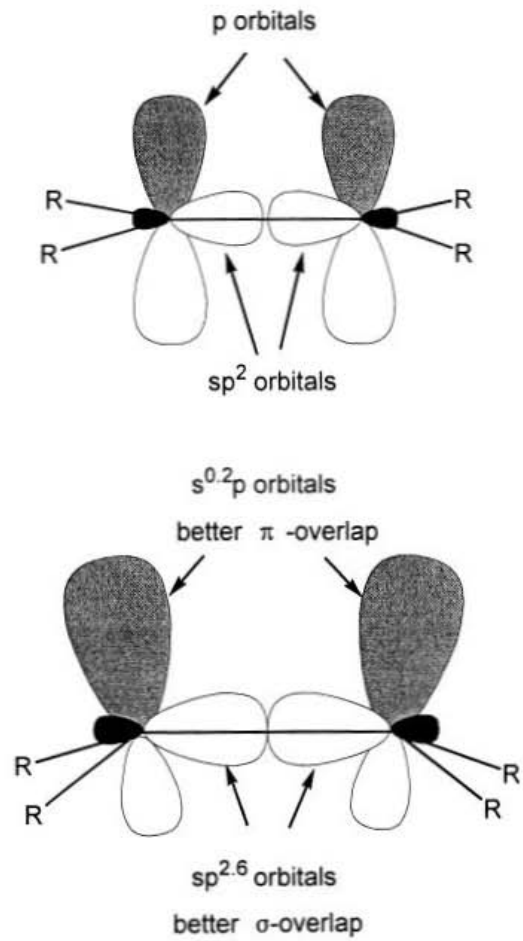

Figure 2-5: Effect of Pyramidalization with Rehybridization.

[7] Luef, W.; Heese, R. *Topics in Stereochem.* **1991**, *20*, 231-318.
[8] Schmalz, T.G.; Seitz, W.A.; Klein, D.J.; Hite, G.E. *J. Am. Chem. Soc.* **1988**, *110*, 1113-1127.

over ground state, planar ethylene.

This increase in energy can be offset through rehybridization, which regenerates the maximum σ and π overlap possible in the pyramidalized geometry (Fig. 2-5).[9] The filled σ and π systems mix, to generate new, hybridized bonding MOs. The p orbital develops some s character, so the π-bond is no longer formed by a pure p orbital but by, for example, an $s^{0.2}p$ hybrid. Meanwhile, since some of the s character has been transferred to the π system, the σ-system is no longer composed of sp^2 orbitals, but of $sp^{2.6}$ orbitals. The unfilled σ* and π* orbitals also mix, resulting in a drop in the energy of the lowest unoccupied molecular orbital (LUMO).[4] This drop in the LUMO is much greater than the increase in the HOMO, and is often invoked to explain the electrophilic nature of pyramidalized alkenes.[10]

Although obviously higher in energy than its planar counterpart, a rehybridized pyramidalized alkene has a π-bond that is essentially intact. When the pyramidalized carbon is part of an aromatic ring, rehybridization therefore allows the π-system, and hence its "aromatic stabilization," to remain largely intact. This may explain why nonplanar aromatic molecules can remain stable and display 'aromatic' properties (such as a ring current) even when severely distorted from planarity. The chemistry of such distorted aromatic systems will be discussed later on in this chapter.

2.2.2 - Quantification of Pyramidalization

Can pyramidalization be quantified? Originally, the degree of pyramidalization was determined by measuring the pyramidalization angle φ, defined as the angle between the plane formed by the C and its two substituents, and a line extended through the C-C bond (Fig. 2-6). Unfortunately, this method is anisotropic – it depends on which bond is chosen to be extended, and is therefore does not provide unequivocal values for atoms in aromatic molecules which, due to Kekulé structures, have two theoretically "double"

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[9] Haddon, R.C. *Acc. Chem. Res.* **1988**, *21*, 243-249.
[10] Smith, J.M.; Hrovat, D.A.; Borden, W.T.; Allan, M.; Asmis, K.R.; Bulliard, C.; Haselbach, E.; Meier, U.C. *J. Am. Chem. Soc.* **1993**, *113*, 3816-3817.

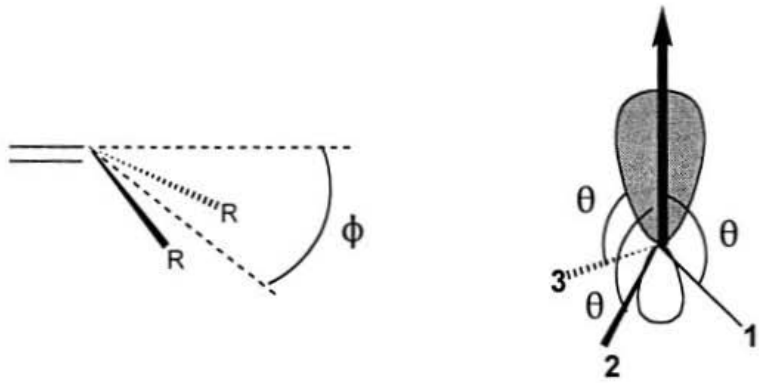
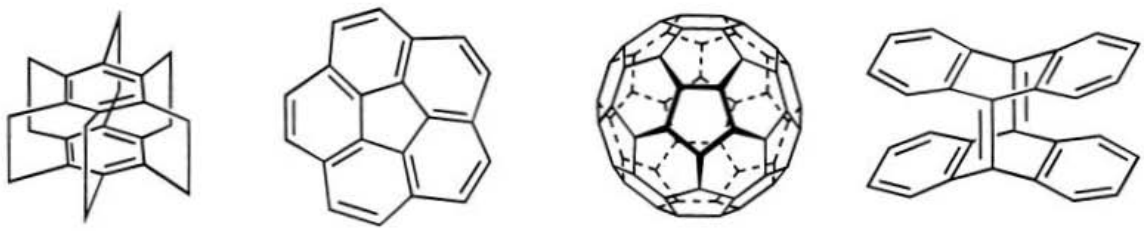


Figure 2-6: Definition of Angles ϕ and θ

bonds. To provide a more general method for the analysis of pyramidalized carbons, the π-orbital axis vector (POAV) analysis was developed by Haddon.[11]

The POAV analysis depends on the construction of a vector along which the π-orbital is assumed to lie. In POAV1, the vector is defined so that it forms an equal angle, $\theta_{\sigma\pi}$, with the three σ substituents 1, 2, and 3 (Fig. 2-6). The more elaborate POAV2 analysis involves determining the hybridization of each of the σ bonds to the carbon in question, and thereby calculating the geometry of the π orbital vector. This vector is identical with that of POAV1 when the σ-σ bond angles are equal, but differs when there is inequality in the three σ-σ bond angles. The POAV1 pyramidalization angle is given by $\theta_{\sigma\pi}$ - 90°. From POAV1, hybridization of the π-orbital ($s^n p$) and the average hybridization of the three σ orbitals (sp^n) can be determined. POAV2 allows the



4 **5** **6** **7**

[11] a) Haddon, R.C.; Scott, L.T. *Pure Appl. Chem.* **1986**, *58*, 137-142. b) Haddon, R.C. *Chem. Phys. Lett.* **1986**, *125*, 231-234. c) Haddon, R.C. *J. Am. Chem. Soc.* **1986**, *108*, 2837-2842. d) Haddon, R.C. *J. Am. Chem. Soc.* **1987**, *109*, 1676–1685. e) Haddon, R.C. *Acc. Chem. Res.* **1988**, *21*, 243-249. f) Haddon, R.C. *J. Am. Chem. Soc.* **1990**, *112*, 3385-3389. g) Haddon, R.C. *Science* **1993**, *261*, 1545-1550.

determination of the exact hybridization of each of the orbitals that form the σ-bonds.

The following table compares POAV1 pyramidalization angle, $\theta_{\sigma\pi} - 90^{\circ}$, for a few well-known compounds. [11f]

Table 2-1: POAV Angles of Distorted Aromatics

Compound	$\theta_{\sigma\pi} - 90^{\circ}$
Superphane, **4** [12]	6.96 °
Corannulene, **5** [13] (central C)	8.72 °
C_{60} Buckminsterfullerene, **6** [14]	11.64 °
9,9',10,10'-Tetradehydrodianthracene, **7** [15]	13.04 °

Since all of these compounds are quite stable under ambient conditions, it seems reasonable to state that aromatic compounds can undergo a (POAV) pyramidalization of well over ten degrees without becoming too unstable to isolate. The synthesis and chemistry of such distorted aromatic compounds will now be discussed.

2.3 - Cyclophanes

2.3.1 - Introduction and Nomenclature

The name "cyclophane" is a contraction of the words *cyclo*, *ph*enyl, and alk*ane*, and refers to cyclic molecules that contain a phenyl (or other aromatic moiety) as part of the ring. Since the first investigations of such compounds in the late 1940s,[16] a vast amount of knowledge about their physical, chemical, and other properties has been obtained. An elaborate system of nomenclature was proposed by Cram and developed by

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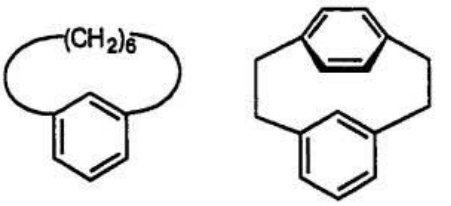
[12] Sekine, Y.; Brown, M.; Boekelheide, V. *J. Am. Chem. Soc.* **1979**, *101*, 3126-3127.
[13] Siegel, J.S.; Seiders, T.J. *Chem. Br.* **1995**, 313-316.
[14] Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature* **1985**, *318*, 162-163.
[15] Viavattene, R.L.; Greene, F.D.; Cheung, L.D.; Majeste, R.; Trefonas, L.M. *J. Am. Chem. Soc.* **1974**, *96*, 4342-4343.
[16] Brown, C.J.; Farthing, A.C. *Nature* **1949**, *164*, 915-916.

Vögtle,[17] which will be used throughout this thesis. In this system, [n] denotes the length of the bridge, and "meta" or "para" (or numbers when a nonbenzenoid aromatic moiety is present) describe the points of connection. To briefly illustrate this system of nomenclature, consider compounds **8**, **9**, and **10**. Compound **8** is [6]metacyclophane. The number in the square bracket denotes the number of atoms in the bridge, and "meta" denotes the substitution pattern on the aromatic ring. Compound **9** is



8 **9** **10**

[2.2]metaparacyclophane, where the number of numbers denotes the number of bridges, the numbers themselves indicate the length of the bridges, and the substitution pattern of each ring is given by "meta" and "para." Finally compound **10** is [8](2,5)furanophane. Again, the number in the square bracket indicates the length (in atoms) of the tether, while the numbers in the parentheses describe the substitution pattern of the aromatic ring, in this case a furan. Numbering of carbons in a cyclophane starts on a bridge carbon adjacent to an aromatic ring, goes along the bridge, around the ring, onto the next bridge, and so on. For a more detailed discussion of cyclophane nomenclature, consult Ref. 17a-c.

Cyclophanes are of interest due to the challenge they pose for synthesis,[18] their interesting chemical,[19] conformational[20] and spectroscopic[20] properties, and the potential for their application as photochromic compounds,[21] as novel ligands and chiral

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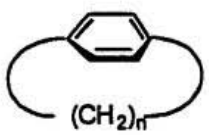
[17] a) Cram, D.J.; Steinberg, H. *J. Am. Chem. Soc.* **1951**, *73*, 5691-5704. b) Vögtle, F.; Neumann, P. *Tetrahedron Lett.* **1969**, 5329-5334. c) Vögtle, F.; Neumann, P. *Tetrahedron* **1970**, *26*, 5847-5863.
[18] Kane, V.V.; de Wolf, W.; Bickelhaupt, F. *Tetrahedron* **1994**, *50*, 4575-4622.
[19] Bickelhaupt, F.; de Wolf, W. H. *J. Phys. Org. Chem.* **1998**, *11*, 362-376.
[20] Mitchell, R.H. in Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, Vol. 1* Academic Press, New York, **1983**; pp. 239-310.
[21] Mitchell, R.H. in Thummel, R.P., Ed. *Advances in Theoretically Interesting Molecules, Vol. 1* JAI Press, London, **1989**; pp. 135-199.

auxiliaries,[22] and as constituents in supramolecular assemblies.[23] They have been reviewed in numerous monographs[24] and articles,[25] and novel syntheses and applications for these compounds continue to be produced. Most of this material will not be dealt with here, but one subdiscipline of cyclophane chemistry, that of the [n]paracyclophanes, is closely related to the topic to be considered later and will therefore be discussed in some detail.

2.3.2 - Paracyclophanes

Chemists once assumed that benzene and other aromatic molecules were rigid and incapable of undergoing significant out-of-plane distortions. However, the discovery and study of non-planar aromatic molecules has resulted in a rethinking of this dogma.[26] The archetypal examples of aromatic molecules undergoing an out-of-plane distortion has always been the [n]paracyclophanes, **11**. Many of these compounds have been prepared and studied over the past 50 years, and their properties have stimulated a great deal of interest in the concept of aromaticity in three dimensions.



11

a: n=4
b: n=5
c: n=6
d: n=7
e: n=8
f: n=9
g: n=10
h: n=12

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[22] Pye, P.J.; Rossen, K.; Reamer, R.A.; Tsou, N.N.; Volante, R.P.; Reider, P.J. *J. Am. Chem. Soc.* **1997**, *119*, 6207-6208. Rossen, K.; Pye, P.J.; Maliakal, A.; Volante, R.P. *J. Org. Chem.* **1997**, *62*, 6462-6463.

[23] Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 362-386. b) Odashima, K.; Koga, K. in Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, Vol. 2* Academic Press, New York, **1983**. pp. 629-678.

[24] a) Smith, B.H. *Bridged Aromatic Compounds* Academic Press, New York, **1964**. b) Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, 2 Vols.* Academic Press, New York, **1983**. c) Vögtle, F. *Cyclophan-Chemie* B.G. Teubner, Stuttgart, **1990**.

[25] a) Cram, D.J.; Cram, J.M. *Acc. Chem. Res.* **1971**, *4*, 204-213. b) Bodwell, G.J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2085-2088.

2.3.2.1 - Synthesis – General Remarks

Prior to embarking on a discourse upon the synthesis of [n]paracyclophanes, it would be useful to consider some of the theoretical aspects of such a synthesis (Fig. 2-7).[27] The usual way to synthesize a cyclic molecule in organic chemistry is through a simple ring closing reaction. In the case of paracyclophanes, such a reaction would involve starting with a *p*-disubstituted benzene derivative and closing the appropriately functionalized tether (Routes **A** and **B**). For larger ($n \geq 9$) [n]paracylophanes, this method proved quite effective. Unfortunately, the smaller (and therefore more interesting) members of the paracyclophane family could not be prepared in this manner, due to the prohibitive increase in strain on ring closure – in simple terms, "the ends do not meet" and polymerization, rather than ring closure, is the result. Most syntheses of small ($n < 9$) paracyclophanes therefore require the preparation of a less strained benzene precursor, **P**, with the tether already in place. The energy released on liberation of the benzene ring, route **C**, an extremely exothermic step in unstrained systems, overcomes the increase in strain energy inherent in a markedly nonplanar aromatic system.

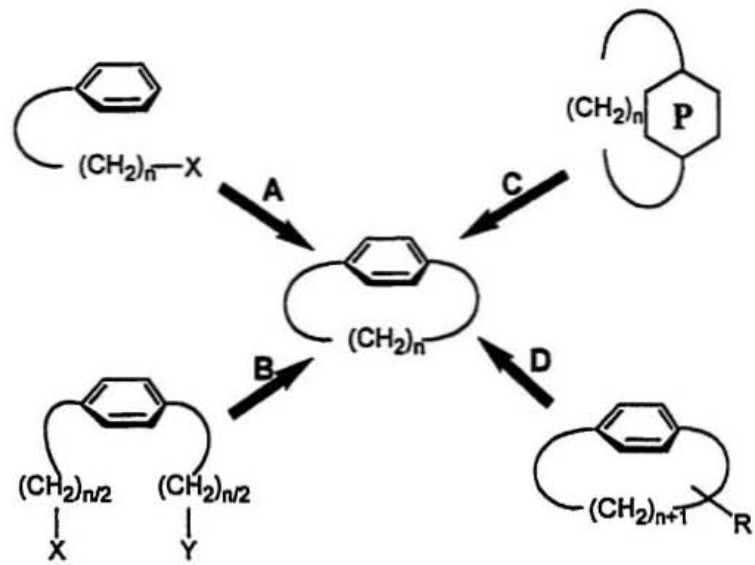


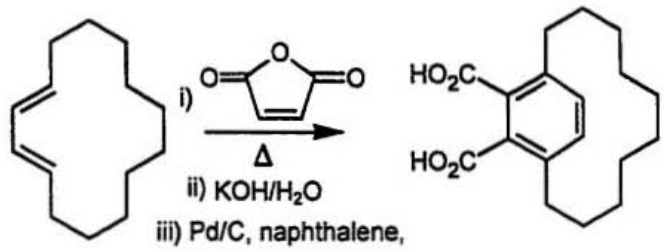
Figure 2-7: Approaches to the Synthesis of [n]Paracyclophanes

[26] a) Wynberg, H.; Nieuwpoort, W.C.; Jonkman, H.T. *Tetrahedron Lett.* **1973**, 4623-4628. b) Lipkowitz, K.B.; Peterson, M.A. *J. Comp. Chem.* **1993**, *14*, 121-125.

Moreover, the benzene ring generation step should occur under as mild conditions as possible, to allow the isolation of highly reactive or thermally labile products. Alternately, highly exothermic ring-contraction methodology can be applied to shorten the tether (Route **D**). Some cyclophane syntheses (such as that of Jones, described below) may not fit into any of these categories.

2.3.2.2 - Synthesis of Paracyclophanes

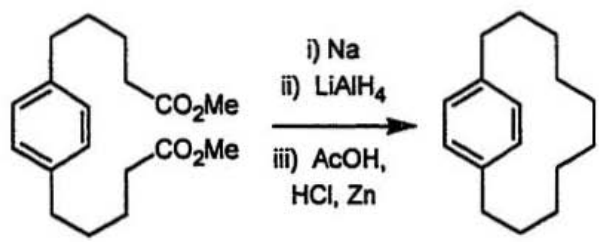
The first synthesis of an [n]paracyclophane was reported by Wiesner's group in



12 **13**

Scheme 2-1: Diels-Alder Synthesis of Paracyclophanes

1950. He described two methods to generate [10]paracyclophane or its derivatives. The first (Scheme 2-1) involved a Diels-Alder reaction of maleic anhydride with cyclotetradeca-1,3-diene, **12**, followed by dehydrogenation to yield the substituted [10]paracyclophane **13**. To check his assignment of the structure, he also conducted an acyloin condensation (Scheme 2-2) on diester **14** (in 70% yield), followed by



14 **11g**

Scheme 2-2: Acyloin Route to Paracyclophanes

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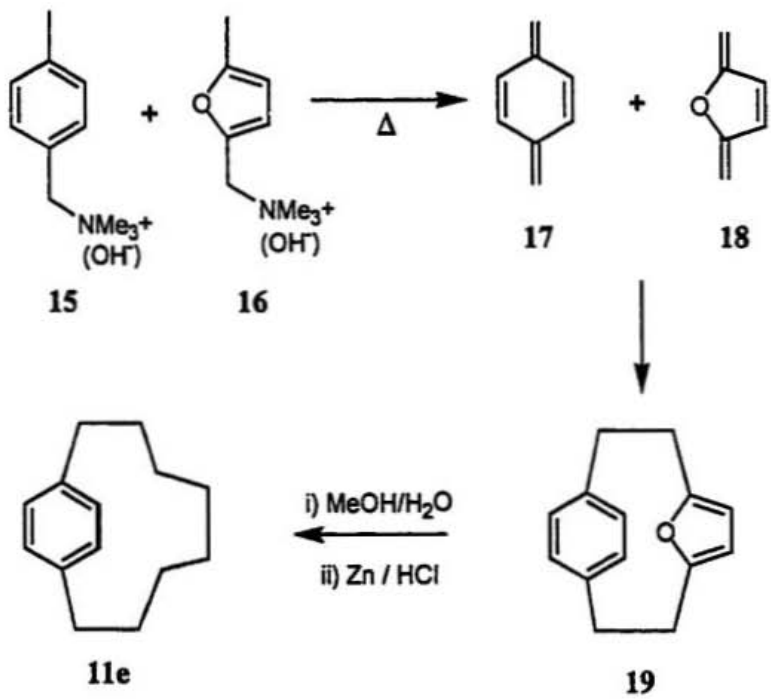
[27] a) Bickelhaupt, F. *Pure Appl. Chem.* **1990**, *62*, 373-382. b) Bickelhaupt, F.; de Wolf, W.H. *Rec. Trav.*

deoxygenation to afford [10]paracyclophane **11g**.[28] Two years later, Wiesner reported that the Diels-Alder/dehydrogenation method failed to generate [9]paracyclophane. However, under drastically forcing dehydrogenation conditions (Se, 370°C) small amounts of a compound with the elemental composition of [9]paracyclophane could be isolated. Under even these conditions, only retro-Diels-Alder products could be isolated from the [8]paracyclophane precursor.[29]

A number of other methods were used to prepare large ($n \geq 9$) paracyclophanes by simple ring-closing techniques, such as the Friedel-Crafts reaction[30] and the Eglington oxidative coupling of alkynes.[31]

D.J. Cram, who first proposed the term 'cyclophane', prepared a number of larger



Scheme 2-3: *p*-Xylylene Route to [8]Paracyclophane

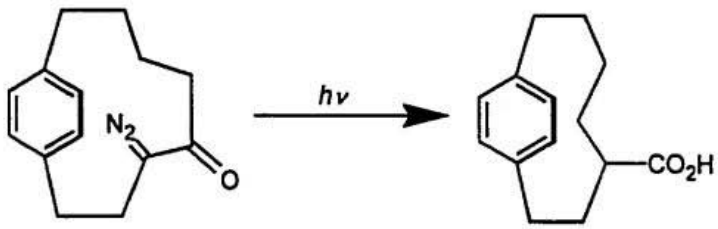
Chim. Pays-Bas **1988**, *107*, 459-478.

[28] Wiesner, K.; MacDonald, D.M.; Ingraham, R.B.; Kelly, R.B. *Can. J. Res. Sec. B.* **1950**, *28*, 561-566.

[29] Bartlett, M.F.; Figdor, S.K.; Wiesner, K. *Can. J. Chem.* **1952**, *30*, 291-294.

[30] a) Schubert, W.M.; Sweeney, W.A.; Latourette, H.K. *J. Am. Chem. Soc.* **1954**, *76*, 5462-5466. b) Huisgen, R.; Ugi, I. *Chem. Ber.* **1960**, *93*, 2693-2704.

[31] a) Matsuoka, T.;. Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1970**, 2549-2552. b) Matsuoka, T.; Negi, T.; Otsubo, Y.; Sakata, Y.; Misumi, S. *Bull. Chem. Soc. Japan* **1972**, *45*, 1825-1833.

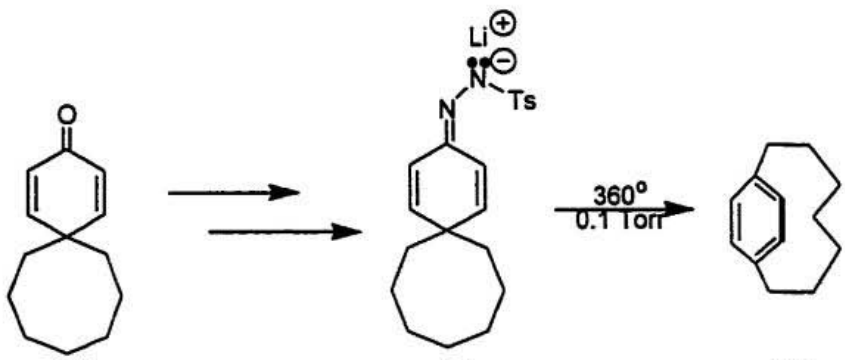


20 **21**

Scheme 2-4: Wolff Rearrangement of **20**

[n]paracyclophanes (n=12,10,9)[32] via the acyloin/dehydrogenation method, but this method did not work for [8]paracyclophane. Cram then (in 1961) applied an ingenious "cross-breeding" reaction (Scheme 2-3), in which *p*-xylylene **17** and furan derivative **18** were prepared together (via a Hofmann elimination of **15** and **16**) and allowed to undergo [6+6] dimerization, a "forbidden" reaction that occurs due to the high energy nature of the reactants.[33] This, of course, led to a mixture of products, but the 'crossed' paracyclofuranophane **19** was the major product (30% yield). Hydrolysis followed by Clemmensen reduction afforded [8]paracyclophane, **11e**. Aberrations in the UV spectrum of this compound suggested that the benzene ring was markedly bent.

It took eleven years for the first [7]paracyclophane derivative to be prepared,



22 **23** **11d**

Scheme 2-5: Synthesis of [7]Paracyclophane

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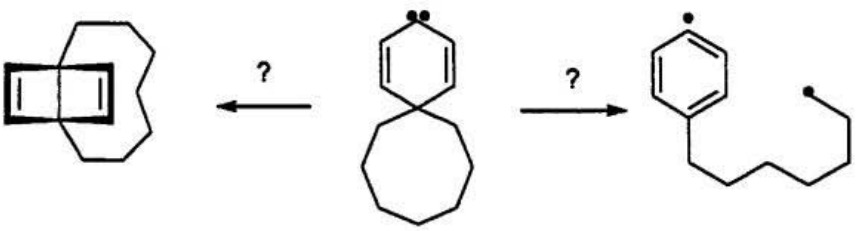
[32] a) Cram, D.J.; Daeniker, H.V. *J. Am. Chem. Soc.* **1954**, *76*, 2743-2752. b) Cram, D.J.; Allinger, N.L.; Steinberg, H. *J. Am. Chem. Soc.* **1954**, *76*, 6132-6141. c) Cram, D.J.; Antar, M.F. *J. Am. Chem. Soc.* **1958**, *80*, 3109-3114.

[33] Cram. D.J.; Knox, G.R. *J. Am. Chem Soc.* **1961**, *83*, 2204-2205. b) Cram. D.J.; Montgomery, C.S.; Knox, G.R. *J. Am. Chem Soc.* **1966**, *88*, 515-525

(Scheme 2-4) by a Wolff rearrangement-ring contraction of the diazoketone **20**, which is highly exothermic due to the loss of N_2.[34] This afforded 3-carboxy[7]paracylophane **21**. Unfortunately, this method could not generate a [6]paracyclophane derivative as the required diazoketone could not be isolated.[34b]

The parent [7]paracyclophane, **11d**, was prepared by Jones a year later, in 1973, by a novel method (Scheme 2-5) involving the rearrangement of a 4,4-spirocyclohexadienylidene **24**, generated by pyrolysis of the tosylhydrazide **23** derivative of dienone **22**.[35] The exact mechanism of this transformation is unknown (Scheme 2-6), but it might involve radicals such as **25** or a carbene insertion to generate a Dewar benzene **26**.[36] The yield for this transformation was around 20%.

Jones used an analogous method to prepare [6]paracyclophane **11c**, isolating the product in low (<5 %) yield, due to the difficulty in separating the paracyclophane from other impurities.[37] This method failed in the synthesis of [5]paracyclophane **11b**.[18] Jones reported heating [6]paracyclophane to 90 °C, and did not mention any decomposition. This is significant, as [6]paracyclophane appears to represent the limit of room-temperature stability in the paracyclophanes.



26 **24** **25**

Scheme 2-6: Possible Intermediates in the Synthesis of **11d** from **24**

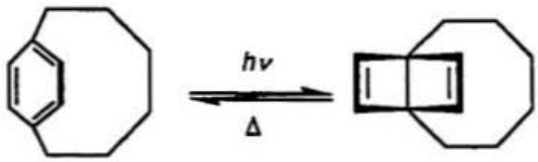
---

[34] a) Allinger, N.L.; Walter, T.J. *J. Am. Chem. Soc.* **1972**, *94*, 9267-9268. b) Newton, M.G.; Walter, T.J.; Allinger, N.L. *J. Am. Chem. Soc.* **1973**, *95*, 5652-5658.

[35] Wolf, A.D.; Kane, V.V.; Levin, R.H.; Jones Jr., M. *J. Am. Chem. Soc.* **1973**, *95*, 1680.

[36] Berdick T.E.; Levin, R.H.; Wolf, A.D.; Jones Jr., M. *J. Am. Chem. Soc.* **1973**, *95*, 5087-5088. b) Jones Jr., M. *Acc. Chem. Res.* **1974**, *7*, 415-421.

[37] Kane, V.V.; Wolf, A.D.; Jones Jr., M. *J. Am. Chem. Soc.* **1974**, *96*, 2643-2644.

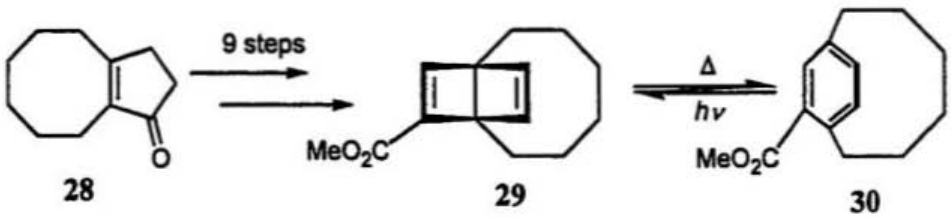


11c **27**

Scheme 2-7: Interconversion of **11c** and **27**

More recently, a method involving the dehydrogenation of a cyclohexene generated by a Diels-Alder reaction of a macrocyclic diene (reminiscent of Wiesner's method) afforded [7]- and [8]paracyclophanes in reasonable yields (79% for the dehydrogenation step).[38]

Bickelhaupt observed that [6]paracyclophane, **11c**, could be converted quantitatively to its Dewar benzene isomer by irradiation with UV light (Scheme 2-7). Heating the Dewar benzene isomer to 60 °C led to rapid and clean reversion to [6]paracyclophane.[39] One interesting feature of this transformation was that it suggested a method to prepare the lower paracyclophanes – the thermal rearrangement of Dewar benzenes. This method was successfully applied (Scheme 2-8) to the synthesis[40] (from cyclopentenone **28**) of a number of [6]paracyclophane derivatives, such as **30**. Attempted syntheses of [5]-,[40b,41] [4]-,[42] and [3]paracyclophanes[43] using this method (flow pyrolysis,



28 **29** **30**

Scheme 2-8: Route to Paracyclophane **30** from Enone **28**

---

[38] Gassman, P.G.; Bailey, T.F.; Hoye, R.C. *J. Org. Chem.* **1980**, *45*, 2923-2924.

[39] a) Kammula, S.L.; Iroff, L.D.; Jones Jr., M.; van Straten, J.W.; de Wolf, W.H.; Bickelhaupt. F. *J. Am. Chem. Soc.* **1977**, *99*, 5815. b) van Straten, J.W.; Turkenburg, L.A.M.; de Wolf, W.H.; Bickelhaupt. F. *Rec. Trav. Chim. Pays-Bas* **1985**, *104*, 89-97.

[40] a) Tobe, Y.; Kakiuchi, K.; Odaira, Y.; Hosaki, T.; Kai, Y.; Kasai, N. *J. Am. Chem. Soc.* **1983**, *105*, 1376-1377. b) Tobe, Y.; Nakayama, A.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *J. Org. Chem.* **1987**, *52*, 2639-2644.

[41] van Straten, J.W.; Landheer, I.J.; de Wolf, W.H.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, 4499-4502.

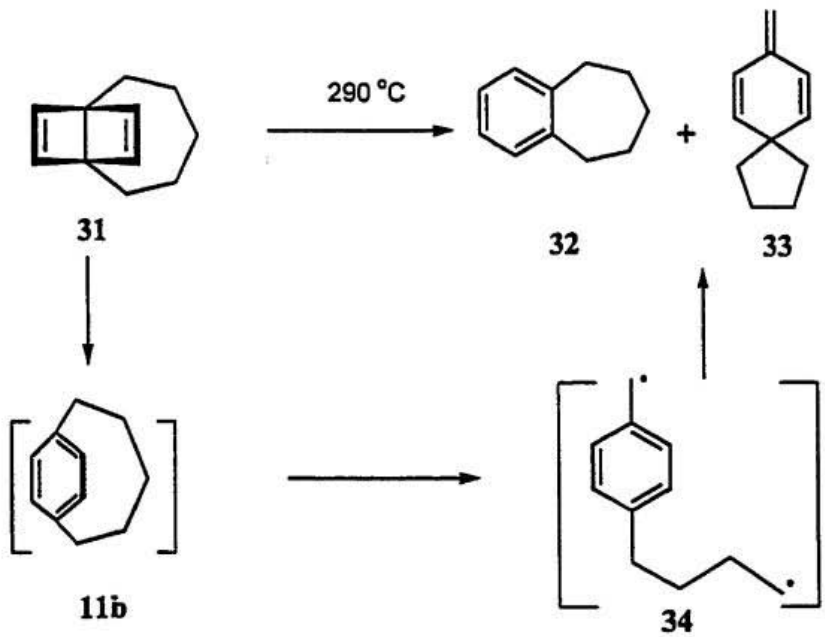
[42] a) Landheer, I.J.; de Wolf, W.H.; Bickelhaupt, F. *Tetrahedron Lett.* **1974**, 2813 - 2816. b) Weinges, K.; Klessing, K. *Chem. Ber.* **1974**, *107*, 1915-1924.

[43] Landheer, I.J.; de Wolf, W.H.; Bickelhaupt, F. *Tetrahedron Lett.* **1975**, 349-352.

approximately 300 °C) did not result in the isolation of any desired products. However, **31** did yield decomposition products **32** and **33** which could be attributed to the formation and subsequent decomposition (perhaps via diradical **34**) of a desired paracyclophane **11b** (Scheme 2-9).[44] A milder method for the Dewar benzene-benzene isomerization was required for the synthesis of the short chain paracyclophanes.

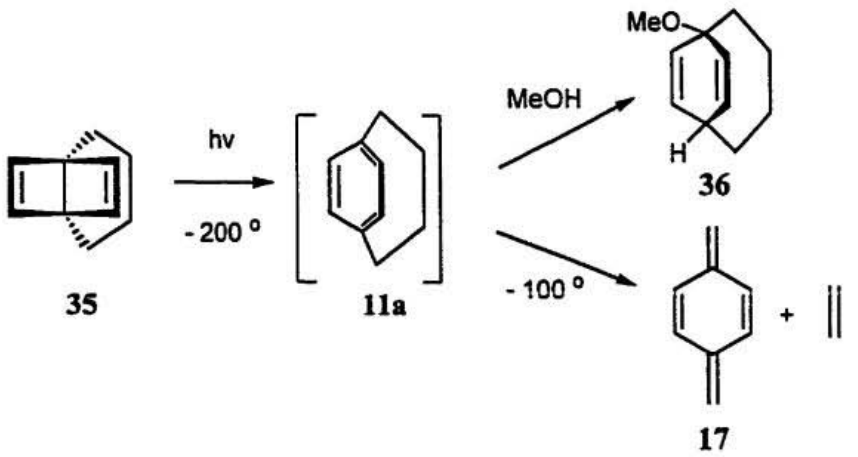
This 'milder method' was finally reported by the groups of Bickelhaupt and Tobe in 1985.[45] [5]Paracyclophane, **11b**, was prepared by mercury lamp irradiation of its Dewar benzene isomer **31** in THF-d_8 at -60 °C. The yield by NMR was 6-7%, and insoluble polymeric material was gradually formed on longer irradiation or on warming to 0 °C. Some kinetically-stabilized, functionalized [5]paracyclophanes were prepared by analogous methods, but even these polymerized slowly in solution at room temperature.[46]

Given the instability of [5]paracyclophane, it was assumed that [4]paracyclophane, **11a**, would be extremely labile and difficult to detect, let alone



Scheme 2-9: Mechanism for Formation of **32** and **33** from **31**

[44] van Straten, J.W.; de Wolf, W.H.; Bickelhaupt. F. *Rec. Trav. Chim. Pays-Bas* **1977**, *96*, 88.
[45] Jenneskens, L.W.; de Kanter, F.J.J.; Kraakman, P.A.; Turkenburg, L.A.M.; Koolhaas, W.E.; de Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716-3717.



Scheme 2-10: Synthesis and Reactions of [4]Paracyclophane

isolate. The observation of the compound **11a** was reported simultaneously and independently by Bickelhaupt and Tsuji in 1987.[47] The two groups used the same method (Scheme 2-10), namely, the photolysis of Dewar benzene **35**. When performed in methanol, the methanol adduct 5,8-dihydro-5-methoxy[4]paracyclophane, **36**, was isolated in high yield. Tsuji also reported that UV bands attributable to a highly strained benzene could be observed when **36** was irradiated in an ethanol matrix at 77 K, but these bands disappeared irreversibly on 'warming' to 173 K (-100 °C). The decomposition products were shown to be *p*-xylylene **17** and ethylene.

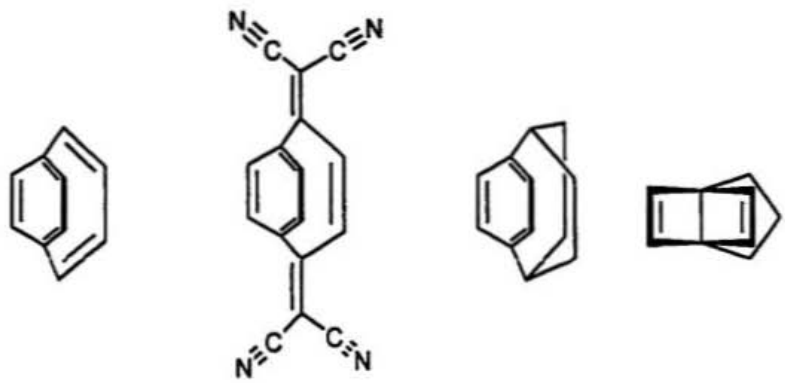
Strained as **11a** is, Tsuji reported an even more strained compound, a [4]paracyclopha-1,3-diene **37**, in 1989.[48] This compound replaces the tetramethylene bridge with a 1,3-butadienylene bridge, which is alleged to be shorter and less flexible and the benzene ring will therefore be even more strained than **11a** (the bond angles in the tether, however, are larger). The compound was observed by UV in a 5:5:2 mixture of ether, isopentane, and ethanol at 77 K and could be trapped as a cyclopentadiene adduct.

---

[46] a) Tobe, Y.; Kaneda, T.; Kakiuchi, K.; Odaira, Y. *Chem. Lett.* **1985**, 1301-1304. b) Kostermans, G.B.M.; de Wolf, W.H.; Bickelhaupt, F. *Tetrahedron Lett.* **1986**, *27*, 1095-1098. c) Kostermans, G.B.M.; de Wolf, W.H.; Bickelhaupt, F. *Tetrahedron* **1987**, *43*, 2955-2966.

[47] a) Tsuji, T.; Nishida, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1189-1190. b) Kostermans, G.B.M.; Bobeldijk, M.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 2471-2475. c) Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1988**, *110*, 2157-2164.

[48] Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1989**, *111*, 368-369. Tsuji, T.; Nishida, S.; Okuyama, M.; Osawa, E. *J. Am. Chem. Soc.* **1995**, *117*, 9804-9813.



37 38 39 40

Tsuji's most recent contribution to the [n]paracyclophane area describes a kinetically stabilized [4]paracyclophane, **38**, whose bridgehead atoms are sterically shielded.[49] This compound was observed to remain intact for over 1 hour in isopentane-ether at -50 °C. The proton spectrum of this compound could therefore be acquired. Tsuji has also prepared an exceptionally strained [1.1]paracyclophane derivative.[50]

Attempts to prepare the ethano-bridged [4]paracyclophane **39** failed.[47c,51] Similarly, attempts to transform trimethylene (Dewar benzene) **40** into [3]paracyclophane by thermolysis (300 °C) resulted in the quantitative recovery of the starting material. The recent literature does not contain any suggestions of methods to prepare and observe paracyclophanes more strained than those already known. These results suggest that the [4]paracyclophanes already prepared might represent the limit of the extent to which benzene can be bent, even as a fleeting intermediate.

2.3.2.3 - Physical and Spectroscopic Properties

Isolable [n]paracyclophanes (n≥6) exist as colorless, volatile liquids, and are thermally stable to at least 90 °C . As described above, [5]paracyclophane **11b** is unstable to polymerization and Dewar-benzene-equilibration at 0 °C in solution, and [4]paracyclophane **11a** can only be observed in a matrix at (or below) 77 K and decomposes to (1,4)addition products or *p*-xylylene at temperatures as low as -130 °C.

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[49] Okuyama, M.; Tsuji, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1085-1086.
[50] Kawai, H.; Suzuki, T.; Ohkita, M.; Tsuji, T. *Angew. Chem. Int. Ed. Engl.* **1998**, *37*, 817-819.
[51] Gleiter, R.; Krennrich, G.; Bischof, P.; Tsuji, T.; Nishida, S. *Helv. Chim. Acta* **1986**, *69*, 962-971.

For this reason, many of the physical properties of the smaller cyclophanes have not been determined experimentally.

2.3.2.3.1 - Ultraviolet Spectroscopy

Before examining the UV/Vis spectrum of the paracyclophanes, the characteristics of the spectrum of benzene itself should be considered.[52] Above 180 nm, the spectrum of benzene shows three absorption bands, resulting from π-π^* transitions. A broad, structureless band (ε_{max} 6.8 x 10^4) is seen at around 185 nm, and (according to the group theoretical notation of the transition) is referred to as the $^1E_{2u}$ transition. Overlapping this absorption at 204 nm (ε_{max} 8.8 x 10^3), with some poorly resolved vibrational structure, is the $^1B_{1u}$ band. The third absorption, at 254 nm, is a low intensity band (ε_{max} 2.5 x 10^2) with clear vibrational structure and is termed the $^1B_{2u}$. The latter two bands ($^1B_{1u}$ and $^1B_{2u}$) are both forbidden; however, the 204 nm band "borrows" intensity from the allowed $^1E_{2u}$ band with which it overlaps. The 254 nm band is symmetry-forbidden, but vibrational distortions result in a small, transitional dipole moment which allows a low intensity absorption.

When benzene is substituted, its absorption bands undergo changes. Because of reduced symmetry, the group theoretical notations used in the previous paragraph no longer apply. Another system of notation, introduced by Clar, is based on the behavior of different bands with varying temperature and solvent.[53] According to this system, the 184 nm band is termed the β band, while the 204 and 254 nm absorptions are called the *p (para)* and α bands, respectively. The spectrum of *p*-diethylbenzene, a good model of an unstrained, *para*-substituted benzene ring, shows the β band at 193 nm, the *p* band at 214, and the α band at 265 nm. All three bands have been red-shifted by about 10 nm relative to benzene itself.

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[52] Lambert, J.B.; Shurvell, H.F.; Lightner, D.A.; Cooks, R.G. *Introduction to Organic Spectroscopy* MacMillan Publishing, New York, 1987. pp. 280-283.
[53] Clar, E. *Spectrochimica Acta* 1950, *4*, 116-121.

Now, let us consider the absorption spectroscopy of paracyclophanes. The following table describes the major experimental UV absorptions of the [n]paracyclophanes.[54]

Table 2-2: UV Spectroscopic Data on [n]Paracyclophanes

Compound	λ_1, β	log ε_1	λ_2, *p*	log ε_2	λ_3, α	log ε_3
p-diethyl-benzene[a]	193[a]	4	214[a]	3	265[a]	
n=10			223[a]	3	268[a]	2
n=9			224[a]	3	271[a]	3
n=8	205[a]	4	224[b]	3.84	274[b]	2.61
n=7	216[c]	4	245[c]	4	283[c]	3
n=6	212[d]	4.3	253[d]	4.0	296[d]	2.8
n=5			280[e]		330[e]	
n=4			260[f]		340[f]	

a) Solvent not specified, ref. 35

b) Solvent not specified, ref. 34

c) EtOH, ref. 36

d) EtOH, ref. 37

e) THF-d_8, -60 °C, ref. 45

f) EtOH matrix, 77 K, ref. 47a

The values quoted above were obtained in different solvents, under different conditions over a time span of almost four decades, and therefore rigorous quantitative comparisons would be unwise. However, certain trends are obvious. First of all, the absorption bands show dramatic red-shifts as the aromatic ring becomes more bent. Secondly, although it is not obvious from the chart, the fine structure in the *p* and α

[54] Allinger, N.L.; Freiberg, L.A.; Hermann, R.B.; Miller, M.A. *J. Am. Chem. Soc.* **1963**, *85*, 1171-1176. See also: Allinger, N.L.; Sprague, J.T.; Liljefors, T. *J. Am. Chem. Soc.* **1974**, *96*, 5100-5104.

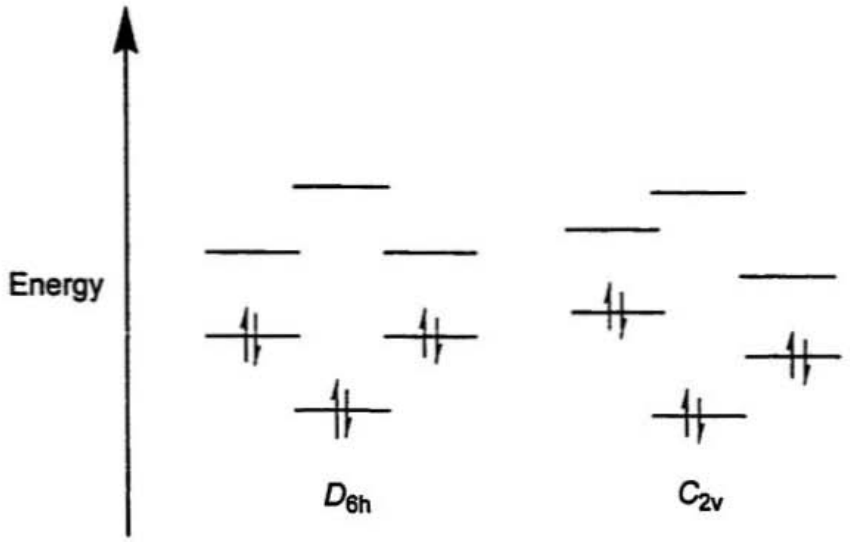

Figure 2-8 : MO Energy Levels of Planar and Nonplanar Benzene π Orbitals (Allinger, Ref. 54)

absorption bands tends to disappear as the distortion of the benzene ring increases.[55] There is surprisingly little information in the literature concerning the theoretical background of these changes in UV spectra. The red-shifts can be attributed to a drop in the HOMO-LUMO gap resulting from poorer π-overlap and the decrease in symmetry of the benzene rings as they are distorted from a D_{6h} to a C_{2v} geometry, as demonstrated (in benzene) by Allinger using a simple Hückel method (Fig. 2-8).[54] The loss of fine structure has been explained as resulting from strong coupling between vibrational and electronic states, which has been attributed to a "high degree of anharmonicity" in the benzene vibrations.[56] This has been termed the "loose bolt" theory, in which electronically excited states transfer their energy to groups capable of low energy vibrations.[57] Of course, why this energy transfer should increase as the tether becomes tighter and more rigid is unclear.

[55] Rosenfeld, S.M.; Choe, K.A. in Ref. 3, p. 336-337.
[56] Ingraham, L.L. *J. Chem. Phys.* **1957**, *27*, 1228-1229.
[57] Lewis, G.N.; Calvin, M. *Chem. Rev.* **1939**, *25*, 273-328.

2.3.2.3.2 - NMR Spectroscopy

The chemical shifts observed for the aromatic and highest-field tether protons for paracyclophanes are listed in Table 2-3:[58]

Table 2-3: ^{1}H NMR Data on [n]Paracyclophanes

Compound	ring, δ	tether, δ	Comments
n = 12		+0.78	
n = 11		+0.68	
n = 10	7.04	+0.48	
n = 9		+0.33	
n = 8		+0.19	
n = 7	7.07	- 0.6	
n = 6[37]	7.13	+ 0.33	At -80 °C, high field signal splits, shifted upfield to δ -0.62 ppm.
n = 5[45]	7.44, 7.38	+ 0.01	Acquired at -72 °C
n = 4[49]	7.97	*	Spectrum obtained on kinetically stabilized derivative **39** – no polymethylene tether.

A useful feature of the [n]paracyclophanes is the presence of an intramolecular ring current probe in the form of the tether. Because the tether is forced to lie directly above the face of the aromatic nucleus, it is affected by the diamagnetic ring current and the ^{1}H chemical shift of some of the tether's protons is shifted upfield. As can be seen, there is a steady increase in shielding as the tether shortens to n=7. After this, the chemical shift appears to return downfield. However, on cooling **11c** (n=6), the tether becomes 'frozen' in one conformation (at the NMR timescale), and one proton is forced directly into the shielding cone. The chemical shift of this proton is – 0.6 ppm, indicating that considerable ring current still exists. When n=5 (**11b**), the chemical shift of the highest field tether protons is at δ=0.01 ppm even at -72 °C, which might suggest the intensity of the ring current is decreasing relative to **11c**. However, as the authors state: "it is not yet clear whether this difference is due to a slightly diminished ring current... or to a less

[58] Agarwal, A.; Barnes, J.A.; Fletcher, J.L.; McGlinchey, M.J.; Sayer, B.G. *Can. J. Chem.* 1977, *55*, 2575-2581.

favorable location within the shielding cone."[45] The only [4]paracyclophane derivative for which NMR data is available does not have a polymethylene tether, so no information on the diatropicity or lack thereof is obtainable from this data. In summary, it seems clear that considerable ring current exists in [n]paracyclophanes for tether lengths at least as short as n=5, which is, of course, markedly non-planar. This seems to support Haddon's contention that rehybridization will allow the π-system to remain intact despite marked non-planarity of the aromatic carbons.

The other observable trend is the *downfield* shift of the aromatic protons. This is more difficult to understand. Allinger[54] proposed that the bending of the aromatic ring should decrease the diatropic ring current, and therefore the aromatic protons should be shifted upfield. Haddon's rehybridization model, which suggests that the carbon orbital contributing to the C-H σ-bonds should have more p-character and therefore be less electronegative, also seems to imply that an upfield shift should be expected. This clearly does not occur. It seems unlikely that the downfield shift of the aromatic protons is a result of an increased ring current. Otherwise, the reason for this unusual phenomenon remains unclear.

Research has shown that the effect of ring currents on ^{13}C NMR shifts are of the same magnitude as their effect on ^{1}H shifts, but in the case of ^{13}C, these effects are usually swamped by other factors.[59] There is a surprising paucity of data concerning ^{13}C spectra of [n]paracyclophanes.[59e] Most papers do not even list ^{13}C data, and no studies on trends in these spectra have been conducted. Some work on the ^{13}C NMR spectra of [2.2] meta- and paracyclophanes has been reported.[60]

2.3.2.4 – Bend Angles

The extent of the deviation from planarity present in [n]paracyclophanes has always been measured using the angles α and β, as shown in Fig. 2-9 (different authors frequently use different Greek letters to represent these angles but α and β will be used

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[59] a) Levin, R.H.; Roberts, J.D. *Tetrahedron Lett.* **1973**, 135-138. b) Günther, H.; Schmickler, H.; Königshofen, H.; Recker, K.; Vogel, E. *Angew. Chem., Int. Ed. Engl.* **1973**, *12*, 243-244. c) Du Vernet, R.; Boekelheide, V. *Proc. Nat. Acad. Sci. U.S.A.* **1974**, *71*, 2961-2964. d) Sakamoto, K.; Oki, M. *Chem. Lett.* **1976**, 267-270. e) Mori, N.; Takemura, T. *J. Chem. Soc., Perkin Trans. 2* **1978**, 1259-1262.

[60] a) Sato, T.; Takemura, T. *J. Chem. Soc., Chem. Comm.* **1974**, 97-98. b) Takemura, T.; Sato, T. *Can. J. Chem.* **1976**, *54*, 3412-3418.

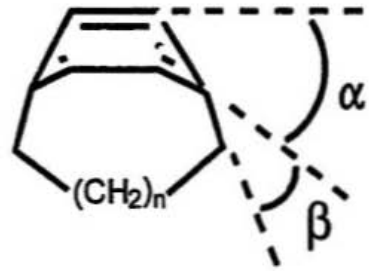

Figure 2-9: Angles α and β

here). There is no direct, (i.e. crystallographic), data regarding the degree of nonplanarity in the [n]paracyclophanes themselves, as all these compounds are liquids at room temperature. However, paracyclophane derivatives have been studied crystallographically, and many semiempirical[54,61] and *ab initio*[62] techniques have been applied to determine the magnitude of α and β. The following table lists the experimental and the calculated bend angles (α and β) of certain [n]paracyclophanes.

Table 2-4: Strain Energy and Bend Angles of [n]Paracyclophanes

Compound	Strain Energy[a] (kcal/mol)	α_{av} (exp.)	β_{av} (exp.)	α_{av} (calc.)	β_{av} (calc.)
n = 8	17 (MM)[3]	9.1°[b]		8.4°[e]	8.9°
n = 7	32	16.8°[c]	6.8°	14.2°[f]	13.9°
n = 6	44	20.7°[d]	18.8°	18.8°[g]	20.6°
n = 5	62			23.5°[g]	28.7°
n = 4	88			29.7°[g]	38.2°

a) MNDO, ref. 27a, except where noted.

b) 4-carboxy[8]paracyclophane, ref. 34b

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[61] a) Carballeira, L.; Casado, J.; Gonzalez, E.; Rios, M.A.; *J. Chem. Phys.* **1982**, 77, 5655-5663. b) Bockisch, F.; Rayez, J.C.; Liotard, D.; Duguay, B. *J. Comp. Chem.* **1992**, *13*, 1047-1056. c) Bockisch, F.; Rayez, J.C.; Dreeskamp, H.; Liotard, D.; Duguay, B. *Theor. Chim. Acta* **1993**, *85*, 69-86. d) Bockisch, F.; Rayez, J.C.; Liotard, D.; Duguay, B. *J. Mol. Struc. (Theochem)* **1993**, *284*, 75-85.

[62] Remington, R.B.; Lee, T.J.; Schaefer III, H.F. *Chem. Phys. Lett.* **1986**, *124*, 199-201. b) Rice, J.E.; Lee, T.J.; Remington, R.B.; Allen, W.D.; Clabo Jr., D.A.; Schaefer III, H.F. *J. Am. Chem. Soc.* **1987**, *109*, 2902-2909. c) Lee, T.J.; Rice, J. E.; Remington, R.B.; Schaefer III, H.F. *Chem. Phys. Lett.* **1988**, *150*, 63-70. d) Grimme, S. *J. Am. Chem. Soc.* **1992**, *114*, 10542-10547. e) Frank, I.; Grimme, S.; Peyerimhoff,

c) 3-carboxy[7]paracyclophane, ref. 34a

d) 8-carboxy[6]paracyclophane, ref. 40a

e) STO – 3G, ref. 62c

f) Double ξ - SCF, ref. 62c

g) SCF – DZP Optimized, ref. 62d

The experimental values are for the functionalized paracyclophanes noted. Obviously, no experimental data exist for those [n]paracyclophanes that are too unstable to be isolable in the solid state (**11a,b**). At the outset of these studies, it was not clear whether semiempirical studies would be appropriate, as it was uncertain whether the available force fields and parameters and assumptions about the quadratic dependence of bonding strain on bend angle were appropriate for the extreme distortions observed for smaller paracyclophanes. On the other hand, the possible role of d-orbitals and configuration interaction called lower-level *ab initio* work into question.[27b] The calculated α and β values listed are all derived *ab initio* methods, as MM and other semiempirical methods tend to overestimate the degree of bending of the aromatic ring.[60a,b] It seems that high-level *ab initio* techniques can predict the degree of bending of a paracyclophane to within 2°. It is also evident that a benzene ring can be bent to around 40° (**11c**, $\alpha + \beta = 20.7° + 18.8° = 39.5°$) while still remaining stable under ambient conditions. The crystal structures also demonstrate bond angle compression at the benzylic carbons, and some bond angle expansion at the bridge methylenes.[40] The effects that crystal packing forces have on the geometry of the aromatic ring in crystalline paracyclophanes is uncertain, although such effects may be considerable, especially in the less strained [n]paracyclophanes.

2.3.2.5 - Chemistry of Paracyclophanes

The marked instability of the short-tether paracyclophanes demonstrates that the chemistry of the benzene ring in these molecules differs markedly from that of benzene

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S.D. *J. Am. Chem. Soc.* **1994**, *116*, 5949-5953. f) Ma, B.; Sulzbach, H.M.; Remington, R.B.; Schaefer III, H.F. *J. Am. Chem. Soc.* **1995**, *117*, 8392-8400.

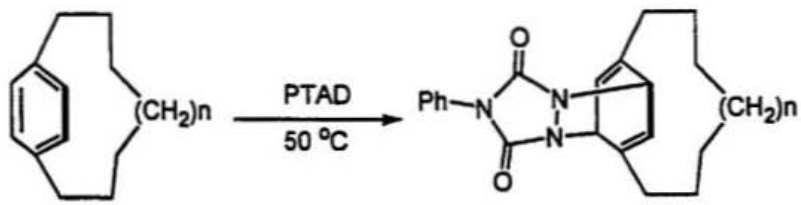
itself. The chemical behavior of strained paracyclophanes will be discussed briefly. Most of the chemistry described in this section has been summarized in a recent review.[19]

2.3.2.5.1 - Thermal and Photochemical Reactions

As discussed above, the thermal stability of small paracyclophanes decreases drastically as the bridge length shortens. Thus, **11b** polymerizes at 0 °C, while **11a** decomposes to ethylene and *p*-xylylene **17** even at -100 °C.

Photochemically, strained paracyclophanes can be transformed to their (less strained) Dewar benzene isomers by irradiation. Of course, irradiation also converts the Dewar benzene back to the paracyclophane, so a photostationary state can be established. For **11c**, the photostationary state (under irradiation by an unfiltered 450 W mercury arc)[39] lies at a ratio of 75:25, while for **11b**, it lies at 7:93.[19] Clearly, the strain imposed by the tether favors the (normally thermodynamically strongly disfavored) Dewar benzene isomer.

Strained paracyclophanes have been shown to undergo Diels-Alder reactions with a number of dienophiles, including *N*-phenyltriazolinedione (PTAD) and perfluoro-2-butyne, to yield 1:1 adducts such as **42** (Scheme 2-11).[37,63] Such reactions do not occur in unstrained model compounds.

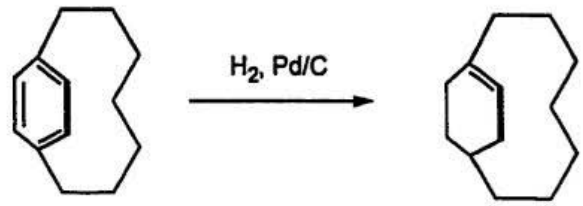


11d,e : n=1,2 **42**

Scheme 2-11: Diels-Alder Reaction of Paracyclophanes

2.3.2.5.2 - Hydrogenation

High temperatures and pressures and powerful catalysts are generally required to hydrogenate benzene. By contrast, [7]paracyclophane **11d** can be hydrogenated (Scheme



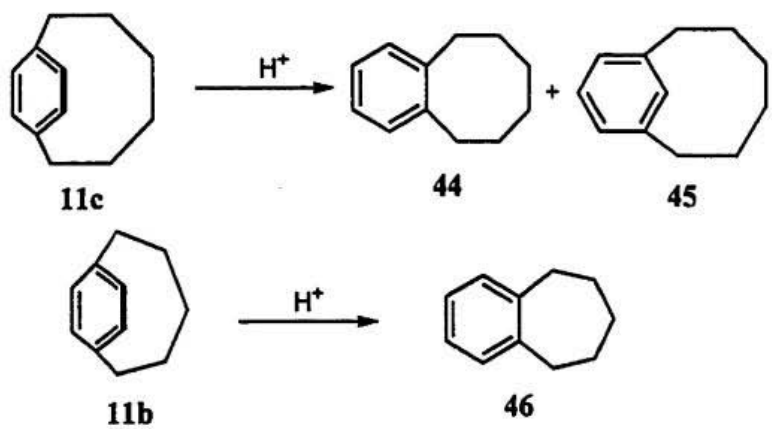
11d **43**

Scheme 2-12: Hydrogenation of [n]Paracyclophane

2-12) to a hyperstable[64] monoolefin **34** at "low pressure" over Pd/C.[65] The exact conditions were not reported. There is no report of such an experiment being conducted on shorter paracyclophanes, but it seems likely that the reaction would be even more facile for more strained compounds.

2.3.2.5.3 - Reactions with Electrophiles

Benzene reacts with electrophiles to give electrophilic substitution products, and it usually requires catalysts to promote such reactions. Paracyclophanes, on the other hand, undergo a number of atypical (for aromatic compounds) reactions.



11c **44** **45**

11b **46**

Scheme 2-13: Acid-Catalyzed Rearrangement of Paracyclophanes

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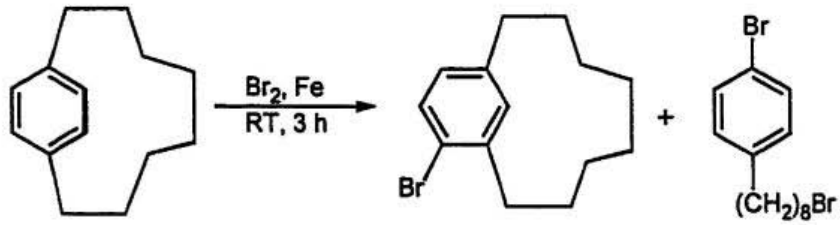
[63] a) Noble, K.-L.; Hopf, H.; Jones Jr., M.; Kammula, S.L. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 602. b) Murad, A.F.; Kleinschroth, J.; Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 389-390.

[64] An hyperstable olefin is a bridgehead alkene that has less strain than its parent saturated hydrocarbon. See Maier, W.F.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1981**, *103*, 1891-1900.

[65] Li, Z.-H.; Jones Jr., M. *Tetrahedron Lett.* **1987**, *28*, 753-754.



11e **47** **48**

Scheme 2-14: Products of Paracyclophane Bromination.

On treatment with acid (Scheme 2-13), [6]paracyclophane, **11c**, rearranges to its less strained meta-, **44**, and ortho-, **45**, isomers.[40b] Treatment of [5]paracyclophane, **10b**, with TFA at -20° affords benzocycloheptene **46** instantaneously and quantitatively.[45] Curiously, [4]paracyclophane does not rearrange to tetralin, but generates 1,4-addition products only.[47] This might be due to excessive strain present in the *meta*-substituted protonated intermediate, which would need to form before the molecule could rearrange to tetralin. Bickelhaupt has estimated that the pK_a of protonated [4]paracyclophane is around 37, as compared to the pK_a of a 'normal' protonated aromatic, around -6.[19] The extraordinary change in the basicity of the benzene ring caused by the short tether reflects the relief in strain permitted when one of the planar sp^2 carbons (neglecting rehybridization) is converted to sp^3 on protonation.

Finally, treatment of [8]paracyclophane, **11e**, with bromine (Scheme 2-14) resulted only in the isolation of products of rearrangement or cleavage, **47** and **48**.[66]

2.3.2.6 - Are Paracyclophanes Aromatic?

We must now return to the topic discussed in Chapter 1, and its implication for the compounds described in this chapter: are paracyclophanes aromatic? Since, as shown previously, there is no universally accepted definition or measurement of aromaticity, the answer to the question will depend on individual preferences. However, the chemical, geometric, magnetic, and energetic properties of paracyclophanes can be compared and contrasted with those of benzene.

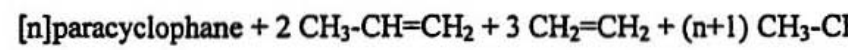
[66] Hopf, H., described in Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, Vol. 1* Academic Press, New York, 1983. pp. 342-343.

2.3.2.6.1 - Reactivity

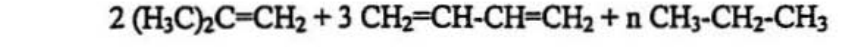
The section prior to this one demonstrated clearly that strained paracyclophanes differ markedly from 'typical' aromatic behavior, showing thermal instability and a tendency to undergo addition, rather than substitution, reactions. By the simplistic "chemistry like that of benzene" criterion, therefore, paracyclophanes are obviously not aromatic. However, it must be remembered that reactivity, unlike aromaticity, is not a ground state property. The transition states of the reactions which [n]paracyclophanes undergo involve the release of strain, and it is this, and other factors such as the asymmetric distribution of electrons on the two faces of the aromatic ring, rather than the absence of resonance stabilization, which results in the atypical chemistry of these molecules.

2.3.2.6.2 – Energetics

The energetic criterion defines an aromatic molecule as being a molecule more stable than a non-delocalized reference structure suggests. Semiempirical MNDO and Molecular Mechanics [60a,b] calculations were used to show that the strain energy present in the bent aromatic ring of [5]metacyclophane far exceeds the resonance energy of benzene (which, incidentally, was quoted as being 36 kcal/mol), and consequently the aromatic character could be said to be lost. However, semiempirical calculations are of limited reliability here as they are not parameterized for such extremely bent and strained compounds.[27b] As described in the previous chapter, the resonance energy of benzene can be determined through the use of a homodesmotic reaction, affording a value of 21.2 kcal/mol.[67] Homodesmotic reactions for [n]paracyclophanes are necessarily more complex than that of benzene, but one was devised by Schaefer and co-workers.[62b,c]



[n]paracyclophane + 2 CH_3-CH=CH_2 + 3 CH_2=CH_2 + (n+1) CH_3-CH_3 →



2 $(H_3C)_2$C=CH_2 + 3 CH_2=CH-CH=CH_2 + n CH_3-CH_2-CH_3

At the DZ SCF level, ΔH values for this reaction are:

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[67] George, P.; Trachtman, M.; Bock, C.W.; Brett, A.M. *J. Chem. Soc., Perkin Trans. 2* **1976**, 1222-1227.

n=5, -55.0 kcal/mol

n=6, -30.6 kcal/mol

n=7, -12.9 kcal/mol

n=8, +6.3 kcal/mol

For n=7 and less, the results are opposite in sign to the value obtained for benzene. In other words, while benzene is stabilized relative to the acyclic olefins it is compared to in a homodesmotic reaction, strained paracyclophanes are markedly *destabilized.* Conversion of **11b, c,** or **d** to 2-methylpropene, 1,3-butadiene, and propane would be *exothermic* reactions. If aromaticity were the stability of a molecule relative to an unstrained, acyclic reference, then by the thermochemical criterion, [5]-, [6]-, and [7]paracyclophanes are clearly *not* aromatic.

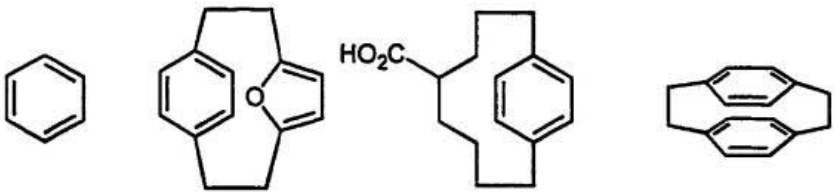
There is, however, a fundamental objection to this reasoning, which Bickelhaupt states as "strain and resonance energies are not quantities which can be subtracted in an arithmetic manner."[27b] As commonly defined, aromaticity does not compare a molecule to a *different, acyclic* molecule, but rather to an *identical but localized* molecule, whose energy is *estimated* using data from acyclic model compounds. The homodesmotic reaction scheme above does not differentiate between the immense strain energy present in **11b-e** and the potential resonance stabilization of **11b-e.** If we take as the reference compound a *localized* [n]paracyclophane, it is easy to see that localizing the molecule does not result in *any* strain relief, as two bridgehead double bonds are still present. Bickelhaupt demonstrated this by showing (at MNDO level) that the distortion of [4]paracyclophane from a bond-equalized to a bond-alternant geometry caused an increase in energy (10.6 kcal/mol) almost identical with the energy required to distort benzene itself from a D_{6h} to a D_{3h} geometry (9.6 kcal/mol).[19] In other words, [4]paracyclophane prefers the delocalized, bond-equalized geometry just as much as planar benzene does. So if aromaticity is taken to be the difference in energy between a molecule and an *identical but geometrically localized* reference, then even [4]paracyclophane should be considered to be aromatic.

Recent work by Schaefer,[62f] however, has partitioned the strain energy in [4]paracyclophane and shown that there is considerable loss of resonance energy (29 kcal/mol) in that compound. Combining this work with that of Bickelhaupt leads to an interesting situation. The resonance energy due to π-electron delocalization has apparently been largely lost. However, the molecule still displays bond equalization, and distortion to a bond-alternant geometry is energetically disfavored. This appears to be independent confirmation of Shaik and co-workers' assertion that bond equalization in benzene is a σ, not a π effect (see Chapter 1). But it again begs the question of what aromaticity exactly is – a compound with resonance energy (in which case [4]paracyclophane is not aromatic, or at least displays reduced aromaticity) or a compound where bond-equalized geometry is more stable than the bond alternant (in which case [4]paracyclophane is aromatic). Once again, the absence of a rigorous definition of aromaticity is illustrated.

2.3.2.6.3 - Magnetic Criteria

The magnetic data on [n]paracyclophanes is quite unambiguous – there is an unequivocal ring current present for n as low as 5 (**11b**), as shown by the shielding of the tether protons. There are no experimental data for **11a**, due to the difficulty of obtaining an NMR spectrum of such an unstable compound. Although it has been suggested that the ring current might be attenuated in **11a** and **11b**, there is little evidence to support this. A high-field deuterium NMR study (mentioned in the previous chapter) on [5]metacyclophane demonstrated that the compound is at least as aromatic as a planar aromatic analogue.[68] If anything, it might be *more* aromatic! IGLO evaluation of the magnetic susceptibility of [4]paracyclophane led the to the conclusion that a "weak ring current" should exist.[62e] NICS and magnetic susceptibility exaltation Λ were calculated for a model of Tsuji's kinetically stabilized [4]paracyclophane.[49] The results (NICS: -9.0, vs. -9.7 for benzene; Λ: -11.6, -15.1 for benzene) both indicated that [4]paracyclophanes retain good electron delocalization in their aromatic rings. From a

[68] van Zijl, P.C.M.; Jenneskens, L.W.; Bastiaan, E.W.; MacLean, C.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1986**, *108*, 1415-1418.



49 **19** **50** **51**

magnetic viewpoint, all evidence indicates that bending benzene rings has little effect on their aromaticity.

2.3.2.6.4 - Geometric and Other Criteria

Both crystallographic[39] and calculated[61,62] geometries suggest that there is little bond alternation present even in the most strained paracyclophanes, but little quantitative analysis of this bond alternation has been published. Krygowski and co-workers examined a few of the paracyclophane crystal structures available in terms of HOMA, GEO, and EN:[69]

Table 2-5: HOMA, GEO, and EN Indices for Selected Aromatics

Compound	HOMA	GEO	EN
Benzene, **49**	0.979	0.00	0.021
[2.2]paracyclofuranophane, **19**	0.963	0.039	-0.002[70]
4-carboxy[8]paracyclophane, **50**	0.989	0.010	0.001
[2.2]paracyclophane, **51**	1.003	0.000	-0.003
[2_6]cyclophane (Superphane), **4**	0.916	0.084	0.000

As Krygowski states, "The main conclusion to be drawn from the data ... is that benzene rings embedded in cyclophane moieties do not loose (*sic*) aromatic character more than any other para- or meta-disubstituted ... benzene derivatives."[69] So, there is little bond alternation or deviation of bond lengths from "optimal" values in the paracyclophanes studied. Of course, the cyclophanes studied here are not nearly as strained as the [5] and

[69] Cyranski, M.K.; Krygowski, T.M.; Bird, C.W. *Tetrahedron* **1998**, *54*, 9711-9720.

[4]paracyclophanes, where the status of the aromaticity is of most interest. The available data, however, strongly suggest that even highly strained paracyclophanes retain a non-alternant geometry.

Two other experiments should be mentioned. Tobe *et al.* used $^4J_{HCCMe}$ to probe bond orders in distorted aromatics.[71] 8-Methyl[6]paracyclophane showed only slight bond order changes from planar aromatic molecules. During their DZ-SCF study of [5]paracyclophane, Schaefer's group evaluated the harmonic vibrational frequencies of [5]paracyclophane.[62b] They found that the correlation between the vibrational spectra of **11b** and *p*-dideuteriobenzene were good, suggesting that the former could be labeled 'benzene-like' or 'aromatic'. The use of IR to diagnose aromaticity is very unusual, but here it supports many other avenues of evidence that imply that [5]paracyclophane is aromatic.

2.3.3 - Paracyclophanes - Conclusion

The paracyclophanes are perhaps the best illustration of the absence of an operational definition of aromaticity. On one hand, they display the increased reactivity and 'non-aromatic' chemical behavior of highly strained molecules. On the other hand, they retain many other 'aromatic' properties such as a ring current and bond equalization. Like the previous chapter, this section ends in ambiguity. The question of whether paracyclophanes are aromatic again depends on the individual's personal definition of the term.

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[70] How a negative number is obtained from a quadratic function such as EN is unknown. Inquiries about this enigmatic result have been directed to members of Prof. Krygowski's group, but no response has been obtained to date.

[71] Gready, J.E.; Hambley, T.W.; Kakiuchi, K.; Kobiro, K.; Sternhell, S.; Tansey, C.W.; Tobe, Y. *J. Am. Chem. Soc.* **1990**, *112*, 7537-7540.

Chapter 3 – Buckyballs and Buckybowls

In the previous chapter, the preparation and chemistry of curved, isolated aromatic rings was discussed. In this chapter, a relatively new topic – curved polycyclic aromatic hydrocarbons, molecules such as buckminsterfullerenes (commonly referred to as fullerenes or, in the case of C_{60}, "buckyball"), and buckminsterfullerene fragments known as buckybowls – will be considered. The amount of research conducted in this area is immense, and a comprehensive coverage is well outside the scope of this thesis. Only a brief summary of the relevant work will be presented.

3.1 - Carbon and its Allotropes

It has long been known that carbon exists in two distinct (ideally) crystalline allotropes: diamond, which is a three-dimensional network of singly bonded, sp^3-hybridized carbons; and graphite, which consists of sp^2-hybridized carbons arranged in stacks of planar, fused hexagonal rings, with a delocalized π-system above and below the plane. Some older (pre-1990 or so) textbooks also refer to a third allotrope, a partially crystalline material usually referred to as carbon black, activated carbon, or soot.[1] Although structurally heterogenous, these allotropes were generally described as consisting of a folded version of the graphite network. However, faint murmurings could be found in the literature[2] about another, molecular form of carbon, in which an sp^2, graphite-like framework is curved into a sphere – a class of molecules that would eventually be called fullerenes.

The first known reference to the structures now known as fullerenes was by the speculative-science writer David Jones (under the *nom-de-plume* Daedalus) who in 1966 proposed large, hollow spheres of carbon with a graphitic structure as a low-density solid.[3] Subsequently, Japanese and Russian groups suggested C_{60}, "carbo-s-icosahedrene," **1**, as a member of a family of large carbon clusters.[4] Davidson, in a 1981

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[1] Shriver, D.F.; Atkins, P.W.; Langford, C.H. *Inorganic Chemistry* W.H. Freeman & Co., New York, 1990. pp. 342-344.
[2] Curl, R.E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1566-1576. (Nobel Lecture)
[3] Jones, D.E.H. *New Scientist* **1966**, *32*, 245.
[4] a) Osawa, E. *Kagaku* **1970**, *25*, 854. b) Yoshida, Z.; Osawa, E. *Aromaticity*. Kagakudojin, Kyoto, 1971. p. 174. c)Stankevich, I.V.; Nikerov, M.V.; Bochvar, D.A. *Russ. Chem. Rev.* **1984**, *53*, 640-655.

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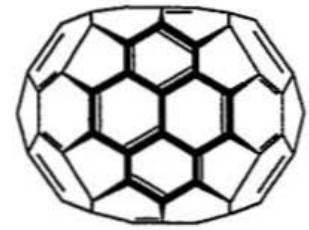

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paper on the applications of graph theory to conjugated hydrocarbons proposed "truncated icosahedrene," C_{60}, and rather prophetically stated:

> "Should such structures ... ever be rationally synthesized or obtained by pyrolytic routes from carbon polymers, they would be the first manifestation of authentic, discrete, three-dimensional aromaticity." [5]

In 1985, the structure **1** was again proposed as an example of 3-dimensional aromaticity and referred to as "footballene" (or "soccerballene" in North America – an extreme example of confusion in nonsystematic nomenclature).[6] While this paper was in press, however, the first experimental detection of fullerenes was reported, by a group who knew nothing of the theoretical papers just described.

3.2 – Buckminsterfullerenes

3.2.1 - Discovery of the Fullerenes

The serendipitous discovery of C_{60} and C_{70} was accomplished by Kroto, Smalley, and Curl, and co-workers in 1985, at Rice University, during an attempt to generate long carbon chains (e.g. HC_7N) by the pulsed laser photolysis of graphite in an inert atmosphere.[2,7] The mass spectrum of the vapor produced by this experiment showed prominent peaks at M=720 and M=840, corresponding to C_{60}^+ and C_{70}^+. The now well-known structures of I_h C_{60}, **1** and D_{5h} C_{70}, **2** were proposed to explain these observations, and the name "buckminsterfullerene" was proposed for these compounds, after the American architect and engineer R. Buckminster Fuller, who first designed geodesic

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[5] Davidson, R.A. *Theor. Chim. Acta* **1981**, *58*, 193-231.
[6] Haymet, A.D.J. *J. Am. Chem. Soc.* **1986**, *108*, 319-321.
[7] Kroto, H.W.; Heath, J.R.; O'Brien, S.C.; Curl, R.F.; Smalley, R.E. *Nature* **1985**, *318*, 162 -163. b) Kroto, H.W. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1578-1593 (Nobel Lecture). Smalley, R.E. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1594-1601 (Nobel Lecture).

domes. However, this method did not allow the preparation of any isolable quantities of the fullerenes, so their chemistry remained unexplored.

The next major step in chemistry came in 1990, when the groups of Krätchmer (Max Planck Institute, Heidelburg) & Huffman (University of Arizona, Tucson) reported the first isolation of C_{60} and C_{70}.[8] They found that a graphite rod, vaporized by resistive heating in a helium atmosphere, produced a sooty condensate from which fullerenes could be isolated in yields of up to 15%, the yield being critically dependent on the pressure of the helium. Chromatography was used to separate **1** (≈75%) and **2** (≈23%) from higher fullerenes. The ability to isolate these compounds in macroscopic amounts allowed experimental investigation of their structure and chemistry to proceed.

3.2.2 - Structure and Physical Properties

Buckminsterfullerenes are composed of sp^2-hybridized carbons arranged in fused 5- and 6-membered rings.[9] The pentagons, which are absent in the ideal structure of graphite,[10] result in the curvature that allows the molecule to close up into a sphere. According to Euler's Theorem, a geometric shape must contain 12 pentagons to close into a sphere. Fullerenes therefore must be composed of 2(10+M) carbon atoms and contain 12 pentagons and M hexagons. Theoretically, the smallest possible fullerene contains 20 carbon atoms, and is a fully unsaturated analogue of dodecahedrane, but it is believed that this structure is so immensely strained that the decadehydrocorannulene **3**

3

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[8] Krätschmer, W.; Lamb. L.D.; Fostiropoulos, K.; Huffman, D.R. *Nature* **1990**, *347*, 354-358.
[9] a) Hirsch, A. *The Chemistry of the Fullerenes* Thieme: New York, 1994. pp. 25-28. b) Curl, R.F.; Smalley, R.E. *Sci. Am.* **1991**, *265 (10)*, 54-63.
[10] True samples of graphite almost certainly contain some five-membered rings. See ref. 1

bowl isomer of C_{20} is actually more stable.[11] Calculations suggest that C_{28} is the smallest structure where the fullerene structure is the most stable isomer, but there is no experimental evidence for the existence of this compound as a stable species.[12]

Why is C_{60} formed preferentially to any other fullerene? In C_{60}, all the pentagons are fused only to hexagons. The structure therefore follows what is called the "isolated pentagon rule" or IPR, which postulates that adjacent pentagons in fullerene-type structures are less stable. This results from pentalene-like 8π "antiaromatic" resonance structures, which destabilize the molecule, and can lead to an increase in strain energy due to unfavorable bond angles. C_{60} is the smallest fullerene that can obey the IPR.

All the atoms in C_{60} are equivalent, giving a single signal in the ^{13}C NMR spectrum.[9] There are two types of bonds, however (Fig. 3-1). One type, at the fusion of a five- and a six-membered ring, is known as a 5-6 bond. The other, at the fusion of two six-membered rings, is called a 6-6 bond. These two types of bonds have been shown to be dramatically nonequivalent in terms of bond length. X-ray crystallographic structures of a transition-metal derivative of C_{60} show the 5-6 bonds are 1.467 Å in length, while the 6-6 bonds are 1.355 Å long.[13] In other words, C_{60} displays considerable (geometric) bond localization. In its lowest energy Kekulé structure, the double bonds are localized at the junction of two hexagons (the 6-6 bonds), so there are no double bonds in the pentagonal rings. Each hexagon therefore resembles a cyclohexatriene, while each pentagon is a [5]radialene moiety. The energetic cost of introducing a double bond into the five-membered ring has been estimated at 8.5 kcal/mol.[14]

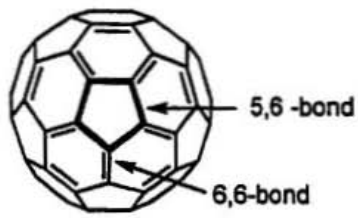

Figure 3-1: C_{60}, Displaying Single and Double Bonds

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[11] Martin, J.M.L.; El-Yazal, J.; François, J.P. *Chem. Phys. Lett.* **1996**, *248*, 345-352, and references therein.
[12] Martin, J.M.L. *Chem. Phys. Lett.* **1996**, *255*, 1-6.
[13] Liu, S.; Lu, Y.J.; Kappes, M.M.; Ibers, J.A. *Nature* **1991**, *254*, 408.

C_{70} (**2**) is less symmetrical than C_{60} (**1**), having five distinct carbons and eight types of C-C bonds. The most curvature (as measured by POAV analysis) [15] occurs at the corannulene-like poles, while the equatorial region, composed of fused hexagons, is less curved.

The standard heat of formation of C_{60} is 10.16 kcal/mol per C atom, and for C_{70} it is 9.65 kcal/mol per C atom. Energetically, therefore, the fullerenes are far less stable than diamond (ΔH_f° = 0.4 kcal/mol) or graphite (ΔH_f° = 0, graphite being considered the standard state of elemental carbon).[16] As fullerenes increase in size, the heat of formation asymptotically approaches that of graphite.[16] This indicates that most of the heat of formation of fullerenes results from the strain imposed by pyramidalization of the carbons.

MO calculations suggest that C_{60} has a triply degenerate, low-lying LUMO, as might be expected for a molecule consisting of pyramidalized alkenes. It should therefore be easily reduced, but difficult to oxidize, and should react with nucleophilic reagents. The question of the aromatic nature of the fullerenes has generated some controversy. In a detailed discussion by Haddon, the arguments against the fullerenes being aromatic are described.[15] The compounds are quite susceptible to addition reactions, do not undergo certain other reactions typical of aromatic hydrocarbons (such as the formation of η^6 – metal compexes), and display marked bond alternation and low magnetic susceptibility. However, as Haddon points out, these characteristics may not imply an absence of resonance stabilization. Unlike other PAHs, fullerenes have no periphery and no hydrogen atoms. Therefore, they cannot undergo substitution with the familiar "retention of type." As with the paracyclophanes, most of the "non-aromatic" behavior of the fullerenes can be explained by the enormous strain involved in bending the ideally planar C atoms. Indeed, the mere existence of fullerenes as isolable compounds suggests that it is resonance-stabilized. As Haddon says: "That C_{60} exists at all with 8 kcal/mol of strain energy at every carbon atom is a testament to the aromaticity of the molecule." Quantifying the resonance stabilization in fullerenes has proven to be very difficult, mostly due to the difficulty in choosing a suitable reference structure. The

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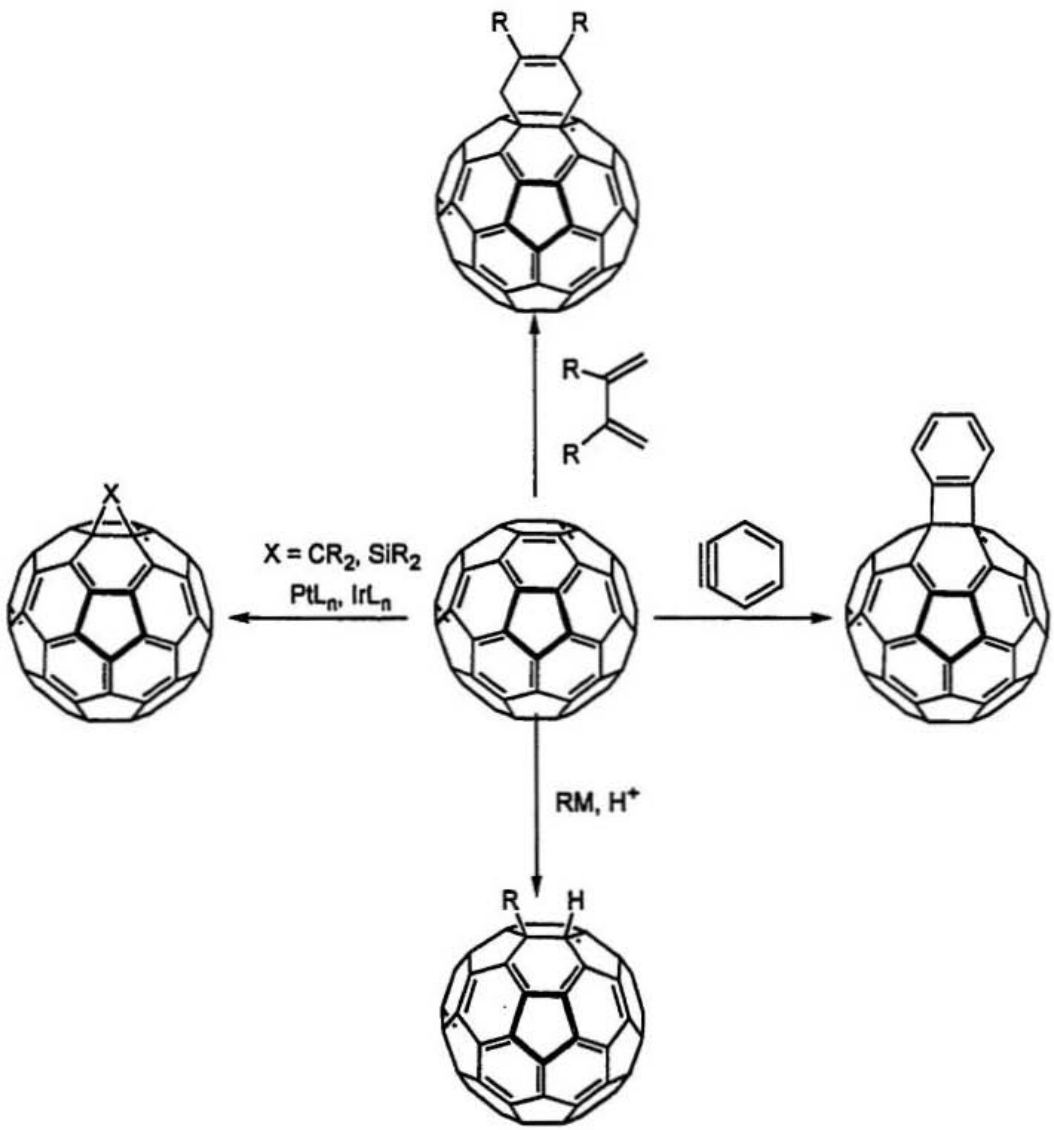
[14] Diederich, F.; Thilgen, C. *Science* **1996**, *271*, 317-323.
[15] a) Haddon, R.C. *Acc. Chem. Res.* **1988**, *21*, 243-249. b) Haddon, R.C. *Science* **1993**, *261*, 1545-1550.

(by now familiar) problems with the definition of aromaticity precludes any definite statements regarding the presence or absence of aromaticity in the fullerenes.

3.2.3 - Chemistry

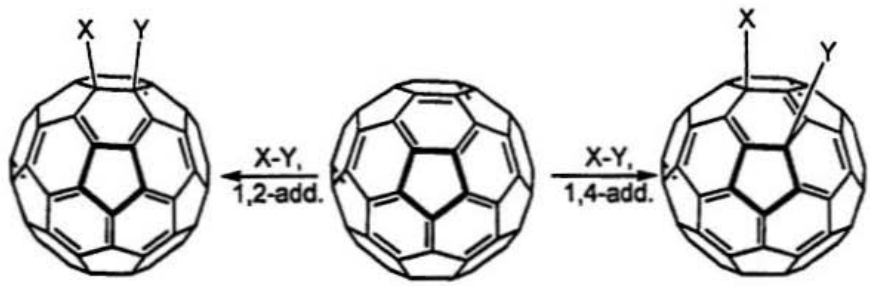
With the development of methodology to prepare gram-scale amounts of fullerenes in 1990, a great deal of their chemistry has been studied.[9a,17] Attention has



Scheme 3-1: Examples of Exohedral Fullerene Derivatives

[16] Ref. 9a, p.29
[17] a) Hirsch, A. *Angew. Chem., Int. Ed. Engl.* **1993**, *32*, 1138-1141. b) Hirsch, A. *Synthesis* **1995**, 895-913.

focused mostly on C_{60}, with some work being done on C_{70}. Chemically, C_{60} acts as a strained, electron-deficient polyalkene with localized double bonds (Scheme 3-1). Almost all addition reactions it undergoes are exothermic, and are presumably driven by the strain relief inherent in converting a pyramidalized sp^2 C to sp^3. Very recent work has suggested that electrophilicity also plays a role in determining the reactivity of the fullerenes.[18] There are two commonly observed modes of addition in C_{60} – 1,2 and 1,4 additions (Scheme 3-2). The latter type of addition results in the introduction of an energetically unfavored 5-6 double bond, and therefore only occurs in the addition of very bulky substrates in which the steric strain resulting from 1,2-eclipsing interactions prevents 1,2-addition. Multiple additions are possible, but eventually the adducts become unstable due to other factors, such as steric repulsion between added groups. A few of the reactions observed in C_{60} and C_{70} will now be described in some detail.



Scheme 3-2: 1,2- and 1,4-addition to C_{60}

3.2.3.1 - Endohedral Adducts

Fullerenes have a large, empty space inside the cage, in which they can entrap atoms. Both noble gases such as He, and metal atoms have been placed in the fullerene cage, but such adducts cannot be prepared in high yields and are usually difficult to separate from the "empty" fullerenes.[19]

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[18] Manoharan, M. *Chem. Phys. Lett.* **1998**, *296*, 429-434.
[19] a) Smalley, R.E. *Acc. Chem. Res.* **1992**, *25*, 98-105. b) Haddon, R.C. *Acc. Chem. Res.* **1992**, *25*, 127-133.

3.2.3.2 - Reduction

Due to its triply degenerate LUMO, C_{60} readily adds up to 6 electrons, to form alkali metal salts.[20] Salts such as K_3C_{60} are conductors,[21] and become superconductors at low temperatures. On the other hand, K_6C_{60}, with no unpaired electrons, is an insulator. These complex redox properties suggest possible uses of the fullerenes in electronic applications.

3.2.3.3 - Addition Products

C_{60} forms adducts (Schemes 3-1, 3-2) with radicals, nucleophiles, carbenes, and transition metals (as η^2 adducts).[22] It can be hydrogenated and halogenated, and acts as an electron-deficient dienophile in Diels-Alder reactions, and a dipolarophile in [3+2] dipolar additions.[17] The overwhelming majority of these additions are 1,2 additions across 6-6 bonds. Halogenation with bromine, however, does generate 1,4 adducts, due to the large amount of steric strain present in the 1,2 adduct.

C_{70}, with its less symmetrical structure, contains four types of 6-6 bonds. Reactions involving C_{70} occur almost exclusively at the poles, involving the most highly pyramidalized carbons.[23] The central belt, consisting of pyrene moieties, is unaffected by most reagents. The highly reactive alkene benzyne forms a number of 1,2-adducts, including (as minor products) adducts at the equatorial belt.[24] Similarly, *o*-quinodimethane produces adducts at the central belt as a minor isomer.

3.3 - Buckybowls

Since the discovery of the fullerenes, one of the "holy grails" of synthetic chemistry has been the preparation of a buckyball through rational chemical synthesis, as well as the preparation of other molecular allotropes of carbon.[25] Considerable effort has therefore been invested into the preparation and study of curved polycyclic aromatic

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[20] Echegoyen, L; Echegoyen, L.E. *Acc. Chem. Res.* **1998**, *31*, 593-601.
[21] Stephens, P.W.; Mihaly, L.; Lee, P.L.; Whetten, R.L.; Huang, S.M.; Kaner, R.; Diederich, F.; Holczer, K. *Nature* **1991**, *351*, 632-634.
[22] Balch, A.L.; Olmstead, M.M. *Chem. Rev.* **1998**, *98*, 2123-2165.
[23] a) Hawkins, J.M.; Meyer, A.; Solow, M.A. *J. Am. Chem. Soc.* **1993**, *115*, 7499-7500. b) Thilgen, C.; Herrmann, A.; Diederich, F. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2268-2280.
[24] Meier, M.S.; Wang, G.W.; Haddon, R.C.; Brock, C.P.; Lloyd, M.A.; Selegue, J.P. *J. Am. Chem. Soc.* **1998**, *120*, 2337-2342.

hydrocarbons that represent fragments of fullerenes, known as buckybowls. Buckybowls are fullerene fragments (carbon skeletons represented on the surface of a fullerene) which assume a bowl shape in their lowest energy conformation. The elucidation of chemical methodology for the synthesis of such bowl-shaped structures will, it is hoped, ultimately permit the controlled synthesis of fullerenes and other potentially useful carbon-containing molecules. Recent work in the area of curved PAH synthesis will now be discussed in some detail.

As mentioned above, a buckybowl is a bowl-shaped hydrocarbon, consisting of fused five- and six-membered rings representing a fragment of the surface of a buckminsterfullerene.[26] Buckybowls are of interest as synthetic intermediates in the total synthesis of fullerenes, as model compounds for fullerene structure and chemistry, and (like the fullerenes) for their potential use in electronic applications. Buckybowl chemistry has witnessed substantial work towards the development of novel synthetic methodology over the past decade; however, major obstacles still must be overcome before the rational synthesis of C_{60} or any other fullerene is likely to be achieved.

3.3.1– Corannulene

The first known, simplest, and most studied buckybowl is the $C_{20}H_{10}$ compound [ghi,mno]dibenzofluoranthene, now known as corannulene, **4**.[27] It consists of a central five membered ring annellated by five six-membered rings, and represents the so-called polar cap of C_{60} and C_{70}. It is a bowl shaped molecule, with a bowl depth of 0.87 Å measured from the plane of the central five-membered ring to the plane of the (hydrogen bearing) rim carbons. The molecule is flexible (Fig. 3-2), and undergoes rapid bowl-to-bowl inversion at room temperature, with an activation barrier of approximately 10 kcal/mol, which implies corannulene inverts 200,000 times a second at room temperature.[28] The first synthesis of this molecule, predating the discovery of the

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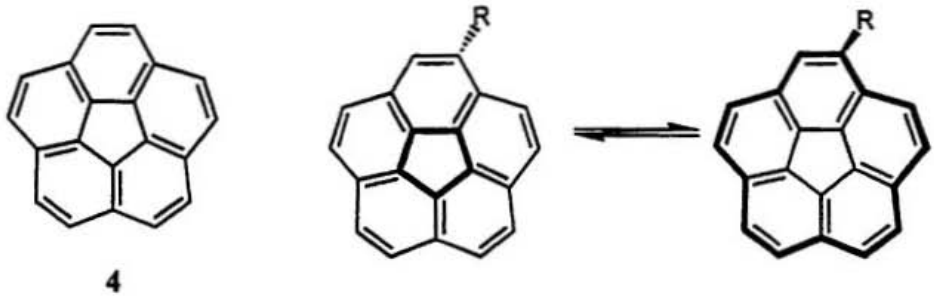
[25] Diederich, F.; Rubin, Y. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 1101-1123.
[26] a) Faust, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1429-1432. b) Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235-242. c) Scott, L.T. *Pure Appl. Chem.* **1996**, *68*, 291-300.
[27] Siegel, J.S.; Seiders, T.J. *Chem. Britain* **1995**, 313-316.
[28] a) Scott, L.T.; Hashemi, M.M.; Meyer, D.T.; Warren, H.B. *J. Am. Chem. Soc.* **1991**, *113*, 7082-7084. b) Scott, L.T.; Hashemi, M.M.; Bratcher, M.S. *J. Am. Chem. Soc.* **1992**, *114*, 1920-1921.

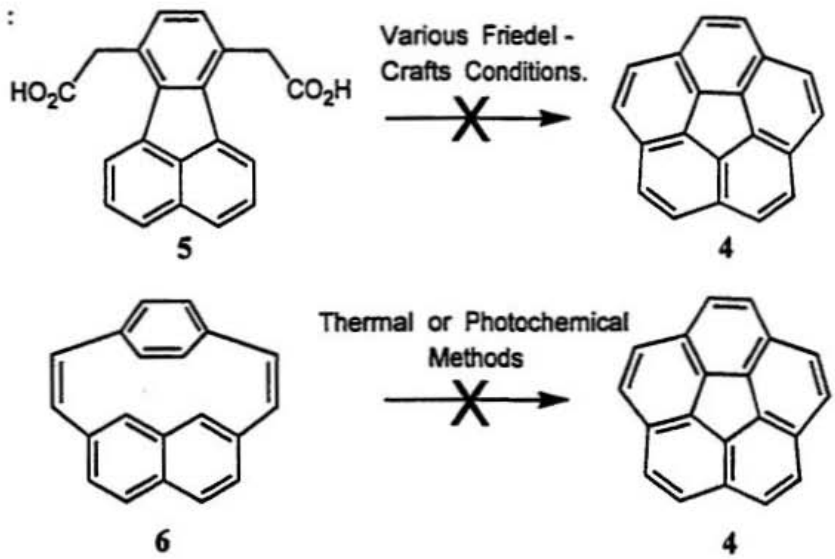


4

Figure 3-2: Corannulene, Illustrating Bowl-to-Bowl Inversion

fullerenes by two decades, was accomplished by Barth and Lawton in 1966.[29] This 17-step classical synthesis did not involve pyrolysis (unlike almost all of the recent syntheses, *vide infra*) but was far too lengthy and low-yielding to be useful when the discovery of the fullerenes transformed corannulene from an obscure laboratory curiosity to a subject of intense interest. The development of an efficient synthetic strategy to **3** then became an important goal.

In the synthesis of curved PAHs, syntheses that fail are frequently as instructive as those that succeed. After 1966, a number of attempts to prepare corannulene by



5 4

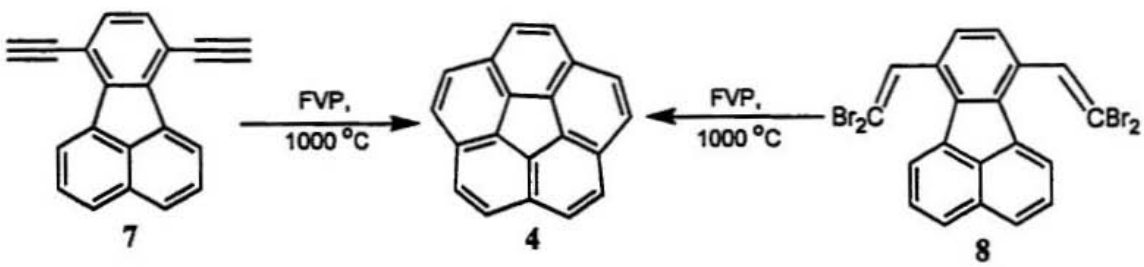
6 4

Scheme 3-3: Failed Corannulene Synthesis Attempts.

[29] a) Barth, W.E.; Lawton, R.G. *J. Am. Chem. Soc.* **1966**, *88*, 380-381. b) Barth, W.E.; Lawton, R.G. *J. Am. Chem. Soc.* **1971**, *93*, 1730-1745.

Australian groups using nonpyrolytic techniques failed (Scheme 3-3).[30] Failed efforts included the double cyclization of fluoranthene-derived diacid **5** using Friedel-Crafts chemistry, and thermal and photochemical approaches to the dehydrogenative cyclization of paracyclonaphthalenophane **6**. These unsuccessful attempts reflect the large amount of strain present in buckybowls, and indicate that only the most forcing conditions will be sufficient to overcome the energetic barriers inherent in the formation of such strained molecules.

A short synthesis of corannulene was finally published by Scott's group in 1992.[28] The synthesis hinged on two principles: the well known thermal isomerization of terminal acetylenes to highly reactive vinylidene carbenes,[31] and the proposition that, at high temperatures, PAHs will fluctuate drastically away from their equilibrium geometries, allowing otherwise remote reactive centers (such as the thermally generated carbene and an aryl-H bond) to approach one another. Thus, flash vacuum pyrolysis of 7,10-diethynylfluoranthene **7** at 1000 °C (Scheme 3-4) afforded corannulene in about a 10% yield. The yield could be improved to 40% by using tetrabromide **8**, which may conceivably react by an electrocyclic ring closure, followed by the pyrolytic loss of the bromine atoms.



Scheme 3-4: Synthetic Approaches to Corannulene.

A year later, Siegel's group reported another synthesis of corannulene (Scheme 3-5) using classical cyclophane chemistry.[32] Pyrolysis (1000 °C) of tetrabromide **9**, or

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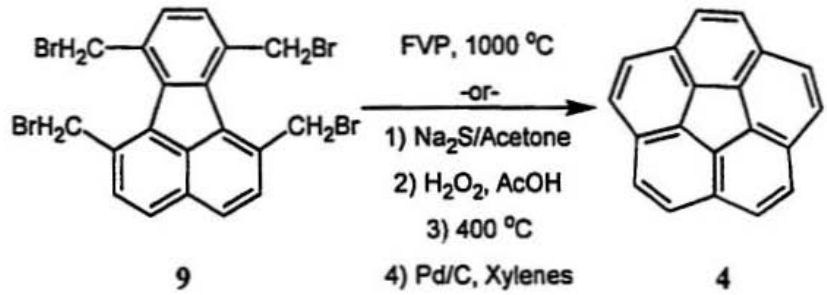
[30] a) Craig, J.T.; Robins, M. D. W. *Aust. J. Chem.* **1968**, *21*, 2237-45. b) Davy, J. R.; Iskander, M.N.; Reiss, J.A. *Aust. J. Chem.* **1979**, *32*, 1067-78.

[31] Brown, R.F.C.; Harrington, K.J.; McMullen, G.L. *J. Chem. Soc., Chem. Comm.* **1974**, 123-124

[32] Borchardt, A.; Fuchicello, A.; Kilway, K. V.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* **1992**, *114*, 1921-1923.

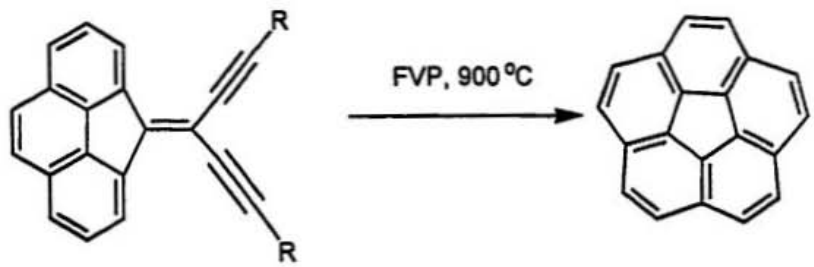


9 4

Scheme 3-5: Nonpyrolytic Synthesis of Corannulene

conversion to the thiacyclophane followed by oxidation, SO_2 extrusion (400 °), and dehydrogenation, afforded corannulene in 18 % and 7 % respectively.

The next approach to be reported was that of Zimmermann (Scheme 3-6), whose approach intended to use phenanthrylidenepentadiyne **10a** as a key intermediate.[33] Unfortunately, this compound was too unstable to isolate, but the silylated derivative **10b** was thermolyzed in H_2 at 900 °C. This afforded corannulene in 15 % yield, along with a number of aromatic hydrocarbons. The mechanism proposed for this reaction involved the formation of vinyl radicals generated by the addition of H· to the alkynes, which then undergo cyclization.



10a - R = H
10b - R = Si(CH$_3$)$_3$

4

Scheme 3-6: Another Pyrolytic Corannulene Synthesis.

In a synthesis closely related to Scott's work, Rabideau showed that pyrolysis of vinyl silyl ether **11** (Scheme 3-7) will generate corannulene in 8 % yield.[34]

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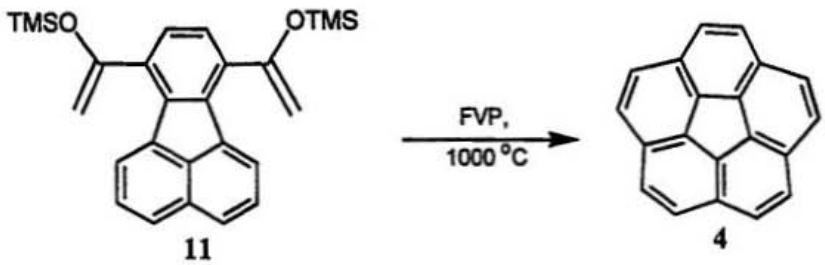
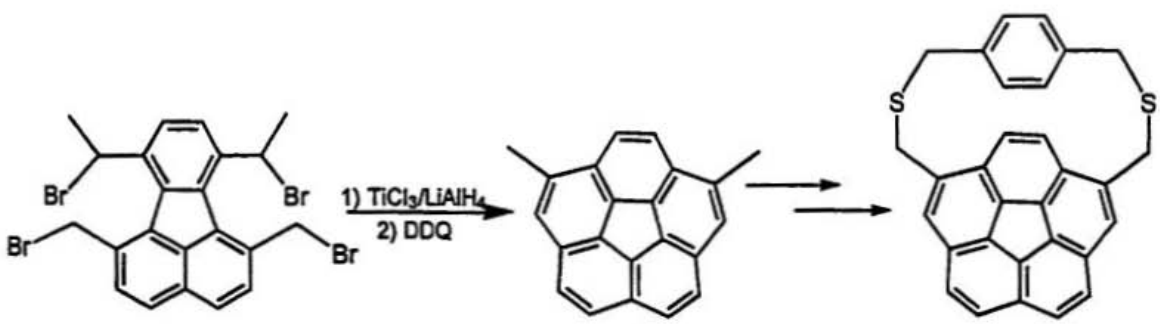
[33] Zimmermann, G.; Nuechter, U.; Hagen, S.; Nuechter, M. *Tetrahedron Lett.* **1994**, *35*, 4747-4750.
[34] Liu, C.Z.; Rabideau, P. W. *Tetrahedron Lett.* **1996**, *37*, 3437-3440.



11 4

Scheme 3-7: Corannulene from Pyrolysis of Silyl Enol Ether **11**

Siegel's most recent contribution to the corannulene synthesis field involved the first truly nonpyrolytic synthesis (Scheme 3-8), in which tetrabromide **12** was reductively coupled with $TiCl_3/LiAlH_4$ or $VCl_3/LiAlH_4$, followed by dehydrogenation with DDQ to afford dimethylcorannulene **13** in 18 % yield over two steps.[35] This was subsequently elaborated to the corannulene cyclophane **14**. This is extremely significant, as it demonstrates that, under proper conditions, strained polycyclic aromatic molecules can be generated via non-pyrolytic methods.



12 13 14

Scheme 3-8: Siegel's Synthesis of Corannulenophane **14**.

Finally, Mehta's syntheses of corannulene (Scheme 3-9) was closely related to that of Scott, involving the thermal cyclization of benzophenanthrenes **15a-d** (presumably via a vinylidene carbene) to afford corannulene in 2-8 % yield depending on the substrate used.[36]

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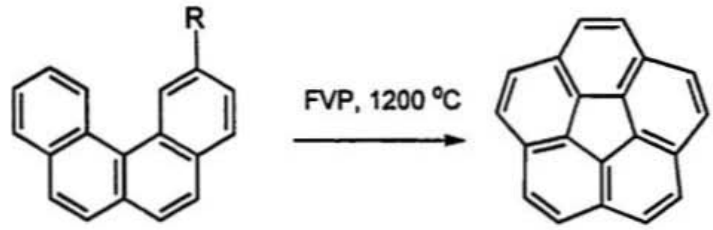
[35] Seiders, T.J.; Baldridge, K.K.; Siegel, J.S. *J. Am. Chem. Soc.* 1996, *118*, 2754-2755.



15a: R = CCH **15c:** R = C(Cl)CH_2 **4**
15b: R = HCCHCl **15d:** R = C(OTMS)CH_2

Scheme 3-9: Mehta's Corannulene Syntheses

3.3.2 - Sumanene and Related C_3 Fragments

With successful syntheses of corannulene accomplished, attention turned to the preparation of larger fullerene fragments, with the ultimate goal being the rational total synthesis of a fullerene. Mehta published detailed retrosynthetic analyses of C_{60} and C_{70}, in which he dismantled the molecules into fragments retaining varying symmetry elements, and then used MNDO or MM2 calculations to evaluate the increase in strain as the molecule was reassembled. In C_{60}, Mehta divided the molecule by three different

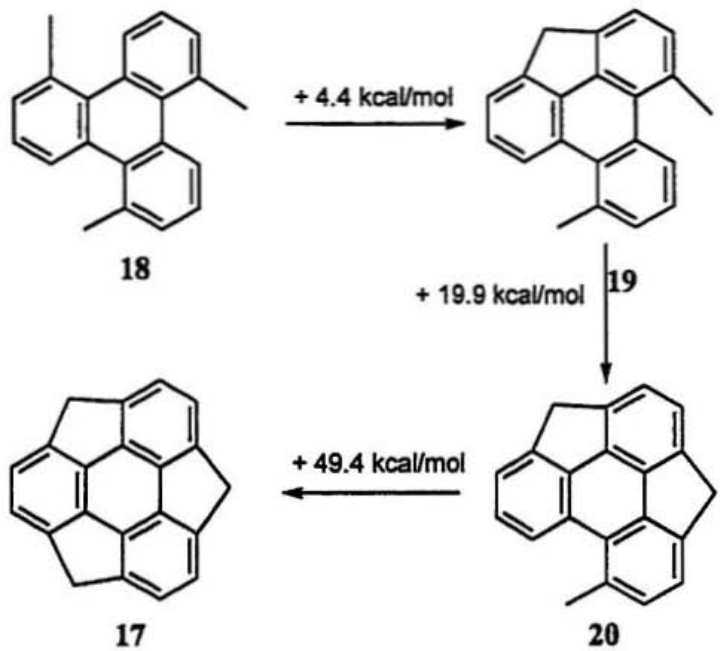
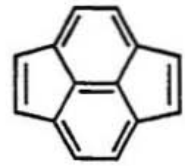


Figure 3-3: Increase in Strain Energy on Formation of Successive Bridges in Sumanene.

[36] Mehta, G.; Panda, G. *Tetrahedron Lett.* **1997**, *38*, 2145-2148.

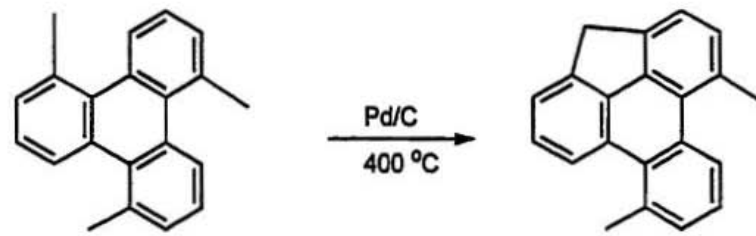


16

17

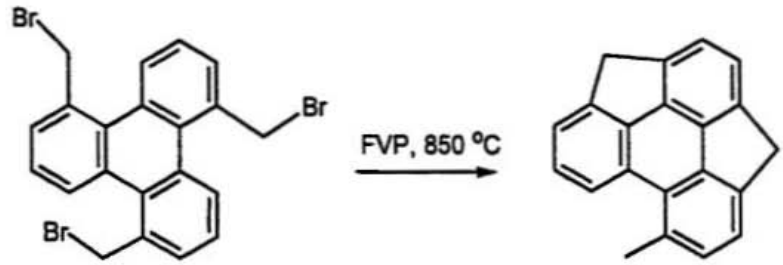
routes, in which the fragments retained C_5, C_3, or C_2 symmetry.[37] The smallest fragment of the C_5 route was corannulene, **4**, and the smallest fragment along the C_2 route was pyracylene, **16**. Both of these molecules were known. Along the C_3 route, however, the smallest subunit was an unknown C_{21} fragment, **17**, which he named sumanene, after the Sanskrit word for flower. Mehta's calculations indicated that sumanene had a curvature which is closer to the curvature of C_{60} than corannulene, which implies that sumanene is more strained than corannulene. In a synthesis of C_{60}, a highly strained early intermediate means that the further increase in strain required to generate the final product is reduced. Therefore, Mehta and others focused on the preparation of sumanene and other C_3–symmetric fullerene fragments.

The calculations on the increase in strain during the assembly of sumanene demonstrated a nonlinear increase in strain on the closure of successive rings (Fig. 3-3). Starting with the trimethyltriphenylene **18**, the closure of the first 5-membered ring resulted in a strain increase of 4.4 kcal/mol. The closure of the second 5-membered ring increased the strain by a much larger 19.9 kcal/mol. The closure of the final 5-membered ring augmented the strain by 49.4 kcal/mol, more than ten times greater than the energy



18 19

Scheme 3-10: Dehydrogenative Cyclization of **18**



21 **20**

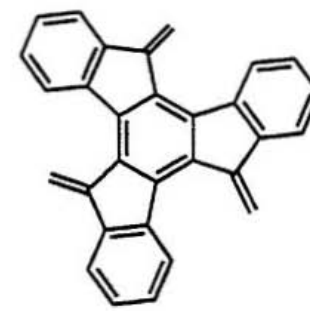
Scheme 3-11: Pyrolytic Dehydrobromination of **21**.

required for the first ring closure. This meant that, in any synthesis of sumanene, while the closure of the first ring should be facile, the closure of the second and especially the third five-membered ring would be the key steps, and highly energetic intermediates will be required for such steps to proceed effectively.

Mehta's attempts at the synthesis of sumanene demonstrated the difficulty in attaining the closure of the third ring.[38] Heating **18** to 400 °C over Pd/C (Scheme 3-10) afforded the mono-bridged compound **19** in up to 70 % yield. FVP of tribromide **21** at 850 °C (Scheme 3-11) generated the doubly bridged compound **20**, along with some mono-bridged **19** (87:13) in 20 % total yield. Even at these temperatures, closure of the third ring did not occur. No other synthetic attempts at sumanene itself have been reported.

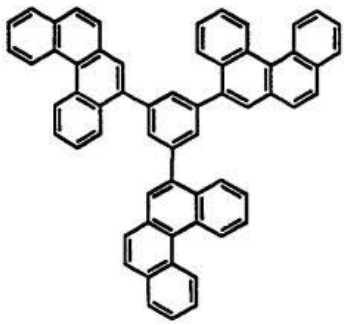
Most of the synthetic efforts in this area have targeted benzoannellated sumanene derivatives, such as triindenotriphenylene, **22**, whose carbon skeleton had been proposed

Triindenotriphenylene, **22**



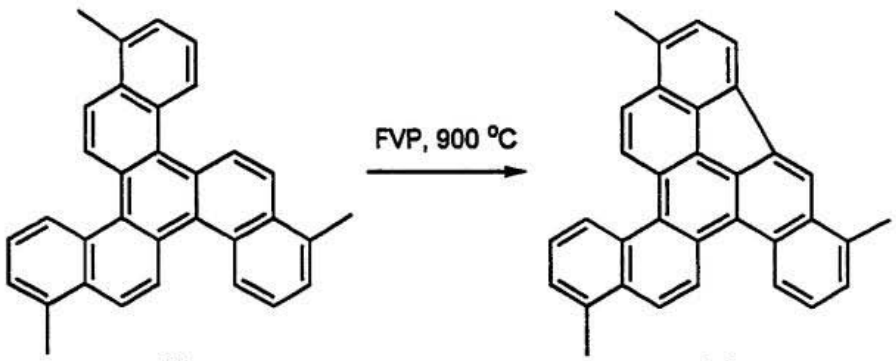
Truxenene, **23**

[37] Sastry, G.N.; Jemmis, E.D.; Mehta, G.; Shah, S.R. *J. Chem. Soc., Perkin Trans 2* **1993**, 1867-1871.



24

as an intermediate in buckyball formation in vaporized graphite.[39] Vollhardt published a computational paper that demonstrated (not surprisingly) that **22** displayed a rigid, bowl-shaped structure,[40] while Plater and Rzepa described a computational study of metal complexes of **22**.[41] De Lucchi reported a synthesis of truxenene, **23**,[42] and Plater reported a triphenyltruxenene,[43] in the hope that electrocyclic ring closure/dehydrogenation to a triphenyl derivative of **22** could be induced. Unfortunately, neither FVT nor photolysis of these products afforded characterizable products of any kind. Plater also reported the synthesis and mass spectroscopic study of a (planar) C_3-C_{60} fragment **24**, but he has never reported any pyrolysis experiments on this compound.[44]



25 **26**

Scheme 3-12: Dehydrogenative Pyrolysis of **26**.

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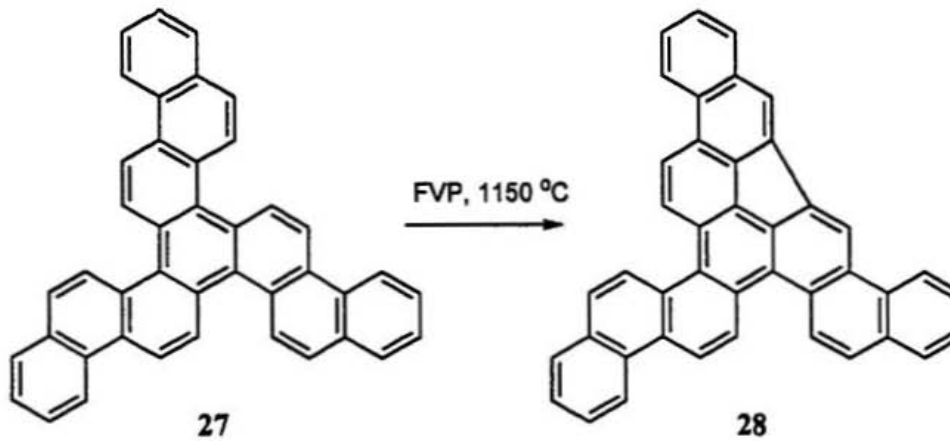
[38] Mehta, G.; Shah, S.R.; Ravikumar, K. *J. Chem. Soc., Chem. Commun.* **1993**, 1006-1008.
[39] McKee, M.L.; Herndon, W.C. *Theochem. J. Mol. Struc.* **1983**, *153*, 75-84.
[40] Faust, R.; Vollhardt, K.P.C. *J. Chem. Soc., Chem. Commun.* **1993**, 1471-1473.
[41] Plater, J.; Rzepa, H.S.; Stoppa, F.; Stossel, S. *J. Chem. Soc., Perkin Trans. 2* **1994**, 399-400.
[42] Sbrogio, F.; Fabris, F.; De Lucchi, O. *Synlett* **1994**, 761-762.
[43] Plater, M.J.; Praveen, M.; Howse, A.R. *J. Chem. Res. (S)* **1997**, 46-47.
[44] a) Plater, M.J. *Synlett* **1993**, 405-406. b) Plater, M. J. *Perkin Trans. 1* **1997**, 2897-2901.

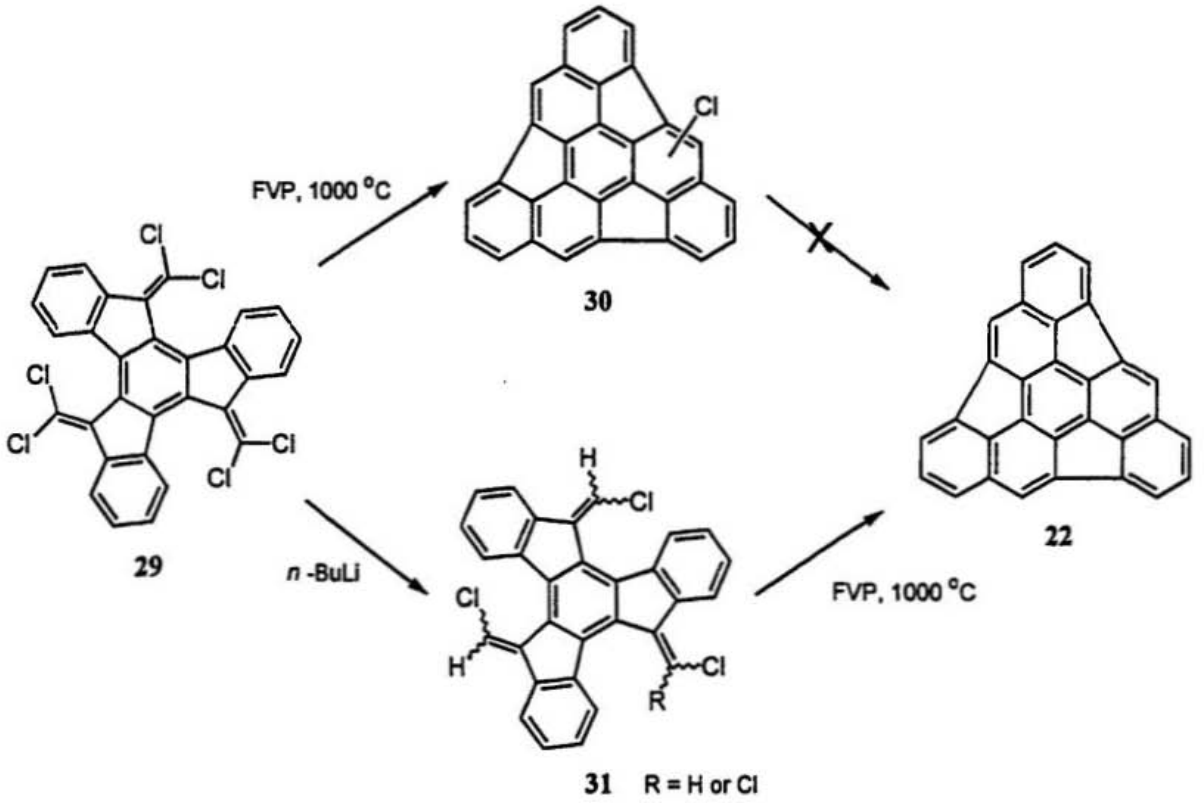
Mehta synthesized trimethyltribenzotriphenylene, **25**, but FVP at 900 °C afforded only mono-ring-closed products **26** in quantitative yield (Scheme 3-12).[45] An attempt to prepare larger C_{35} - C_3[46] and C_{48} - C_3[47] fragments failed to even generate the desired precursors. A trinaphthotriphenylene **27** was prepared (Scheme 3-13), but again only a mono-ring-closed product **28** could be isolated after FVP at 1150 °C.[48]



Scheme 3-13: Dehydrogenative Pyrolysis of **27**.

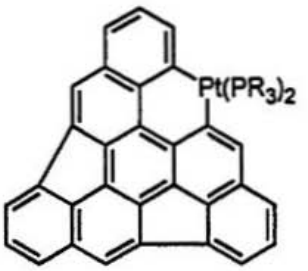
Rabideau's approach to this problem (Scheme 3-14) involved the synthesis of a hexachlorotruxenene **29**, whose pyrolysate (1000 °C) suggested the presence of chlorinated triindenotriphenylene, **30**.[49] By removing some of the chlorines from **30** with *n*-BuLi, a mixture of tri- and tetrachlorotruxenes (**31**) could be generated, which on pyrolysis afforded triindenotriphenylene **22** in low (5-10 %) yield. This was the first successful synthesis of a C_3-symmetric, sumanene-containing buckybowl. Subsequently, in an attempt to generate a π-transition metal complex between **23** and $Pt(CH_2{=}CH_2)(PPh_3)_2$, an oxidative addition to form a σ-bonded Pt(II)-buckybowl

[45] Mehta, G.; Raghava Sharma, G.V.; Krishna Kuvar, M.A.; Vedavyasa, T.V.; Jemmis, E.D. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2529-2530.
[46] Mehta, G.; Rao, K.V. *Synlett* **1995**, 319-320.
[47] Mehta, G.; Rao, K.V.; Ravikumar, K. *J. Chem. Soc., Perkin Trans. 1* **1995**, 1787-1788.
[48] Mehta, G.; Panda, G.; Shah, S.R.; Kunwar, A.C. *J. Chem. Soc., Perkin Trans. 1* **1997**, 2269-2271.
[49] Abdourazak, A.H.; Marcinow, Z.; Sygula, A.; Sygula, R.; Rabideau, P.W. *J. Am. Chem. Soc.* **1995**, *117*, 6410-6411.



Scheme 3-14: Rabideau's Synthesis of Triindenotriphenylene **22**

compound **32** was observed.[50] This unusual reaction testifies as to the considerable strain present in **22**.

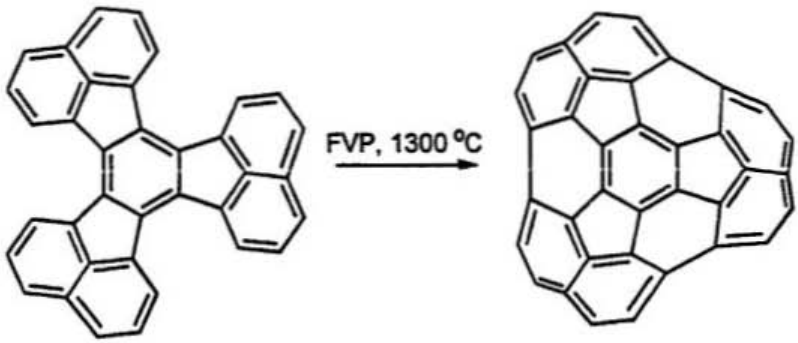


32

More recently, Scott's group reported a successful pyrolytic synthesis of a C_3-$C_{36}H_{12}$ fullerene subunit, **34**, by the pyrolysis of decacyclene, **33**.[51] At 1100 °C, this

[50] Shaltout, R.M.; Sygula, R.; Sygula, A.; Fronczek, F.R.; Stanley, G.G.; Rabideau, P.W. *J. Am. Chem. Soc.* **1998**, *120*, 835-836.
[51] Scott, L.T.; Bratcher, M.S.; Hagen, S. *J. Am. Chem. Soc.* **1996**, *118*, 8743-8744.

reaction failed, but at 1200-1300 °C (Scheme 3-15), **34** could be isolated in 0.2 % yield. Among the other products isolated from this reaction was a trace of C_{60}, which begs a

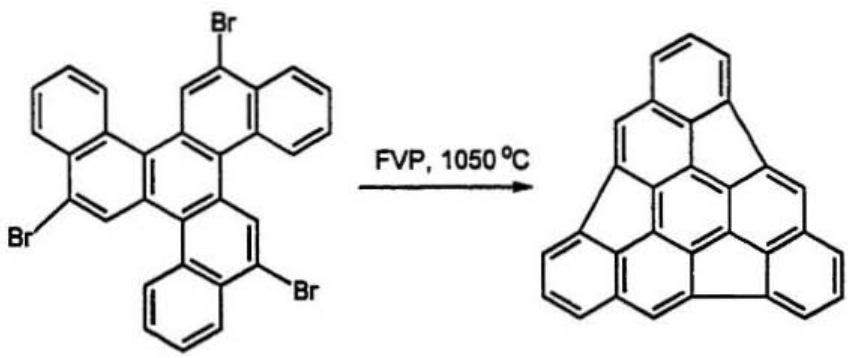


33 **34**

Scheme 3-15: Scott's Synthesis of **34**

difficult question: at sufficiently high temperatures, how can a "rational synthesis" of C_{60} be distinguished from the simple vaporization/condensation of carbon compounds, by which fullerenes are currently prepared? After all, pyrolysis/controlled combustion of smaller buckybowls and even planar aromatics such as benzene can generate fullerenes.[52] The dividing line between rational synthesis and simple "thermal generation" becomes fuzzy in cases like this.

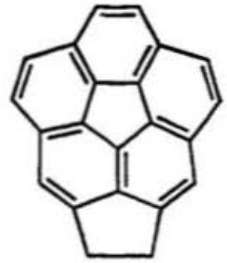
Recently, Scott, Zimmermann, and co-workers reported a triindenotriphenylene



35 **22**

Scheme 3-16: Synthesis of **22** by Pyrolysis of Tribromoarene **35**

[52] Howard, J.B.; McKinnon, J.T.; Marovsky, Y.; LaFleur, A.; Johnson, M.E. *Nature* **1991**, *352*, 139-141.



36

37

synthesis (Scheme 3-16) using different methodology than the other syntheses reported here.[53] With considerable understatement, they state that "synthetic routes to strained bowl-shaped PAH based on uncatalyzed cyclodehydrogenation reactions of hydrocarbons rarely work well and sometimes fail completely." Pyrolysis of the tribromobenzo[c]naphtho[2.1-p]chrysene, **35**, at 1050 °C afforded **22** in an excellent (by buckybowl-synthesis standards) yield of 7.5 - 9%. The reaction is believed to proceed by radical formation, 1,2-H migration, cyclization, and loss of H·. Clearly, the generation of reactive centers (such as radicals) on buckybowl precursors assists in the formation of strained rings.

3.3.3 - Corannulene-Containing PAHs

The C_5-symmetric disconnection of C_{60} could be fragmented to corannulene, which has been synthesized, as described above. Although little effort has focused on preparing larger C_5-symmetric buckybowls, larger corannulene-containing fragments have been prepared.

Rabideau's group, in an extension of Scott's methodology, generated cyclopentacorannulene, **36**, and its dehydrogenated analogue **37**, and demonstrated **36**'s much higher (relative to corannulene, **4**) inversion barrier (27.7 kcal/mol at 100 °C).[54] Later, they pyrolyzed **38** (1000 °C) to generate the $C_{30}H_{12}$ "semibuckminsterfullerene" **39** in 5% yield (Scheme 3-17).[55] Interestingly, an attempt to generate benzocorannulene by

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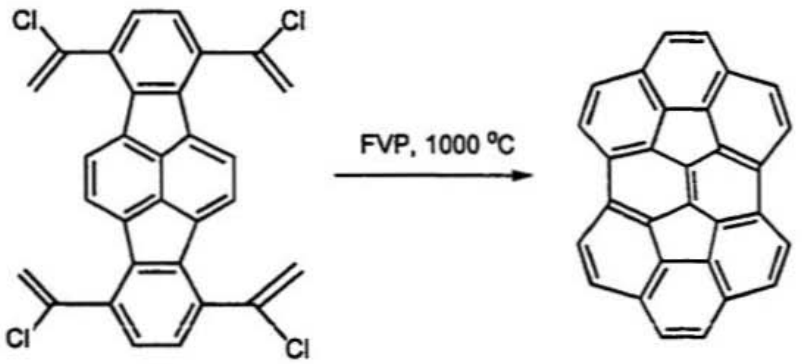
[53] Hagen, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew Chem., Int. Ed. Engl.* **1997**, *36*, 406-408.
[54] Abdourazak, A.H.; Sygula, A.; Rabideau, P.W. *J. Am. Chem. Soc.* **1993**, *115*, 3010-3011.
[55] Rabideau, P.W.; Abdourazak, A.H.; Folsom, H.E.; Marcinow, Z.; Sygula, A.; Sygula, R. *J. Am. Chem. Soc.* **1994**, *116*, 7891-7892.

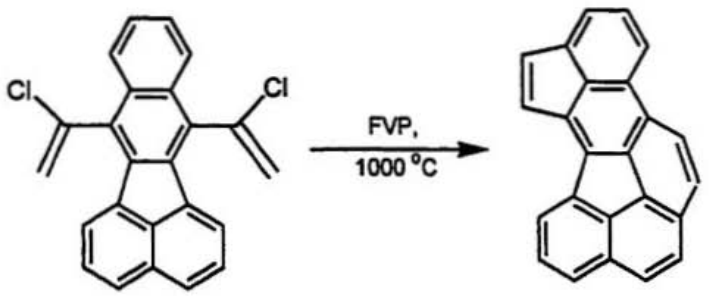


38 **39**

Scheme 3-17: Rabideau's Synthesis of **39**

the pyrolysis of **40** (Scheme 3-18) afforded only planar hydrocarbon **41**.[56] Even at 1000 °C, there appears to be a highly favored, lower energy pathway for the formation of planar over curved products.

Zimmermann's attempted synthesis of **39** (Scheme 3-19) involved the pyrolysis of **42**, which afforded 4.4% of **43** and 15% of the rearranged product **44**.[57] The Stone-Wales-type rearrangement that generated **44** was believed to be catalyzed by radical addition (Fig. 3-4).[58] By including toluene as a radical scavenger, the relative yield of **43** can be improved somewhat. Further pyrolysis of **43** afforded only traces (0.6 %) of the corannulene-containing hydrocarbon **39**. This result indicates another problem with the



40 **41**

Scheme 3-18: Pyrolysis of **40** Generates Planar **41**

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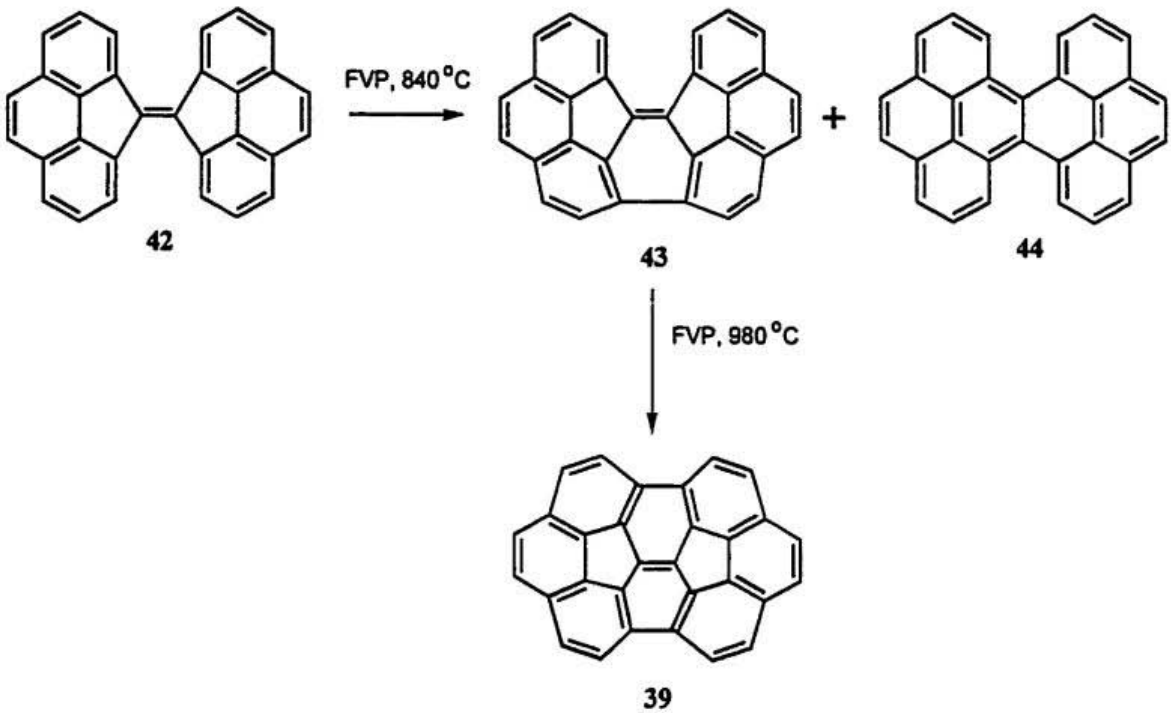
[56] Marcinow, Z.; Fronczek, F.R.; Liu, Y.-H.; Rabideau, P.W. *J. Org. Chem.* **1995**, *60*, 7015-7016.
[57] a) Hagen, S.; Nuechter, U.; Nuechter, M.; Zimmermann, G. *Tetrahedron Lett.* **1994**, *35*, 7013-7014. b) Hagen, S.; Christoph, H.; Zimmermann, G. *Tetrahedron* **1995**, *51*, 6961-6970.
[58] a) Alder, R.W.; Whittaker, G. *J. Chem. Soc., Perkin Trans. 2* **1975**, 712-713. b) Scott, L.T. *Acc. Chem. Res.* **1982**, *15*, 52-58. c) Stone, A.J.; Wales, D.J. *Chem. Phys. Lett.* **1986**, *128*, 501-503.



Scheme 3-19: Pyrolysis Products from Bis-Fluoranthrylidene **42**

synthesis of many buckybowls – their propensity to rearrange to more stable isomers, if possible. Consequently, the designer of any synthetic route to a buckyball or fullerene must be wary of undesirable rearrangements.

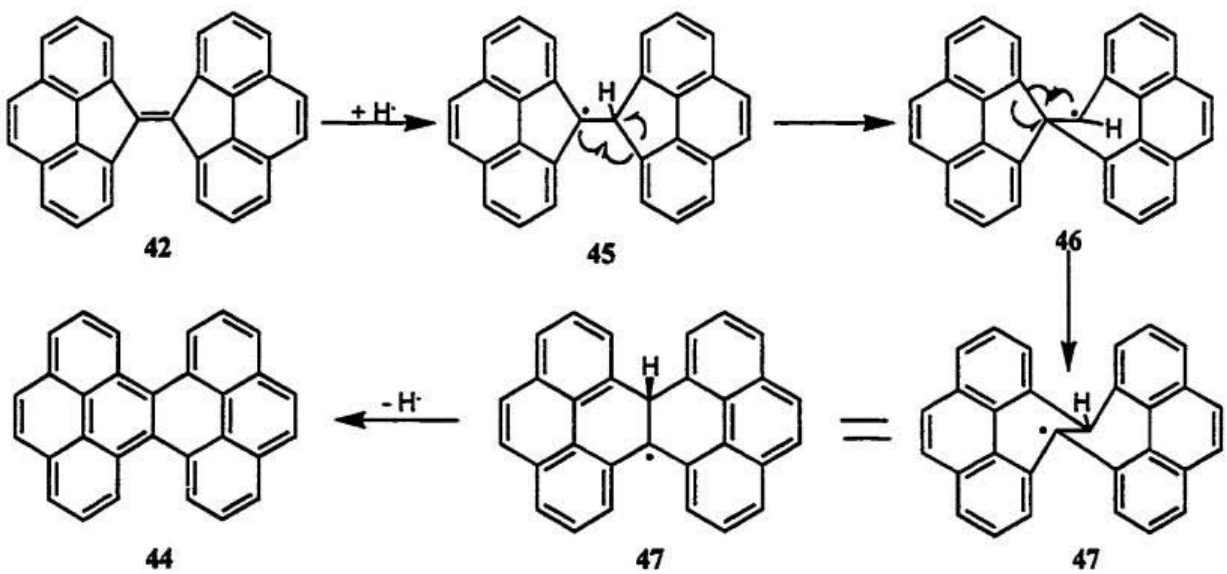
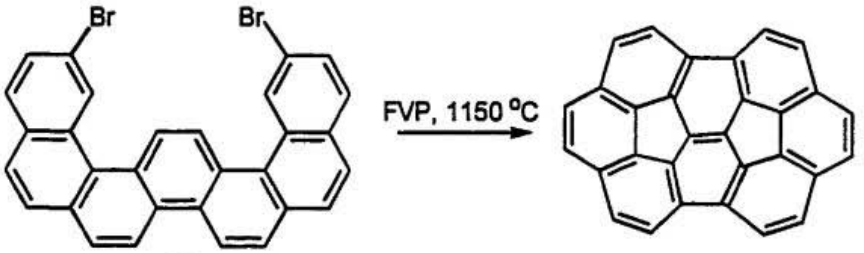


Figure 3-4: Possible Mechanism for Rearrangement of **42** to **44**

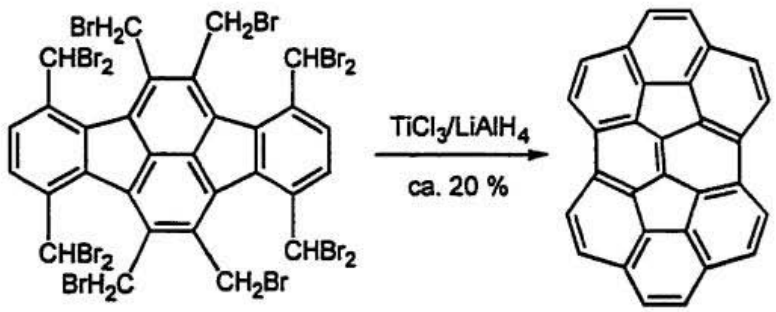
Mehta's synthesis of semibuckminsterfullerene **49** followed on Scott and co-workers' report of their successful synthesis of the C_3-buckybowl **23** using aryl bromides as a radical precursor. The pyrolysis (Scheme 3-20) of dibromo-PAH **48** at 1150 °C affords **39** in 2-3% yield.[59]



48 **39**

Scheme 3-20: **39** from Pyrolysis of **48**

Finally, Rabideau's group achieved what could be a major advance in buckybowl synthesis methodology by reporting the first non-pyrolytic synthesis of semibuckminsterfullerene **39** in about 20 % yield from dodecabromide **49** (Scheme 3-21) using the low-valent titanium reductive coupling first used by Siegel in a synthesis of the corannulene nucleus.[60] This demonstrates conclusively that, if sufficiently reactive intermediates can be generated, the strain present in buckybowls can be introduced at low (nonpyrolytic) temperatures.



49 **39**

Scheme 3-21: Rabideau's Nonpyrolytic Synthesis of **39**

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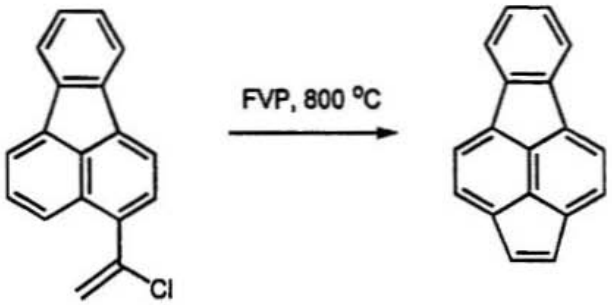
[59] Mehta, G.; Panda, G. *J. Chem. Soc., Chem. Commun.* **1997**, 2081-2082.



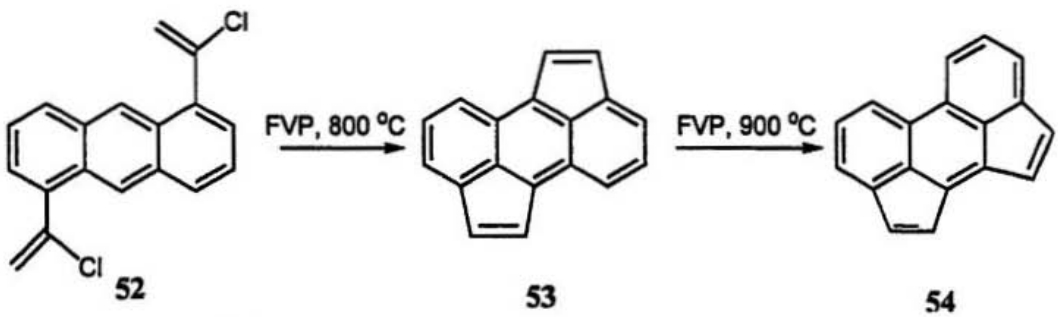
50 **51**

Scheme 3-22: Jenneskens' Synthesis of **51**

3.3.4 – C_2 Buckybowls

The smallest C_2-symmetric C_{60} fragment is pyracylene, **17**, but this molecule is not bent sufficiently to be termed a buckybowl. Comparatively little effort has been invested into the preparation of other C_2-buckybowls. In yet another application of Scott's methodology, Jenneskens' group reported the pyrolysis (800 °C) of chloroethenylfluoranthene **50** to afford acefluoranthylene **51** (Scheme 3-22) in 27 % yield.[61] Jenneskens also (Scheme 3-23) pyrolyzed the anthracene derivative **52** to afford cyclopent[*hi*]aceanthrylene **53** (not a fragment of C_{60} or C_{70}), which then isomerizes to cyclopent[*hi*]acephenanthrylene, **54**.[62] The ratio of the products depends on the pyrolysis temperature, and the total mass recovered drops steadily as the temperature increases.

Agranat reported a nonpyrolytic synthesis (Scheme 3-24) of **56** by a Pd-catalyzed



52 **53** **54**

Scheme 3-23: Synthesis and Rearrangement of **53**

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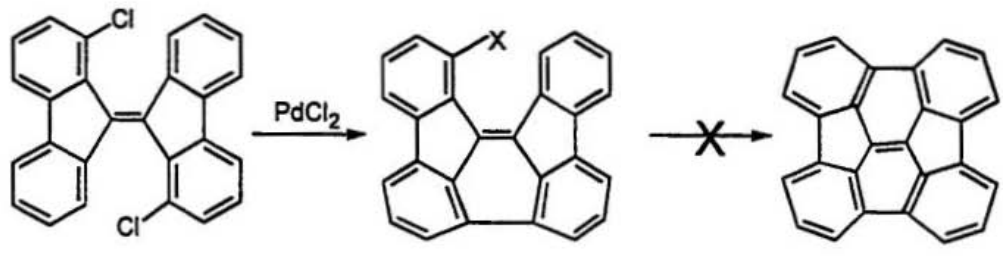
[60] Sygula, A.; Rabideau, P. *J. Am. Chem. Soc.*, **1998**, *120*, 12666-12667.
[61] Sarobe, M.; Snoeijer, J.D.; Jenneskens, L.W.; Slagt, M.Q.; Zwikker, J.W. *Tetrahedron Lett.* **1995**, *36*, 8489-8492.
[62] Sarobe, M.; Snoeijer, J.D.; Jenneskens, L.W.; Zwikker, J.W.; Wesseling, J. *Tetrahedron Lett.* **1995**, *36*, 9565-9566.



55 56 57

X = H or Cl

Scheme 3-24: Agranat's Pd-Catalyzed Synthesis of **56**

cyclization of **55**, but not surprisingly, the second cyclization does not occur, and no **57** is produced.[63]

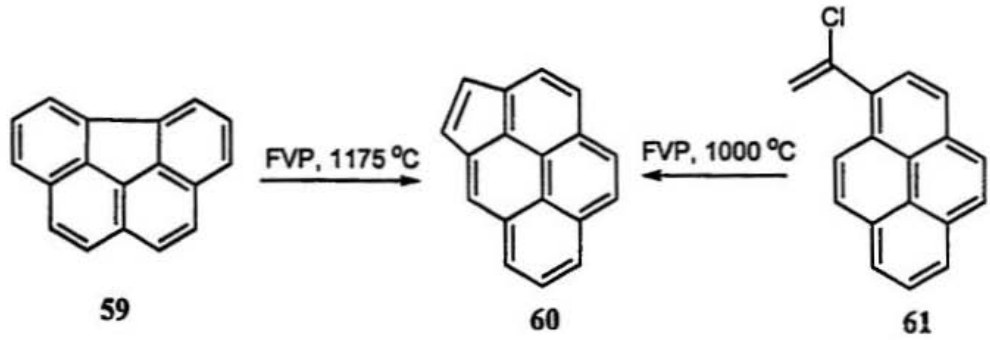
3.3.5 – C_{70} Buckybowls

Mehta's retrosynthesis of C_{70} revealed a new C_2-symmetric $C_{28}H_{14}$ pyrene containing buckybowl, which he named pinakene, **58**, after the Sanskrit work "pinak" describing a curved surface.[64] This paper also described a number of belt-shaped molecules resembling the pyrenoid equatorial belt of C_{70}, **2**. Although some generalized

Pinakene, **58**

synthetic schemes towards these molecules were discussed, no experimental work towards their synthesis has ever been described by Mehta. Plater reported that the pyrolysis of benzo[ghi]fluoranthene **59** (Scheme 3-25) afforded Stone-Wales rearranged cyclopenta[cd]pyrene **60** in 12 % yield.[65] Jenneskens has pyrolyzed 1-(pyren-1-

[63] Pogodin, S.; Biedermann, U.; Agranat, I. *J. Org. Chem.* **1997**, *62*, 2285-2287.
[64] Jemmis, E.V.; Sastry, G.N.; Mehta, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 437-441.
[65] Plater, M.J. *Tetrahedron Lett.* **1994**, *35*, 6147-6150.



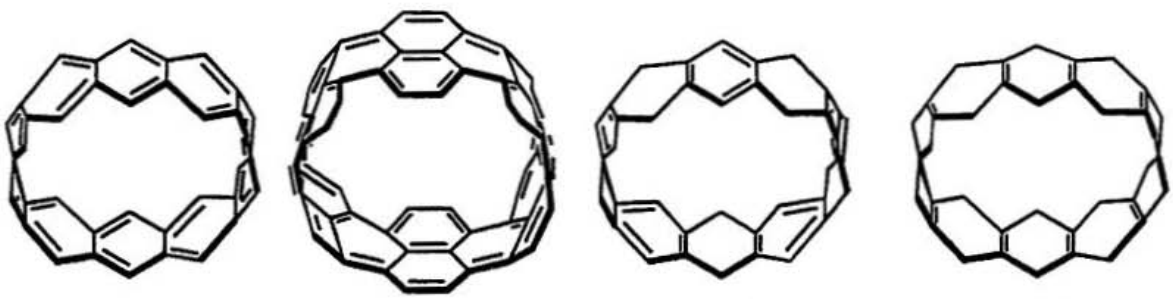
59 60 61

Scheme 3-25: Synthetic Approaches to Cyclopenta[c,d]pyrene **60**

yl)ethyne **61** to afford the same cyclopenta[cd]pyrene **60**.[66] Scott and co-workers have used similar methodology to prepare three isomeric dicyclopentapyrenes.[67] Work (by Jenneskens' group) at extending this methodology to multiple-five-membered ring containing structures such as **58** is now reportedly underway.[68]

3.4 - Aromatic Belts

The preceeding paragraph briefly mentioned belt-shaped molecules corresponding to the equatorial pyrenoid belt of C_{70}. Although not considered to be buckybowls, molecules such as cyclacenes, e.g. **62**,[69] or pyrenoid belts as first proposed by Vögtle, e.g. **63**, are fullerene fragments, and their partially hydrogenated derivatives, collarenes, **64**, and beltenes, **65**,[70] are expected to have applications in host-guest chemistry. The



62 63 64 65

[66] Sarobe, M.; Zwikker, J.W.; Snoeijer, J.D.; Wiersum, U.E.; Jenneskens, L.W. *J. Chem. Soc., Chem. Commun.* **1994**, 89-90

[67] Scott, L.T.; Necula, A. *J. Org. Chem.* **1996**, *61*, 386-388.

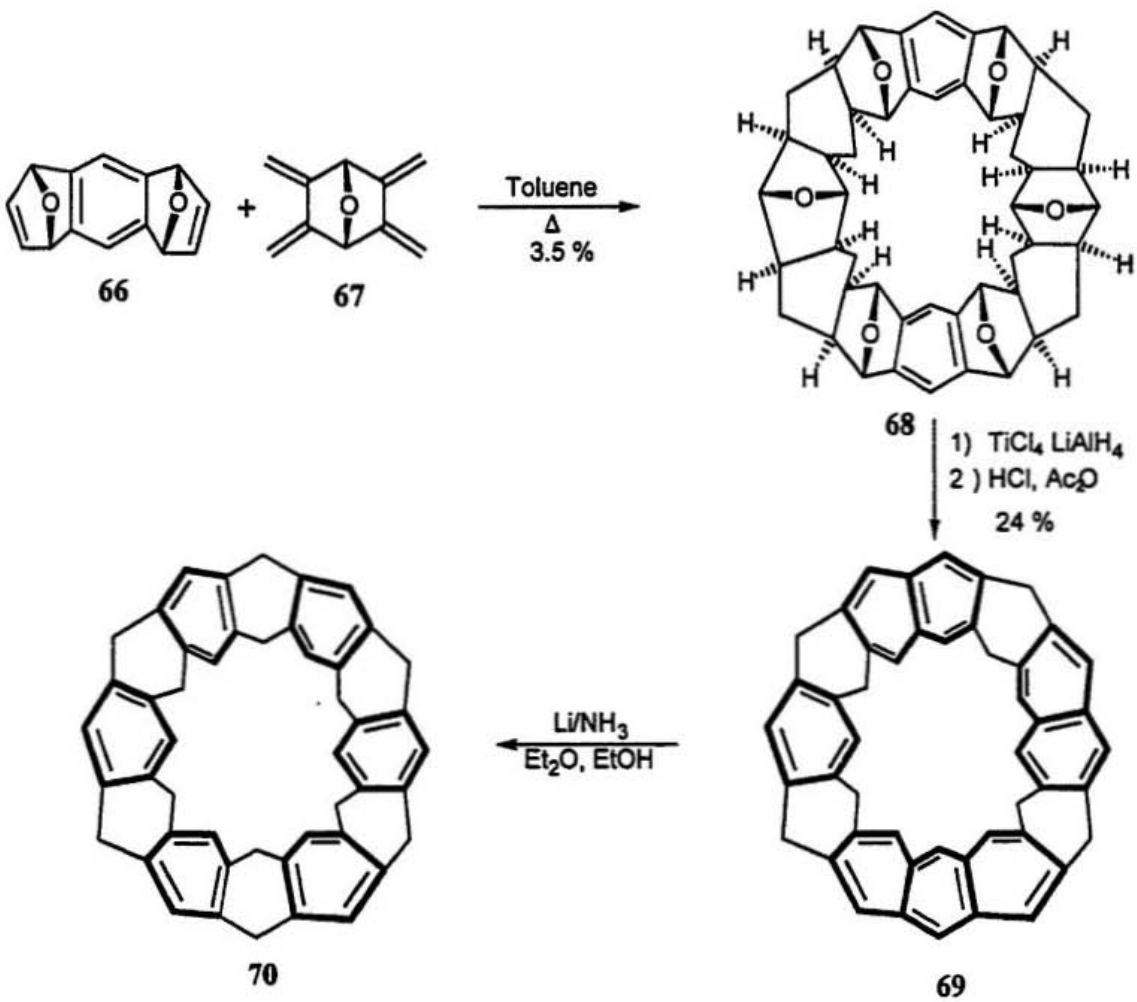
[68] Sarobe Ugarriza, M. Ph. D. Thesis, Universiteit Utrecht, **1998**.

[69] a) Balaban, A.T. *Pure Appl. Chem.* **1980**, *52*, 1409-1429. b) Kivelson, S.; Chepman, O.L. *Phys. Rev. B.* **1983**, *28*, 7236-7243.

[70] Alder, R.W.; Sessions, R.B. *J. Chem. Soc. Perkin Trans. 2* **1985**, 1849-1854.

synthesis of such compounds, however, is notoriously difficult, and a number of approaches have been attempted, with limited successes to date.

An early approach to such molecules was that of Stoddart's group (Scheme 3-26), who used a Diels-Alder reaction of bis(dienophile) **66** and bis(diene) **67** and a final head-to-tail intramolecular Diels-Alder to generate oxygenated molecular belt **68** in low yield (3.5 %).[71] An even larger oxygenated belt has been reported recently.[72] Reduction and dehydration of **68** afforded partially hydrogenated [12]cyclacene **69**. Birch reduction of



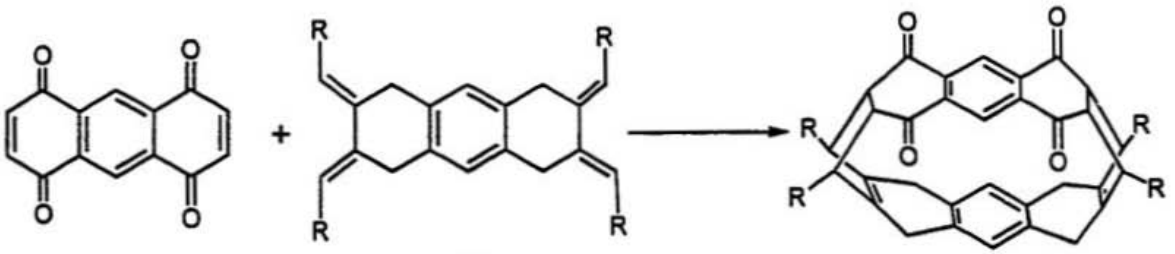
Scheme 3-26: Stoddart's Synthesis of [12]Collarene **70**

[71] a) Ashton, P.R.; Isaacs, N.S.; Kohnke, F.H.; Slawin, A.M.Z.; Spencer, C.M.; Stoddart, J.F.; Williams, D.J. *Angew. Chem., Int. Ed. Engl.* **1988**, *27*, 966-969. b) Kohnke, F.H.; Stoddart, J.F. *Pure Appl. Chem.* **1989**, *61*, 1581-1586 c) Mathias, J.P.; Stoddart, J.F. *Chem. Soc. Rev.* **1992**, 215-225. d) Kohnke, F.H.; Mathias, J.P.; Stoddart, J.F. *Top. Curr. Chem.* **1993**, *165*, 1-69.

[72] Kintzel, O.; Luger, P.; Weber, M.; Schluter, A-D. *Eur. J. Org. Chem.* **1998**, 99-105.

this compound yielded a compound believed to be [12]collarene, **70**, although no yield was reported. Further reduction to the beltene did not occur. There was no report of any attempt to dehydrogenate **69** to the fully aromatic [12]cyclacene. Alder also planned a Diels-Alder approach to collarenes, but failed to isolate the required precursors.[73] More recently, Paquette applied a similar Diels-Alder strategy in preliminary studies towards a beltene/cyclacene synthesis.[74] Unfortunately, his approach was hindered by the extreme insolubility of some of his synthetic intermediates.

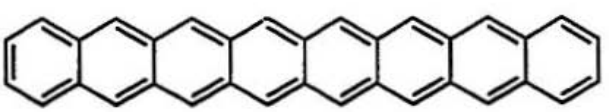
Cory's work in this area also resembles that of Stoddart, except that while Stoddart's approach uses *rigid* bisdienes and dienophiles, Cory's approach relies on *flexible* bisdienes, such as **72**, capable of bending to close onto a shorter, rigid dienophile **71**.[75] This method allowed the preparation (Scheme 3-27) of quinoid cyclophane **73**, which, it was hoped, could be elaborated to the fully aromatic [8]cyclacene **62**. Unfortunately, no successful dehydrogenation to the cyclacene has been reported to date.



71 **72** **73**

Scheme 3-27: Cory's Diels-Alder Route to Cyclacene Derivative **73**

None of the papers cited above comment on the question of the stability of the target cyclacenes. Linear acenes become increasingly unstable with increasing length,

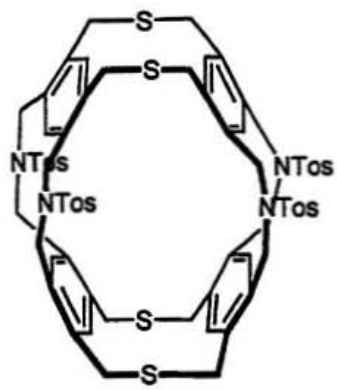


74

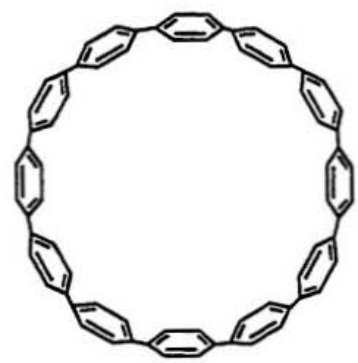
[73] Alder, R.W.; Allen, P.R.; Edwards, L.S.; Fray, G.I.; Fuller, K.E.; Gore, P.M.; Hext, N.M.; Perry, M.H.; Thomas, A.R.; Turner, K.S. *J. Chem. Soc., Perkin Trans. 1* **1994**, 3071-3077.
[74] Graham, R.J.; Paquette, L.A. *J. Org. Chem.* **1995**, *60*, 5770-5777.
[75] a) Cory, R.M.; McPhail, C.L.; Dikmans, A.J.; Vittal, J.J. *Tetrahedron Lett.* **1996**, *37*, 1983-1986. b) Cory, R.M.; McPhail, C.L. *Tetrahedron Lett.* **1996**, *37*, 1987-1990.

and octacene **74** is too unstable to be isolated under ambient conditions.[76] Cyclization of octacene to [8]cyclacene **62** involves the pyramidalization (i.e., straining) of the preferentially planar sp^2 carbons, and also destroys the only intact aromatic sextet resonance structure present in the molecule. Finally, note that [8]cyclacene can be viewed as two antiaromatic, 16-electron π-systems stacked on one another. All this suggests that the [8]cyclacene, whose synthesis is being attempted here, might display extremely low kinetic stability, and its isolation or even detection may well be an insurmountable challenge. However, an odd-numbered cyclacene would at least have two stacked, formally aromatic, (4n+2) annulenes and might therefore be more amenable to synthesis.

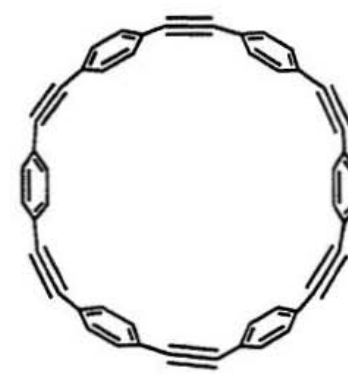
Another class of aromatic belts are the pyrenoid nanotubes proposed by Vögtle (e.g. **63**), corresponding to the equatorial belt of C_{70} and hereafter referred to as Vögtle belts. Vögtle has reported the synthesis (in low yield) of a tetrathiatetraazacyclophane **75** which might be a precursor to a Vögtle belt, but no attempt to remove the sulfurs and nitrogens has ever been reported.[77] Closely related to Vögtle belts are the macrocyclic [0_n]paracyclophanes, such as **76**. Vögtle has described a number of strategies towards such molecules, but again, no successful synthesis has ever been reported.[78] An "expanded" version of these molecules, in which the arene rings are bridged by acetylene



75



76

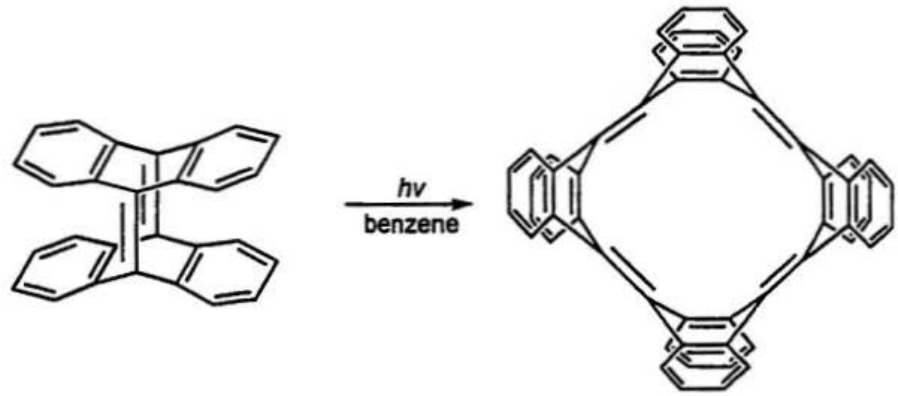


77

[76] Clar, E. *Polycyclic Hydrocarbons* Academic Press, London, **1964**, pp. 462-463.
[77] Schroder, A.; Karbach, D.; Guther, R.; Vögtle, F. *Chem. Ber.* **1992**, *125*, 1881-1887.
[78] Friederich, R.; Nieger, M.; Vögtle, F. *Chem. Ber.* **1993**, *126*, 1723-1732.

units, **77**, has been reported.[79] These molecules are unstable in air and can explode on heating.

An ingenious method for the construction of beltlike aromatic molecules, reported by Herges, involves the ring-expanding metathesis (Scheme 3-28) of tetradehydrodianthracene **78** to afford "picotube" **79**.[80] This molecule is extremely unreactive, being stable at 450 °C, and unreactive to *m*-CPBA and bromine at room temperature. Dehydrogenation and C-C bond formation would afford a buckytube, which would be the first rationally synthesized, fully aromatic belt. Experiments towards this goal are underway.



78 **79**

Scheme 3-28: Herges' Ring Expansion of **78** to Picotube **79**

3.5 - Conclusions

The discovery of the fullerenes has inspired a great deal of work towards the synthesis of buckybowls and other strained fullerene fragments. Most of this work has not been very successful, at best generating the desired products in extremely low yields. Current synthetic methodology appears rather inadequate for the task of generating strained aromatic compounds efficiently and in high yield, and higher yields than those

[79] Kawase, T.; Darabi, H.R.; Oda, M. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2664-2666.
[80] a) Kammermeier, S.; Jones, P.G.; Herges, R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2669-2671. b) Kammermeier, S.; Jones, P.G.; Herges, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2200-2202.

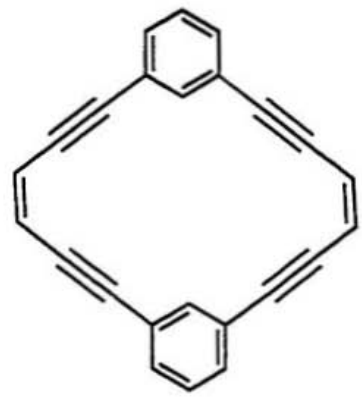
observed up to now will be necessary for the method to be applicable to a rational total synthesis of C_{60} or any other fullerene. The development of more effective methods for the construction of strained C-C bonds will be required before any realistic synthesis of a fullerene is likely to be achievable.

Chapter 4 – A Bergman/Radical Cyclization Approach to Fullerene Fragments

4.1 – The Bergman Cycloaromatization

4.1.1 – Introduction

Our group's interest in metacyclophane chemistry, and our development of a simple and effective synthetic route to dithiametacyclophanes,[1] led to the consideration of novel metacyclophane-related molecules as targets for synthesis. One such target was the



1

"enediyne metacyclophane" or enediynophane, **1**, which is an example of a "carbomer" or "expanded molecule," in which C-C bonds have been elongated by the insertion of alkyne moieties.[2] The enediyne fragments in this molecule appeared to be ideal substrates for a double Bergman cyclization, which would sequentially generate two highly energetic diradicals which, as will be described, might prove to be precursors for highly strained polycyclic aromatic hydrocarbons. Our rapid success in the synthesis of pyrenophanes (See Chapters 5 & 6) had piqued our interest in fullerene fragments and buckybowls, and it was therefore decided to explore the possibility of using molecules such as **1** as precursors for curved aromatic molecules. Progress in this area is described in this chapter.

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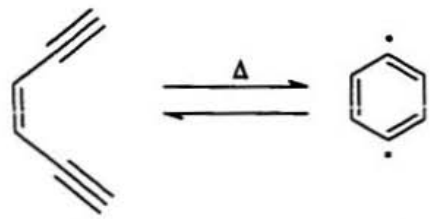
[1] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett* **1995**, 751-752.

[2] a) Sworski, T.J. *J. Chem. Phys.* **1948**, *16*, 550. b) Kuwatani, Y.; Ueda, I. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1892-1894. c) Chauvin, R. *Tetrahedron Lett.* **1995**, *36*, 397-400. d) Chauvin, R. *Tetrahedron Lett.* **1995**, *36*, 401-404.

4.1.2 - Enediynes and the Bergman Reaction

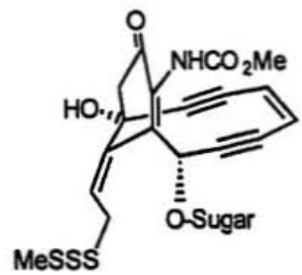
For almost two decades, it has been known that hexa-3-ene-1,5-diyne **2**, at high temperatures (> 200 °C), undergoes a thermal cycloaromatization to the diradical *p*-



2 **3**

Scheme 4-1: The Bergman Cycloaromatization

benzyne (1,4-dehydrobenzene) **3**, known as the Bergman cycloaromatization (Scheme 4-1).[3] This isomerization languished in relative obscurity until it was discovered to be the key reaction in the activation of the enediyne antibiotics,[4] such as calicheamicin, **4**, a class of molecules that attracted wide attention in the late 1980s and early 1990s. With the realization that the enediyne moiety could be a pharmacophore of considerable practical value, a number of methods for its synthesis were developed (Schemes 4-2 and 4-3).[5]



Calicheamicin, **4**

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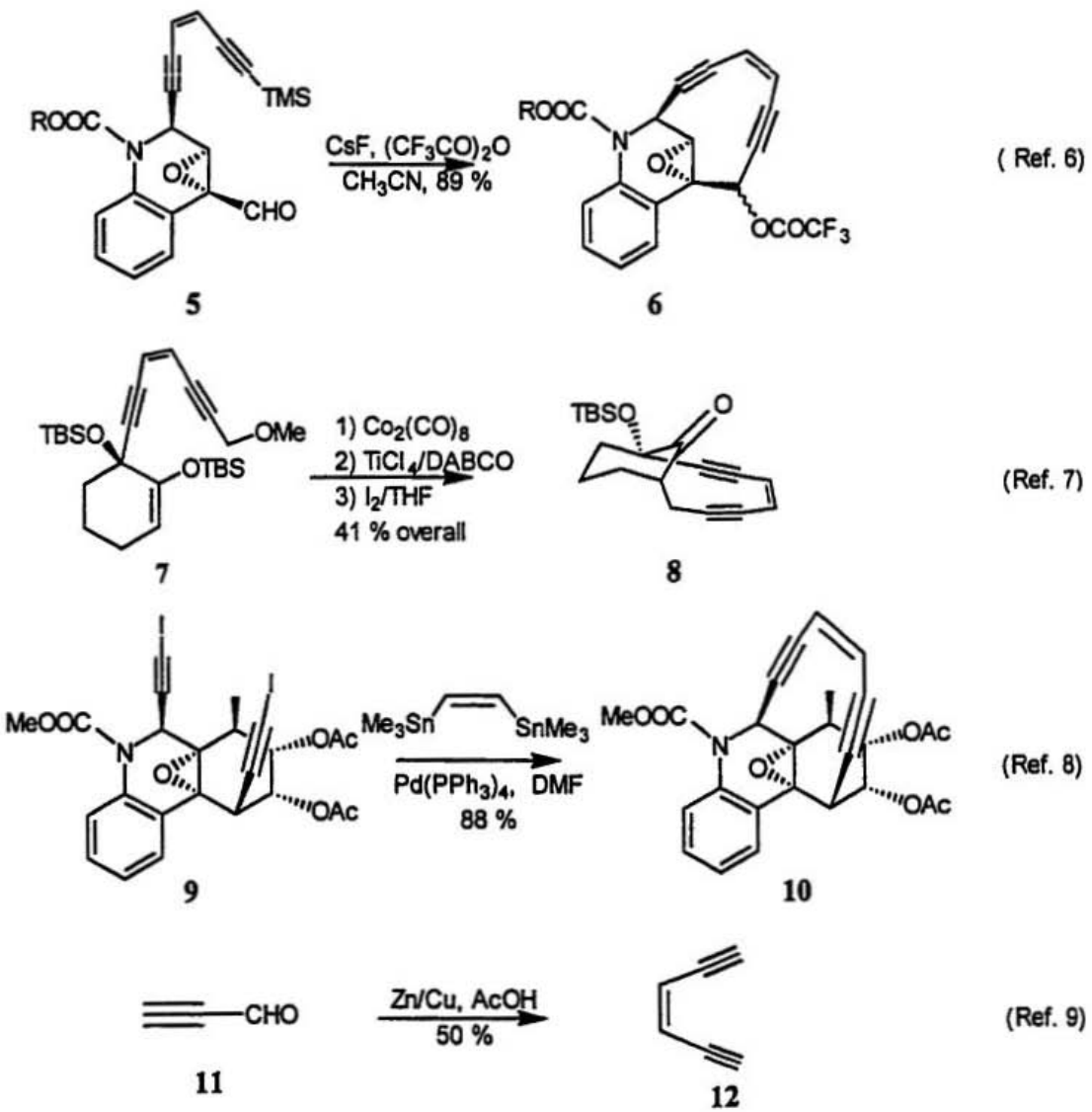
[3] a) Bergman, R.G.; Jones, R.R. *J. Am. Chem. Soc.* **1972**, *94*, 660-661. b) Bergman, R.G. *Acc. Chem. Res.* **1973**, *6*, 25-31. c) Lockhart, T.P.; Comita, P.B.; Bergman, R.G. *J. Am. Chem. Soc.* **1981**, *103*, 4082-4090. d) Lockhart, T.P.; Bergman, R.G. *J. Am. Chem. Soc.* **1981**, *103*, 4091-4096

[4] Lee, M.D.; Ellestad, G.A.; Borders, D.B. *Acc. Chem. Res.* **1991**, *24*, 235-243.

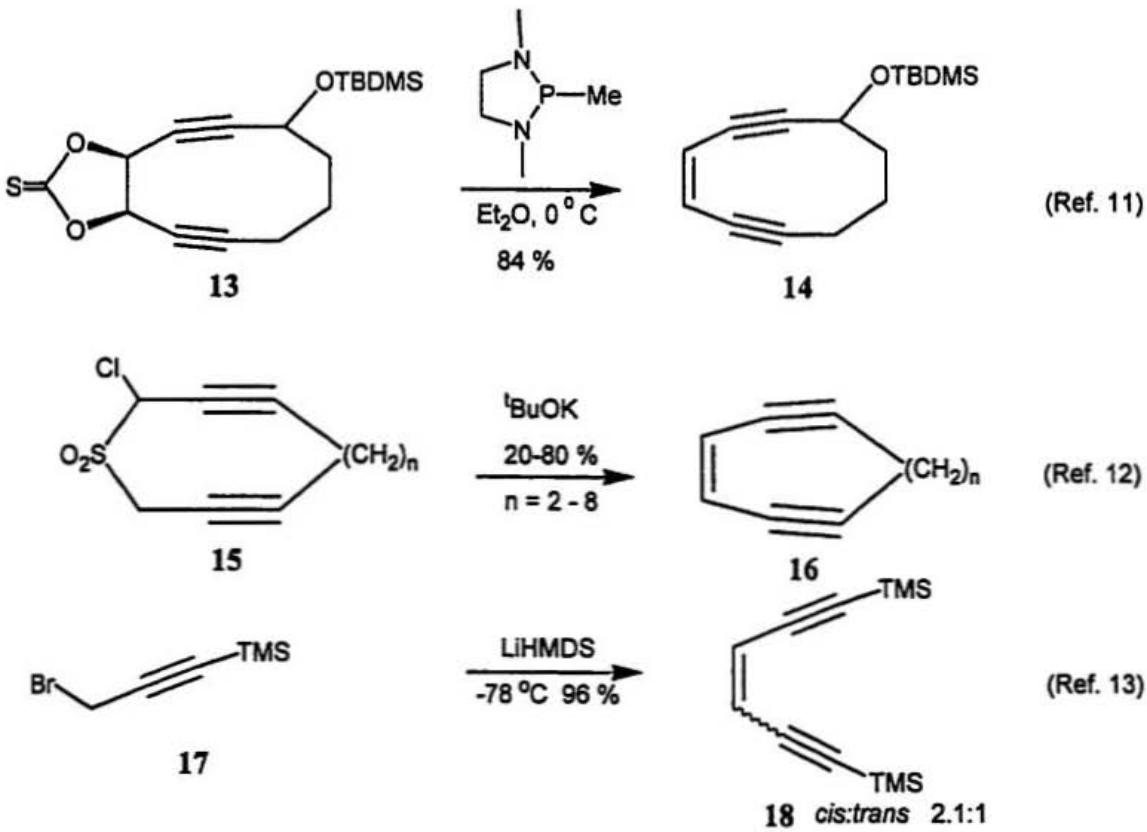
[5] König, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 165-166.

The most common method for the introduction of an enediyne unit into a cyclic molecule is by a ring closure of an existing acyclic enediyne, as exemplified in



Scheme 4- 2: Syntheses of Enediyne Moieties

syntheses by Wender[6] and Magnus.[7] In another approach, Danishefsky used a double Stille coupling to bridge terminal iodoacetylene **9** with (*Z*)-1,2-bis(trimethylstannyl)ethylene to afford **10**, a model of dynemicin.[8] An early approach to an *acyclic* enediyne **12** involved a reductive pinacol-like coupling of propynal, **11**, followed by reductive elimination.[9] A more recent approach to this deoxygenation has been advanced by Semmelhack, who used a modification of the Corey-Winter reaction[10] to reduce the diol derivative **13** to the alkene **14**.[11] Nicolaou used a Ramberg–Bäcklund ring



Scheme 4-3: More Syntheses of Enediyne Moieties

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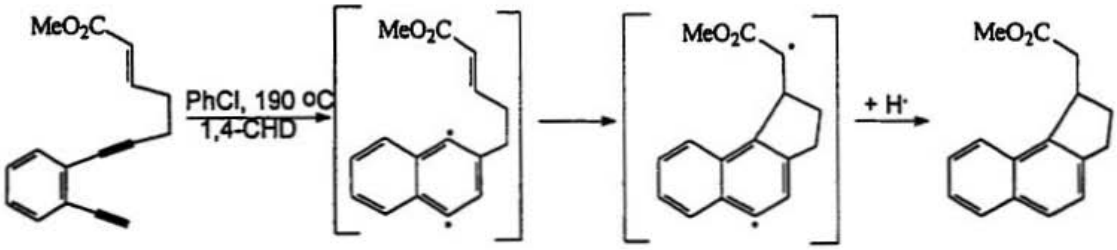
[6] Wender, P.A.; Beckham, S.; Mohler, D.L. *Tetrahedron Lett.* **1995**, *36*, 209-212.
[7] Magnus, P. *Tetrahedron* **1994**, *50*, 1397-1418.
[8] Shair, M.D.; Yoon, T.; Danishefsky, S.J. *J. Org. Chem.* **1994**, *59*, 3755-3757.
[9] Figeys, H.P.; Gelbcke, M. *Tetrahedron Lett.* **1970**, *11*, 5139-5142.
[10] Corey, E.J.; Winter, R.A.E. *J. Am. Chem. Soc.* **1963**, *85*, 2677-2678.
[11] Semmelhack, M.F.; Gallagher, J. *Tetrahedron Lett.* **1993**, *34*, 4121-4124.

contraction/SO_2 extrusion to generate a cyclic enediyne **16** from a *bis*-propargylic sulfone **15**.[12] Possibly the most ingenious approach to the enediyne skeleton was that of Jones, using propargylic bromide **17** and base, generating predominantly the *cis* product **18**, and presumably involving a carbenoid intermediate.[13] Clearly, there is no shortage of methods for the preparation of enediyne-containing compounds.

Another important discovery in the enediyne field was the demonstration by Grissom that the radicals generated by the Bergman reaction could undergo conjugate radical addition to generate a benzanellated cyclopentene (Scheme 4-4).[14] By appending an α,β-unsaturated ester onto the incipient benzene ring, as in **19a**, the highly reactive aryl diradical formed by cycloaromatization (**19b**) underwent conjugate addition to generate **19c**, followed by trapping with a H· source such as cyclohexadiene or γ-terpinene, to form cyclized products such as **20**.



19a **19b** **19c** **20**

Scheme 4-4: Grissom's Tandem Enediyne-Radical Cyclization

Examination of the structure of enediyneophanes, such as **1**, suggested that a Bergman cycloaromatizaion, followed by Grissom's radical conjugate addition, might allow the combination of our interest in cyclophanes with a synthetic route to previously unknown buckybowls such as pinakene, **21**.

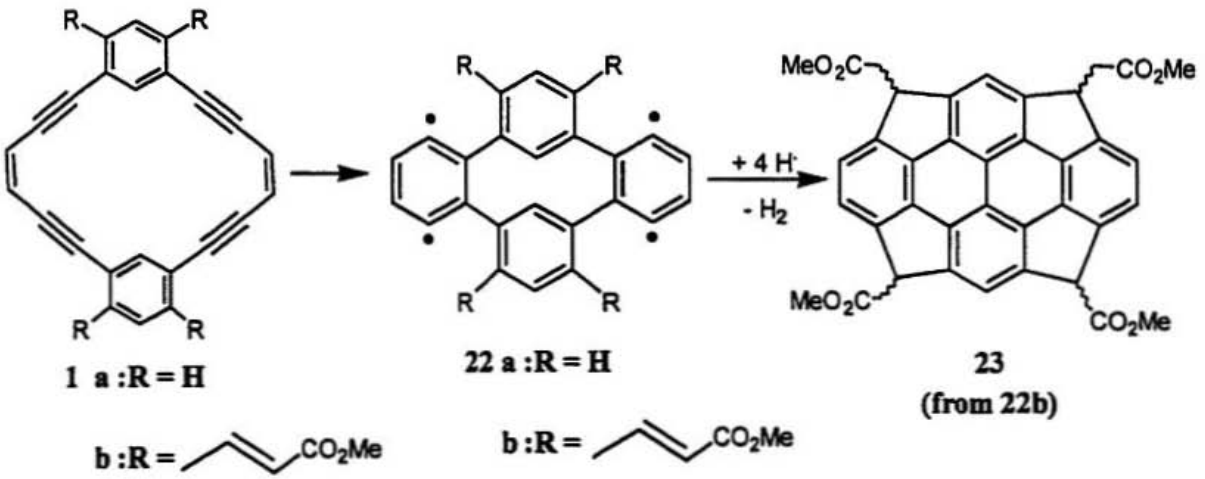
Pinakene, **21**

[12] Nicolaou, K.C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E.J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866-4868.
[13] Huber, R.S.; Jones, G.B. *Tetrahedron Lett.* **1994**, *35*, 2655-2658. b) Jones, G.B.; Huber, R.S.; Mathews, J.E. *J. Chem. Soc., Chem. Commun.* **1995**, 1791-1792.

4.2 – Attempted Synthesis of Bowl-Shaped Molecules - Theory

4.2.1 - The Idea

As described above, the Bergman reaction involves the thermochemical electrocyclization of enediyne **2** into *p*-benzyne **3**. Grissom demonstrated how the *p*-benzyne can undergo intramolecular radical cyclizations to form products containing fused aromatic and five-membered rings. Consider now the structure of **1** (Scheme 4-5). A Bergman reaction of **1a** would generate (at least formally) tetraradical **22a**. If α,β-unsaturated ester groups were appended onto the benzene rings of **1**, as in **1b**, each of the radicals in **22b** could undergo 5-exo-trig cyclizations to form (after central bond



Scheme 4- 5: Bergman-Radical Cyclization Cascade

formation, loss of H_2 and quenching with H·) compound **23**. This compound would be a derivative of pinakene, **21**, a C_2 symmetric fragment of C_{70}, with pendant alkoxycarbonylmethyl groups. By starting with doubly benzanellated enediynophane **24** (as in Grissom's work), the product of such a cyclization (Scheme 4-6) would be a dibenzopinakene derivative **25**, from which removal of the pendant groups would afford dibenzopinakene, **26**. If successful, this would be the first successful synthesis of the pinakene skeleton. Mehta's paper[15] describes the large amount of strain inherent in the pinakene skeleton, and discusses the difficulty which might be expected in the synthesis

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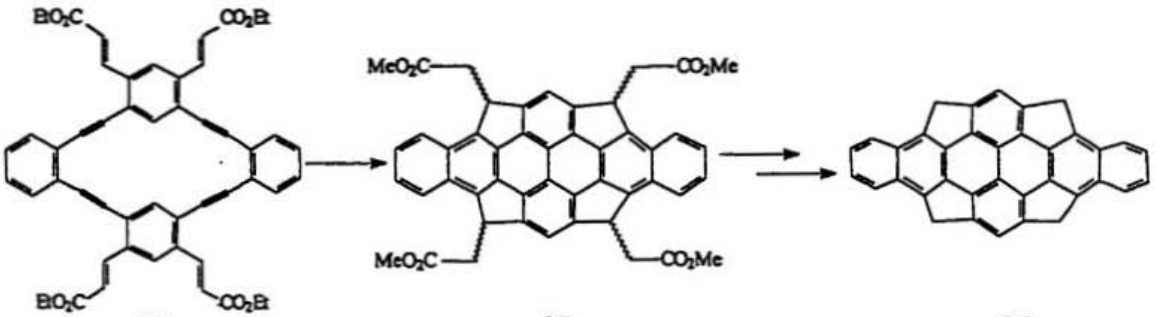
[14] Grissom, J.W.; Calkins, T.L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744-11752.
[15] Jemmis, E.V.; Sastry, G.N.; Mehta, G. *J. Chem. Soc., Perkin Trans. 2* **1994**, 437-441



24 25 26

Scheme 4-6: Enediyne-Cyclization Route to Dibenzopinakene Skeleton

of molecules containing such strain. Aryl radicals, however, are sufficiently energetic to lead to the formation of highly strained molecules.[16] It was hoped that such highly reactive aryl radicals, combined with the high temperatures required to initiate the Bergman reaction in the first place, would provide adequate energy to allow the formation of pinakene derivative **25**.

The challenge therefore became the synthesis of enediynophane **1b** and/or dibenzoenediynophane **24**. Since the bridges of **1b** consisted of enediyne moieties, it seemed likely that the synthesis would involve one of the previously mentioned synthetic methods for the enediyne antibiotics. Other methods would have to be found for the synthesis of **24**.

4.2.2 - Retrosynthetic Analysis

Retrosynthetic analysis (Fig. 4-1) of the enediynophane **1b** suggested three possible disconnections. Either the enediyne moiety **2** could be prepared separately and added to a suitably functionalized isophthalate derivative such as **28** (Path ***A***), or two dialkynylisophthalates **29** could be coupled by any one of several C-C bond forming reactions (Path ***B***). A less symmetrical disconnection (Path ***C***) would involve the coupling of terminal diyne **31** with a homopropargylic *bis*-electrophile **30**. In any case, the pendant acrylate groups could be added to **27** by modifying the oxidation state of the ester groups, followed by Horner-Wadsworth-Emmons chemistry.[17]

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[16] Hagen, S.; Bratcher, M.S.; Erickson, M.S.; Zimmermann, G.; Scott, L.T. *Angew Chem., Int. Ed. Engl.* **1997**, *36*, 406-408.

[17] a) Wadsworth, W.S.; Emmons, W.D. *J. Am. Chem. Soc.* **1961**, *83*, 1733 -1738. b) Wadsworth, W.S. *Org. React. (N. Y.)* **1977**, *25*, 73.

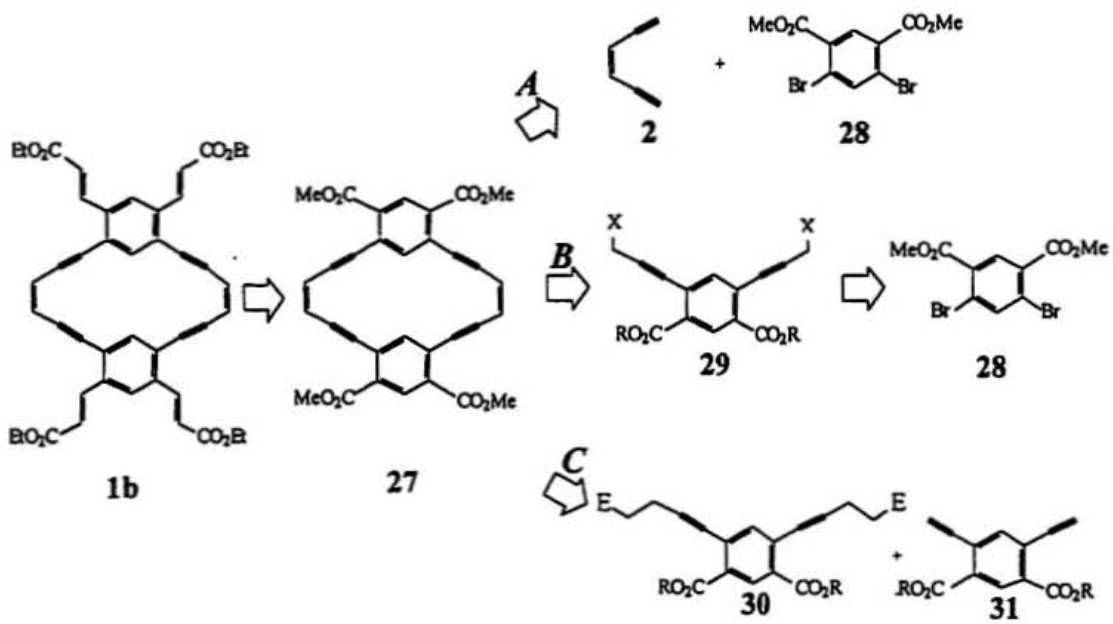
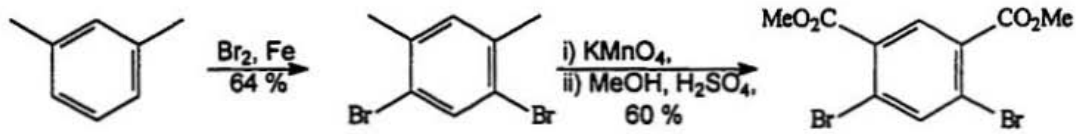


Figure 4-1: Retrosynthetic Analysis of Enediynophane **1b**

4.3 – Attempted Synthesis of Bowl-Shaped Molecules - Results and Discussion

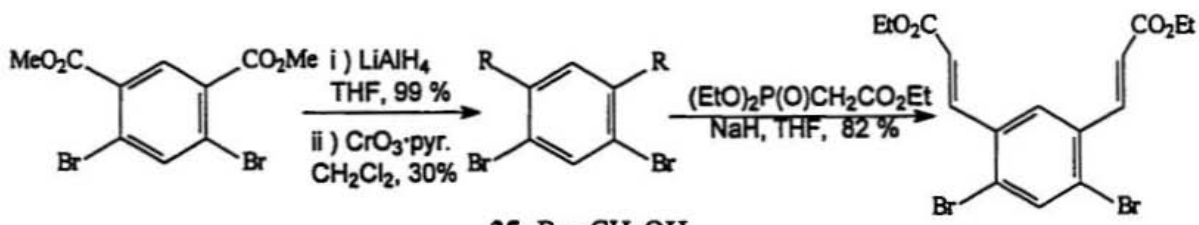
The first goal was the preparation of the key intermediate dimethyl 4,6-dibromoisophthalate **28** (Scheme 4-7). This was accomplished using classical chemistry. 4,6-Dibromo-*m*-xylene, **33**, could be prepared by slow addition of Br_2 to neat *m*-xylene, **32**, at room temperature with a trace of iron filings as a catalyst. Recrystallization of the crude product afforded pure **33** (64 %). Oxidation of **33** to 4,6-dibromoisophthalic acid **34** was accomplished in refluxing aqueous $KMnO_4$ with vigorous stirring.[18] With less agitation, the yield was markedly reduced. The crude acid was not purified, but it was converted to the desired ester **28** using the Fischer-Speier procedure by boiling in methanol with a trace of H_2SO_4, yielding **28** (60 %).[19]



32 **33** **28**

Scheme 4-7: Synthesis of Diester **28**

To ensure that the conjugated ester groups could be installed onto this isophthalate derivative, **28** was converted (Scheme 4-8) to the analogous dialdehyde **36** by reduction ($LiAlH_4$, 99%, affording diol **35**) and oxidation (CrO_3/pyridine, 30 %). Horner-Emmons reaction[17] of **36** with triethyl phosphonoacetate and NaH afforded the



28

35: R = CH_2OH
36: R = CHO

37

Scheme 4-8: Synthesis of Vinylogous Diester **37**

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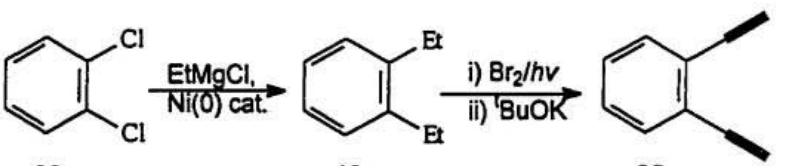
[18] a) March, J. E. *Advanced Organic Chemistry, 4th Ed.* J. Wiley and Sons, 1992, New York. pp. 1183-1184. b) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis, Vol. 1* John Wiley and Sons, New York, 1967. pp. 942-944.

[19] Fischer, E.; Speier, A. *Ber. Dtch. Chem. Ges.* **1895**, *28*, 3252-3258.

vinylogous diester **37** in 82% yield. Attention was next focused on the preparation of the enediynophane itself.

The simplest approach to **1b** or **24** would involve coupling of dibromodiester **28** with an enediyne moiety. 1,2-Diethynylbenzene, **38**, was chosen as the enediyne due to its ease of preparation and its immunity to possibly facile photochemical *cis-trans* isomerization after arylation, a transformation for which there is literature precedent.[20]

1,2-Dichlorobenzene, **39**, and ethylmagnesium bromide were coupled (Scheme 4-9) with a nickel catalyst, $(Ph_2P(CH_2)_3Ph_2P)NiCl_2$, which was reduced *in situ* to Ni(0), to afford *o*-diethylbenzene, **40** in 74% yield.[21] A two-step literature preparation, bromination followed by elimination, then gave **38** (17 % over two steps) as a clear, colorless liquid.[22]



39 **40** **38**

Scheme 4-9: Synthesis of 1,2-Diethynylbenzene, **38**

The first, "shotgun" synthetic approach to **24** simply involved mixing **38** and **28** in equal proportions with a Pd(0) catalyst, in the optimistic hope that cyclization would occur. The usual conditions for a Sonogashira coupling involve catalytic $Pd(PPh_3)_2Cl_2$ and CuI in either triethylamine or *n*-butylamine as base/solvent.[23] Problems had already been experienced with aromatic esters in *n*-butylamine, in that significant transacylation to the amide was observed.[24] It was then discovered that diester **28** was insoluble in triethylamine. Therefore, **28** and **38** were dissolved in DMF and heated (80 °C), with

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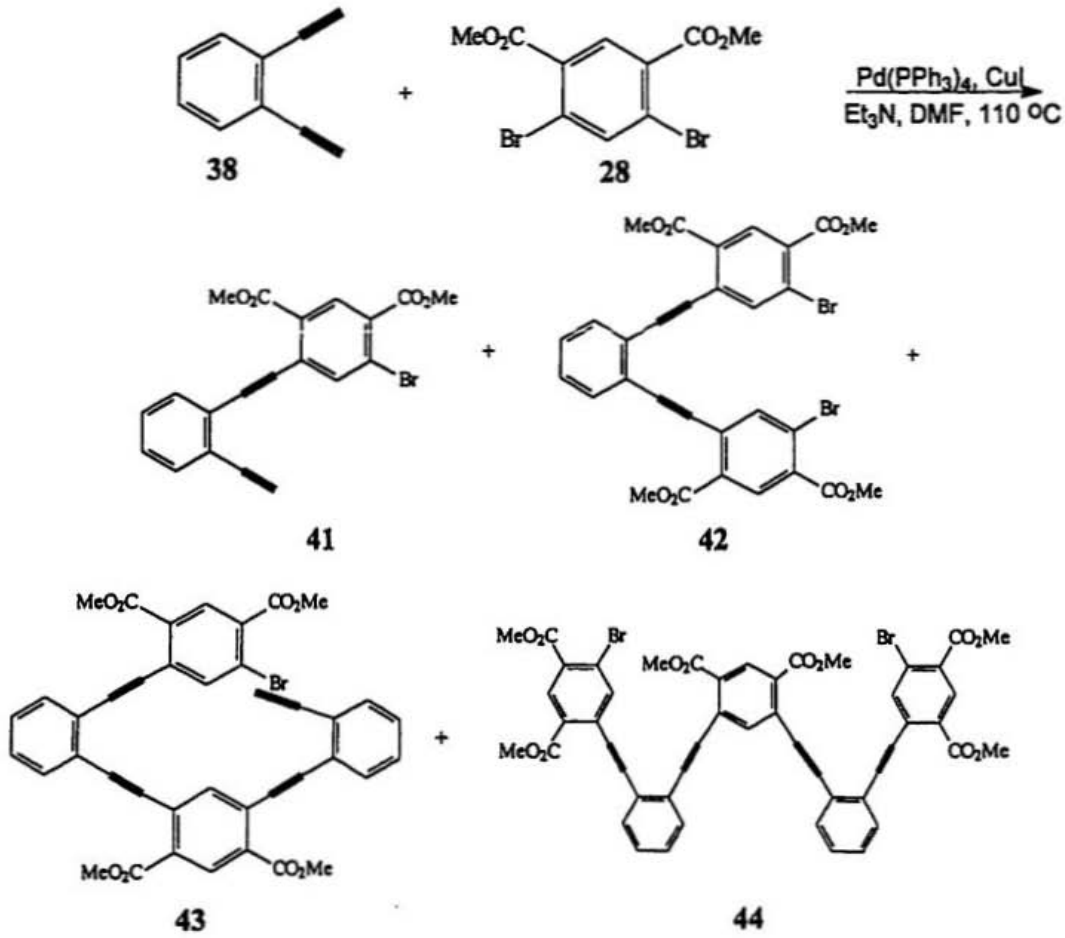
[20] König, B.; Schofield, E.; Bubenitschek, P.; Jones, P.G. *J. Org. Chem.* **1994**, *59*, 7142-7143.

[21] Sumitani, K.; Tamao, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374-4376. b) Tamao, K.; Sumitani, K.; Kiso, Y.; Zembayashi, M.; Fujioka, A.; Kodama, S.; Nakajima, I.; Minato, A.; Kumada, M. *Bull. Chem. Soc. Japan* **1976**, *49*, 1958-1969.

[22] a)Behr, O.M.; Eglinton, G.; Galbraith, A.R.; Raphael, R.A. *J. Chem. Soc.* **1960**, 3614-3625. b) Behr, O.M.; Eglinton, G.; Lardy, I.A.; Raphael, R.A. *J. Chem. Soc.* **1964**, 1151-1154.

[23] Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470 ; Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253-257; Dieck, H.A.; Heck, F.R. *J. Organomet. Chem.* **1975**, *93*, 259-263; Trost, B.M.; Fleming, I., Eds. *Comprehensive Organic Synthesis, Vol. 3* Pergamon Press, New York, **1991**. p. 521.

[24] Bodwell, G.J.; Chen, S.-L. unpublished results



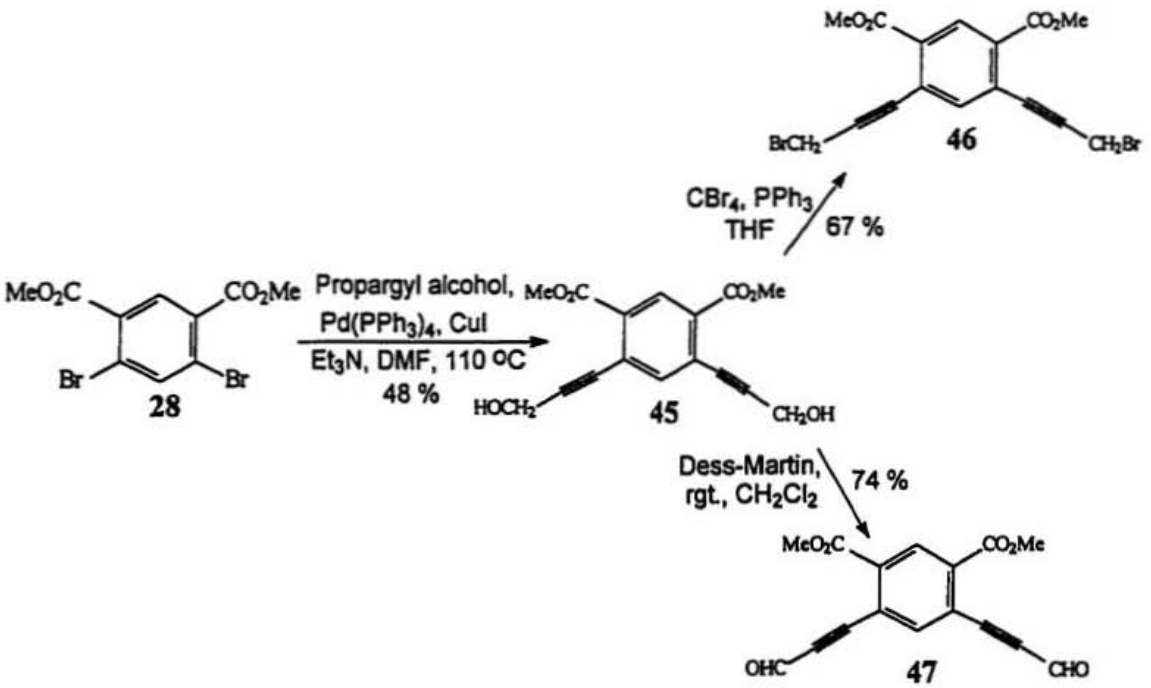
Scheme 4-10: Products of Coupling Reaction

triethylamine as the base. Unfortunately, although **28** was almost totally consumed, an extremely complex mixture of products resulted (Scheme 4-10), with no evidence of any enediynophane. Some of these products **41-44** could be isolated by careful chromatography, and were found to be short linear co-oligomers of **28** and **38**. TLC analysis of the highly polar column washings suggested that longer co-oligomers might be present as well, but these were not isolated. Changing the proportions of diester to diyne to 3:1 only changed the product ratio of the acyclic products.

Clearly, the Sonogashira coupling was occurring; however, no cyclization could be observed. This might be attributed to the geometric constraints of palladium-catalyzed couplings. The geometries required for the final, reductive elimination are first a *trans*, then a *cis* arrangement of the two groups, in this case the aryl and the alkynyl groups, in

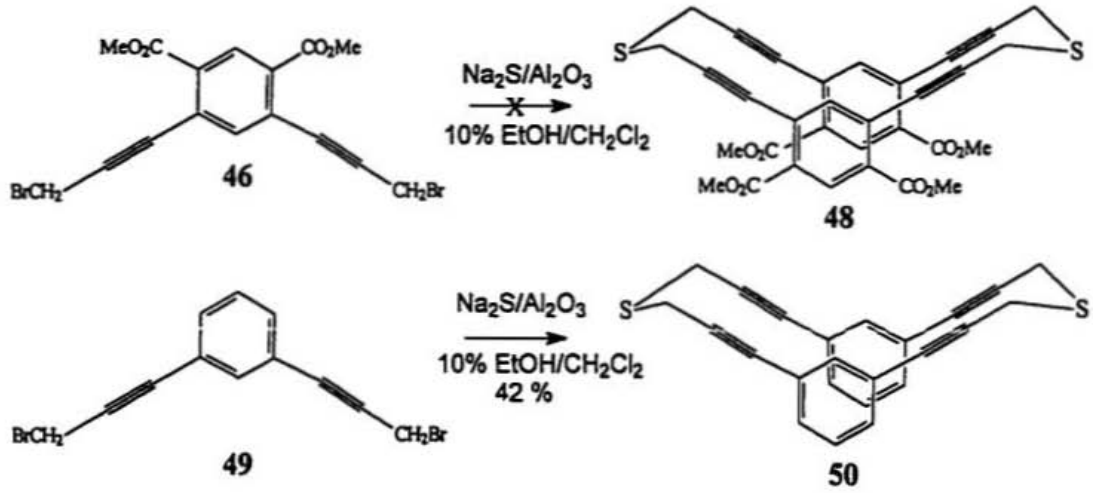
the square planar Pd(II) complex.[25] Examination of molecular models shows clearly that these arrangements would be highly strained, and therefore, presumably, this cyclization cannot occur. The only other option for the molecule is linear chain elongation, and this is what is observed. It is also possible that the product is generated, but is extremely insoluble and cannot be separated from the other products by chromatography. Consequently, approaches to **24** or **27** in which the enediyne moiety is already in place appeared unlikely to succeed, and no further approaches along the lines of Path ***A*** were considered.

Attention was next focussed on path ***B***, along which a number of C-C bond-forming reactions were available. Sonogashira coupling of **28** with propargyl alcohol afforded diol **45** (Scheme 4-11) in moderate yield (48 %). The product appeared to be unstable under the reaction conditions, forming uncharacterizable tar-like material if left too long or if heated excessively. This diol could be transformed into dibromide **46** under mild bromination conditions (67 %),[26] and **45** could be oxidized to dialdehyde **47** with



Scheme 4-11: Synthesis of Enediyne Precursors **46** and **47**

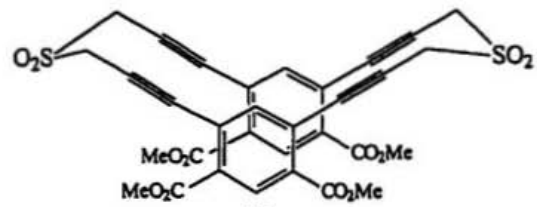
[25] Hegedus, L. in M. Schlosser, Ed. *Organometallics in Synthesis*. J. Wiley & Sons, Chichester, 1994; pp. 406-407.
[26] Hooz, J.; Gilani, S.S.H. *Can. J. Chem.* 1968, *46*, 86-87.



Scheme 4-12: Approaches to Expanded Thiacyclophanes

Dess-Martin reagent (74 %).[27]

First, an approach similar to Nicolaou's (via a Ramberg-Bäcklund ring contraction/SO_2 extrusion) was considered, which would entail preparation of dithiacyclophane **48**. Under normal Na_2S/Al_2O_3 coupling conditions, **46** was rapidly and quantitatively consumed to afford intractable, colored material. No thiacyclophane could be detected (Scheme 4-12). This result was especially surprising as the parent dibromodiyne **49** afforded thiacyclophane **50** in 42 % yield.[28] Disulfone **51** could therefore not be obtained via this route.



Next, a modification of the Wittig reaction to form the two double bonds was explored. However, the attempted Arbuzov reaction[29] (Scheme 4-13) to prepare the

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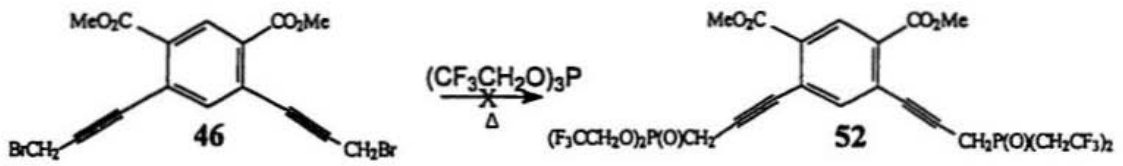
[27] Dess, D.B.; Martin, J.C. *J. Org. Chem.* **1983**, *48*, 4155-4156. A better method for the preparation of the periodinane has been published: Ireland, R.E.; Liu, L. *J. Org. Chem.* **1993**, *58*, 2899.
[28] Bodwell, G.J.; Houghton, T.J.; Miller, D. *Tetrahedron Lett.* **1998**, *39*, 2231-2234.
[29] Arbuzov, B.A. *Pure Appl. Chem.* **1964**, *9*, 307-335.

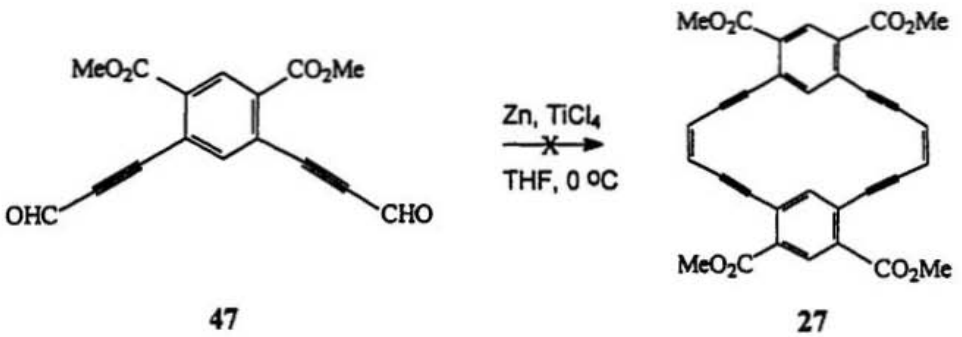
bis(bis(trifluoroethyl)phosphonate) **52** from dibromide **46** failed, producing a complex



Scheme 4-13: Failed Arbuzov Reaction

mixture of products. This prevented a Still-Gennari coupling of **47** and **52**.[30]

McMurry coupling of dialdehyde **47** also failed (Scheme 4-14), the reaction producing only an intractable black solid.[31]

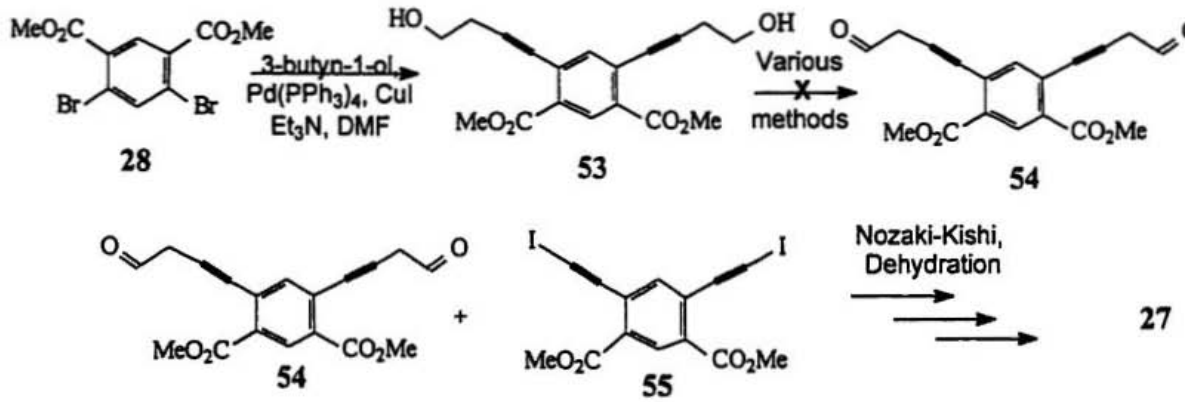


Scheme 4-14: Failed McMurry Coupling

[30] Still, W.C.; Gennari, C. *Tetrahedron Lett.* **1983**, *24*, 4405-4408.

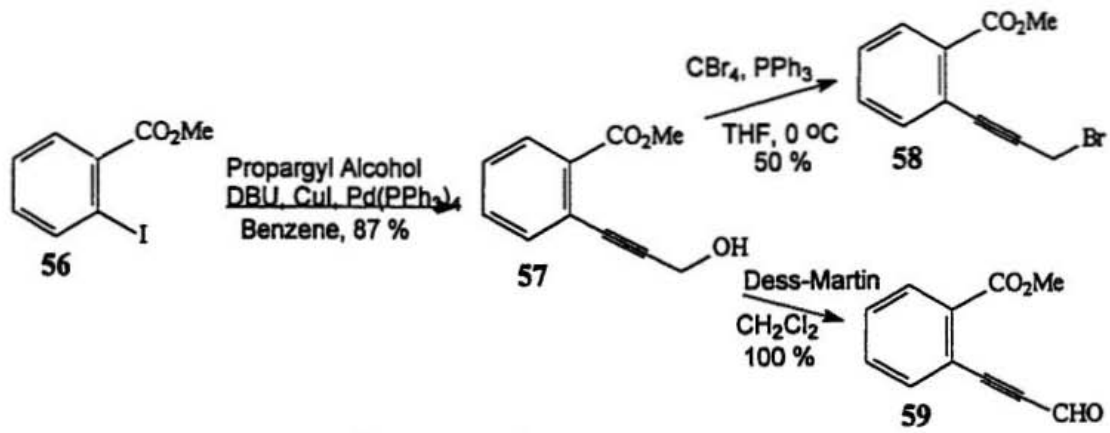
[31] a) McMurry, J.E. *Chem. Rev.* **1989**, *89*, 1513-1524. b) McMurry, J.E. *Acc. Chem. Res.* **1983**, *16*, 405-411. c) Furstner, A.; Bogdanovic, B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2442-2469.

Attention was next focused on Path *C*. Homopropargylic dialdehyde **54** and iodinated diyne **55** were synthetic targets, which could be coupled by a Nozaki-Kishi coupling.[32] Elimination of the resultant alcohols would afford enediynophane **27**. Homopropargylic diol **53** could be prepared (27 %) by the familiar Sonogashira route (Scheme 4-15). However, numerous attempts to oxidize this diol to dialdehyde **54** (Dess-



Scheme 4-15: Approaches to Path *C*

Martin, Swern,[33] CrO_3/pyridine) all failed, affording only intractable material. It was concluded that this aldehyde was extremely unstable, perhaps polymerizing spontaneously by aldol condensations or other reactions. This failure prevented further

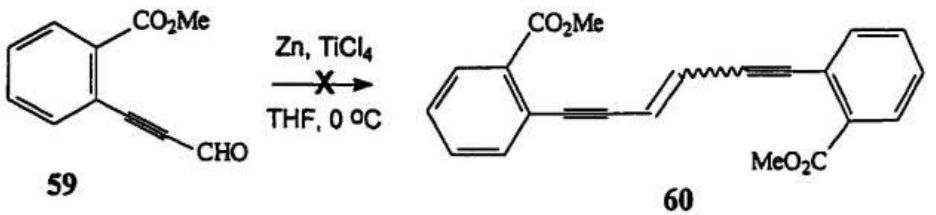


Scheme 4-16: Synthesis of **58** and **59**

[32] a) Takai, K.; Kimura, K.; Kuroda, T.; Hiyama, T.; Nozaki, H. *Tetrahedron Lett.* **1983**, *24*, 5281–5284. b) Jin, H.; Uenishi, J.; Christ, W.J.; Kishi, Y. *J. Am. Chem. Soc.* **1986**, *108*, 6048-6050. c) Cintas, P. *Synthesis* **1992**, 248 -257.

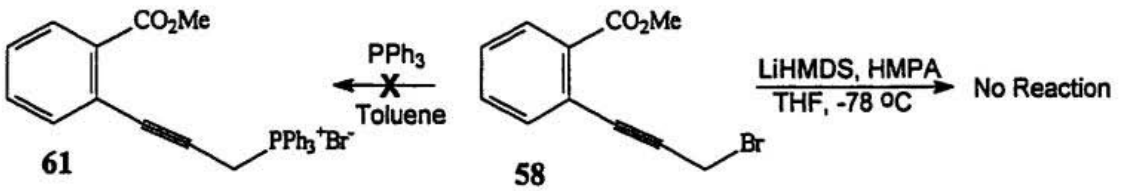
exploration of Path *C*.

All attempts at simultaneous alkene/cyclization reactions having failed, it was decided to prepare simpler model compounds, on which to test alkene-forming reactions. Alcohol **57** was therefore prepared from methyl *o*-iodobenzoate **56** (87 % yield) and then converted to bromide **58**, or to aldehyde **59** (Scheme 4-16). Again, a McMurry reaction (Scheme 4-17) of aldehyde **59** provided no useful products.



Scheme 4-17: Attempted McMurry Coupling of **59**

A Jones carbenoid coupling of **58** (Scheme 4-18),[13] afforded no reaction at -78 °C. Warming the reaction seemed to bring about extensive decomposition. This failure might



Scheme 4-18: Transformations of Propargylic Bromide **58**

have been due to the inability to add the bromide sufficiently slowly. Extremely slow addition is apparently crucial to the success of this reaction and, on such a small scale, dropwise addition from a dropping funnel may simply have been too rapid.

Finally, an attempt at a Wittig coupling of **58** and **59** (Scheme 4-18) was thwarted when an attempt to make the triphenylphosphonium salt **61** by treatment of **58** with PPh_3 in toluene afforded an unidentified, deeply colored product whose NMR spectrum clearly did not correspond to **61**. This result proved difficult to duplicate; however, in all cases the treatment of **58** with PPh_3 in a number of solvents generated a deep brown color and little or no anticipated precipitate of the desired triphenylphosphonium salt.

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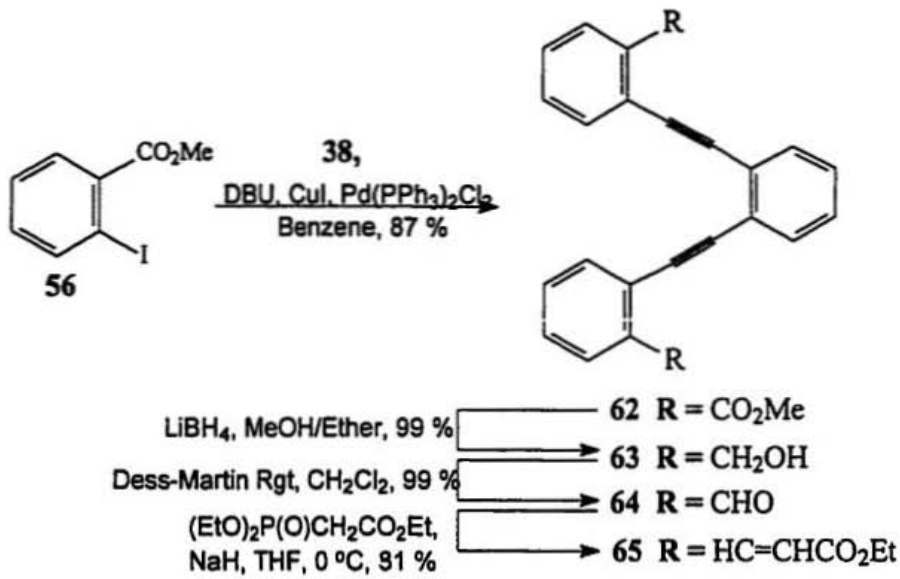
[33] Omura, K.; Swern, D. *Tetrahedron* **1978**, *34*, 1651-1660.



Scheme 4-19: Synthesis of Enediynes **62** and **65**

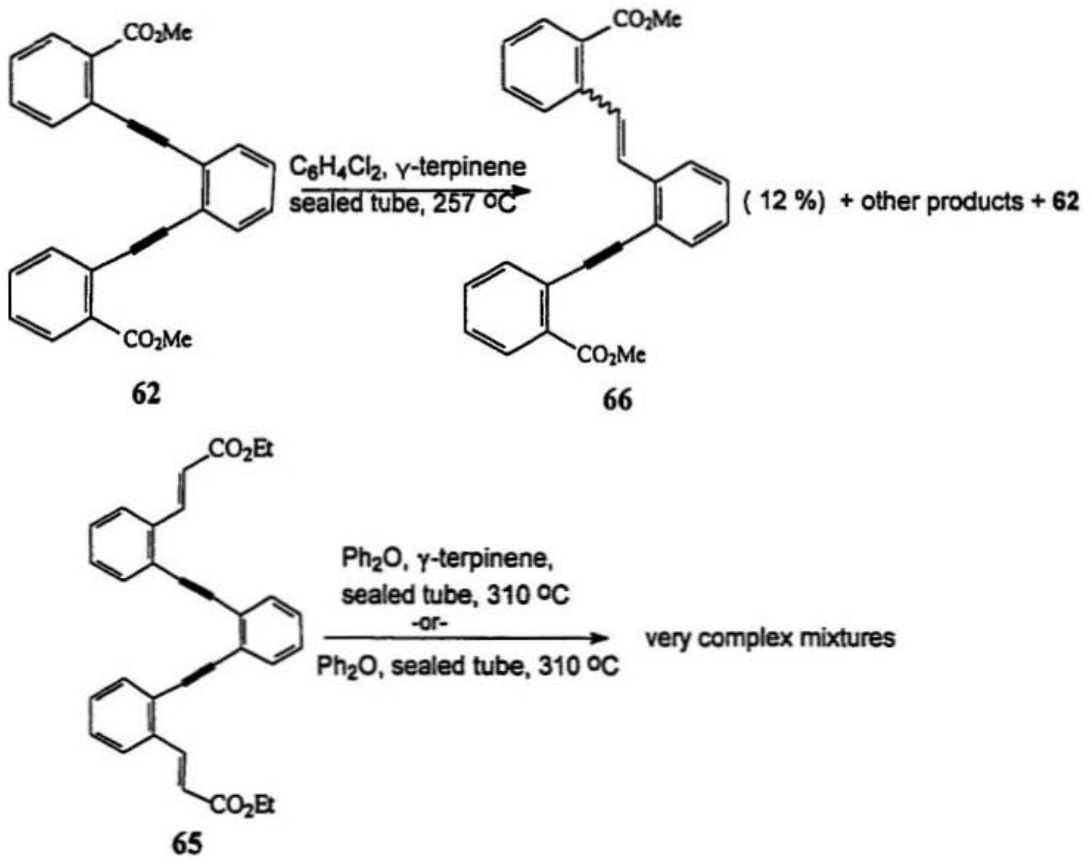
Frustration at the failure of all attempts at alkene-forming reactions led to the decision to prepare simpler "half enediynophanes," specifically terphenyl **62**, and its *bis*-vinylogous analogue **65**. These were prepared (Scheme 4-19) uneventfully using previously described chemistry in excellent overall yield.

The Bergman cyclizations of enediynes **62** and **65** could now be investigated in order to examine the feasibility of the proposed pinakene synthesis described above. After 3 hours at 190 °C in chlorobenzene with γ-terpinene as H· source in a sealed tube, **62** could be recovered quantitatively. At 257 °C, however, **62** was consumed, and a mixture of products was obtained. Only one compound could be isolated (Scheme 4-20), and this was tentatively identified (from NMR and mass spectral data) as the partially hydrogenated product **66**. This was alarming, as it suggested that hydrogen transfer from γ-terpinene occurred more rapidly than the Bergman reaction.[34] Hoping to overcome this potentially catastrophic side reaction, the vinylogous diester **65** was heated to 310 °C in diphenyl ether in a sealed tube. Again, only an extremely complex mixture of products was obtained, from which, despite considerable efforts, no pure products could be isolated. A last ditch effort to salvage the project by leaving the γ-terpinene out of the

[34] For a recent review of this type of reaction, see: Ruchardt, C.; Gerst, M.; Eberhach, J. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1407-1430.

reaction (which should have eliminated unwanted reduction of the starting material) was not effective, with a complex mixture of products still being generated.

At this point, a re-evaluation of the prospects of this project was required. Although the failure of the Path *A* approach was not surprising, the abundance of alkene-

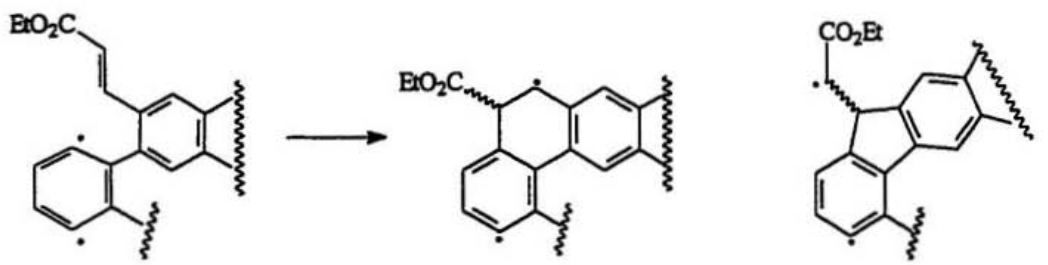


Scheme 4-20: Results of Cycloaromatization Experiments

forming methodology available (McMurry, Wittig, SO_2 extrusion) had led to an overly optimistic assumption that **27** could be prepared with relatively little difficulty. On the contrary, every coupling method that was attempted had unexpectedly failed, even though there were literature precedents for closely related compounds which reacted normally. The failure of many of these coupling methods might be attributable to the highly electron-deficient nature of these substrates, combined with the presence of the alkyne groups, leading to atypical reactivity. The failure of the synthesis of phosphonium salt **61**, for instance, might have been due to PPh_3 attacking the alkyne rather than the

alkyl halide. Under McMurry conditions, reduction of the triple bond might have been followed by aldol reactions, producing polymeric products. On the other hand, many of these methods also failed during attempted syntheses of the parent system **1a**, so factors other than the highly electron-deficient nature of the intermediates must be at least partially responsible for their lack of success here.

The abject failure of the attempted Bergman reactions to generate isolable products, cyclized or otherwise, was more discouraging. The synthetic approach to pinakene demanded efficient cycloaromatization followed by reasonably selective 5-exo-trig cyclization of the resulting aryl radicals onto the acrylate acceptors. This would certainly have to work well in the "half-enediynophane" **65** (in which a much less strained product would be generated) for the parent systems **1b** or **24** to have any chance of cyclizing successfully. Of course, no cyclized products were isolated. The inseparable mixture afforded by the various sealed tube reactions of **62** and **65** was presumably due to the completely nonselective formation of all possible combinations of 5-exo-trig and 6-endo-trig additions (Scheme 4-21), as well as non-cyclized and partially cyclized products. Reduction of the alkynes, presumably by the γ-terpinene (when present), may also have contributed to the multitude of products visible by tlc analysis in the crude reaction mixture. The production of a small amount of each of a very large number of products was the worst-case scenario for this reaction, spelling disaster for the project as a synthetic venture. It now seemed very unlikely that a Bergman/radical cyclization route would allow efficient generation of the pinakene skeleton. Although all possible routes to enediynophane **1b** had by no means been exhausted, the knowledge that it likely could

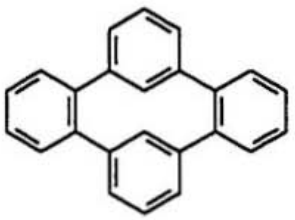


22b **67,** 6-endo-trig product **68,** 5-exo-trig product

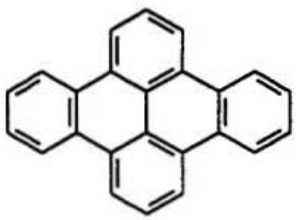
Scheme 4-21: Competing 5-Exo and 6-Endo Modes of Cyclization.

not be transformed to buckybowl **25** made it a much less compelling synthetic target. Facing the likely prospect of many more months exploring other enediyne-forming methodologies, it was decided to abandon this project in favor of pursuing other, more successful lines of research.

Some time after this project was terminated, the synthesis of the parent enediynophane **1a** was accomplished by another researcher in this group,[35] albeit it in very low yield. Even with this compound, the Bergman cyclization to dibenzometacyclophanediene **69** has proven very difficult to accomplish, and neither **69** nor the dehydrogenated product **70** have been successfully isolated (by our group) to date.[36] The



69



70

complex and unpredictable chemistry of this system and the synthetic precursors described above are very puzzling. It is perhaps best seen as a synthetic cautionary tale. Although most of the transformations attempted above had reasonable precedents in the literature, under these circumstances they proved ineffective. As all practising synthetic chemists learn, chemical transformations that look plausible on paper may well fail utterly in practice.

4.4 - Experimental

Reactions were performed under air unless otherwise indicated. THF was distilled from sodium benzophenone ketyl under N_2 prior to use. All other solvents were used as received. "Ether" refers to diethyl ether. Chromatographic purification was accomplished with 230-400 mesh silica gel. Tlc plates were visualized using a short wave (254 nm) UV lamp. Melting points were obtained on a Thomas Hoover 7427-H10

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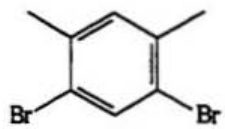
[35] Houghton, T.J. Ph.D. Thesis, Memorial University of Newfoundland, 1999.

[36] A molecule similar to 69 has been isolated by other workers, using a different method. See: Mitchell, R.H.; Chen, Y.S. *Tetrahedron Lett.* **1996**, *37*, 5239-5242.

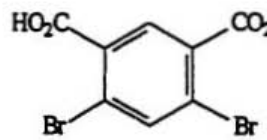
Melting Point Apparatus and are uncorrected. IR spectra (ν in cm^{-1}) were recorded on a Perkin Elmer 1320 spectrophotometer in solution in 1 mm NaCl cells. ^1H NMR spectra were obtained on a GE-300 NB at 300.1 MHz in $CDCl_3$ unless otherwise noted; shifts are relative to an internal TMS standard; coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 MHz in $CDCl_3$ unless otherwise noted; chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$). Selected NMR spectra from this Chapter are reproduced in Appendix B. Low resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta, and are stated as percentages.



33

4,6-Dibromo-*m*-xylene, 33. Iron filings (1.6 g, 28 mmol) and *m*-xylene (63.4 mL, 55.0 g, 0.518 mol) were stirred and cooled on ice as Br_2 (56.0 mL, 174 g, 1.08 mol) was added dropwise. When addition was complete, the mixture was dissolved in CH_2Cl_2 (200 mL) and washed repeatedly with aqueous 5% $Na_2S_2O_3$ (5 x 100 mL), aqueous saturated $NaHCO_3$ (2 x 100 mL), and once with brine (50 mL). The solution was dried (K_2CO_3), filtered, and concentrated to afford a yellow-white solid. Recrystallization from MeOH afforded **33** (87.8 g, 0.333 mmol, 60 %) as a colorless solid.

33: mp 68-70 °C (MeOH); lit. mp. 72 °C;[37] ^1H NMR δ 7.66 (s, 1H), 7.08 (s, 1H), 2.30 (s, 6H); ^{13}C NMR δ 136.8, 134.8, 132.5, 122.0, 22.2.



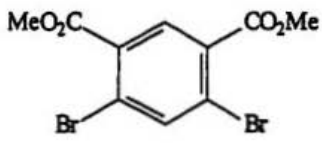
34

4,6-Dibromoisophthalic acid, 34. 4,6-Dibromo-*m*-xylene, **33** (7.66 g, 29.0 mmol) was suspended in a solution of K_2CO_3 (5.20 g, 37.6 mmol) and $KMnO_4$ (10.0 g, 63.3 mmol) in H_2O (200 mL) and heated at reflux with vigorous magnetic stirring. When the purple solution had faded to black (6 h), more $KMnO_4$ (10.0 g, 63.3 mmol) was added, and the solution was refluxed for 24 h. The reaction was cooled and poured into an aqueous 5 % $NaHSO_3$ solution (200 mL). This was then acidified with aqueous HCl (6

[37] Fittig, R.; Ahrens, W.; Mattheides, L. *Liebigs Ann.* **1868**, *147*, 15-39.

M) until a colorless precipitate formed. This was isolated by suction filtration, washed with water, and dried *in vacuo* to afford crude diacid **34** (5.63 g, 17.4 mmol, 60 %). Recrystallization from water yielded colorless needles of **34**.

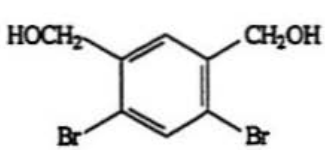
34: mp 259-262 °C (H_2O), lit. mp. 250-254 °C;[38] ^{1}H NMR (DMSO-d_6) δ 13.79 (br s, 2H), 8.16-8.13 (m, 2H); ^{13}C NMR (DMSO-d_6) δ 165.9, 138.5, 132.7, 132.4, 123.7.



28

Dimethyl 4,6-dibromoisophthalate, 28. Crude diacid **34** (3.21 g, 9.91 mmol) was dissolved in MeOH (50 mL) and H_2SO_4 (1 mL) was added. This solution was heated at reflux for 12 h. The reaction was cooled and the solvent removed under reduced pressure. The residue was redissolved in diethyl ether (50 mL) and washed with water (50 mL), aqueous saturated $NaHCO_3$ (3 x 50 mL), brine (50 mL), dried, filtered, and concentrated to afford **28** (3.44 g, 9.81 mmol, 60 % from **33**) as a colorless solid.

28: mp 97.5-98.5 °C (heptane); IR ($CDCl_3$) 2955 (m), 1735 (s), 1585 (m), 1435 (m), 1260 (s), 1220 (s); ^{1}H NMR δ 8.30 (s, 1 H), 8.03 (s, 1H), 3.95 (s, 6H); ^{13}C NMR δ 164.9, 139.9, 134.0, 130.7, 125.9, 52.8; EI-MS *m/z* (%) 354 (17), 352 (32, M^+), 350 (18), 323 (53), 321 (100), 319 (52), 278 (10), 74 (31). Anal. Calc'd for $C_{10}H_8Br_2O_4$: C, 34.12; H, 2.29. Found: C, 34.19; H, 1.95.



35

4,6-Dibromo-1,3-*bis*(hydroxymethyl)benzene, 35. Diester **28** (1.11 g, 3.15 mmol) was dissolved in dry THF (50 mL) and cooled to 0°C. $LiAlH_4$ (0.155 g, 4.1 mmol) was added slowly while purging with N_2. The reaction was stirred and allowed to warm to room temperature. After 18 h, the reaction was quenched with ethyl acetate (5 mL), and then poured into aqueous 1 M HCl (50 mL). This was saturated with NaCl and extracted with ether (3 x 50 mL). The organic layer was dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford pure **35** (0.86 g, 2.9 mmol, 93 %) as a colorless solid.

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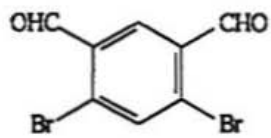
[38] Rodd, E.H., Ed. *Chemistry of Carbon Compounds, Vol. III (B)* Elsevier Publishing, Amsterdam, 1956. p. 559.

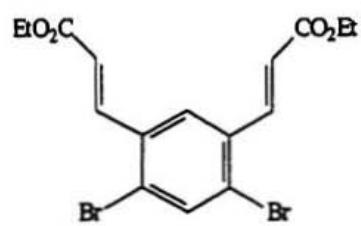
35: mp 179-181 °C (ether); ^{1}H NMR δ 7.77 (s, 1H), 7.75 (s, 1H), 5.55 (t, *J*=5.4, 2H), 4.48 (d, *J*=5.5, 4H); ^{13}C NMR δ 140.5, 134.0, 127.4, 119.2, 62.3; EI-MS *m/z* (%) 298 (14), 296 (28, M^+), 294 (15), 264 (17), 173 (57), 171 (33), 169 (38), 165 (36), 120 (100), 92 (25), 89 (18), 77 (49). Anal. Calc'd for $C_8H_8Br_2O_2$: C, 32.47; H, 2.72. Found: C, 32.73; H, 2.43.



36

4,6-Dibromoisophthalaldehyde, 36. Pyridine (3.5 mL) was dissolved in CH_2Cl_2 (75 mL) and cooled to 0 °C. CrO_3 (2.00 g, 20.0 mmol) was added, and the reaction was allowed to warm to room temperature. This was then stirred for 30 min. Diol **35** (0.78 g, 2.64 mmol) was dissolved in dry THF (25 mL) and added to the solution dropwise. After 24 h, the reaction was washed with aqueous 5 % KOH (3 x 100 mL), aqueous 10 % H_2SO_4 (3 x 100 mL), aqueous saturated $NaHCO_3$ (100 mL), and brine (100 mL). The solution was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown solid. Chromatography (CH_2Cl_2) afforded pure dialdehyde **36** (0.21 g, 27 %) as a colorless solid.

36: mp 185.5-186.5 °C, lit. mp. 190-192 °C.[39]

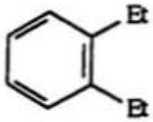


37

Diethyl 4,6-dibromobenzene-1,3-*Bis*(acrylate), 37. NaH (60 % dispersion in mineral oil, 0.041 g, 1.0 mmol) was suspended in dry THF (20 mL) and cooled to 0°C. To this was added triethyl phosphonoacetate (*ca.* 0.2 mL) dropwise until the solution became clear. Then, dialdehyde **36** (0.140 g, 0.48 mmol) in THF (25 mL) was added under N_2. After 5 min, the solvent was removed under reduced pressure, and the residue partitioned between ether (50 mL) and water (50 mL). The organic layer was washed with brine (50 mL) then dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a colorless solid. Column chromatography (CH_2Cl_2) afforded **37** (0.170 g, 0.39 mmol, 82 %) as a colorless solid.

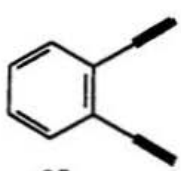
[39] Jakobs, A.; Christiaens, L.; Renson, M. *Bull. Soc. Chim. Belg.* **1991**, *100*, 1-4.

37: mp 137-137.5 °C (heptane); IR ($CHCl_3$) 3035 (w), 2960 (w), 1710 (s), 1640 (m), 1450 (m), 1370 (m), 1315 (s), 1180 (m); ^{1}H NMR δ 7.93 (d, *J*=16.2, 2H), 7.89 (s, 1H), 7.78 (s, 1H), 6.43 (d, *J*=16.0, 2H), 4.29 (q, *J*=7.1, 4H), 1.36 (t, *J*=7.2, 6H); ^{13}C NMR) δ 165.9, 141.3, 137.3, 134.3, 126.4, 126.0, 122.3, 60.9, 14.3; EI-MS *m/z* (%) 434 (6, M^+) 432 (12, M^+), 430 (6, M^+), 387 (23), 353 (53), 350 (50), 339 (23), 337 (23), 325 (98), 323 (100), 311 (18), 309 (18), 229 (12), 215 (61), 199 (22), 171 (27), 126 (32). Anal. Calc'd for $C_{16}H_{16}Br_2O_4$: C, 44.47; H, 3.73. Found: C, 44.40; H, 3.67.



40

1,2-Diethylbenzene, 40. Mg (37.2 g, 1.53 mol) was covered with anhydrous ether (200 mL). Bromoethane (112 mL, 164 g, 1.59 mol) was dissolved in anhydrous ether (200 mL) and added dropwise to the Mg, with stirring. When the addition was complete, the reaction was allowed to reflux for 10 min. The cloudy liquid was then filtered under N_2 and added dropwise to a solution of *o*-dichlorobenzene (75.0 mL, 98.0 g, 0.666 mmol) and $[(Ph_2P)_2(CH_2)_3]NiCl_2$[40] (2.50 g, 4.61 mmol) in ether (300 mL). This was heated to reflux overnight. The reaction was poured onto crushed ice (500 mL) and conc. HCl (100 mL). The resulting aqueous solution was extracted with ether (3 x 100 mL), washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford brown liquid. Distillation under reduced pressure (130 - 150 °C, 20 mm Hg; Lit. b.p. 183 °C 760 mm Hg)[41], afforded **40** (66.5 g, 0.495 mol, 74 %) as a colorless liquid.



38

1,2-Diethynylbenzene, 38. Diethylbenzene (20.0 g, 149 mmol) was heated to 130 °C in an oil bath, and Br_2 (~32 mL) was added slowly, with irradiation from a visible-light lamp (150 W). When the solution no longer decolorized the Br_2, addition was stopped, and the liquid was purged with N_2 to remove excess Br_2 and HBr. On cooling, the liquid solidified, and was crystallized twice from absolute EtOH to afford a colorless crystalline solid (20.1 g, 44.7 mmol, 30 %).

To freshly distilled ^{t}BuOH (130 mL) was carefully added K (5.90 g, 150 mmol), which was stirred at room temperature under N_2 until all the metal had dissolved. Part of

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[40] Booth, G.; Chatt, J. *J. Chem. Soc.* **1965**, 3238-3241.

the bromination product (9.1 g, 20 mmol) was dissolved in dry THF (40 mL) and added to the ^{t}BuOK solution. This was refluxed for 1 h, then the reaction was *cautiously* quenched by the addition of H_2O in small portions (5 mL). The solvent was removed under reduced pressure, and the residue extracted into ether (100 mL) and washed with aqueous saturated NH_4Cl (50 mL), then dried ($MgSO_4$), filtered, and concentrated under reduced pressure yielding a liquid. Vacuum distillation (60-70 °C, 1 mm Hg, lit. b.p. 80-82 °C, 14 mm Hg)[22a] afforded **38** (1.45 g, 11.5 mmol, 58 %) as a colorless liquid. This was used in subsequent reactions without further characterization.

Attempted Endiynophane Synthesis – Sonogashira Route – Diester **28** (1.00 g, 2.84 mmol) and *o*-diethynylbenzene **38** (0.50 g, 4.0 mmol, 1.4 eq.) Et_3N (1.1 mL, 7.9 mmol), $Pd(PPh_3)_4$ (0.100 g, 0.087 mmol), and CuI (50 mg, 0.26 mmol) were mixed in DMF (25 mL). The resulting solution was heated to 80 °C for 6 h under N_2. The reaction was then poured into aqueous 1 M HCl (50 mL) and then extracted with Et_2O (3 x 50 mL) which was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a brown oil. Chromatography (1:1 CH_2Cl_2/petroleum ether, then neat CH_2Cl_2, then 1:1 ethyl acetate/hexanes) afforded a complex mixture of products, some of which could be isolated and tentatively identified based on NMR and mass spectral data (yields based on initial amount of diester **28**). Starting material **28** (0.010 g, 0.028 mmol, 1 %), **41** (0.040 g, 0.10 mmol, 4 %), **42** (0.25 g, 0.35 mmol, 25 %), **43** (0.036 g, 0.054 mmol, 4 %), **44** (0.20 g, 0.20 mmol, 21 %). Washing the column with methanol eluted a mixture of very polar materials (by tlc) which were not characterized further.

41: ^{1}H NMR δ 8.46 (s, 1H), 8.01 (s, 1H), 7.64-7.56 (m, 2H), 7.39-7.35 (m, 2H), 3.98 (s, 3H), 3.97 (s, 3H), 3.41 (s, 1H).

42: ^{1}H NMR δ 8.47 (s, 2H), 8.03 (s, 2H), 7.68-7.65 (m, 2H), 7.43-7.40 (m, 2H), 3.96 (s, 6H), 3.91 (s, 6H); 13C NMR δ (obvious peaks only) 162.4, 162.1, 137.1, 130.8, 129.9, 126.4, 93.9, 87.9, 50.0, 49.8; EI-MS *m/z* (%) 668 (2, M^+), 653 (100).

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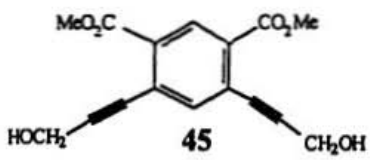
[41] *Aldrich Catalogue Handbook of Fine Chemicals* Aldrich Co., Milwaukee, 1997, p. 510.

43: ^{1}H NMR δ 8.64 (s, 1H), 8.41 (s, 1H), 8.03 (s, 2H), 7.58-7.50 (m, 4H), 7.38-7.32 (m, 4H), 3.98 (s, 3H), 3.91 (s, 3H), 3.89 (s, 3H), 3.87 (s, 3H), 3.27 (s, 1H).

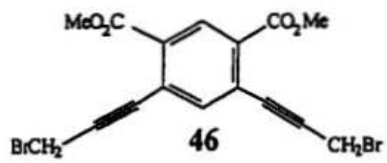
44: ^{1}H NMR δ 8.68 (s, 1H), 8.34 (s, 2H), 8.17 (s, 1H), 7.92 (s, 2H), 7.66-7.62 (m, 4H), 7.32-7.38 (m, 4H), 3.94 (s, 6H), 3.90 (s, 6H), 3.85 (s, 6H).



45

Dimethyl 4,6-*bis*(3-hydroxy-1-propynyl)isophthalate, 45. Diester **28** (2.00 g, 5.68 mmol), propargyl alcohol (2.0 mL, 2.9 g, 51 mmol), triethylamine (2.0 mL, 14.1 mmol), $Pd(PPh_3)_4$ (0.10 g, 0.087 mmol) and CuI (0.10 g, 0.53 mmol) were dissolved in dry DMF (25 mL), and the reaction was stirred at room temperature under N_2. After 7 days, the reaction was poured into saturated aqueous $NH_4Cl_{(aq)}$ (50 mL). This was extracted with diethyl ether (3 x 50 mL), which was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Column chromatography (1:1 ethyl acetate/hexanes) yielded **45** (0.82 g, 2.71 mmol, 48 %) as a colorless solid.

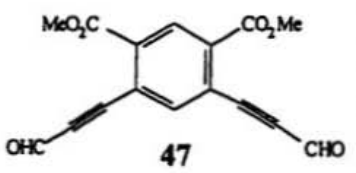
45: mp 132-133 °C (ethyl acetate/60-80 petroleum ether); IR ($CHCl_3$) 3660 (m), 3620 (m), 3510 (s), 3030 (s), 2890 (s), 2400 (s), 2230 (s), 1720 (s), 1595 (m), 1535 (s), 1435 (s); ^{1}H NMR δ 8.32 (s, 1H), 7.67 (s, 1H), 5.43 (t, *J*=6.0, 2H), 4.37 (d, *J*=5.9, 4H), 3.87 (s, 6H); ^{13}C NMR δ 164.5, 138.7, 131.8, 130.5, 126.0, 98.6, 80.7, 52.5, 49.6; EI-MS *m/z* (%) 302 (M^+, 96), 287 (73), 273 (100), 259 (54), 241 (31), 215 (40), 199 (28), 127 (32), 115.0 (34), 75 (37). Anal. Calc'd for $C_{16}H_{14}O_6$: C, 63.24; H, 4.47. Found: C, 63.57; H, 4.67.



46

Dimethyl 4,6-*bis*(3-bromo-1-propynyl)isophthalate, 46. Diester **28** (0.240 g, 0.79 mmol) and CBr_4 (0.99 g, 2.99 mmol) were dissolved in THF (50 mL) and cooled to 0 °C. PPh_3 (0.83 g, 3.16 mmol) was dissolved in THF (10 mL) and added to the diester solution dropwise under N_2. The reaction was then allowed to warm to room temperature and stirred for 1 day. The solvent was then removed under reduced pressure, and column chromatography (20 % ethyl acetate/hexanes) yielded pure **46** (0.21 g, 0.49 mmol, 62 %) as a colorless solid.

46: mp 131-133 °C (EtOAc/hexanes). IR ($CHCl_3$) 3040 (m), 2960 (m), 2400 (m), 1720 (s), 1600 (m), 1550 (m), 1435 (s). ^{1}H NMR δ 8.56 (s, 1H), 7.73 (s, 1H), 4.21 (s, 4H), 3.97 (s, 6H). ^{13}C NMR δ 164.9, 139.8, 132.8, 131.2, 126.1, 92.6, 83.5, 52.6, 14.5; EI-MS *m/z* (%) 350 (16), 349 (91), 348 (16), 347 (89), 253 (100), 223 (38), 138 (20), 87 (18), 82 (19), 80 (19), 75 (25.0). Anal. Calc'd for $C_{16}H_{12}Br_2O_4$: C, 44.89; H, 2.82. Found: C, 44.78; H, 2.58.



47

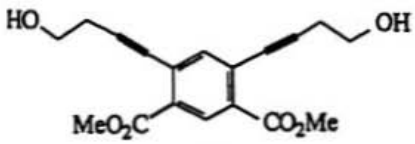
Dimethyl 4,6-*bis*(3-oxo-1-propynyl)isophthalate, 47. Freshly prepared Dess-Martin reagent (0.53 g, 1.3 mmol)[27] was dissolved in CH_2Cl_2 (25 mL). Diester **28** (0.19 g, 0.62 mmol) was dissolved in CH_2Cl_2 (40 mL). This was added to the periodinane solution dropwise at room temperature. After 40 min, the reaction was not complete, so another 0.25 g (0.59 mmol) of Dess-Martin reagent was added. The reaction was then poured into 1 M aqueous NaOH (50 mL) and ether (150 mL). The organic layer was washed with 1 M aqueous NaOH (50 mL), water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography (CH_2Cl_2) afforded pure **47** (0.14 g, 0.47 mmol, 76 %) as an unstable white solid (identified by a 100 MHz NMR spectrum) that darkened in the solid state and in solution. The compound was not characterized further but was used immediately in the next step.

Attempted Synthesis of Thiacyclophane 48. Dibromodiester **46** (0.39 g, 0.91 mmol) was dissolved in 10 % EtOH / CH_2Cl_2 (100 mL). Freshly prepared Na_2S/Al_2O_3[1] (1.10 g, 2.29 mmol) was added in portions over 40 min. The reaction turned black. Filtration followed by concentration afforded a brown oil (0.37 g), which was insoluble in CH_2Cl_2 but somewhat soluble in acetone. The product spot on tlc did not move in CH_2Cl_2, and streaked severely in more polar solvents. Further isolation was not attempted.

Attempted McMurry Reaction. Dioxodiester **47** (0.040 g, 0.13 mmol) was dissolved in THF (30 mL) and cooled to 0 °C under N_2. $TiCl_4$ (0.1 mL) was added, forming a yellow solution. Freshly activated Zn powder (0.10 g, 1.5 mmol) was added, and the reaction turned black. Tlc analysis indicated that all starting material had been consumed, but all

tlc spots remained on the baseline even in neat ethyl acetate. Heating the reaction to reflux did not generate any mobile spots. Further manipulation was not undertaken.

Attempted Still-Gennari Coupling, 60. Dibromodiester **46** (0.035 g, 0.082 mmol) was suspended in tris(2,2,2-trifluoroethyl)phosphite (10 mL). This was heated to reflux under an air condenser. After 3 h, tlc analysis revealed most of the starting material was still present, with a number of faint spots in evidence. The reaction was heated for a further 5 days, after which the starting material had been consumed but a complex mixture of product spots remained on tlc. Isolation was not attempted.



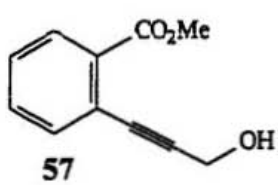
53

Dimethyl 4,6-*bis*(4-hydroxy-1-butynyl)isophthalate, 53. Dibromodiester **28** (1.00 g, 2.84 mmol), 3-butyn-1-ol (0.63 g, 9.0 mmol, 3.5 eq.), triethylamine (1.0 mL, 7.3 mmol), $Pd(PPh_3)_4$ (50 mg, 0.043 mmol), and CuI (56 mg) were mixed in DMF (25 mL). The resulting solution was heated to 110 °C for 1 h. The mixture was then cooled and poured into aqueous 1 M HCl (100 mL). This was extracted with Et_2O (3 x 50 mL) which was washed with brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a yellow-brown oil. Chromatography (1:1 ethyl acetate/hexane) gave the desired product **53** (0.25 g, 0.76 mmol, 27 %) as a colorless solid.

53: mp 96-97 °C (ethyl acetate/hexanes); IR ($CHCl_3$) 3510 (s), 3030 (s), 2400 (s), 1720 (s), 1600 (m), 1535 (s), 1425 (s); ^{1}H NMR δ 8.53 (s, 1H), 7.61 (s, 1H), 3.93 (s, 6H), 3.88 (q, *J*=5.9, 4H), 3.58 (t, *J*=6.5, 2H), 2.74 (t, *J*=5.7, 4H). ^{13}C NMR δ 165.0, 138.6, 132.8, 129.5, 127.9, 97.3, 80.4, 60.6, 52.5, 24.4; EI-MS *m/z* (%) 330 (M^+, 11), 313 (20), 301 (20), 300 (100), 299 (24), 227 (42). Anal. Calc'd for $C_{20}H_{18}O_6$: C, 65.45; H, 5.49. Found: C, 65.09; H, 5.27.

Attempted Syntheses of Dimethyl 4,6-bis(4-oxo-1-butynyl)isophthalate, 54. Oxalyl chloride (0.12 g, 0.94 mmol) in CH_2Cl_2 (10 mL) was cooled to -78 °C, and DMSO (0.160 g, 2.05 mmol) in CH_2Cl_2 (10 mL) was added dropwise. The reaction was stirred at -78 °C for 15 minutes. The diol **53** (0.050 g, 0.15 mmol) in CH_2Cl_2 (10 mL) was added, then the reaction was allowed to warm to room temperature, turning black as it did so. A drop of

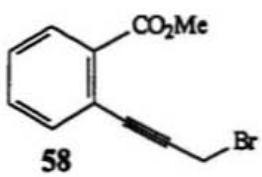
Et_3N in CH_2Cl_2 (2 mL) was added. A smell of Me_2S was observed, but TLC showed only baseline material present. The reaction was quenched and washed with H_2O (30 mL). A intractable solid gradually was deposited from the organic solution, which showed only baseline spots by tlc. Similar results were observed for test-tube tests of **53** (10 mg) with PCC and Dess-Martin reagent.[27]



57

Methyl 2-(3-hydroxy-1-propynyl)benzoate, 57. Methyl 2-iodobenzoate (5.10 g, 19.5 mmol), propargyl alcohol (1.58 g, 28.2 mmol), DBU (4.58 g, 28.2 mmol), $Pd(PPh_3)_4$ (0.100 g, 0.087 mmol), and CuI (0.73 g, 3.8 mmol) were dissolved in distilled benzene (100 mL) and degassed under vacuum. The solution was stirred at room temperature under N_2. After 48 h, the dark reaction mixture was filtered and the filtrate was concentrated. Chromatography of the residue (CH_2Cl_2, then 10 % ethyl acetate/CH_2Cl_2), yielded **57** (3.21 g, 16.9 mmol, 87 %) as a colorless oil.

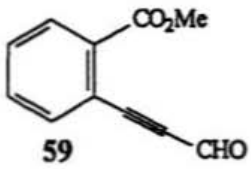
57: ^{1}H NMR δ 7.95 (d, *J*=7.9, 1H), 7.56 (d, *J*=7.7, 1H), 7.47 (t, *J*=7.4, 1H) 7.38 (t, *J*=7.9, 1H), 4.57 (s, 2H), 3.92 (s, 3H), 2.45 (br s, 1H); ^{13}C NMR δ 166.5, 134.1, 131.8, 130.3, 128.0, 123.3, 92.7, 84.3, 52.2, 51.7; EI-MS *m/z* (%) 190 (M^+, 25), 175 (88), 161 (37), 159 (33), 149 (26), 147 (100), 129 (51), 103 (31), 102 (32), 101 (40), 91 (33), 77 (51);



58

Methyl 2-(3-bromo -1-propynyl)benzoate, 58. Hydroxyester **57** (0.51 g, 2.68 mmol) and CBr_4 (2.61 g, 7.87 mmol) were dissolved in THF (50 mL). PPh_3 (2.11 g, 8.04 mmol) was added, and the solution was stirred at room temperature for 6 h. It was then filtered, diethyl ether was added, and the organic solution was washed with H_2O (50 mL), saturated aqueous $NaHCO_3$ (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Column chromatography (30 % CH_2Cl_2/hexanes) afforded pure **58** (0.34 g, 1.3 mmol, 50 %) as a colorless oil.

58: ^{1}H NMR δ 7.93 (d, *J*=7.8, 1H), 7.55-7.36 (m, 3H), 4.23 (s, 2H), 3.93 (s, 3H); ^{13}C NMR δ 166.1, 134.0, 131.8, 131.5, 130.2, 128.3, 122.3, 88.8, 85.1, 52.0, 15.2; EI-MS *m/z* (%) 223 (3), 221 (2.5), 174 (12), 173 (100), 143 (22), 114 (15), 102 (14). Anal. Calc'd for $C_{11}H_9BrO_2$: C, 52.20; H, 3.58. Found: C, 51.73; H, 3.48.



59

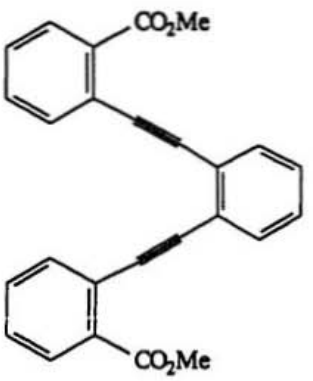
Methyl 2-(3-oxo-1-propynyl)benzoate, 59. Dess-Martin reagent (1.00 g, 2.37 mmol) was dissolved in CH_2Cl_2 (40 mL). Hydroxyester **57** (0.400 g, 2.10 mmol) was dissolved in CH_2Cl_2 (20 mL) and added dropwise to the periodinane solution. After 30 min, the reaction was poured into diethyl ether (100 mL) and washed with saturated aqueous NH_4Cl (2 x 50 mL) containing 10 g $Na_2S_2O_3$. The organic layer was then washed with water (50 mL) and brine (50 mL) dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Column chromatography (CH_2Cl_2) afforded pure **59** (0.40 g, 2.1 mmol, 100 %) as a colorless oil. This compound darkened slowly when pure, so no satisfactory elemental analysis results was obtained.

59: ^{1}H NMR δ 9.50 (s, 1H), 8.08-8.04 (m, 1H), 7.74-7.68 (m, 1H), 7.62-7.51 (m, 2H), 3.97 (s, 3H); ^{13}C NMR δ 176.9, 165.6, 135.3, 132.9, 132.1, 130.8, 130.6, 120.1, 93.2, 91.9, 52.5; EI-MS *m/z* (%) 188 (9, M^+), 173 (100), 157 (38), 129 (22), 102 (29), 101 (66), 89 (20).

Attempted McMurry Coupling of 59: Oxoester **59** (0.150 g, 0.8 mmol) was dissolved in dry THF (50 mL) under N_2 and cooled to 0 °C. $TiCl_4$ (0.3 mL) was added by syringe, then Zn powder (0.300 g, 4.59 mmol) was added. The reaction went black and tlc showed mostly baseline material, and a mixture of faint spots above baseline

Attempted Wittig Coupling of 58 and 59. Bromoester **58** (0.300 g, 1.18 mmol) was dissolved in toluene (10 mL). PPh_3 (0.371 g, 1.41 mmol) was added. The reaction gradually turned dark brown, but no precipitate was observed. The reaction was concentrated and column chromatography (CH_2Cl_2) gave PPh_3 (0.175 g, 0.667 mmol) and an unidentified colored compound (0.120 g). No compound corresponding to phosphonium salt **61** was isolated.

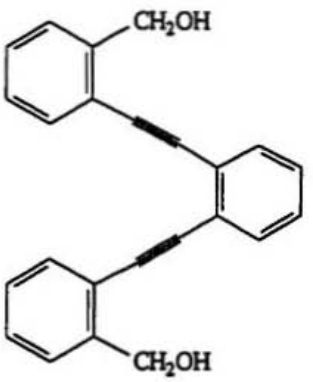
1,2-*Bis*(4-(methoxycarbonyl)phenylethynyl)benzene, 62. Methyl 2-iodobenzoate (2.28 g, 8.72 mmol), *o*-diethynylbenzene **38** (0.55 g, 4.4 mmol), and DBU (1.66 g, 10.9 mmol) were dissolved in distilled benzene (100 mL) and degassed. $Pd(PPh_3)_2Cl_2$ (0.120 g) and CuI (0.10 g) were added, and the reaction was stirred under N_2, cooling in an ice bath due to exothermic reaction. After 6 h, The reaction was filtered and the filtrate was



62

concentrated under reduced pressure, yielding a brown oil. Column chromatography (70 % CH_2Cl_2/hexanes) afforded diester **62** (1.58 g, 4.01 mmol, 92 %) as a colorless solid.

62: mp (benzene/hexane) 72-73 °C; ^{1}H NMR δ 7.97 (d, *J*=7.7, 2H), 7.70-7.61 (m, 4H), 7.46-7.31 (m, 6H), 3.86 (s, 6H). ^{13}C NMR δ 166.4, 134.2, 132.2, 131.6, 131.5, 130.4, 128.2, 127.9, 125.7, 123.6, 93.1, 92.1, 52.0; EI-MS *m/z* (%) 394 (M^+, 3), 380 (27), 379 (100), 365 (20), 364 (75), 320 (21), 274 (21), 263 (34), 138 (22). Anal. Calc'd for $C_{26}H_{18}O_4$: C, 79.17; H, 4.60. Found: C, 79.06; H, 4.71.

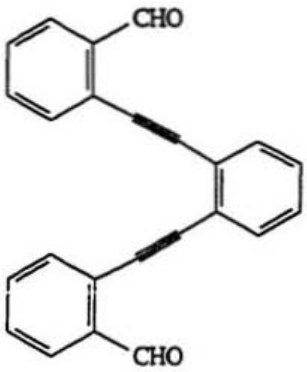


63

1,2-*Bis*(4-(hydroxymethyl)phenylethynyl)benzene, 63. Diester **62** (0.49 g, 1.24 mmol) was dissolved in diethyl ether (100 mL). $LiBH_4$ (0.068 g, 3.1 mmol.) was added, and 5 drops of MeOH was slowly added with stirring.[42] After 10 min., the reaction was quenched with 1 mL ethyl acetate, then aqueous saturated NH_4Cl (50 mL) was added. The mixture was stirred for 15 min, the layers were separated, and the organic layer was washed with aqueous saturated NH_4Cl (50 mL), water (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography of the residue (50 % ethyl acetate/hexanes) afforded diol **63** (0.42 g, 1.24 mmol, 100 %) as a colorless solid.

63: mp 116-117 °C ($CHCl_3$); ^{1}H NMR (acetone-d_6) δ 7.67-7.27 (m, 12H), 4.92 (s, 4H), 4.52 (s, 2H); ^{13}C NMR(acetone-d_6) δ 141.5, 129.5, 129.0, 126.1, 125.8, 124.0, 123.6, 122.4, 117.3, 89.7, 88.1, 59.3; EI-MS *m/z* (%) 338 (M^+, 24), 320 (60), 303 (83), 291 (85), 290 (60), 289 (100), 276 (59), 219 (47), 202 (48), 145 (61), 138 (48), 119 (58), 28 (74). Anal. Calc'd for $C_{24}H_{18}O_2$: C, 85.18; H, 5.36. Found: C, 84.81, H, 5.29.

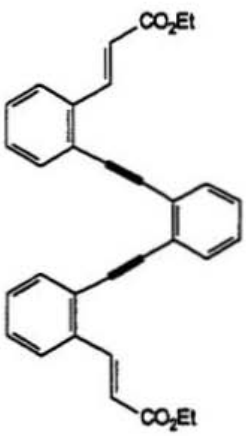
[42] Soai, K.; Ookawa, A. *J. Org. Chem.* **1986**, *51*, 4000-4005.



64

1,2-*Bis*(4-formylphenylethynyl)benzene, 64. Dess-Martin reagent (1.30 g, 3.08 mmol) was dissolved in CH_2Cl_2 (20 mL) and diol **63** (0.42 g, 1.24 mmol) was suspended in CH_2Cl_2 (20 mL) and added slowly to the periodinane solution. After five min., the reaction was poured into diethyl ether (100 mL) and aqueous 2 M NaOH (50 mL). The layers were separated, and the organic layer washed with aqueous 2 M NaOH (50 mL), then aqueous saturated NH_4Cl (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. This afforded **64** (0.41 g, 1.23 mmol, 99 %) as a colorless solid. Elemental analysis results for this compound were consistently very poor.

64: ^{1}H NMR δ 10.72 (s, 2H), 7.95 (d, *J*=7.8, 2H), 7.69-7.40 (m, 10H); ^{13}C NMR δ 191.5, 135.9, 133.9, 133.3, 132.4, 129.2, 129.0, 128.9, 127.3, 124.9, 120.2, 94.7, 89.2; EI-MS *m/z* (%) 334 (19, M^+), 306 (34), 305 (100), 277 (28), 276 (66), 274 (21), 138 (40).



65

1,2-*Bis*(4-(2-(ethoxycarbonyl)vinyl)phenylethynyl)benzene, 65: NaH (0.109 g, 2.72 mmol) was suspended in dry THF (50 mL). Triethyl phosphonoacetate (0.5 mL) was added by syringe until the solution was clear. Dialdehyde **64** (0.41 g, 1.2 mmol) was dissolved in dry THF (50 mL) and added to the ylide solution dropwise at room temperature, turning the solution brown. The reaction was stirred under N_2 overnight. The reaction was quenched with aqueous saturated NH_4Cl (1 mL) and the solvent was removed under reduced pressure. The residue was redissolved in diethyl ether (40 mL) and washed with aqueous saturated NH_4Cl (50 mL) and brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to yield a yellow oil. Chromatography (30 % ethyl acetate/hexanes) afforded pure **65** (0.41 g, 0.76 mmol, 63 %) as a colorless solid.

65: mp 75.5-77 °C (benzene/heptane); ^{1}H NMR δ 8.31 (d, *J*=16.1, 2H), 7.67-7.62 (m, 4H), 7.57-7.53 (m, 2H), 7.37-7.26 (m, 6H), 6.52 (d, *J*=16.2, 2H), 4.10 (d, *J*=7.1, 4H), 1.25 (t, *J*=7.0, 6H); ^{13}C NMR δ 166.5, 142.1, 135.7, 133.0, 132.0, 129.5, 128.6, 128.5, 128.3, 126.0, 125.3, 123.9, 119.8, 94.1, 91.1, 60.3, 14.1; EI-MS *m/z* (%) 474 (M^+, 8), 399 (25), 371 (28), 355 (38), 343 (33), 328 (40), 327 (100), 326 (98), 324 (29), 313 (21), 163 (23). Anal. Calc'd for $C_{32}H_{26}O_4$: C, 80.99; H, 5.52. Found: C, 81.01; H, 5.36.

Sample Bergman Reaction: Diester **62** (1.05 g, 2.65 mmol) was dissolved in freshly distilled *o*-dichlorobenzene (5 mL) and placed in a glass tube with γ-terpinene (2 mL). The solution was degassed by freezing in liquid N_2 and thawing under reduced pressure (1 mm Hg). The tube was then sealed and heated to 257 °C in a muffle furnace. After 6 h, the tube was removed and allowed to cool. The flask was broken and the volatile solvents removed by vacuum distillation. Column chromatography in 60 % CH_2Cl_2/hexanes which afforded a number of impure, unidentified products, as well as partially hydrogenated **66** (0.130 g, 0.33 mmol, 12 %) and recovered **62** (0.77 g, 2.0 mmol, 75 %).

Chapter 5 – Synthesis of [n]Pyrenophanes

5.1 Nonplanar PAHs

5.1.1 – Introduction

The previous chapters have described aromatic compounds that feature nonplanar aromatic systems and the formidable synthetic challenges that such compounds pose, as well as some of the unusual conformational, spectroscopic, and chemical behavior these compounds display. The question of to what extent an aromatic ring can be bent while remaining stable and isolable under ambient conditions, and retaining its "aromatic" properties, has been probed in great detail through experimental and theoretical studies of, for example, the [n]metacyclophanes and [n]paracyclophanes, as described in Chapter 2. In summary, for the latter class of compounds, it has been shown that, while

1a **1b** **1c**

[6]paracyclophane, **1a**, is stable under ambient conditions,[1] [5]paracyclophane, **1b**, exists only in solution as a minor component (6-7 %) in equilibrium with its Dewar benzene isomer and is unstable even at 0 °C.[2] [4]Paracyclophane, **1c**, has never been isolated and has only been detected by trapping reagents or by UV spectroscopy in a matrix at very low temperatures,[3] although some functionalized derivatives are slightly more stable.[4] The stability normally associated with benzene is clearly attenuated drastically by the strain imposed by short tethers. It is nevertheless clear that benzene rings can be distinctly bent without losing many of their other normal 'aromatic' characteristics, such as a diatropic ring current and a high degree of bond equalization.

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[1] Kane, V.V.; Wolf, A.D.; Jones Jr., M. *J. Am. Chem. Soc.* **1974**, *96*, 2643-2644.

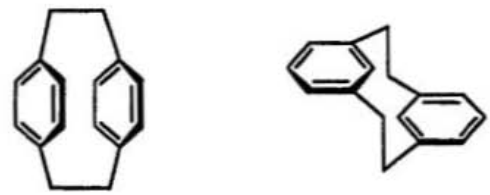
[2] Jenneskens, L.W.; de Kanter, F.J.J.; Kraakman, P.A.; Turkenburg, L.A.M.; Koolhaas, W.E.; de Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716-3717.

[3] a) Tsuji, T.; Nishida, S. *J. Chem. Soc., Chem. Commun.* **1987**, 1189-1190. b) Kostermans, G.B.M.; Bobeldijk, M.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 2471-2475. c) Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1988**, *110*, 2157-2164.

[4] a) Tsuji, T.; Nishida, S. *J. Am. Chem. Soc.* **1989**, *111*, 368-369. b) Tsuji, T.; Nishida, S.; Okuyama, M.; Osawa, E. *J. Am. Chem. Soc.* **1995**, *117*, 9804-9813. c) Okuyama, M.; Tsuji, T. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 1085-1086.

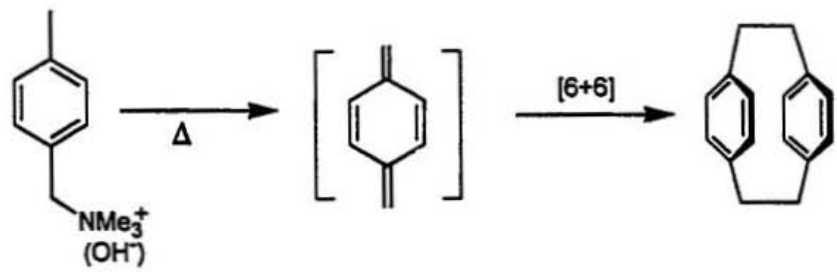
5.1.2 – Synthetic Methods For [2.2]Cyclophanes

A large proportion of the theoretically interesting cyclophanes, including many of those to be described in this chapter, are [2.2]cyclophanes, with two 2-atom bridges. A brief discussion of the methodology available for the preparation of [2.2]cyclophane frameworks (such as [2.2]paracyclophane, **2**, and [2.2]metacyclophane, **3**, shown here in



2 **3**

its more stable, *anti* conformation) is necessary.[5] The classical method (Scheme 5-1) for the synthesis of [2.2]paracyclophane **2** involves the thermolysis (110-150 °C) of benzylic trimethylammonium hydroxides, such as **4**, which, after a Hofmann elimination, generates *p*-xylylene intermediate **5**, which then dimerizes to form paracyclophane **2** in 17 % yield.[6] This dimerization is presumed to be stepwise, as a [6+6] dimerization is



4 **5** **2**

Scheme 5-1: [2.2]Paracyclophane Synthesis by Hofmann Elimination

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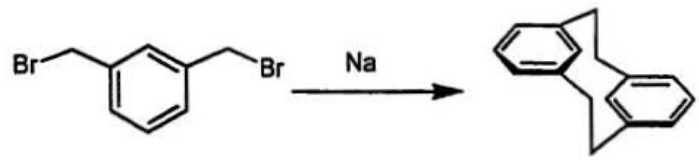
[5] For reviews of cyclophane synthesis methodology, see: a) Vögtle, F.; Neumann, P. *Synthesis* **1972**, 85-103. b) Keehn, P.M.; Rosenfeld, S.M., Eds. *Cyclophanes, Vol. 1* Academic Press, New York, **1983**. c) - Vögtle, F. *Cyclophan-Chemie* B.G. Teubner, Stuttgart, **1990**.

[6] Wynberg, H.E.; Fawcett, F.S.; Mochel, W.E; Theobald, C.W. *J. Am. Chem. Soc.* **1960**, *83*, 1428-1435.



6 3

Scheme 5-2: [2.2]Metacyclophane Synthesis by Wurtz Coupling

thermally disallowed according to the Woodward-Hoffmann rules.[7]

Such methodology is not applicable to the preparation of metacyclophane **3**, as a "*m*-xylylene" intermediate would be a highly energetic diradical. Compound **3** was first prepared by a simple Wurtz coupling (Scheme 5-2) of benzylic dibromide **6**, in a yield of 12 %.[8] Modifications of this Wurtz methodology have sometimes generated metacyclophane **3** in yields up to 35 %.[9]

2,11-Dithia[3.3]metacyclophane frameworks have proven to be very versatile precursors for the preparation of saturated and unsaturated [2.2]metacyclophane frameworks (Scheme 5-3). From dithiacyclophane **7**, sulfur extrusion can be achieved by photolysis in triethyl phosphite, or by oxidation to disulfone **8** and vacuum thermolysis to extrude SO_2.[10] Ring contraction can also be achieved by either a Wittig[11] or a Stevens[12] rearrangement, to generate a *bis*(methylthioether) **9**. Hofmann elimination of a derivative of this compound will afford the cyclophanediene **10**, which can (in theory) be hydrogenated to the cyclophane **3** or dehydrogenated to pyrene, **11**.[13] The application of these methodologies to the preparation of polycyclic aromatic hydrocarbon (PAH)-containing cyclophanes will now be considered.

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[7] a) Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* **1965**, *87*, 2046-2048 b) Longone, D.T.; Reetz, M.T. *J. Chem. Soc., Chem. Commun.* **1967**, 46-47.

[8] a) Pellegrin, M. *Rec. Trav. Chim. Pays-Bas* **1899**, *18*, 457. b) Baker, W.; McOmie, J. F.W.; Norman, J.M. *J. Chem. Soc.* **1951**, 1114-1118.

[9] a) Burri, K.; Jenny, W. *Helv. Chim. Acta* **1967**, *50*, 1978-1993. b) Flammang, R.; Figeys, H.P.; Martin, R.H. *Tetrahedron* **1968**, *24*, 1171-1185.

[10] a) Vögtle, F.; Schunder, L. *Chem. Ber.* **1969**, *102*, 2677-2683. b) Vögtle, F. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 274.

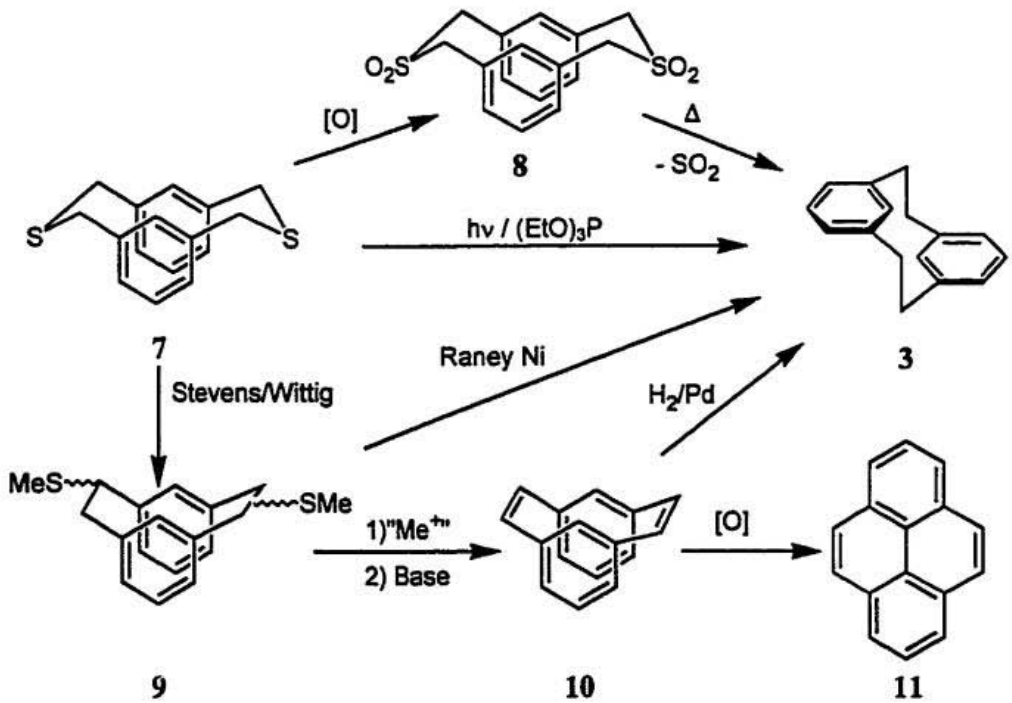
[11] Mitchell, R.H.; Otsubo, T.; Boekelheide, V. *Tetrahedron Lett.* **1975**, 219-222.

[12] Thomson, T.; Stevens, T. S. *J. Chem. Soc.* **1932**, 69-73. For the mechanism of the Stevens Rearrangement, see Baldwin, J.E.; Erickson, W.F.; Hackler, R.E.; Scott, R.M. *J. Chem. Soc., Chem. Commun.* **1970**, 576-578.

[13] Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1974**, *96*, 1547-1557.

5.1.3 - PAH – Containing Cyclophanes

In contrast with isolated benzene rings, the tolerance of polycyclic aromatic frameworks to distortion from planarity has received sparse and non-systematic attention. Many cyclophanes containing polycyclic aromatic hydrocarbons have been reported over the past four decades.[14] Among the first PAH-containing cyclophanes prepared were the [2.2](1,4)naphthalenoparacyclophane **12** and the [2.2](1,4)naphthalenophane **13**. The syntheses of these compounds illustrate the classical methods described in the previous paragraphs. Cram's synthesis of **12**[15] and Wassermann's preparation of **12**[16] and **13**[17] both rely on the Hoffmann elimination route, via benzo-*p*-xylylene **14**. Sondheimer's synthesis of **13**,[18] by the solvolysis of ditosylate **15** in pyridine, is also believed to involve



Scheme 5-3: Synthetic Pathways from Dithia[3.3]metacyclophane, **7**

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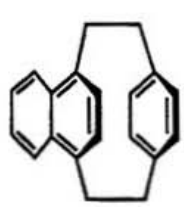
[14] Reiss, J.A. in Keehn, P.M.; Rosenfeld, S.M. Eds. *Cyclophanes, Vol. II* Academic Press, New York, 1983, pp. 443-484.
[15] Cram, D.J.; Dalton, C.K.; Knox, G.R. *J. Am. Chem. Soc.* 1963, *85*, 1088-1093.
[16] Wassermann, H.H.; Keehn, P.M. *J. Am. Chem. Soc.* 1972, *94*, 298-300.
[17] Wassermann, H.H.; Keehn, P.M. *J. Am. Chem. Soc.* 1969, *91*, 2374-2375.
[18] Brown, G.W.; Sondheimer, F. *J. Am. Chem. Soc.* 1967, *89*, 7116-7117.



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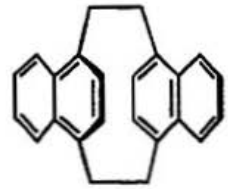

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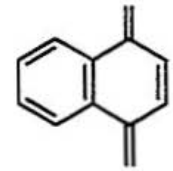

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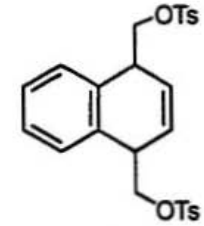
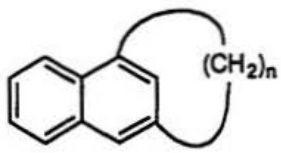


15

intermediates such as **14**, but proceeds in an extraordinarily high yield of 90%. Compound **13** has also been prepared via the sulfur extrusion route, as in Bruhin and Jenny's work.[19] Other methods to (1,4)[2,2]naphthalenophanes have also been reported.[20]

Other naphthalenophanes have also been prepared. Examples include [n](1,3)naphthalenophane **16** (essentially a benzo[n]metacyclophane),[21] [n](1,4)naphthalenophane **17** (a benzo[n]paracyclophane),[22] [2.2](2,7)naphthalenophane **18** (prepared via a Wurtz coupling route),[23] and [2.2](2,6)naphthalenophanes such as **19** (prepared from the corresponding [3.3]dithiacyclophane by oxidation and SO_2 extrusion).[24]

Anthracene-containing cyclophanes have also been prepared, such as an early



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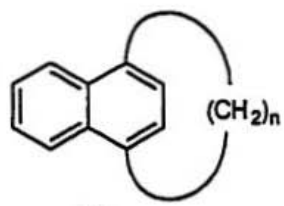

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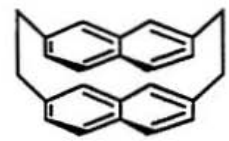

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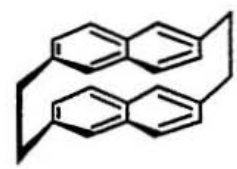

19

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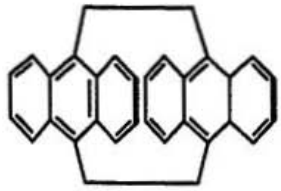
[19] Bruhin, J.; Jenny, W. *Tetrahedron Lett.* **1973**, 1215-1218.

[20] Kleinschroth, J.; Hopf, H. *Tetrahedron Lett.* **1978**, 969-972.

[21] a) Parham, W.E.; Johnson, D.R.; Hughes, C.T.; Meilahn, M.K.; Rinehart, J.K. *J. Org. Chem.* **1970**, *35*, 1048-1052. b) Parham, W.E.; Egberg, D.C.; Montgomery, W.C. *J. Org. Chem.* **1973**, *38*, 1207-1210. c) Parham, W.E.; Montgomery, W.C. *J. Org. Chem.* **1974**, *39*, 3411-3412. d) Grice, P.; Reese, C.B. *J. Chem. Soc., Chem. Commun.* **1980**, 424-425.

[22] a) Wiberg, K.B.; O'Donnell, M.J. *J. Am. Chem. Soc.* **1979**, *101*, 6660-6663. b) Tobe, Y.; Takahashi, T.; Ishikawa, T.; Yoshimura, M.; Suwa, M.; Kobiro, K.; Kakiuchi, K.; Gleiter, R. *J. Am. Chem. Soc.* **1990**, *112*, 8889-8894. A [5](1,4)naphthalenophane derivative has been reported by Bickelhaupt and co-workers: Van Es, D.S.; de Kanter, F.J.J.; de Wolf, W.H.; Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2553-2555.

[23] Baker, W.; McOmie, J.F.W.; Warburton, W.K. *J. Chem. Soc.* **1952**, 2991-2993.



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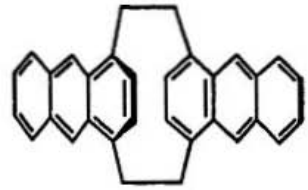

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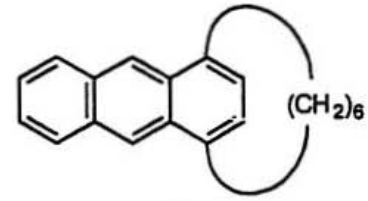
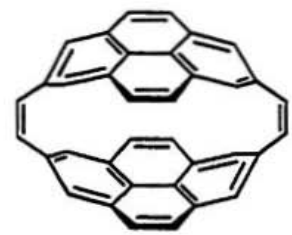


22

synthesis of [2.2](9,10)anthracenophane **20** by the treatment of 9,10-*bis*(chloromethyl)anthracene with NaI in acetone, an alternate method for the generation of a *p*-xylylene structure.[25] [2.2](1,4)Anthracenophane **21** has also been prepared by a Hofmann elimination/dimerization route.[26] A [6](1,4)anthracenophane, **22**, and a [6](9,10)anthracenophane have also been reported recently by Tobe.[22b]

A few pyrenophanes have also been reported, the ones most significant to this discussion being the [2.2](2,7)pyrenophane **23** and its 1,13-diene **24**. These two molecules were first prepared in 1975 by a Japanese group.[27] Subsequently, **23** was also reported by Canadian[28] and German[29] researchers. In all three cases, the molecule was constructed using some variant of the sulfur extrusion/ring contraction methodology.

23



24

5.2 – Synthesis and Chemistry of 1,n-Dioxa[n](2,7)pyrenophanes

5.2.1 – The Project

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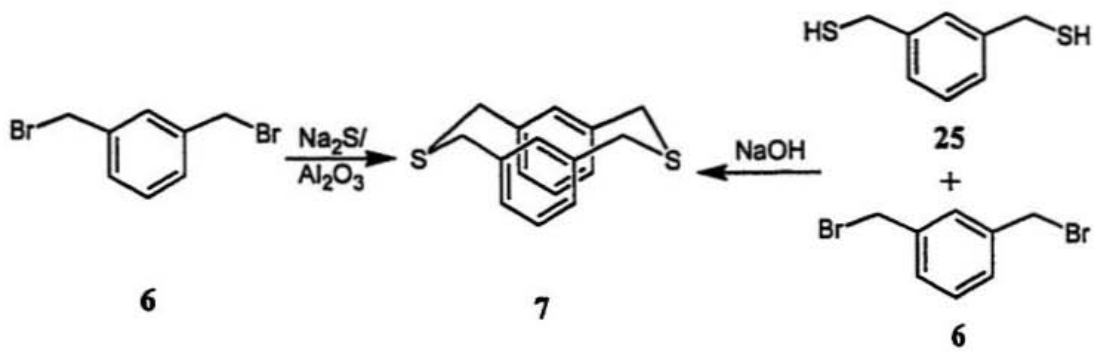
[24] a) Staab, H.A.; Haenel, M. *Tetrahedron Lett.* **1970**, 3585-3588. b) Haenel, M.W. *Tetrahedron Lett.* **1977**, 4191-4194.
[25] Golden, J.H. *J. Chem. Soc.* **1961**, 3741-3747.
[26] Toyoda, T.; Otsubo, I.; Otsubo, T.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1972**, 1731-1734.
[27] Umemoto, T.; Satani, S.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1975**, 3159-3162.
[28] Mitchell, R.H.; Carruthers, R.J.; Zwinkela, J.C.M. *Tetrahedron Lett.* **1976**, 2585-2588.
[29] Imgartinger, H.; Kirrstetter, R.G.H.; Krieger, C.; Rodewald, H.; Staab, H.A. *Tetrahedron Lett.* **1977**, 1425-1428.

Examination of the cyclophanes described to this point reveals that most are simply benzanellated [n]metacyclophanes and [n]paracyclophanes, in which the nonplanar distortion is still effectively localized to a single benzene ring. Helicenes,[30] buckybowls, such as corannulene (as described in Chapter 3),[31] and a few novel cyclophanes such as the naphthalenophane **19** and the pyrenophane **23** are among the few examples of PAHs in which nonplanarity is spread over the entire aromatic surface. However, at the outset of our work in this area no systematic study of the tolerance of any PAH to distortion over its entire aromatic surface had ever been undertaken.

Prior to this worker's involvement in this research project, our group had developed a reagent, sodium sulfide adsorbed on alumina, which allowed the efficient synthesis of 2,11-dithia[3.3]metacyclophanes, **7**, from benzylic bromide precursors, **6**.[32] The older methodology for the synthesis of such compounds involved the slow addition of an equimolar solution of dithiol **25** and dibromide **6** to an alkaline medium (Scheme 5-4). This reaction demanded high dilution, vigorous mechanical stirring, and required a long time (several days at gram scales) for the addition (and hence the reaction) to be complete. By contrast, the Bodwell method could be carried out at moderate dilutions, in an Erlenmeyer flask open to the air, and was often complete in less than an hour. Also, because these conditions permitted nucleophilic ring closure of the cyclophane by a



Scheme 5-4: Two Methods for Dithiametacyclophane Synthesis

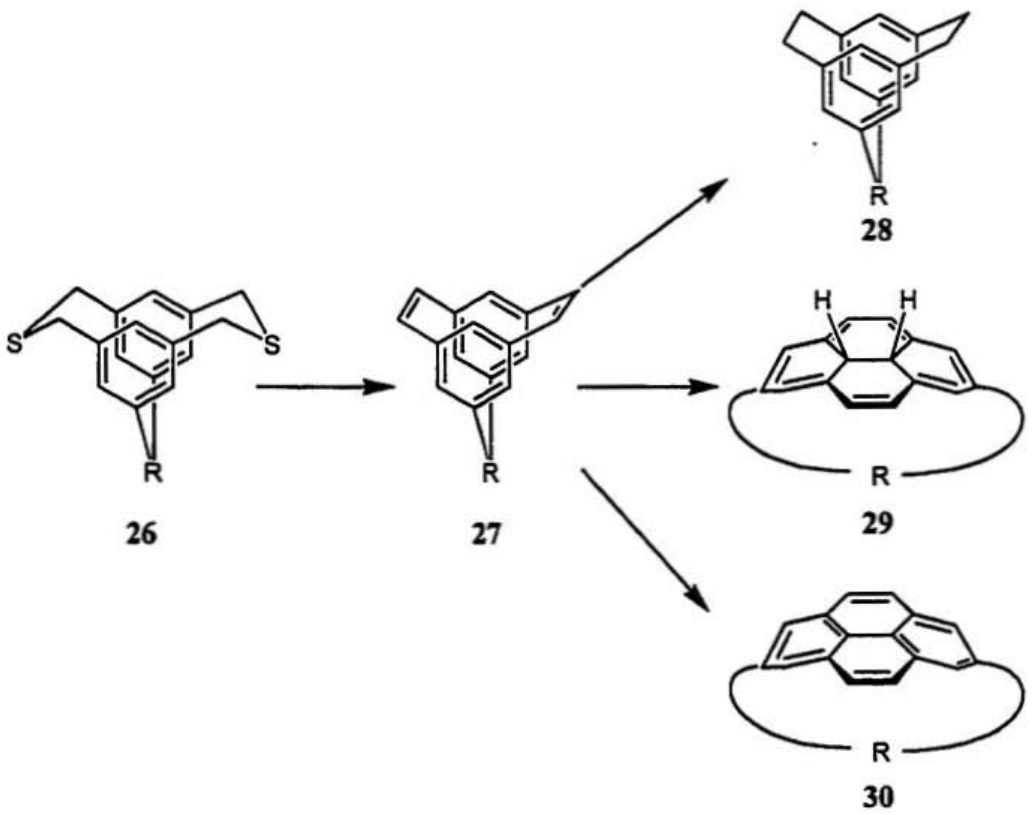
[30] a) Laarhoven, W.H.; Prinsen, W.J.C. *Top. Curr. Chem.* **125**, Springer Verlag, Berlin, **1984**. b) Meurer, K.P.; Vögtle, F. *Top. Curr. Chem.* **127**, Springer Verlag, Berlin, **1985**.

[31] For recent reviews on bowl-shaped fullerene fragments, see: a) Siegel, J.S.; Seiders, T.J. *Chem. Britain* **1995**, 313-316. b) Faust, R. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1429-1432. c) Rabideau, P.W.; Sygula, A. *Acc. Chem. Res.* **1996**, *29*, 235-242.

[32] Bodwell, G.J.; Houghton, T.J.; Koury, H.E.; Yarlagadda, B. *Synlett* **1995**, 751-752.

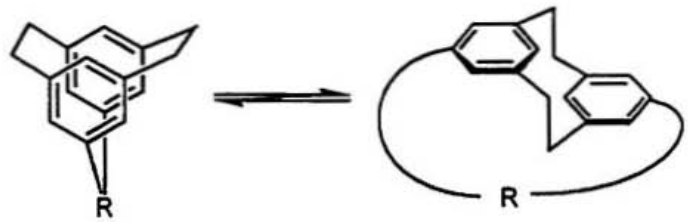
sulfide anion, "tethered" cyclophanes such as **26** could be synthesized, a transformation extremely difficult to achieve using the older method.

Tethered dithiametacyclophanes, **26** (in effect [n.3.3](1,3,5)cyclophanes, with n denoting the number of atoms in the tether), were plausible precursors for a number of novel cyclophanes (Scheme 5-5). The conversion of these compounds into tethered [2.2] metacyclophanedienes, **27**, by a ring contraction/elimination sequence seemed feasible. At this stage, a number of transformations could be envisioned. The dienes could be hydrogenated to generate the saturated tethered [2.2]metacyclophanes, **28**, which might display interesting conformational properties, as illustrated in Scheme 5-6.[33] These compounds were eventually prepared by thermolytic sulfur extrusion of an oxidized derivative of **26**. This work has been presented elsewhere[34] and will not be discussed



Scheme 5-5: Possible Transformations of Tethered Dithiametacyclophanes, **26**

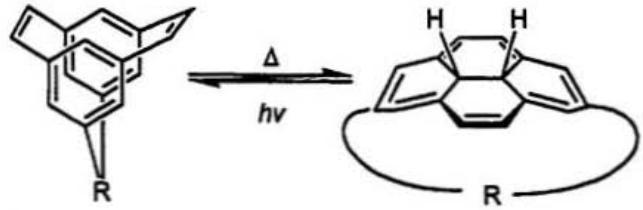
[33] Houghton, T. Ph.D. Thesis, Memorial University of Newfoundland, 1999.
[34] Bodwell, G.J.; Houghton, T.J.; Kennedy, J.W.J.; Mannion, M.R. *Angew. Chem., Int. Ed. Engl.* 1996, *35*, 2121-2123.



syn - **28** *anti* - **28**

Scheme 5-6: Conformational Properties of Cyclophane **28**

here. Another possibility for cyclophanediene **27** involved the valence isomerization of [2.2]metacyclophane-1,9-dienes, **27** to 10b,10c-dihydropyrenes, **29**.[35] The equilibrium for this isomerization, which is known in the parent (untethered) system bearing internal methyl groups, strongly favors the deep green dihydropyrene structure, with its 14-electron cyclic π-system in the periphery, over the colorless cyclophanediene isomer. The dihydropyrene can nevertheless be (at least partially) converted to the cyclophanediene by irradiation with visible light. The equilibrium can be restored by mild heating or by irradiation with ultraviolet light. Possibly, by adjusting the length of the tether in **29**, the equilibrium between the two could be modulated to produce a



Cyclophanediene, Colorless **27**

Dihydropyrene, Green **29**

Scheme 5-7: Possible Photochromism of **27** and **29**

photochromic compound (Scheme 5-7): one that loses its color (bleaches) on irradiation with light, and regenerates its color when heated. Work in this area has been conducted with limited success, and will not be discussed further here.[36]

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[35] Mitchell, R.H. *Adv. Theor. Interesting Mol.* **1989**, *1*, 135-199.
[36] Bodwell, G.J.; Chen, S.-L., unpublished results.

Another possibility was the dehydrogenation of the cyclophanedienes to generate the 'tethered pyrenes' or pyrenophanes, **30**. By varying the tether length in the acyclic precursor, a series of increasingly strained pyrenophanes could be prepared, allowing the systematic study of the effects of nonplanarity on a polycyclic aromatic hydrocarbon. In this chapter, the synthesis of a number of these [n]pyrenophanes will be described. The physical, chemical and spectroscopic properties of these compounds will be discussed in the next chapter.

5.2.2 - 1,n-Dioxa[n](2,7)pyrenophanes: Retrosynthesis

The first synthetic targets chosen were the pyrenophanes with oxygen atoms at either end of the tether, namely the 1,n-dioxa[n](2,7)pyrenophanes, **31**. The oxygens were required only as "synthetic handles" to allow the efficient introduction of the polymethylene tether. They would also allow easy removal of the tether, if so desired. As described in the previous section, a dioxa[n](2,7)pyrenophane **31** (Fig. 5-1) could be derived from a cyclophanediene **32**, which could in turn result from the ring contraction and elimination of a dithiacyclophane **33**. These compounds could be prepared from a tetrabromide such as **34**, which might arise by functional group interconversion of

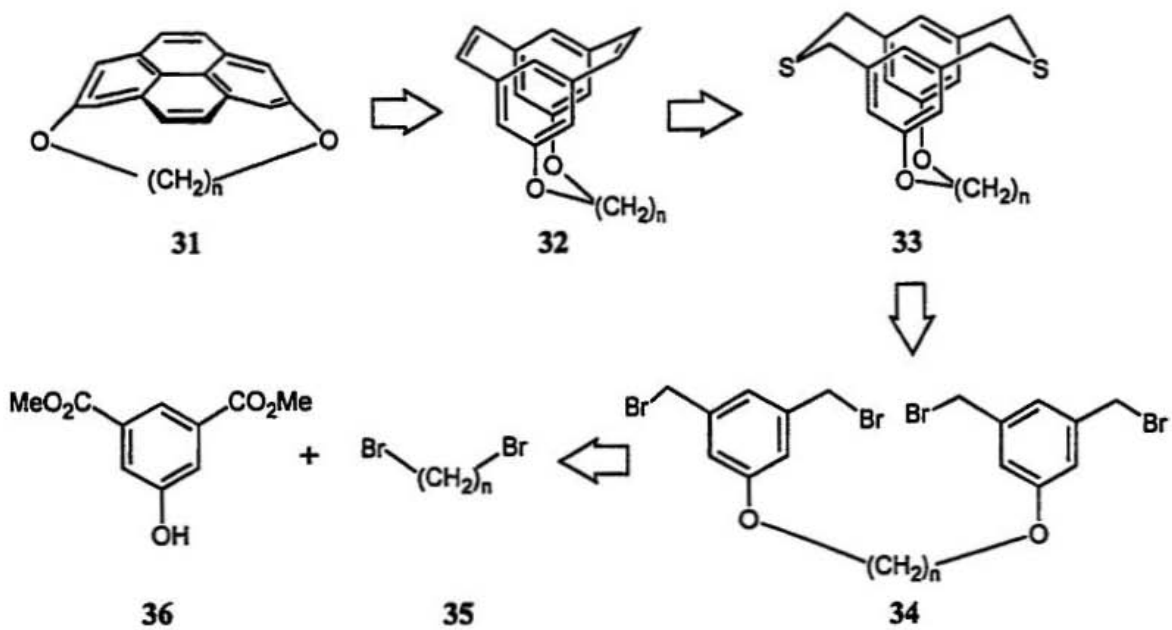
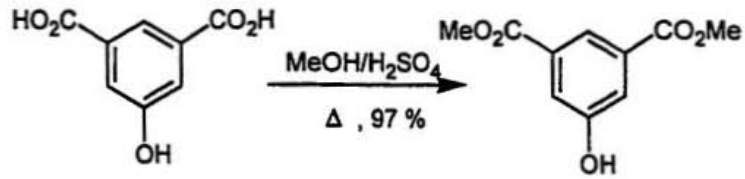


Figure 5-1: Retrosynthetic Analysis of 1,n-Dioxa[n](2,7)pyrenophane, **31**

tetraester synthesized by an etherification of a 5-hydroxyisophthalate such as **36** with an α,ω-dibromoalkane **35**.

5.2.3 - 1,n-Dioxa[n](2,7)pyrenophanes: Synthesis

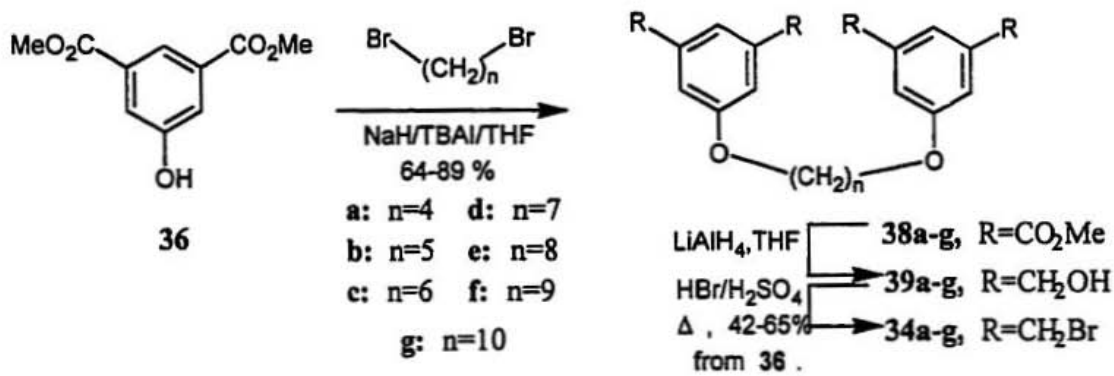
The synthesis of **31** began with commercially available 5-hydroxyisophthalic acid **37**, which was esterified (Scheme 5-8) under Fischer-Speier conditions



37 **36**

Scheme 5-8: Esterification of **37**

(methanol/H_2SO_4)[37] to afford dimethyl 5-hydroxyisophthalate, **36**, in 95 % yield. The tether was then introduced (Scheme 5-9) with a Williamson ether synthesis,[38] treating



36

Scheme 5-9: Synthesis of Tetrabromides **34** from Diester **36**

diester **36** with NaH and a 1,n-dibromoalkane in THF with TBAI as an ion pair disruptor[39] to afford tetraesters **38a-g**. These could be isolated by chromatography, but due to their insolubility in most useful chromatography solvents, the tetraesters were

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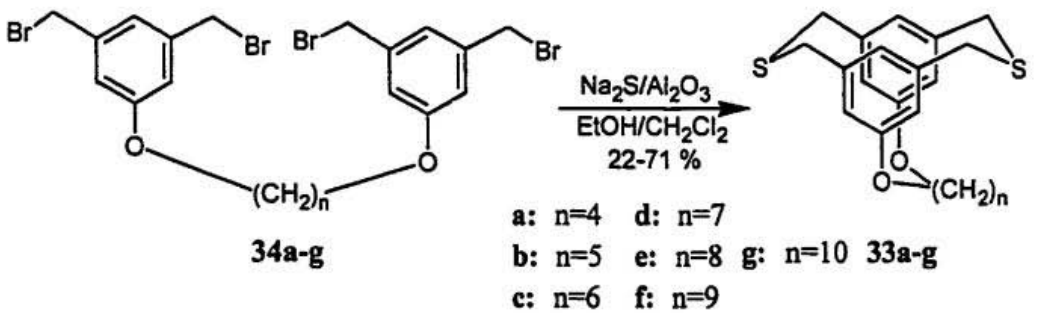
[37] Fischer, E.; Speier, A. *Ber. Dtch. Chem. Ges.* **1895**, *28*, 3252-3258.
[38] a) Williamson, A.W. *J. Chem. Soc.* **1851**, 106-112; b) Williamson, A.W. *J. Chem. Soc.* **1851**, 229-239; c) Vogel, A.I. *J. Chem. Soc.* **1948**, 616-624.
[39] Dehmlow, E. V.; Schmidt, J. *Tetrahedron Lett.* **1976**, 95-96.

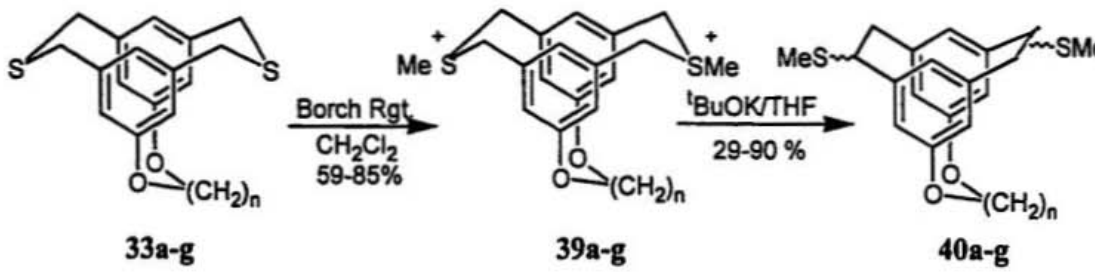
normally carried through the next two reactions crude. Reduction with $LiAlH_4$ in THF at room temperature afforded tetraalcohols **39a-g**. These compounds were extremely insoluble in most organic solvents and water, and were therefore difficult to extract. Consequently, the crude reaction products from the reduction, after quenching and the removal of the THF, were simply treated with 2:1 (v/v) 48 % HBr/H_2SO_4 and heated to give, after chromatography, the CH_2Cl_2-soluble and crystalline tetrabromides **34a-g**. The yield for this sequence was usually between 40 and 60 % from diester **36**, which may seem modest. However, when it is considered that ten individual transformations have occurred (2 etherifications, 4 reductions, 4 brominations) the yield for each individual reaction must average 92 %.

The crucial thiacyclophane synthesis (Scheme 5-10) using Na_2S/Al_2O_3 proceeded effectively, generating thiacyclophanes **33a-g** in moderate to good yield. It was found that the reaction could be performed in an Erlenmeyer flask with vigorous magnetic



Scheme 5-10: Synthesis of Dithiacyclophanes **33**

stirring. Without this stirring, both the rate and yield of the reaction were markedly reduced. Although thiacyclophanes are generally considered to be very robust chemical species, those prepared here degraded to an intractable polymer if left impure in the solid state. Once the thiacyclophane was purified, however, this decomposition was usually not observed. The reason for this unexpected instability is unclear. Perhaps the conformationally labile ("floppy") polymethylene tether reduces the ability of these thiacyclophanes to crystallize, especially when impure, which renders them more susceptible to air oxidation. Or, perhaps microscopic Al_2O_3 fragments or some other impurities from the reaction, which were not removed by filtration, catalyze some

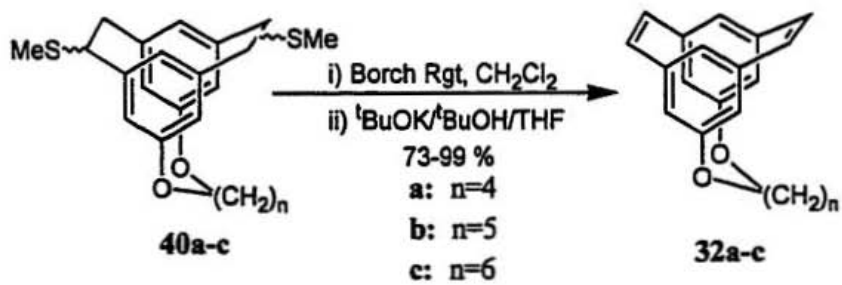


Scheme 5-11: Stevens Rearrangement of **33**

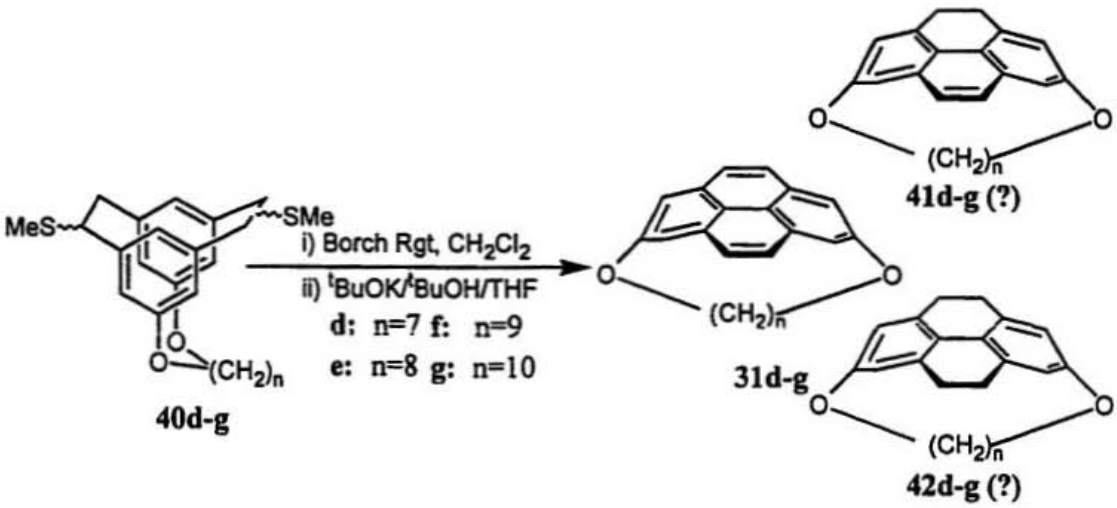
polymerization or oxidation process. In any event, once purified, the thiacyclophanes **33** were reasonably stable.

Methylation of **33a-g** with Borch reagent ($(MeO)_2CHBF_4$)[40] in CH_2Cl_2 produced *bis*-(sulfonium) salts **39a-g** as white powders, insoluble in most organic solvents. The structure **39** could, however, be confirmed by NMR in d_6-DMSO. Stevens rearrangement[12] (Scheme 5-11) of **39** by treatment with potassium *tert*-butoxide in THF gave thioethers **40a-g** as a mixture of isomers and in variable yields. Treatment of **40** with Borch reagent afforded a dark oil that was presumably methylated **40**; however, no solid pure product could be isolated in any case. The low yields observed for some of these reactions (and all subsequent reactions in this sequence) could most likely be improved, as many of them were only performed once and were not optimized.

The product composition of the next step, potassium *tert*-butoxide-induced Hofmann elimination of dimethyl sulfide, depended on the product's tether length. For the shorter tethers (n = 4–6, Scheme 5-12) the cyclophanediene **32a-c** could be isolated as colorless crystalline solids. Longer tethers (n=7-10, Scheme 5-13), by contrast, afforded



Scheme 5-12: Cyclophanediene **32** by Hofmann Elimination



Scheme 5-13: Products of Hofmann Elimination of Longer-tether Cyclophanes **40**

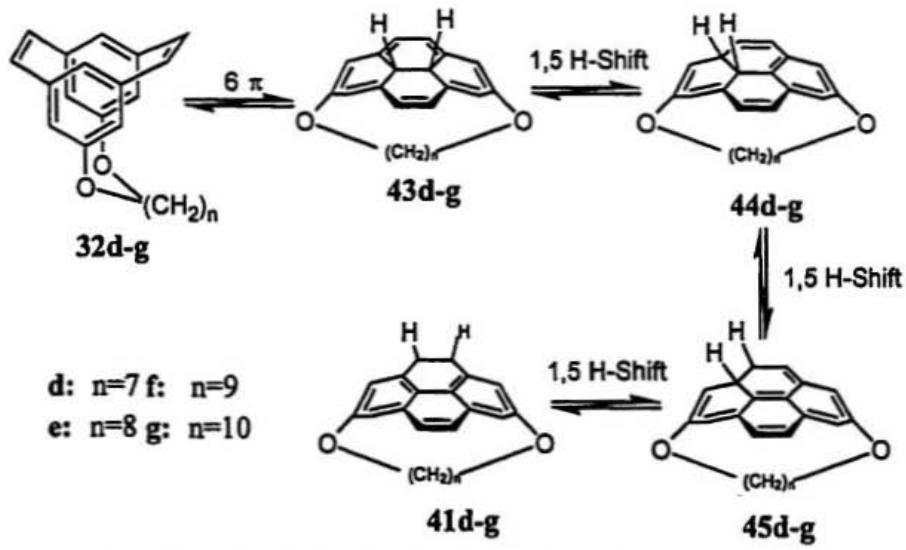
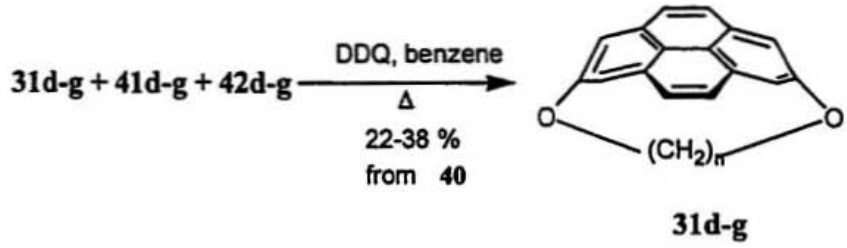


Figure 5-2 : Possible Mechanism for Formation of **41** from **32**

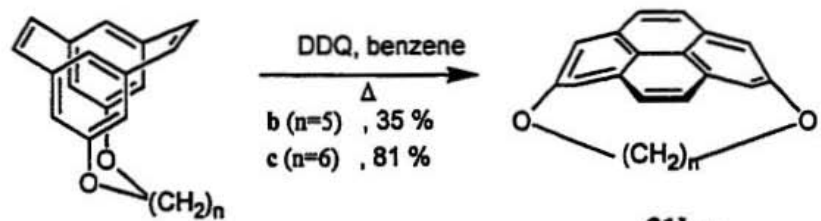
[40] Borch, R.F. *J. Org. Chem.* **1969**, *34*, 627-629.



31d-g

Scheme 5-14: Dehydrogenation of Mixture to Produce Pyrenophane

an inseparable mixture of products, consisting of some pyrenophane **31d-g** and another product (less symmetrical, judging from the ^{1}H NMR spectrum) that has not been identified unequivocally. Treatment of the mixture with DDQ cleanly affords pure pyrenophanes **31d-g** (Scheme 5-14). From this observation, and an apparent AA'BB' signal observed in the ^{1}H NMR of the mixture, the impurity is believed to consist of partially hydrogenated pyrenophanes, possibly dihydropyrenophane **41** and/or tetrahydropyrenophane **42**. This would be consistent with the observations of Boekelheide and co-workers in their work on the parent (untethered) system.[13,41] Dihydropyrenophane **41** can be envisioned as forming from **32** by a 6π electrocyclization, followed by a series of (suprafacial) sigmatropic [1,5]-hydrogen shifts (Fig. 5-2).[42] Compound **41** might then undergo a disproportionation by H_2 transfer to form pyrenophane **31** and tetrahydropyrenophane **42**. This would explain the formation of **31** despite the absence of any obvious oxidizing agent in the system. However, the spontaneous loss of H_2 from the untethered diene system **10** has been observed even in



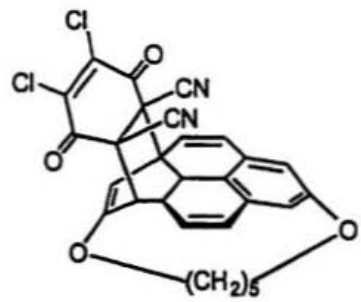
32b,c **31b,c**

Scheme 5-15: Dehydrogenation of **32** to Pyrenophane **31**

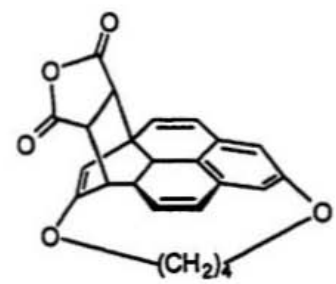
[41] Boekelheide, V.; Sturm, E. *J. Am. Chem. Soc.* **1969**, *91*, 902 - 908. b) Mitchell, R.H.; Boekelheide, V. *J. Am. Chem. Soc.* **1970**, *92*, 3510-3512.

sealed, degassed tubes,[41b] so no adventitious oxidant need be invoked to explain the formation of pyrenophane **31** from diene **32**.

Treatment of cyclophanediene **32c** with DDQ in refluxing benzene (Scheme 5-15) afforded pyrenophane **31c** in good yield (81%). Cyclophanediene **32b** also produced the corresponding pyrenophane **31b** on reaction with DDQ, albeit in a markedly reduced yield (35 %) and impure by ^{1}H NMR after *rapid* chromatography. The product **31b** is unstable on silica, as attempted slow chromatography resulted in yields as low as zero. Unidentified by-products have also been observed in the product mixture, accounting for some of the lost starting material. One yellow by-product could be isolated by chromatography, and appeared by NMR to resemble known Diels-Alder adducts of **31** (see Chapter 6). However, the product could not be crystallized, so x-ray crystallographic data could not be obtained. The EI-MS spectrum was almost identical with that of the parent pyrenophane (a common feature of Diels-Alder adducts of pyrenophanes, see Chapter 6), and no M^+ corresponding to the by-product could be observed. The most plausible structure for this by-product, given the limited data available, was that of a Diels-Alder adduct of **31b** with DDQ, such as **46**.



46



47

After treatment with DDQ in refluxing benzene, cyclophanediene **32a** was recovered almost quantitatively after 1 hour, with no evidence of pyrenophane (**31a**) formation. At higher temperatures (refluxing xylenes, 137 °C) slow decomposition to a baseline spot (on tlc analysis) was observed, again without evidence of the generation of **31a**. Carrying out this reaction in the presence of maleic anhydride as a trapping agent

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[42] Klärner, F.G. *Top. Stereochem.* **1984**, *15*, 1-42.

did not result in any "trapped" pyrenophane **47**. There is therefore no evidence yet, direct or indirect, for the formation of the 1,6-dioxa[6](2,7)pyrenophane **31a**.

5.3 – Synthesis and Chemistry of [n](2,7)Pyrenophanes

5.3.1 - [n](2,7)Pyrenophanes - Retrosynthesis

The retrosynthesis of the "hydrocarbon" pyrenophanes **48** will be very similar to the synthesis of the dioxa-analogues described previously (Fig. 5-3). Indeed, the only significant difference will be in the very last retrosynthetic (the first synthetic) step – the introduction of a polymethylene tether to a suitably functionalized benzene. A Sonogashira[43] coupling of triflate **52** with diynes **53** was chosen to form the required carbon-carbon bonds, which could be followed by hydrogenation to transform the alkyne groups into the desired methylenes, as in tetraester **51**.

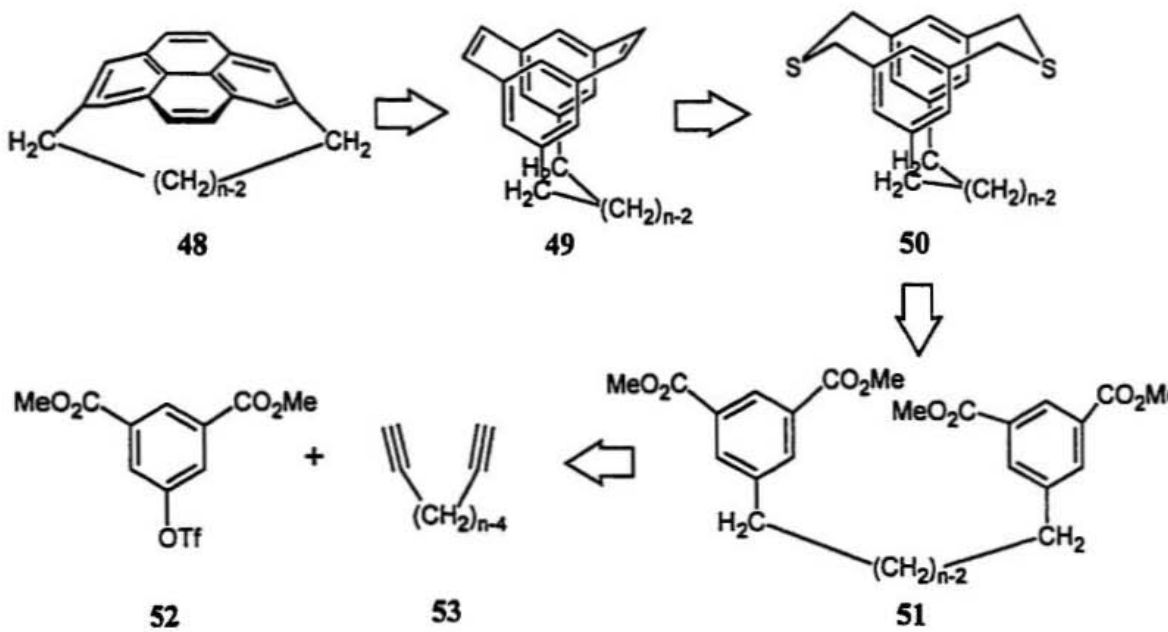
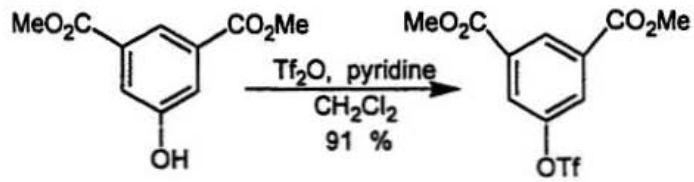


Figure 5-3: Retrosynthetic Analysis of [n](2,7)Pyrenophane, **48**

[43] a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467-4470. b) Cassar, L. *J. Organomet. Chem.* **1975**, *93*, 253 –257. c) Dieck, H.A.; Heck, F.R. *J. Organomet. Chem.* **1975**, *93*, 259-263.

5.3.2 - [n](2,7)Pyrenophanes - Synthesis

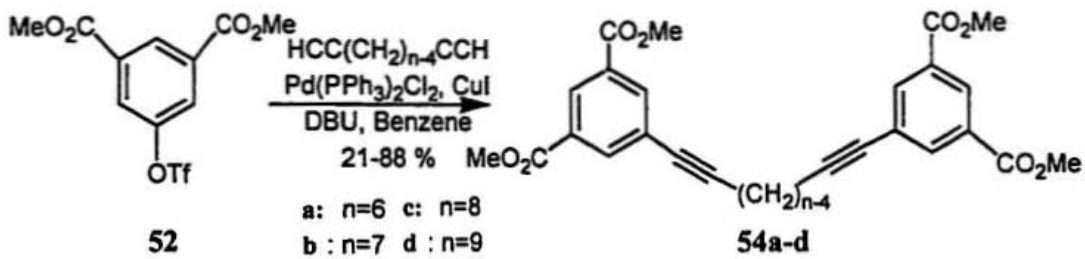
As with the dioxapyrenophanes, the synthesis began with commercially available 5-hydroxyisophthalic acid, **37**, which was converted to the diester **36** and then to the aryl



36 **52**

Scheme 5-16: Synthesis of Aryl Triflate **52**

trifluoromethanesulfonate **52** (Scheme 5-16). This could be coupled to straight-chain terminal diynes under standard Sonogashira conditions (Scheme 5-17) to yield diynetetraesters **54a-d**, which could be isolated by chromatography.[44] The yields for this



52 **54a-d**

Scheme 5-17: Sonogashira Coupling of **52** to Afford Diynetetraesters **54**

reaction were over 80 % with the exception of the product with the six-carbon tether **54a**, which was consistently below 25%. The reasons for this are unclear, but the reduced yield might result from the increased volatility of the diyne. Treating **54a-d** with H_2 over palladium hydroxide on carbon resulted in clean hydrogenation (Scheme 5-18) to the tetraesters **51a-d**. Reduction by $LiAlH_4$ afforded tetraols **55a-d**, which (unlike their dioxa-analogues, **39**) could be isolated by extraction into hot ethyl acetate. These were, however, almost insoluble at room temperature in ethyl acetate, so purification was not attempted, and they were used crude in the next step.

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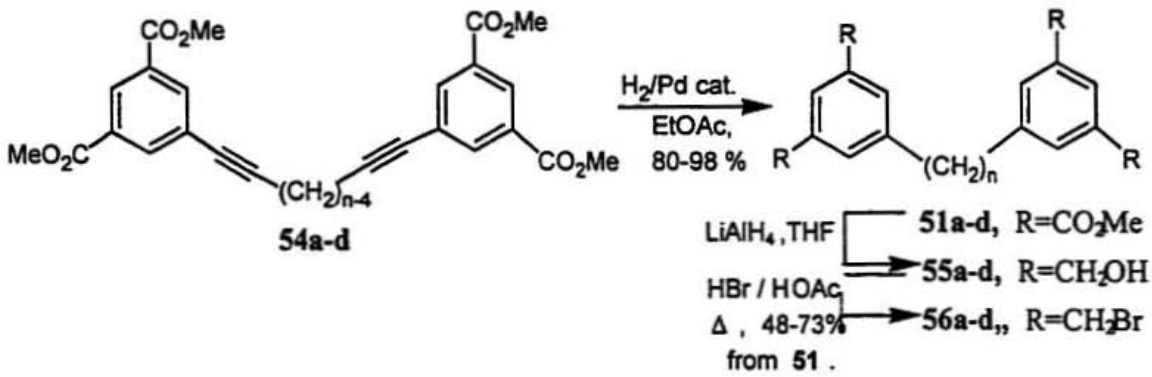
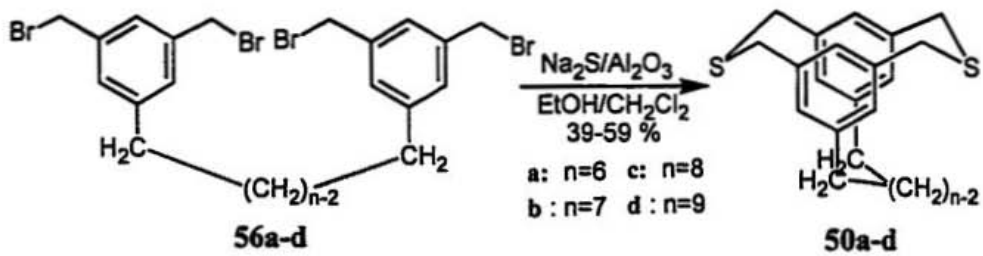
[44] a) Ritter, K. *Synthesis* **1993**, 735-762. b) de Meijere, A.; Meyer, F.E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379-2411. c) Ensley, H.E.; Mahadevan, S.; Mague, J. *Tetrahedron Lett.* **1996**, *37*, 6255-6258.



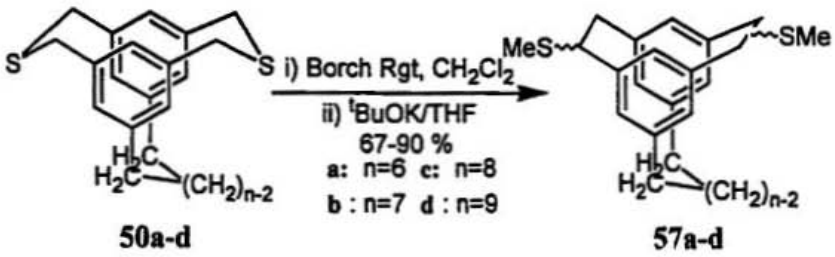
Scheme 5-18: Synthesis of Tetrabromides **56**

Bromination by treatment of **55a-d** with aqueous 48% HBr produced very low yields of the desired tetrabromide products, presumably due to the insolubility of the partially brominated intermediates in the aqueous medium. Consequently, bromination by treatment of **55** with HBr in glacial acetic acid yielded tetrabromides **56a-d** in good yield. These were converted to the [n.3.3]dithia(1,3,5)cyclophanes **50a-d** by treatment with Na_2S/Al_2O_3 (Scheme 5-19).[32] The yields were slightly lower than those observed for the dioxathiacyclophanes **33**, but the reasons for this are uncertain. One possible explanation is that chelation of the Na^+ cation by oxygens in the tether takes place, which holds the two aryl rings close together and favors ring closure over polymerization. This hypothesis is supported by the observation that a cyclophane with a polyether tether was formed in a yield of over 90% under normal Na_2S/Al_2O_3 coupling conditions.[33,45]



Scheme 5-19: Synthesis of Thiacyclophanes **50**

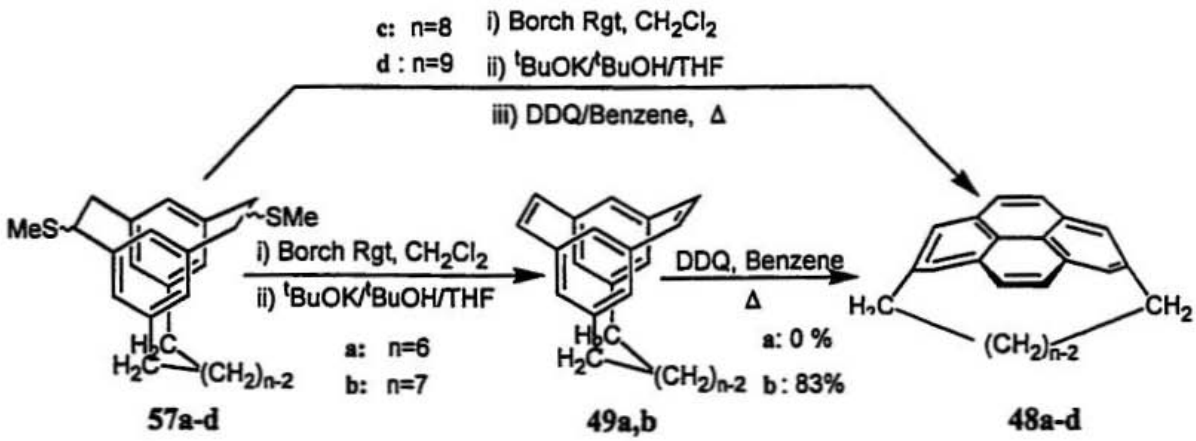
[45] a) Bodwell, G.J.; Houghton, T.J., unpublished results.



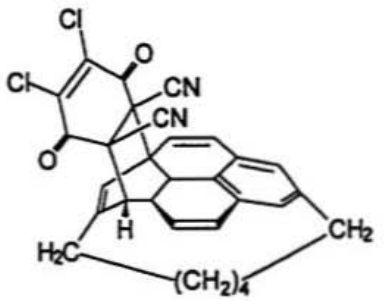
Scheme 5-20: Stevens Rearrangement of **50**

A methylation/Stevens rearrangement procedure (Scheme 5-20) afforded *bis*(thiomethyl)cyclophanes **57a-d** as a mixture of isomers. No attempt was made to purify these mixtures, which were simply carried on through a second methylation/elimination sequence (Scheme 5-21) to yield cyclophanedienes **49a,b**. In the case of the longer tethers investigated (n=8,9), this reaction yielded a mixture of inseparable products, including pyrenophanes **48c,d**. Treatment of either this mixture or of cyclophanediene **49b** with a small excess of DDQ in refluxing benzene cleanly afforded the pyrenophanes **48b-d**. No by-products were observed in these cases.

Cyclophanediene **49a**, when heated with DDQ in C_6D_6 in an NMR tube, displayed no signals attributable to pyrenophane **48a** in the ^1H NMR, and most of the starting material could be recovered after 20 h. However, a trace (<2 mg) of a second



Scheme 5-21: Synthesis of Pyrenophanes **48**

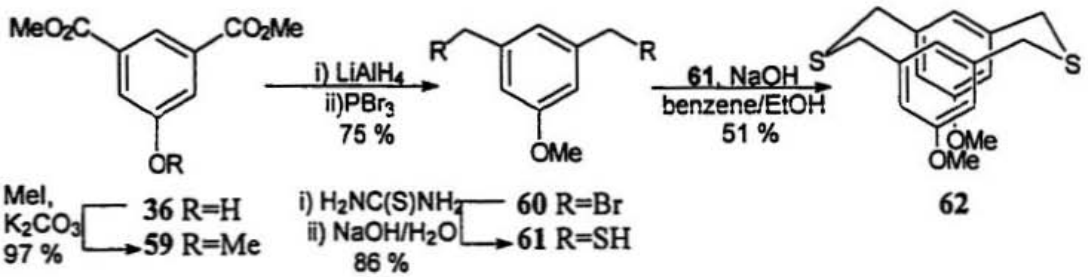


58

compound could be isolated from this mixture by column chromatography. This compound has ^{1}H NMR signals similar to known Diels-Alder adducts of pyrenophane **48a** (n=6), and displays a strong peak at *m/z*=284 (which corresponds to **48a**) in the mass spectrometer. This *might* suggest that **48a** is being slowly generated, then trapped as a Diels-Alder adduct (with DDQ?, e.g. **58**) which undergoes a retro-Diels-Alder reaction in the mass spectrometer. This can hardly be considered conclusive evidence for the formation of **48a**, as it might involve, for example, a Lewis-acid catalyzed rearrangement of the tether to a less strained position (see Chapter 6). However, it is a hint at how such 'impossibly' strained molecules might be produced, even if only as fleeting intermediates.

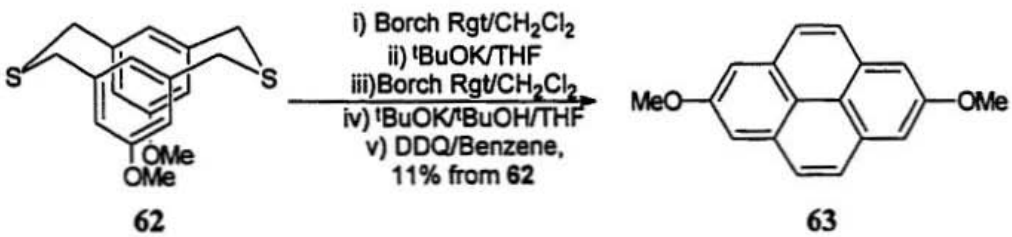
5.4 – 2,7-Dimethoxypyrene

To compare the properties of the tethered pyrenophanes with an untethered reference compound, 2,7-dimethoxypyrene **63** was prepared using methodology

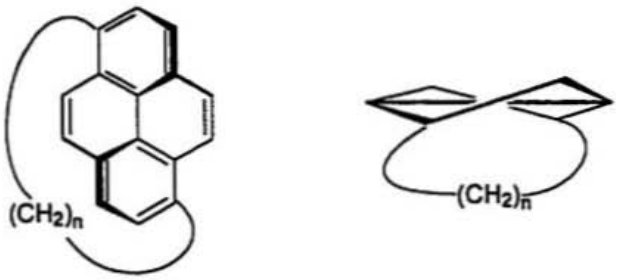


Scheme 5-22: Synthesis of Dimethoxythiacyclophane **62**

analogous to the previously described syntheses (Schemes 5-22, 5-23). Compound **63** was obtained from thiacyclophane **62** in low yield, however the amount isolated was sufficient for spectroscopic characterization.



Scheme 5-23: Synthesis of Dimethoxypyrene **63**



64 **64**, side view

Figure 5-4: Views of (1,6)Pyrenophane **64**

5.5 - [n](1,6)Pyrenophanes

5.5.1 – Introduction - PAHs With a Twist

Having successfully prepared a number of [n](2,7)pyrenophanes, it was realized that the sodium sulfide on alumina methodology might be applicable to the preparation of other, less symmetrical pyrenophanes, such as the [n](1,6)pyrenophanes, **64**. These structures would be interesting because, in addition to a bend around the short axis of the molecule (as already seen in the [n](2,7)pyrenophanes), the tether (if short enough) would impose a *longitudinal twist* or torsion around the long axis of the molecule, as illustrated in Fig. 5-4. This sort of twisting in polycyclic aromatic molecules has received very little attention, although some examples are known.[46] This twist would render **64** C_2 symmetric and chiral, which would make separation of its two enantiomers an additional challenge.

A molecule such as **64** could arise from the corresponding cyclophane **65** by the now-familiar ring contraction/elimination and oxidation route. Thiacyclophane **65** could be generated from tetrabromide **66**, which could be prepared in a manner analogous to **56**. A novel problem, not observed in the preparation of the more symmetrical (2,7)pyrenophanes, presents itself here. From tetrabromide **66**, two modes of ring closure can be envisioned (Scheme 5-24). One will produce the C_2 symmetric thiacyclophane **65**, the precursor for **64**. Compound **65** is also chiral and will obviously be generated as a racemic mixture.[47] The other mode of ring closure will generate the C_s symmetric

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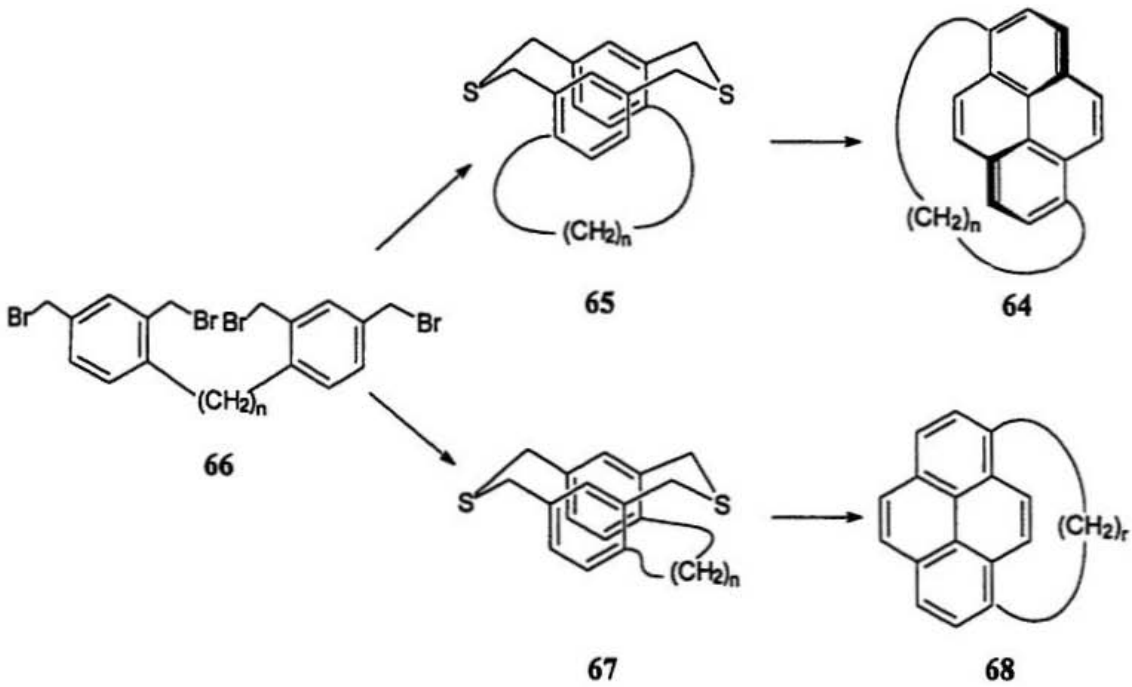
[46] Pascal, Jr., R.A.; McMillan, W.D.; van Engen, D. *J. Am. Chem. Soc.* **1986**, *108*, 5652-5653. b) Pascal, Jr., R.A.; McMillan, W.D.; van Engen, D.; Eason, R.G. *J. Am. Chem. Soc.* **1987**, *10*, 4660-4665.

[47] Chirality in cyclophanes is an interesting topic in its own right, but out of the scope of this discussion. For a review, see: Schlögl, K. *Top. Curr. Chem.* **1984**, *125*, 27-62.



Scheme 5-24: Possible Route to Pyrenophanes **64** and **68**

thiacyclophane **67**, which is a *meso* compound (with respect to the planar chirality observed in **64**). After rearrangement and elimination, **67** would generate the [n](1,8)pyrenophane **68**.

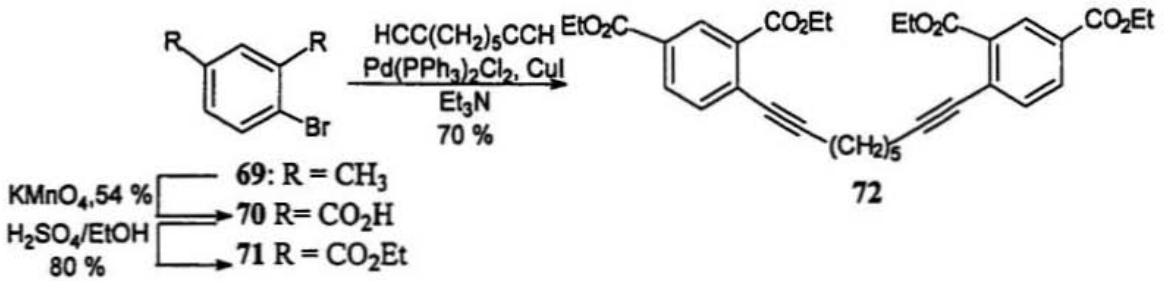
It is difficult to predict which product, **65** or **67**, will predominate when **66** is treated with Na_2S/Al_2O_3. It could be argued that transannular steric repulsions between the tether's benzylic methylenes would destabilize **67** (where the methylenes are *pseudo-ipso* to one another) relative to **65** (where they are *pseudo-meta*), in which **65** might therefore be the thermodynamically favored product Alternately, the bromomethyl groups *para* to the tether might react with nucleophiles (e.g. S^{2-} or RS^-) more rapidly than the *ortho* bromomethyl groups, due to the former being less sterically hindered. If this were the case, the two unhindered bromomethyls might be preferentially coupled by a sulfur, resulting in the undesired dithiacyclophane **67** as the predominant product.

Since predicting the outcome of the Na_2S coupling of tetrabromide **65** was difficult, it was decided to pursue the synthesis and determine experimentally which

product, if any, predominated, and if the resultant thiacyclophanes could be converted to pyrenophanes.[48]

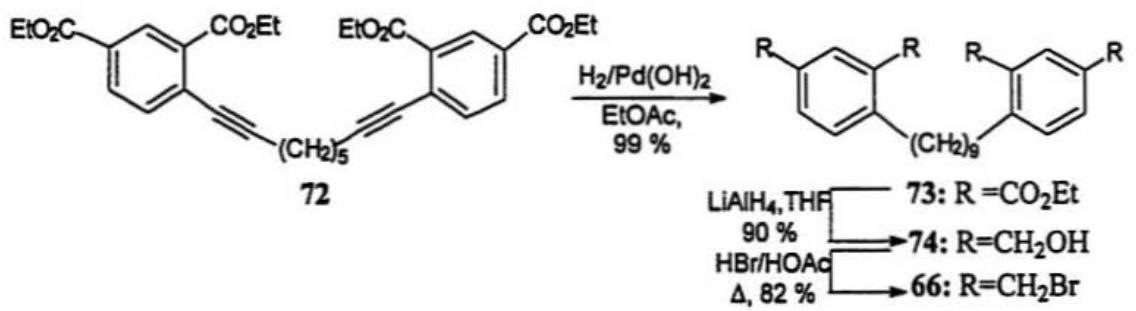
5.5.2 - (9)[1,6]Pyrenophane – Synthesis

The synthesis began with 4-bromo-*m*-xylene, **69**, which was oxidized with aqueous $KMnO_4$ (Scheme 5-25)[49] to 4-bromoisophthalic acid **70**, then esterified using a



Scheme 5-25: Synthesis of Diynetetraester **72**

literature procedure[50] to afford diethyl 4-bromoisophthalate, **71**. The longest tether length available was chosen, to minimize any strain-related instability in the final product, so **71**



Scheme 5-26: Preparation of Tetrabromide **66**

was coupled with nonadiyne under Sonogashira conditions to afford diynetetraester **72** in 70 % yield. Compound **72** was hydrogenated under 1 atm H_2 over wet palladium

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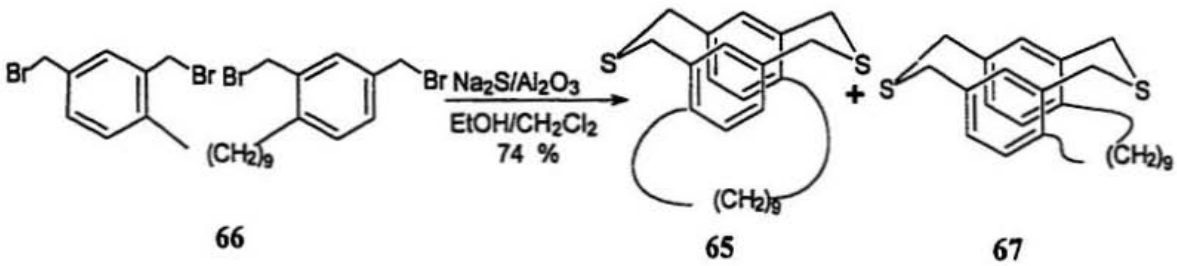
[48] An early attempt at the synthesis of this type of molecule was made some years ago in our group, but it failed before the thiacyclophane stage. See: Kennedy, C. B. Sc. Honours Thesis, Memorial University of Newfoundland, 1995.

[49] a) March, J. E. *Advanced Organic Chemistry, 4th Ed.* J. Wiley and Sons, 1992, New York. pp. 1183-1184. b) Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis Vol. 1.* J.Wiley and Sons, New York, 1967. pp. 942-944.

[50] Schöpff, M. *Ber. Dtch. Chem. Ges.* **1891**, *24*, 3771-3784.

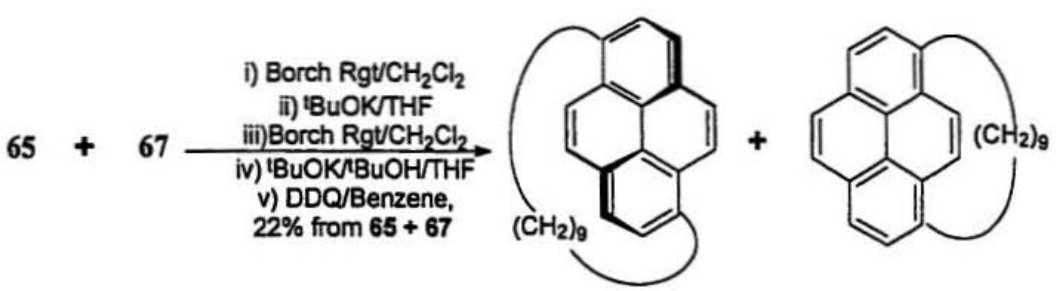


66 65 67

Scheme 5-27: Preparation of Thiacyclophanes **65** and **67**

hydroxide on C (Pearlman's catalyst) (Scheme 5-26) to provide tetraester **73** in near quantitative yield. Reduction with $LiAlH_4$ produced tetraol **74**, which was brominated with HBr in acetic acid, yielding tetrabromide **66** in excellent yield over the last two steps.

The Na_2S/Al_2O_3 coupling of **66** (Scheme 5-27) resulted in the rapid consumption of **66** as observed by tlc analysis, with the appearance of a number of new, more polar spots. Filtration followed by chromatography (CH_2Cl_2/hexanes) afforded a single major spot by tlc (74 % recovery). However, the ^1H NMR spectrum of this product clearly revealed the fraction to be a mixture of at least two compounds, which displayed a strong M^+ at *m/z*=396, which corresponded to **65** and/or **67**. Chromatography in a number of different solvents did not result in any effective separation. Recrystallization appeared to have resulted in some enrichment of one of the products, but the impure thiacyclophane mixture appeared to be susceptible to the same polymerization that had been observed for other such compounds, and prolonged experimentation with different recrystallization



64 68

Scheme 5-28: Synthesis of Pyrenophanes **64** and **68**

solvent mixtures simply resulted in product loss. It was therefore decided to carry the

impure thiacyclophanes through the ring contraction/elimination sequence in the hope that **64** and **68** might be easier to separate.

Disappointingly, the separation of **64** and **68** turned out to be problematic. After the Stevens rearrangement procedure, followed by the elimination of Me_2S, (Scheme 5-28) a complex mixture of products was isolated. The presence of signals well below δ = -1 ppm in the ^{1}H NMR spectrum hinted at the presence of some pyrenophane. Unfortunately, after treatment with DDQ, a single spot (by tlc analysis) was isolated after chromatography which again appeared to consist of at least two products, and the spectrum was too complex to assign any definite structures to the products. Recrystallization from hexanes afforded small, colorless needles which, on isolation, were shown to have a strong peak at *m/z*=326 in the mass spectrum – the correct mass for either **64** or **68**. Unfortunately, ^{1}H NMR analysis of this product revealed that it was still impure, apparently consisting of a major and a minor isomer. Most interestingly, the ^{1}H NMR spectrum of the recovered crystals showed no peaks below 0 ppm – peaks that were clearly present in the product prior to recrystallization. Attention was therefore turned to the mother liquor from the recrystallization.

^{1}H NMR of the mother liquor revealed a mixture of the two compounds present in the crystalline fraction, as well as another compound (the major constituent of the mixture) which was clearly not present at all in the crystals. By comparing the spectra of the hexane-soluble fraction with the crystalline fraction and by mentally "subtracting" the peaks present in both, the spectrum of the major hexane-soluble product could be discerned. The splitting pattern of the aromatic region, which consists of two pairs of doublets; and the presence of tether peaks in the δ -1 - -1.5 ppm range, which indicates the tether is directly underneath the aromatic rings, allowed structure **64** to be assigned to the major component of the hexane-soluble fraction. Compound **68**, whose tether is not necessarily constrained to lie under the aromatic system, might be the major component of the crystalline fraction. The identity of the third product, a minor constituent of both the soluble and crystalline fractions, is unknown.

To date, it has not been possible to purify either **64** or **68**, or to obtain crystals of either that are adequate for x-ray diffraction analysis. In hexanes, **68** appears to co-crystallize with a minor, unidentified impurity. Compound **64** is soluble even in hexanes

at -20 °C, and the sample is contaminated with less soluble impurities. The challenge of obtaining clean crystals of such compounds is considerable, and, in the case of a compound soluble in cold hexanes, there are probably very few useful recrystallization solvents that the compound will *not* be soluble in.

Evidence for the synthesis of twisted pyrenophane **64** has been presented. The most promising method for the preparation of pure **64** will probably involve a separation (by recrystallization) of thiacyclophanes **65** and **67**, a route that was not extensively explored during these studies. An alternate, but more technically demanding, route, might involve a low temperature (- 78 °C ?) crystallization of **64** from, for example, hexane or pentane. The isolation of **64** still appears to be a viable goal for a dedicated researcher willing to perform the (possibly onerous) task of finding effective recrystallization (or perhaps HPLC) conditions that would allow the separation of **64** from **68**, and **65** from **67**. If the isolation of these compounds is achieved, this methodology might then be extended to allow the systematic study of the effects of longitudinal twisting on aromatic molecules, an area of research that has received almost no attention to date. In addition, with a sufficiently short tether (short enough to prevent spinning of the pyrene moiety with respect to the tether), **64** will be chiral and, if resolvable (perhaps by HPLC on an asymmetric solid phase), might demonstrate interesting chiroptical properties. More research in this area is certainly warranted.

5.6 - Conclusions

In general, the syntheses described here proceeded exactly as planned, a relative rarity in organic synthesis. Despite certain surprises, such as the instability of the thiacyclophanes when crude, the work afforded the desired pyrenophanes within a few months of the start of the project. The syntheses of **31** and **48** could be conducted on a reasonably large scale, allowing the preparation of gram-quantities of the pyrenophanes. Starting with ten grams of 5-hydroxyisophthalic acid, about a gram of pyrenophane could be prepared over a week. In the case of the twisted pyrenophane **64**, NMR and EI-MS evidence for its existence were presented, although it was not isolated. Time constraints prevented further pursuit of the isolation of this product, but more work in this area might prove very rewarding.

The most notable aspect of these syntheses is the production of a highly strained polycyclic aromatic hydrocarbon using extremely mild conditions – the highest temperature used in each of the synthetic sequences is that of refluxing benzene, 80 °C. This is in marked contrast with most buckybowl syntheses, which frequently utilize pyrolytic conditions. Of course, this might be an indication that, despite their marked bend, the pyrenophanes prepared here are far less strained than bowl-shaped compounds such as corannulene.

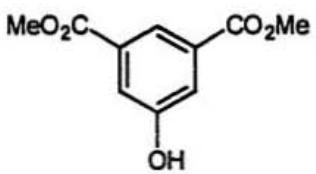
5.7 – Experimental

General: Compounds are reported in the order in which their *synthesis* was mentioned in the text. Reactions were performed open to the air unless otherwise indicated. THF was distilled from sodium benzophenone ketyl under N_2 immediately prior to use. Spectroscopic grade benzene was degassed under reduced pressure prior to use. All other solvents were used as received. Chromatographic purification was accomplished with 230-400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp. Melting points were obtained on a Thomas Hoover 7427-H10 Melting Point Apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on a Perkin Elmer 1320 spectrophotometer in solution in 1 mm NaCl cells. ^1H NMR spectra were obtained on a General Electric GE-300 NB at 300.1 MHz in $CDCl_3$; shifts relative to internal TMS standard; coupling constants are reported in Hertz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 MHz; chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$), number of attached protons was determined by attached proton test experiment. Selected NMR spectra from this Chapter are reproduced in Appendix C. Low and high resolution mass spectroscopic data were obtained on a V.G. Micromass 7070 HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta.

Dimethoxycarbonium tetrafluoroborate (Borch Reagent, $(CH_3O)_2CHBF_4$).[40] $BF_3{\cdot}Et_2O$ (36.5 mL, 0.297 mol) in CH_2Cl_2 (30 mL) was added slowly, with stirring, to $(CH_3O)_3CH$ (27.5 mL, 0.251 mol) at -30 °C under N_2. After the addition was complete, the reaction

was warmed to 0 °C and stirred for 20 min. The two phases of the reaction were then allowed to separate and the upper (CH_2Cl_2) layer was removed by cannula. The lower layer was washed with CH_2Cl_2 (4 x 50 mL) with vigorous stirring; each wash solution being removed by cannula. The remaining yellow oil (fumes in air) was dried *in vacuo* for 6 h and stored under N_2 at -20 °C.

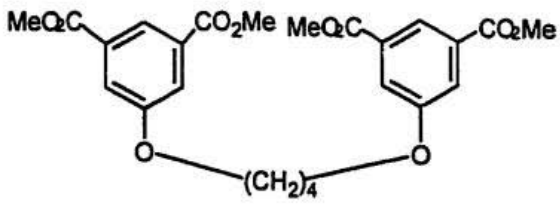
Sodium Sulfide on Alumina (Na_2S/Al_2O_3). $Na_2S{\cdot}9H_2O$ (10.73 g, 44.7 mmol) was dissolved in deionized H_2O (400 mL) and filtered onto basic alumina (Fluka Basic 5016A, 10.49 g). The water was then removed at reduced pressure and the resulting pink solid (17.3 g) was dried *in vacuo* and stored under N_2. The loading of Na_2S was calculated to be 2.58 mmol/g.



36

Dimethyl 5-hydroxyisophthalate, 36. 5-Hydroxyisophthalic acid **37** (51.5 g, 283 mmol) was dissolved in methanol (150 mL) and concentrated H_2SO_4 (10 mL) was added. The solution was refluxed for 4 h then concentrated under reduced pressure. The resultant oily white solid was dissolved in ethyl acetate (500 mL) and washed with aqueous saturated $NaHCO_3$ (3 x 150 mL), H_2O (150 mL), and brine (150 mL). The organic layer was then dried ($MgSO_4$), filtered and concentrated to give the crude product, which was crystallized from xylenes to give fine colorless needles of the diester **36** (55.9 g, 266 mmol, 95%). mp 165-166°C (xylenes). Lit. mp. 162-164 °C.[51]

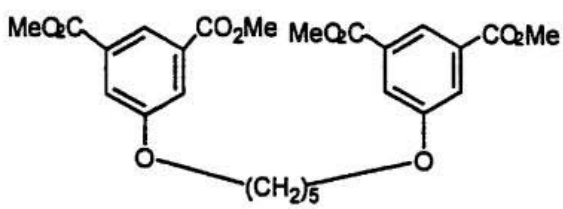
[51] *Aldrich Catalogue Handbook of Fine Chemicals, 1998-1999* Sigma-Aldrich Co., Milwaukee, 1998 p. 656.



38a

1,4-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)butane, 38a. Tetraester **38a** was prepared analogously to **38c** below, using dimethyl 5-hydroxyisophthalate (3.98 g, 18.9 mmol), 1,4-dibromobutane (2.00 g, 9.26 mmol), TBAI (0.997 g, 2.70 mmol) and NaH (0.790 g, 19.8 mmol) yielding **38a** (2.85 g, 6.01 mmol, 64%) %) after chromatography as a colorless solid.

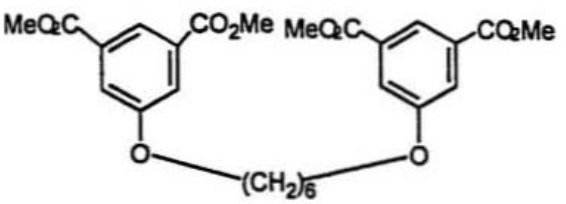
38a: mp 152-153 °C (heptane); IR (CH_2Cl_2) 2920 (m), 2860 (m), 1730 (s, br), 1580 (s), 1100 (s), 1050 (s); ^{1}H NMR δ 8.27 (t, *J*=1.4 Hz, 2H); 7.74 (d, *J*=1.4 Hz, 4H), 4.14 (t, *J*=4.8 Hz, 4H), 3.94 (s, 12H), 2.05-2.01 (m, 4H); ^{13}C NMR δ 166.2, 159.0, 131.8, 123.0, 119.8, 67.9, 52.4, 25.8; EI-MS *m/z* (%) 474 (10, M^+), 443 (13), 265 (100), 223 (33); HRMS: Calc'd for $C_{24}H_{26}O_{10}$ 474.1524, found 474.1535.



38b

1,5-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)pentane, 38b. Tetraester **38b** was prepared analogously to **38c** below, using dimethyl 5-hydroxyisophthalate **36** (8.13 g, 38.7 mmol), 1,5-dibromopentane (4.47 g, 19.4 mmol), TBAI (0.74 g, 2.0 mmol) and NaH (1.64 g, 41.0 mmol) yielding **38b** (7.16 g, 14.7 mmol, 76 %) %) after chromatography as a colorless solid.

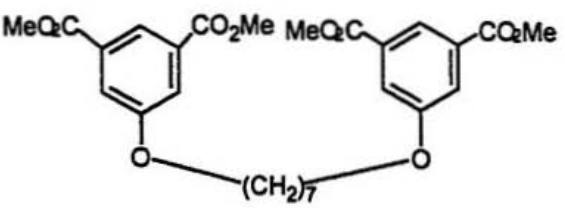
38b: mp 111-113 °C (heptane); IR ($CHCl_3$) 2950 (m), 2860 (w), 1720 (s), 1590 (m), 1340 (s), 1310 (s); ^{1}H NMR δ 8.27 (t, *J*=1.4, 2H), 7.74 (d, *J*=1.4, 4H), 4.08 (t, *J*=6.2, 4H), 3.94 (s, 12 H), 1.93-1.88 (m, 4H), 1.73-1.67 (m, 2H); ^{13}C NMR δ 166.2, 159.1, 131.7, 122.9, 119.8, 68.3, 52.4, 28.8, 22.6; EI-MS *m/z* (%) 488 (17, M^+), 457 (27), 279 (84), 223 (20), 211 (43), 210 (26), 179 (50), 151 (18), 69 (100). HRMS: Calc'd for $C_{25}H_{28}O_{10}$ 488.1681, Found 488.1685.



38c

1,6-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)hexane, 38c. To a solution of **36** (2.05 g, 9.75 mmol), 1,6-dibromohexane (1.20 g, 4.92 mmol), and tetrabutylammonium iodide (TBAI, 0.40 g, 1.1 mmol) in dry THF (125 mL) under N_2 was added NaH (60% dispersion in paraffin oil, 0.43 g, 11 mmol) in small portions. The cloudy mixture was then refluxed for 3 h, after which the reaction was quenched with aqueous saturated NH_4Cl (2 mL), and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), washed with H_2O (150 mL), brine (25 mL), dried ($MgSO_4$), filtered, and concentrated to yield crude **38c** as a yellow solid. This was normally carried on without purification, but pure **38c** could be obtained by flash chromatography in 5% ethyl acetate/hexanes (1.97 g, 3.92 mmol, 80 %)

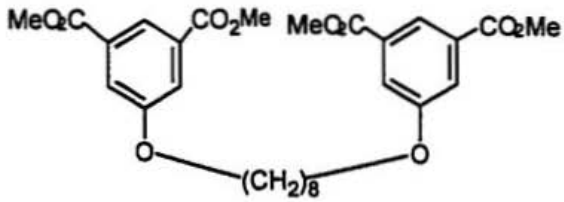
38c: mp 135-136 °C (heptane); IR ($CHCl_3$) 2940 (w), 1720 (s), 1590 (m), 1340 (m), 1310 (m); ^{1}H NMR δ 8.26 (t, *J*=1.4 Hz, 2H), 7.74 (d, *J*=1.4 Hz, 4H), 4.06 (t, *J*=6.4 Hz, 4H), 3.94 (s, 12H), 1.90-1.81 (m, 4H), 1.59-1.54 (m, 4H); ^{13}C NMR δ 166.1, 159.1, 131.6, 122.6, 119.7, 68.5, 52.3, 29.2, 25.9; EI-MS *m/z* 502 (18, M^+), 471 (17), 293 (9), 211 (44), 210 (30), 179 (37), 83 (76), 55 (100). Anal. Calc'd for $C_{26}H_{30}O_{10}$: C, 64.50; H, 6.86. Found: C, 64.35; H, 6.98.



38d

1,7-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)heptane, 38d. Tetraester **38d** was prepared analogously to **38c** above, using dimethyl 5-hydroxyisophthalate **36** (6.43 g, 30.6 mmol), 1,7-dibromoheptane (3.99 g, 15.5 mmol), TBAI (2.46 g, 6.66 mmol) and NaH (1.40 g, 3.50 mmol), yielding **38d** (5.44 g, 10.5 mmol, 69 %) after chromatography as a white solid.

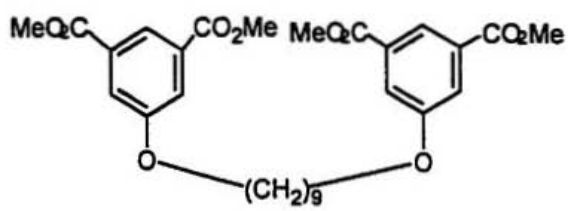
38d: mp 79-85 °C; IR (CH_2Cl_2) 2950 (m), 2860 (w), 1720 (s), 1590 (s); ^{1}H NMR δ 8.26 (t, *J*=1.4 Hz, 2H), 7.74 (d, *J*=1.3 Hz, 4H), 4.05 (t, *J*=6.4 Hz, 4H), 3.94 (s, 12 H), 1.86-1.81 (m, 4H), 1.53-1.48 (m, 6H); ^{13}C NMR δ 166.1, 159.1, 131.6, 122.7, 119.7, 68.4, 52.3, 29.0, 25.9; EI-MS *m/z* (%) 516 (32, M^+), 485 (13), 211 (29), 210 (27), 179 (28), 97 (35), 96 (31), 55 (100). Anal. Calc'd for $C_{27}H_{32}O_{10}$: C, 62.78; H, 6.24. Found C, 63.05; H, 6.19.



38e

1,8-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)octane, 38e. Tetraester **38e** was prepared analogously to **38c** above, using dimethyl 5-hydroxyisophthalate **36** (2.13 g, 10.1 mmol), 1,8-dibromooctane (1.43 g, 5.26 mmol), TBAI (0.50 g, 1.35 mmol), and NaH (0.43 g, 10.8 mmol), yielding **38e** (2.37 g, 4.47 mmol, 89 %) after chromatography as a colorless solid.

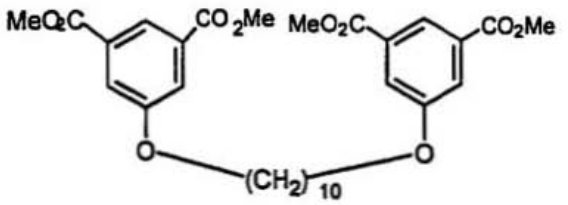
38e: mp 116-117 °C (heptane); IR ($CHCl_3$) 2930 (m), 2860 (w), 1720 (s), 1590 (m), 1340 (m), 1310 (m); ^{1}H NMR δ 8.26 (s, 2H); 7.74 (s, 4H), 4.04 (t, *J*=6.2, 4H), 3.94 (s, 12H), 1.84-1.80 (m, 4H), 1.52-1.40 (m, 8H); ^{13}C NMR δ 166.8, 158.9, 131.3, 122.4, 119.4, 68.2, 52.1, 29.0, 28.8, 25.6; EI-MS *m/z* (%) 531 (14). 530 (44, M^+), 499 (31), 211 (96), 210 (91), 179 (83), 69 (100), 55 (63); HRMS Calc'd for $C_{28}H_{34}O_{10}$ 530.2150, found 530.2138.



38f

1,9-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)nonane, 38f. Tetraester **38f** was prepared analogously to **38c** above, using dimethyl 5-hydroxyisophthalate **36** (6.31 g, 30.0 mmol), 1,9-dibromononane (4.31 g, 15.1 mmol), TBAI (2.14 g, 5.79 mmol), and NaH (1.20 g, 30.0 mmol), yielding **38f** (5.71 g, 10.5 mmol, 70 %) after chromatography as a colorless solid.

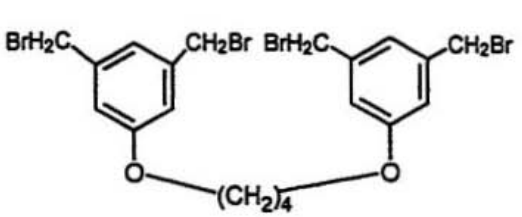
38f: mp 79-81 °C (heptane); IR (CH_2Cl_2) 2940 (m), 1720 (s), 1590 (s), 1340 (s); ^1H NMR δ 8.25 (t, *J*=1.4, 2H), 7.74 (d, *J*=1.4, 4H), 4.04 (t, *J*=6.4, 4H), 3.94 (s, 12H), 1.84-1.75 (m, 4H), 1.49-1.34 (m, 10H); ^{13}C NMR δ 166.1, 159.1, 131.6, 122.6, 119.7, 68.5, 52.3, 29.4, 29.2, 29.0, 25.9; EI-MS *m/z* (%) 544 (8, M^+), 513 (4), 211 (31), 210 (30), 179 (32), 83 (47), 69 (100), 55 (86). Anal. Calc'd for $C_{29}H_{36}O_{10}$: C, 63.96; H, 6.66. Found: C, 64.40; H, 6.82.



38g

1,10-*Bis*(3,5-*bis*(methoxycarbonyl)-phenoxy)decane, 38g. Tetraester **38g** was prepared analogously to **38c** above, using dimethyl 5-hydroxyisophthalate **36** (4.91 g, 23.4 mmol), 1,10-dibromodecane (3.54 g, 11.8 mmol), TBAI (2.32 g, 6.28 mmol) and NaH (1.10 g, 27.5 mmol), yielding **38g** (4.66 g, 8.34 mmol, 71 %) after chromatography as a colorless solid.

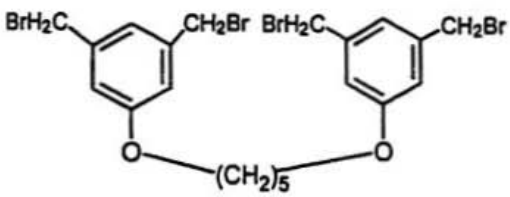
38g: mp 103-104 °C (heptane); IR ($CHCl_3$) 2920 (m), 2860 (w), 1720 (s), 1590 (m), 1340 (s); ^1H NMR δ 8.26 (t, *J*=1.4, 2H), 7.74 (d, *J*=1.4, 4H), 4.04 (t, *J*=6.4, 4H), 3.94 (s, 12H), 1.86-1.76 (m, 4H), 1.50-1.45(m, 4H), 1.35 (m, 8H); ^{13}C NMR δ 166.2, 159.2, 131.6, 122.7, 119.8, 68.6, 52.4, 29.5, 29.3, 29.1, 25.9; EI-MS *m/z* (%) 559 (19), 558 (55, M^+), 527 (24), 211 (100), 210 (98), 179 (78), 109 (22), 97 (47), 96 (38), 95 (33), 83 (90), 82 (40), 69 (67). Anal. Calc'd for $C_{30}H_{38}O_{10}$: C, 64.50; H, 6.86. Found: C, 64.35; H, 6.98.



34a

1,4-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-butane, 34a. Compound **34a** was prepared analogously to **34c** below, using crude tetraester **38a** (11.3 g) and $LiAlH_4$ (8.55 g, 225 mmol) to yield **34a** (6.16 g, 10.0 mmol, 42 % from diester **36**) as a white solid.

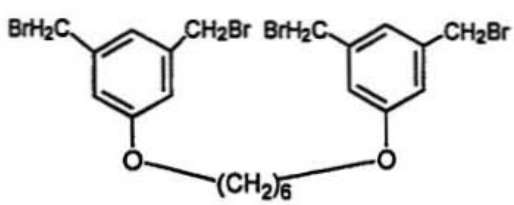
34a: mp 127-128 °C (heptane), IR (CH_2Cl_2) 2920 (w), 2870 (w), 1590 (m), 1050 (w); ^1H NMR δ 7.00 (s, 2H), 6.86 (s, 4H), 4.43 (s, 8H), 4.05 (t, *J*=2.5, 4H), 1.98 (t, *J*=2.5, 4H); ^{13}C NMR δ 159.3, 139.6, 121.8, 115.2, 67.6, 32.9, 25.9; EI-MS *m/z* (%) 616 (10, M^+), 614 (16, M^+); 612 (10, M^+), 535 (24), 533 (25), 337 (51), 335 (100), 333 (55), 228 (26), 227 (36), 120 (23), 103 (27), 91 (36). Anal. Calc'd for $C_{20}H_{22}Br_4O_2$: C, 39.12; H, 3.61. Found: C, 39.11.



34b

1,5-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-pentane, 34b. Compound **34b** was prepared analogously to **34c** below, using crude tetraester **38b** (9.34 g) and $LiAlH_4$ (7.61 g, 201 mmol) to yield **34b** (6.56 g, 10.4 mmol, 53 % from diester **36**) as a white solid.

34b: mp 105-106 °C (heptane), IR (CH_2Cl_2) 2940 (w), 2880 (w), 1590 (s), 1160 (m), 1050 (m); ^1H NMR δ 7.00 (t, *J*=1.3, 2H), 6.86 (d, *J*=1.4, 4H), 4.43 (s, 8H), 4.00 (t, *J*=6.4, 4H), 1.89-1.82 (m, 4H), 1.68-1.64 (m, 2H); ^{13}C NMR δ 159.4, 139.5, 121.7, 115.2, 67.9, 32.9, 28.9, 22.7; EI-MS *m/z* (%) 630 (5, M^+), 628 (8, M^+), 626 (6, M^+), 547 (6), 351 (20), 349 (39), 347 (22), 60 (100). Anal. Calc'd for $C_{21}H_{24}Br_4O_2$: C, 40.16; H, 3.85. Found C, 39.77; H, 3.62.

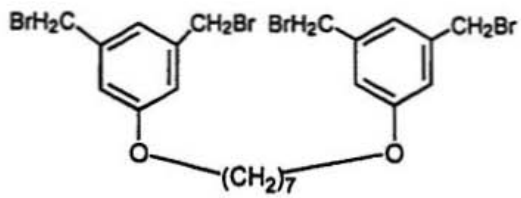


34c

1,6-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-hexane, 34c. Crude tetraester **38c** (9.25 g) was dissolved in dry THF (200 mL) and the solution was added dropwise, with stirring, to a suspension of $LiAlH_4$ (7.65 g, 202 mmol) in dry THF (150 mL) under N_2 at 0 °C. When the addition was complete, the mixture was warmed to room temperature and stirred for 14 h. The reaction was quenched by slow addition of ethyl acetate (40 mL) and H_2O (1 mL), with cooling. The solvents were then removed under reduced pressure, and the gray solid

residue was redissolved in 2:1 aqueous 48 % HBr/H_2SO_4 (200 mL). The mixture was heated for 1 h, then allowed to cool and diluted with H_2O (400 mL). The aqueous solution was extracted with CH_2Cl_2 (3 x 100 mL) and the combined organic layers were washed with H_2O (100 mL), aqueous saturated $NaHCO_3$ (100 mL), and H_2O (100 mL), dried ($MgSO_4$), filtered and concentrated to yield a brown oil. Flash chromatography (35 % CH_2Cl_2/hexanes) afforded pure **34c** (8.32 g, 13.0 mmol, 65 % from diester **36**) as a white solid.

34c: mp 99-101 °C (heptane); IR ($CHCl_3$) 2920 (m), 2860 (m), 1590 (s), 1050 (m); ^{1}H NMR δ 6.99 (s, 2H), 6.86 (s, 4H), 4.43 (s, 8H), 3.98 (t, *J*=6.4, 4H), 1.86-1.82 (m, 4H), 1.57-1.53 (m, 4H); ^{13}C NMR δ 159.3, 139.5, 121.7, 115.2, 68.0, 32.9, 29.1, 25.8; EI-MS *m/z* (%) 644 (8, M^+), 642 (13, M^+), 640 (9, M^+), 563 (6), 561 (6), 481 (6), 363 (9), 241 (27), 83 (90), 55 (100). Anal. Calc'd for $C_{22}H_{26}Br_4O_2$: C, 41.16; H, 4.08. Found: C, 41.16; H, 4.02.

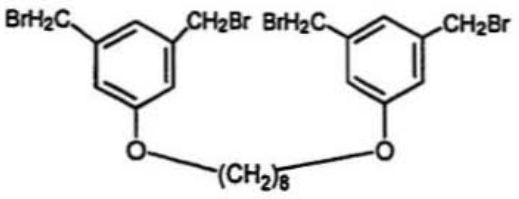


34d

1,7-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-heptane, 34d. Compound **34d** was prepared analogously to **34c** above, using crude tetraester **38d** (10.0 g) and $LiAlH_4$ (7.11 g, 187 mmol) to yield **34d** (5.40 g, 8.23 mmol, 46% from diester **36**) as a white solid.

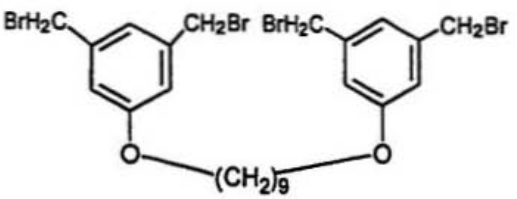
34d: mp 105-106 °C (heptane); IR (CH_2Cl_2) 2940 (w), 2880 (w), 1590 (s), 1450 (m), 1330 (m), 1300 (m); ^{1}H NMR δ 6.98 (t, *J*=1.3, 2H), 6.85 (d, *J*=1.4, 4H), 4.43 (s, 8H), 3.97 (t, *J*=6.4, 4H), 1.83-1.78 (m, 4H), 1.53-1.47 (m, 8H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.0, 33.0, 29.0, 26.0; EI-MS *m/z* (%) 658 (11, M^+), 656 (16, M^+), 654 (11, M^+), 577 (11), 575 (11), 249 (18), 248 (23), 247 (10), 97 (43), 55 (100). Anal. Calc'd for $C_{23}H_{28}Br_4O_2$: C, 42.11; H, 4.30. Found: C, 41.46; H, 4.34.

1,8-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-octane, 34e. Compound **34e** was prepared analogously to **34c** above, using crude tetraester **38e** (13.7 g) and $LiAlH_4$ (9.35 g, 246 mmol) to yield **34e** (9.02 g, 13.5 mmol, 55 % from diester **36**) as a white solid.



34e

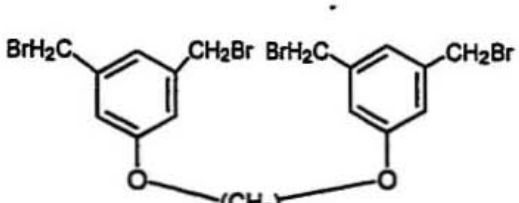
34e: mp 103-104 °C (heptane); IR (CCl_4), 2940 (w), 2860 (w), 1600 (s), 1450 (m), 1330 (m), 1300 (m); ^{1}H NMR δ 6.99 (t, *J*=1.3, 2H), 6.86 (d, *J*=1.4, 4H), 4.43 (s, 8H), 3.96 (t, *J*=6.4, 4H), 1.84-1.74 (m, 4H), 1.52-1.40 (m, 8H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.1, 33.0, 29.2, 29.1, 25.9; EI-MS *m/z* (%) 672 (6, M^+), 670 (9, M^+), 668 (6, M^+), 589 (2), 509 (4), 255 (25), 201 (27), 199 (26), 69 (100), 55 (72). Anal. Calc'd for $C_{24}H_{30}Br_4O_2$: C, 43.02; H, 4.51. Found: C, 43.27; H, 4.32.



34f

1,9-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-nonane, 34f. Compound **34f** was prepared analogously to **34c** above, using crude tetraester **38f** (6.72 g) and $LiAlH_4$ (1.86 g, 49.0 mmol) to yield **34f** (3.65 g, 5.34 mmol, 56 % from diester **36**) as a white solid.

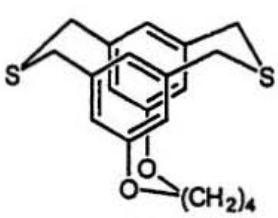
34f: mp 109-110 °C (heptane); IR ($CHCl_3$) 2940 (m), 2860 (m), 1600 (m), 1450 (m), 1330 (m), 1300 (m); ^{1}H NMR δ 6.98 (t, *J*=1.3, 2H), 6.85 (d, *J*=1.4, 4H), 4.42 (s, 8H), 3.96 (t, *J*=6.5, 4H), 1.83-1.73 (m, 4H), 1.52-1.32 (m, 10H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.1, 32.9, 29.4, 29.2, 29.1, 26.0; EI-MS *m/z* (%) 686 (4, M^+), 684 (5, M^+), 682 (3, M^+), 605 (3), 523 (3), 263 (11), 262 (13), 201 (30), 199 (29), 81 (57), 69 (100). Anal. Calc'd for $C_{25}H_{32}Br_4O_2$: C, 43.89; H, 4.71. Found: C, 43.86; H, 4.53.



34g

1,10-*Bis*(3,5-*bis*(bromomethyl)phenoxy)-decane, 34g. This compound was prepared analogously to **34c** above, using crude tetraester **38g** (4.67 g), and $LiAlH_4$ (2.97 g, 78.3 mmol) to yield **34g** (3.79 g, 5.43 mmol, 65 % from diester **36**) as a white solid.

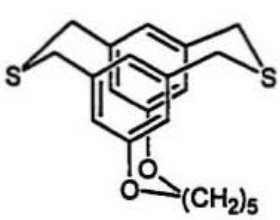
34g: mp 124-125 °C (heptane); IR ($CHCl_3$) 2940 (m), 2860 (m), 1600 (m), 1550 (m), 1330 (m), 1300 (m); ^{1}H NMR δ 6.98 (t, *J*=1.3, 2H), 6.85 (d, *J*=1.3, 4H), 4.43 (s, 8H), 3.96 (t, *J*=6.6, 4H), 1.80-1.75 (m, 4H), 1.50-1.34 (m, 12H); ^{13}C NMR δ 159.5, 139.5, 121.6, 115.2, 68.1, 32.9, 29.5, 29.3, 29.2, 26.0; EI-MS *m/z* (%) 700 (6, M^+), 698 (9, M^+), 696 (6, M^+), 619 (3), 617 (3), 537 (3), 418 (2), 269 (17), 201 (43), 199 (41), 120 (31), 95 (49), 83 (66), 81 (57), 69 (71), 55 (100). Anal. Calc'd for $C_{26}H_{34}Br_4O_2$: C, 44.73; H, 4.91. Found C, 44.56, H, 5.00.



33a

1,6-Dioxa-14,23-dithia[6.3.3](1,3,5)cyclophane, 33a. This compound was prepared analogously to **33c** below, using tetrabromide **34a** (6.09 g, 9.92 mmol) and Na_2S/Al_2O_3 (11.0 g, 28.9 mmol), yielding **33a** (0.778 g, 2.17 mmol, 22 %)[52] as white crystals.

33a: mp 187-188 °C (heptane); IR ($CHCl_3$) 2940 (w), 2880 (w), 1590 (m); ^{1}H NMR δ 6.76 (s, 2H), 6.44 (s, 4H), 4.20-4.18 (m, 4H), 3.78 (d, *J*=14.7, 4H), 3.73 (d, *J*=14.7, 4H), 1.84-1.80 (m, 4H); ^{13}C NMR δ 157.2, 138.4, 125.0, 116.1, 67.6, 38.5, 23.3; EI-MS *m/z* (%) 359 (23), 358 (100, M^+), 294 (8), 237 (28), 122 (7), 121 (12), 91 (13), 55 (18); HRMS Calc'd for $C_{20}H_{22}O_2S_2$: 358.1060, found 358.1042.



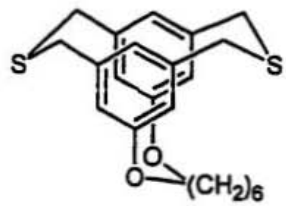
33b

1,7-Dioxa-15,24-dithia[7.3.3](1,3,5)cyclophane, 33b. This compound was prepared analogously to **33c** below, using tetrabromide **34b** (7.21 g, 11.5 mmol) and Na_2S/Al_2O_3 (10.4 g, 28.5 mmol), yielding **33b** (3.02 g, 8.11 mmol, 71 %) as colorless crystals.

33b: mp 126-128 °C (heptane); ^{1}H NMR δ 6.75 (s, 2H), 6.40 (s, 4H), 4.11-4.07 (m, 4H), 3.78 (d, *J*=14.8, 4H), 3.74 (d, *J*=14.8, 4H), 1.76-1.67 (m, 4H), 1.64-1.55 (m, 2H); ^{13}C

[52] A better yield for this compound (62 %) was obtained by another worker, (Ref. 32) demonstrating that many of these reactions (which were often performed only once) have not been optimized.

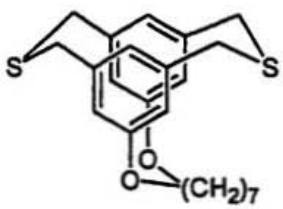
NMR δ 158.0, 138.5, 124.2, 113.5, 65.7, 38.8, 27.3, 21.8; EI-MS *m/z* (%) 373 (25), 372 (100, M^+), 308 (12), 122 (34), 121 (17), 69 (30); HRMS Calc'd for $C_{21}H_{24}O_2S_2$ 372.1216, found 372.1219.



33c

1,8-Dioxa-16,25-dithia[8.3.3](1,3,5)cyclophane, 33c. Tetrabromide **34c** (2.10 g, 3.27 mmol) was dissolved in 18% EtOH/CH_2Cl_2 (1000 mL) in an Erlenmeyer flask and Na_2S/Al_2O_3 (2.67 g, 7.05 mmol) was added in four portions over 2 hours. The reaction was stirred vigorously for 12 h with magnetic stirring, then filtered and concentrated. Flash chromatography of the residue (CH_2Cl_2) afforded colorless crystals of **33c** (0.860 g, 2.22 mmol, 68 %).

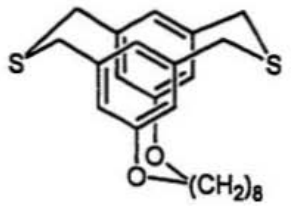
33c: mp 165-167 °C (heptane); ^{1}H NMR δ 6.70 (s, 2H), 6.38 (s, 4H), 3.88-3.84 (m, 4H), 3.79 (d, *J*=14.7, 4H), 3.75 (d, *J*=14.7, 4H), 1.75-1.69 (m, 4H), 1.58-1.55 (m, 4H); ^{13}C NMR δ 159.0, 138.5, 124.4, 113.3, 64.6, 38.8, 28.0, 20.7; EI-MS *m/z* (%) 387 (25), 386 (100, M^+), 353 (10), 322 (12), 122 (40), 120 (19), 91 (31); HRMS Calc'd for $C_{22}H_{26}O_2S_2$: 386.1372, found 386.1373.



33d

1,9-Dioxa-17,26-dithia[9.3.3](1,3,5)cyclophane, 33d. This compound was prepared analogously to **33c** above, using tetrabromide **34d** (14.8 g, 22.5 mmol) and Na_2S/Al_2O_3 (44.3 g, 110.7 mmol), yielding **33d** (4.40 g, 11.0 mmol, 49 %) as white crystals.

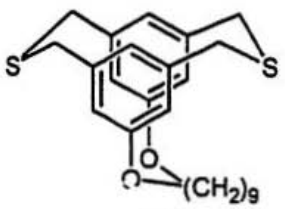
33d: mp 158-159 °C (heptane); ^{1}H NMR δ 6.79 (s, 2H), 6.38 (s, 4H), 3.85-3.81 (m, 4H), 3.79 (d, *J*=14.8, 4H), 3.75 (d, *J*=14.8, 4H), 1.80-1.73 (m, 4H), 1.58-1.52 (m, 4H), 1.40-1.32 (m, 2H); ^{13}C NMR δ 158.8, 138.4, 124.2, 112.8, 65.5, 38.8, 27.1, 24.7, 24.1; EI-MS *m/z* (%) 401 (26), 400 (100, M^+), 367 (11), 336 (11), 122 (42), 121 (18), 55 (54), HRMS Calc'd for $C_{23}H_{28}O_2S_2$: 400.1529, found 400.1557.



33e

1,10-Dioxa-18,27-dithia[10.3.3](1,3,5)cyclophane, 33e. This compound was prepared analogously to **33c** above, using tetrabromide **34e** (4.06 g, 6.06 mmol) and Na_2S/Al_2O_3 (7.19 g, 19.6 mmol) yielding **33e** (1.46 g, 3.52 mmol, 58 %) as colorless crystals.

33e: mp 139-140 °C (heptane); IR (CCl_4) 2950 (s), 2860 (m), 1450 (s), 1320 (s), 1290 (s), 1160 (s), 1050 (m); ^{1}H NMR δ 6.81 (s, 2H), 6.37 (s, 4H), 3.82-3.78 (m, 4H), 3.80 (d, *J*=14.7, 4H), 3.75 (d, *J*=14.7, 4H), 1.76-1.68 (m, 4H), 1.58-1.48 (m, 4H), 1.42-1.36 (m, 4H); ^{13}C NMR δ 158.8, 138.4, 124.1, 112.9, 66.3, 38.8, 28.4, 27.1, 23.7; EI-MS *m/z* (%) 415 (28), 414 (100, M^+), 381 (11), 350 (9), 122 (38), 121 (16); HRMS Calc'd for $C_{24}H_{30}O_2S_2$: 414.1686, found 414.1688.

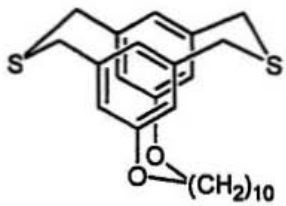


33f

1,11-Dioxa-19-28-dithia[11.3.3](1,3,5)cyclophane, 33f. This compound was prepared analogously to **33c** above, using tetrabromide **34f** (1.69 g, 2.47 mmol) and Na_2S/Al_2O_3 (2.65 g, 6.37 mmol) yielding **33f** (0.700 g, 1.63 mmol, 66 %) as white crystals.

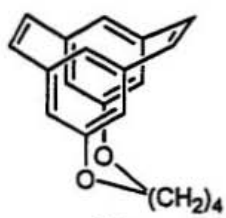
33f: mp 116-118 °C (heptane); ^{1}H NMR δ 6.81 (s, 2H), 6.37 (s, 4H), 3.78 (d, *J*=14.7, 4H), 3.76-3.72 (m, 4H), 3.73 (d, *J*=14.7, 4H), 1.74-1.66 (m, 4H), 1.53-1.36 (m, 10H); ^{13}C NMR δ 159.0, 138.3, 124.0, 112.8, 66.7, 38.8, 28.0, 26.5, 25.7, 23.7; EI-MS *m/z* (%) 429 (29), 428 (100, M^+), 395 (16), 364 (14), 122 (75), 121 (32). Anal. Calc'd for $C_{25}H_{32}O_2S_2$ C, 70.05; H, 7.52. Found C, 69.92; H, 7.40.

1,12-Dioxa-20,29-dithia[12.3.3](1,3,5)cyclophane, 33g. This compound was prepared analogously to **33c** above, using tetrabromide **34g** (1.50 g, 2.14 mmol) and Na_2S/Al_2O_3 (2.02 g, 5.20 mmol) yielding **33g** (0.496 g, 11.2 mmol, 52 %) as white crystals.



33g

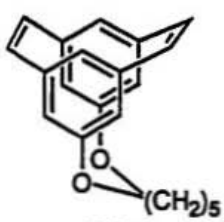
33g: mp 126-127 °C (heptane), IR (CCl_4) 2940 (m), 2860 (w), 1600 (m), 1450 (m), 1330 (w), 1290 (m); ^{1}H NMR δ 6.78 (s, 2H), 6.35 (s, 4H), 3.77 (d, *J*=14.8, 4H), 3.71 (d, *J*=14.7, 4H), 3.73-3.69 (m, 4H), 1.77-1.68 (m, 4H), 1.51-1.30 (m, 12H); ^{13}C NMR δ 158.9, 138.1, 124.0, 112.8, 66.9, 38.6, 28.5, 26.4, 24.3; EI-MS *m/z* (%) 443 (29), 442 (100, M^+), 409 (14), 378 (14), 122 (72), 121 (31), 91 (20), 60 (21), 55 (56); HRMS Calc'd for $C_{26}H_{34}O_2S_2$: 442.1998, found 442.1997.



32a

1,6-Dioxa[6.2.2](1,3,5)cyclophane-13,21-diene, 32a. This compound was synthesized analogously to **32c**, below. Starting with thiacyclophane **33a** (0.477 g, 1.33 mmol) and Borch reagent (0.6 mL, 1.0 g, 6.2 mmol) and yielding *bis*(tetrafluoroborate) salt **39a** (0.487 g, 65 %). Then ^{t}BuOK (0.233 g, 2.08 mmol) was added, yielding isomeric mixture **40a** (0.147 g, 0.354 mmol, 29 % from thiacyclophane **33a**). Borch reagent (0.8 mL, 1.3 g, 7.9 mmol) followed by ^{t}BuOK (0.80 g, 7.1 mmol) yielded **32a** (0.102 g, 0.351 mmol, 99 % from **40a**) as a white crystalline solid.

32a: mp 167-172 °C (heptane); IR (CCl_4) 3010 (m), 2990 (m), 2880 (m), 1400 (m), 1290 (s), 1155 (s); ^{1}H NMR δ 7.17 (s, 4H), 6.77 (s, 2H), 6.15 (s, 4H), 4.13-4.09 (t, *J*=5.7, 4H), 1.58-1.54 (m, 4H); ^{13}C NMR δ 154.8, 136.7, 136.4, 135.1, 117.4, 67.4, 23.0; EI-MS *m/z* (%), 291 (20), 290 (100, M^+), 207 (21), 206 (48), 205 (31), 189 (44), 178 (57), 177 (31), 176 (21), 95 (34); HRMS Calc'd for $C_{20}H_{18}O_2$: 290.1306, found 290.1300.

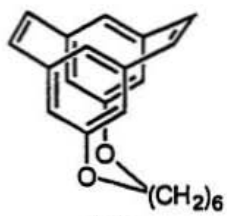


32b

1,7-Dioxa[7.2.2](1,3,5)cyclophane-(14,22)diene, 32b. This compound was synthesized analogously to **32c**, below, starting with thiacyclophane **33b** (3.02 g, 8.11 mmol) and Borch reagent (2.0 mL, 3.2 g, 19.8 mmol) and yielding *bis*(tetrafluoroborate) salt **39b** (3.10 g). Then ^{t}BuOK (2.46 g, 21.9 mmol) was added, yielding isomeric mixture **40b** (1.92 g, 4.82 mmol, 59 % from thiacyclophane **33b**).

Finally, Borch reagent (2.0 mL, 3.2 g, 20 mmol) followed by ^{t}BuOK (5.61 g, 50.0 mmol) yielded **32b** (1.07 g, 3.69 mmol, 73 % from **40b**) as a white, crystalline solid.

32b: mp 138-140 °C (heptane); IR (CCl_4) 3000 (m), 2950 (m), 2890 (m), 1400 (s), 1300 (s), 1270 (s), 1160 (s), 1050 (m); ^{1}H NMR δ 7.14 (s, 4H), 6.87 (s, 2H), 6.12 (s, 4H), 4.08-4.04 (m, 4H), 1.54-1.45 (m, 4H), 1.19-1.09 (m, 2H); ^{13}C NMR δ 155.9, 136.3, 135.9, 134.6, 114.0, 66.7, 29.1, 22.7; EI-MS *m/z* (%) 304 (100, M^+), 207 (33), 206 (96), 205 (32), 189 (63), 178 (51), 41 (31); HRMS Calc'd for $C_{21}H_{20}O_2$: 304.1462, found 304.1440. Anal. Calc'd for $C_{21}H_{20}O_2$: C, 82.86; H, 6.62. Found: C, 82.66; H, 6.65.



32c

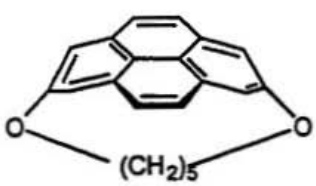
1,8-Dioxa-[8.2.2](1,3,5)cyclophane-(15,23)diene, 32c. Dithiacyclophane **33c** (2.50 g, 6.47 mmol) was dissolved in CH_2Cl_2 (50 mL) and stirred as Borch reagent (1.6 mL, 2.6 g, 16 mmol) was added by syringe under N_2. The reaction was stirred for 3 h. The solvent was removed under reduced pressure and the residue was quenched with aqueous 80% methanol (50 mL). The resulting suspension was filtered to yield the crude *bis*(tetrafluoroborate) salt **39c** (3.25 g, 5.51 mmol, 85 %). This was used without further purification in the next step.

The *bis*(tetrafluoroborate) salt **39c** (3.25 g, 5.51 mmol) was slurried in dry THF (50 mL) and ^{t}BuOK (2.51 g, 22.4 mmol) was added. The reaction mixture was stirred at room temperature under N_2 for 3 h. The reaction was then quenched with aqueous saturated NH_4Cl (1 mL) and the solvents were removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (50 mL), and washed with aqueous saturated NH_4Cl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered through a plug of silica and concentrated to yield a foamy yellow solid **40c** (1.71 g, 4.14 mmol, 63 % from thiacyclophane **33c**) as a complex mixture of isomers. This was used without further purification in the next step.

The isomeric mixture **40c** (1.71 g, 4.14 mmol) was dissolved in CH_2Cl_2 (50 mL) and stirred as Borch reagent (1.4 mL, 2.2 g, 14 mmol) was added by syringe under N_2. The reaction was then stirred at room temperature for 3 h. The solvents were then removed under reduced pressure and the brown oily residue was suspended in 1:1 THF/

^{t}BuOH (80 mL) and treated with ^{t}BuOK (3.55 g, 31.9 mmol) for 6 h with stirring under N_2. The reaction was quenched with aqueous saturated NH_4Cl (1 mL) and the solvents were removed under reduced pressure. The residue was redissolved in CH_2Cl_2 (50 mL) and washed with aqueous saturated NH_4Cl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated to yield a yellow solid. Flash chromatography (CH_2Cl_2) yielded pure diene **32c** (1.15 g, 3.63 mmol, 89 % from **40c**) as a white crystalline solid.

32c: mp 117-118 °C (heptane); IR (CCl_4) 3005 (m), 2940 (s), 2880 (m), 1400 (s), 1300 (s), 1270 (s), 1160 (s), 1115 (m), 1040 (m); ^{1}H NMR δ 7.15 (s, 4H), 6.95 (t, *J*=1.1, 2H), 6.11 (d, *J*=1.0, 4H), 3.93-3.89 (m, 4H), 1.53-1.49 (m, 4H), 1.29-1.25 (m, 4H); ^{13}C NMR δ 155.8, 136.2, 135.5, 134.7, 113.9, 67.4, 27.8, 22.8; EI-MS *m/z* (%) 319 (11), 318 (46, M^+), 207 (28), 206 (100), 205 (20), 189 (27), 178 (48); HRMS: Calc'd for $C_{22}H_{22}O_2$: 318.1619, found 318.1623.

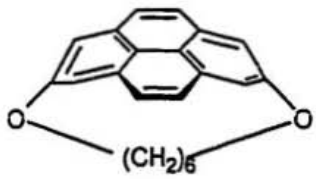


31b

1,7-Dioxa[7](2,7)pyrenophane, 31b. Diene **32b** (0.552 g, 1.90 mmol) was dissolved in benzene (50 mL) and DDQ (0.441 g, 1.94 mmol) was added. The solution was refluxed for 12 h. The solvent was removed under reduced pressure, and the residue was dissolved in CH_2Cl_2 (25 mL). The solution was washed with aqueous 1 M NaOH (20 mL), brine (20 mL), dried ($MgSO_4$) and concentrated. The residue was subjected to flash chromatography (CH_2Cl_2). Two products were obtained, pyrenophane **31b** (0.189 g, 0.626 mmol, 35 %) and an unidentified compound, possibly **46** (0.163 g). Analysis was performed on a small amount of sample crystallized from xylenes.

31b: mp 155 °C (dec.) (xylenes); IR ($CDCl_3$) 3040 (w), 2920 (s), 2840 (s), 1570 (m), 1540 (s), 1420 (m), 1250 (s), 1140 (s); ^{1}H NMR: δ 7.72 (s, 4H), 7.22 (s, 4H), 3.31 (m, 4H), -0.04 (m, 4H), -2.10 (m, 2H); ^{13}C NMR: δ 152.0, 133.4, 126.7, 126.3, 123.1, 76.3, 27.9, 26.9; EI-MS *m/z* (%) 303 (22), 302 (93, M^+), 274 (14), 234 (36), 218 (21), 216

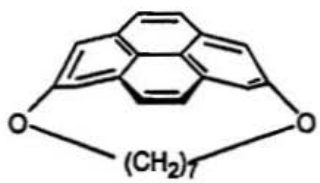
(20), 206 (15), 204 (64), 189 (39), 188 (100), 187 (33), 177 (20), 176 (74), 94 (39). Anal. Calc'd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.40; H, 6.00.



31c

1,8-Dioxa[8](2,7)pyrenophane, 31c. Diene **32c** (1.15 g, 3.63 mmol) was dissolved in benzene (100 mL) and DDQ (1.66 g, 7.30 mmol) was added. The solution was refluxed for 12 h. The solvent was removed under reduced pressure and the residue dissolved in CH_2Cl_2 (25 mL). The solution was washed with 1M NaOH (20 mL), brine (10 mL), dried ($MgSO_4$) and concentrated. It was then redissolved in CH_2Cl_2 (5 mL) and the solution was subjected to flash chromatography (CH_2Cl_2) to yield pyrenophane **31c** (0.92 g, 2.93 mmol, 81%) as a white crystalline solid.

31c: mp 190 °C (dec.) (xylenes); IR (CCl_4) 3040 (w), 2970 (m), 2940 (m), 2880 (m), 1460 (m), 1430 (m), 1290 (m), 1270 (m); ^{1}H NMR δ 7.84 (s, 4H), 7.44 (s, 4H), 3.61-3.57 (m, 4H), 0.10-0.08 (m, 4H), -1.43 – -1.48 (m, 4H); ^{13}C NMR δ 153.6, 132.7, 127.4, 126.9, 123.2, 77.7, 27.9, 26.7; EI-MS *m/z* (%) 317 (24), 316 (100, M^+), 288 (11), 234 (58), 206(49), 205 (62), 188 (56), 176 (70); HRMS Calc'd for $C_{22}H_{20}O_2$: 316.1462, found 316.1451.

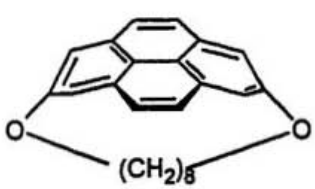


31d

1,9-Dioxa[9](2,7)pyrenophane, 31d. This compound was synthesized analogously to **32c**, above, starting with thiacyclophane **33d** (4.30 g, 10.7 mmol), Borch reagent (2.7 mL, 4.3 g, 26.7 mmol) and CH_2Cl_2 (200 mL) and yielding *bis*(tetrafluoroborate) salt **39d** (4.35 g, 67 %). Then ^{t}BuOK (2.60 g) was added, to yield isomeric mixture **40d** (2.63 g, 6.14 mmol, 57.3 % from thiacyclophane **33d**). Next, Borch reagent (2.5 mL, 4.0 g, 25 mmol) followed by ^{t}BuOK (6.46 g, 57.6 mmol) afforded an inseparable mixture of pyrenophane **31d** and (possibly) dihydropyrenophane **41d** (1.5:1, 0.761 g). Treatment of this mixture with DDQ (0.52 g, 2.3 mmol) in refluxing benzene (50 mL) afforded, after

flash chromatography (CH_2Cl_2), pure pyrenophane **31d** (0.454 g, 1.37 mmol, 23 % from *bis*(methylthio)cyclophane **40d**) as a white crystalline solid.

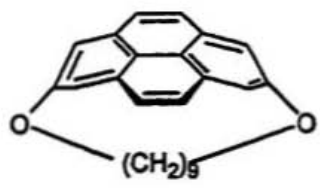
31d: mp 248-250 °C (xylenes); IR ($CHCl_3$) 2920 (s), 2860 (m), 1580 (s), 1540 (m); ^1H NMR δ 7.91 (s, 4H), 7.64 (s, 4H), 3.78-3.74 (m, 4H), 0.73-0.64 (m, 4H), -0.71 – -0.74 (m, 2H), -1.87 – -1.91 (m, 4H); ^{13}C NMR δ 153.6, 132.7, 127.0, 125.3, 122.0, 75.8, 28.9, 28.8, 28.3; EI-MS *m/z* (%) 331 (25), 330 (100, M^+), 234 (75), 206 (35), 205 (42), 188 (33), 176 (27), 55 (90); HRMS Calc'd for $C_{23}H_{22}O_2$: 330.1617, found 330.1608.



31e

1,10-Dioxa[10](2,7)pyrenophane, 31e. This compound was synthesized analogously to **32c**, above, starting with thiacyclophane **33e** (1.46 g, 3.52 mmol) and Borch reagent (1.4 mL, 2.2 g, 14 mmol) and yielding *bis*(tetrafluoroborate) salt **39e** (1.66 g, 76 %). Then ^{t}BuOK (1.00 g, 8.91 mmol) was added, yielding isomeric mixture **40e** (1.01 g, 2.28 mmol, 65 % from thiacyclophane **33e**). Next, Borch reagent (1.0 mL, 1.6 g, 9.9 mmol) followed by ^{t}BuOK (2.14 g, 19.1 mmol) afforded an inseparable mixture of pyrenophane **31e** and (possibly) dihydropyrenophane **41e** (1:1, 0.501 g). Treatment of the mixture with DDQ (0.581 g, 2.56 mmol) in refluxing benzene (50 mL) afforded, after flash chromatography (CH_2Cl_2), **31e** (0.386 g, 1.13 mmol, 50 % from *bis*(methylthio)cyclophane **40e**) as a white crystalline solid.

31e: mp >250 °C (xylenes); IR (CCl_4) 3060 (m), 2960 (m), 2940 (s), 2860 (m), 1450 (m), 1430 (s); ^1H NMR δ 7.92 (s, 4H), 7.72 (s, 4H), 4.04-4.00 (m, 4H), 0.97-0.88 (m, 4H), -0.66 – -0.74 (m, 4H), - 1.12 – -1.22 (m, 4H); ^{13}C NMR δ 154.8, 132.3, 127.1, 123.6, 121.0, 76.3, 30.1, 30.0, 28.3; EI-MS *m/z* (%) 345 (26), 344 (100, M^+), 234 (60), 206 (30), 205 (34), 188 (22), 176 (20), 69 (36). Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02. Found: C, 83.55; H, 7.06.

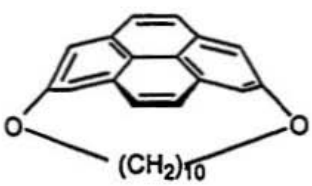


31f

1,11-Dioxa[11](2,7)pyrenophane, 31f. This compound was synthesized analogously to **32c**, above, starting with

thiacyclophane **33f** (0.700 g, 1.63 mmol) and Borch reagent (0.9 mL, 1.4 g, 9 mmol) and yielding *bis*(tetrafluoroborate) salt **39f** (0.608 g, 59 %). Then ^{t}BuOK (0.331 g, 2.95 mmol) was added, yielding isomeric mixture **40f** (0.438 g, 0.97 mmol, 59 % from thiacyclophane **33f**). Next, Borch reagent (0.8 mL, 1.3 g, 8 mmol) followed by ^{t}BuOK (0.937 g, 8.34 mmol) afforded an inseparable mixture of pyrenophane **31f** and (possibly) dihydropyrenophane **41f**, which was treated with DDQ (0.261 g, 1.15 mmol) in refluxing benzene (50 mL) and afforded, after flash chromatography (CH_2Cl_2), pure pyrenophane **31f** (0.099 g, 0.28 mmol, 29 % from *bis*(methylthio)cyclophane **40f**) as a white crystalline solid.

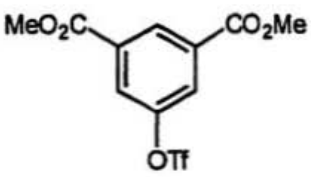
31f: mp 207-210 °C (xylenes); IR (CH_2Cl_2) 3040 (w), 2930 (s), 1595 (s), 1455 (m), 1150 (m); ^{1}H NMR δ 7.98 (s, 4H), 7.83 (s, 4H), 4.21-4.17 (t, 4H), 1.26-1.12 (m, 4H), -0.21 – -0.33 (m, 4H), -0.58 – -0.69 (m, 4H), -1.01 – -1.08 (m, 2H); ^{13}C NMR δ 155.1, 132.0, 127.2, 122.5, 120.3, 75.3, 31.3, 29.2, 29.0, 28.9; EI-MS *m/z* (%) 359 (25), 358 (100, M^+), 234 (44), 206 (29), 205 (37), 188 (19), 176 (20); HRMS Calc'd for $C_{25}H_{26}O_2$: 358.1931, found 358.1920.



31g

1,12-Dioxa[12](2,7)pyrenophane, 31g. This compound was synthesized analogously to **32c**, above, sarting with thiacyclophane **33g** (0.733 g, 1.66 mmol) and Borch reagent (0.4 mL, 0.6 g, 3.9 mmol) and yielding *bis*(tetrafluoroborate) salt **39g** (0.825 g, 1.28 mmol, 77 %). Then ^{t}BuOK (0.401 g, 3.57 mmol) was added, yielding a mixture of isomers **40g** (0.173 g, 0.368 mmol, 22% from thiacyclophane **33g**). Next, Borch reagent (0.2 mL, 0.3 g, 1.9 mmol) followed by ^{t}BuOK (0.50 g, 4.46 mmol) afforded an inseparable mixture of pyrenophane **31g** and (possibly) dihydropyrenophane **41g** (3:2, 0.067 g). Treatment of this mixture with DDQ (0.060 g, 0.26 mmol) in refluxing benzene (15 mL) afforded, after flash chromatography (CH_2Cl_2), pyrenophane **31g** (0.052 g, 0.14 mmol, 38 % from *bis*(thiomethyl)cyclophane **40g**) as a white crystalline solid. Unfortunately, despite repeated chromatography and recrystallization, **31g** could not be separated from a trace contaminant visible in the NMR.

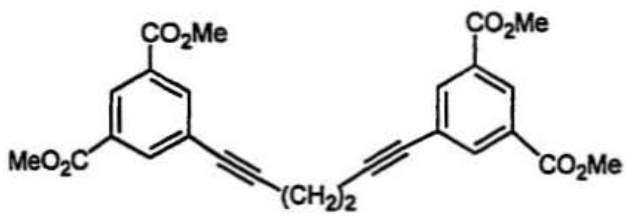
31g: mp 171-173 °C (xylenes); IR ($CDCl_3$) 3045 (w), 2960 (s), 2920 (s), 1600 (s), 1440 (s); ^{1}H NMR δ 7.96 (s, 4H), 7.85 (s, 4H), 4.33-4.29 (t, *J*=4.7, 4H), 1.41 (m, 4H), -0.14 (m, 8H), -0.63 (m, 4H); ^{13}C NMR δ 156.9, 131.9, 127.2, 121.8, 118.7, 74.2, 31.0, 29.8, 29.0, 27.8; EI-MS *m/z* (%) 373 (28), 372 (100, M^+), 234 (45), 206 (21), 205 (19); HRMS Calc'd for $C_{26}H_{28}O_2$: 372.2088, found 372.2064.



52

3,5-*Bis*(methoxycarbonyl)phenyl triflate, 52. Dimethyl 5-hydroxyisophthalate **36** (10.1 g, 48.1 mmol) and pyridine (5.7 mL, 5.6 g, 71 mmol) were dissolved in CH_2Cl_2 (200 mL) and cooled to 0 °C. Trifluoromethanesulfonic anhydride (8.4 mL, 14 g, 49 mmol) was added by syringe under N_2. The solution was stirred for 20 min., then quenched with aqueous 5% HCl (100 mL). The organic layer was washed with aqueous 1M HCl (100 mL), aqueous saturated $NaHCO_3$ (100 mL), brine, then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. The residue was washed through a ~10 cm column of silica with CH_2Cl_2 and the eluate was concentrated to yield pure **52** (14.9 g, 43.6 mmol, 91 %), a white crystalline solid.

52: mp 68.5-69 °C (hexanes); ^{1}H NMR δ 8.71 (m, 1H), 8.13 (s, 2H), 4.00 (s, 6H); ^{13}C NMR δ 164.3, 149.2, 133.0, 130.3, 126.5, 118.6 (q, *J*=320.6), 52.8; EI-MS *m/z* (%) 342 (M^+, 52), 311 (100), 247 (91), 219 (20), 179 (21), 178 (21), 150 (34), 119 (21). Anal. Calc'd for $C_{11}H_9F_3O_7S$: C, 38.60; H, 2.65. Found: C, 38.55; H, 2.49.

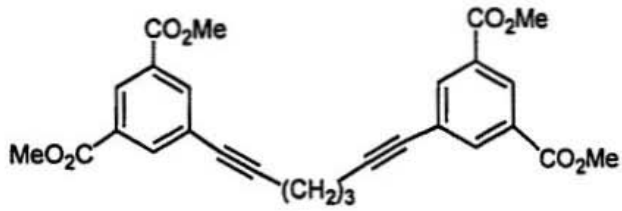


54a

1,6-*Bis*(3,5-*bis*(methoxycarbonyl)-phenyl)-1,5-hexadiyne, 54a: This compound was prepared analogously to **54c**, below, using triflate **52** (6.85 g, 20.0 mmol), 1,6-heptadiyne (0.80 g, 10.0 mmol), DBU (3.60 g, 23.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.30 g, 0.43 mmol) and CuI (0.50 g, 2.63 mmol) in degassed

benzene (60 mL) affording **54a** (0.99 g, 2.14 mmol, 21%) after chromatography (CH_2Cl_2) as a white solid.

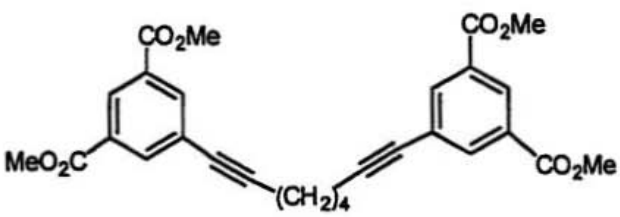
54a: mp: 133-135 °C (cyclohexane); ^{1}H NMR δ 8.58 (s, 2H), 8.25 (s, 4H), 3.94 (s, 12H), 2.77 (s, 4H); ^{13}C NMR δ 165.6, 136.9, 130.8, 129.7, 124.5, 90.2, 80.0, 52.4, 19.5; EI-MS *m/z* (%) 462 (6, M^+), 431 (13), 403 (10), 232 (14), 231 (100), 200 (18). Anal. Calc'd for $C_{26}H_{22}O_8$: C, 67.53; H, 4.79.



54b

1,7-*Bis*(3,5-*bis*(methoxycarbonyl)-phenyl)-1,6-heptadiyne, 54b: This compound was prepared analogously to **54c**, below, using triflate **52** (7.50 g, 21.9 mmol), 1,6-heptadiyne (1.00 g, 10.9 mmol), DBU (4.10 g, 26.9 mmol), $Pd(PPh_3)_2Cl_2$ (0.20 g, 0.28 mmol) and CuI (0.210 g, 1.10 mmol) in degassed benzene (100 mL) affording **54b** (4.47 g, 9.38 mmol, 86%) after chromatography (CH_2Cl_2) as a white solid.

54b: mp 105-107 °C (EtOAc/hexanes); ^{1}H NMR δ 8.57 (s, 2H), 8.24 (s, 4H), 3.95 (s, 12 H), 2.64 (t, *J*=7.0, 4H), 1.94 (quintet, *J*=7.0, 2H); ^{13}C NMR δ 165.7, 136.6, 130.7, 129.6, 124.8, 91.2, 79.6, 52.5, 27.4, 18.6; EI-MS *m/z* (%) 477 (20), 476 (68, M^+), 445 (57), 413 (32), 411 (100), 385 (25), 239 (27), 207 (60). Anal. Calc'd for $C_{27}H_{24}O_8$: C, 68.06; H, 5.08. Found: C, 67.61; H, 4.81.

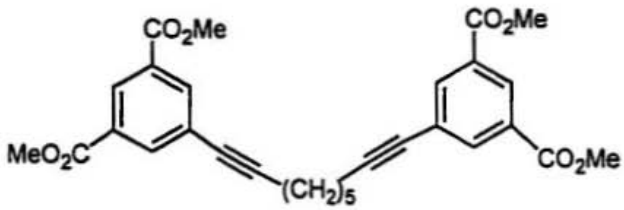


54c

1,8-*Bis*(3,5-*bis*(methoxycarbonyl)-phenyl)-1,7-octadiyne, 54c: Triflate **52** (1.10 g, 3.21 mmol), 1,7-octadiyne (0.171 g, 1.61 mmol) and DBU (0.63 g, 4.1 mmol) were dissolved in benzene (50 mL) and the

solution was degassed. $Pd(PPh_3)_2Cl_2$ (0.050 g, 0.071 mmol) and CuI (0.110 g, 0.578 mmol) were added, and the reaction mixture was stirred at room temperature under N_2 for 24 h. The mixture was washed with 1M HCl (2 x 100 mL), brine (100 mL), then dried ($MgSO_4$), filtered and concentrated under reduced pressure. Column chromatography (CH_2Cl_2) afforded **54c** as a white solid (0.62 g, 1.26 mmol, 79 %).

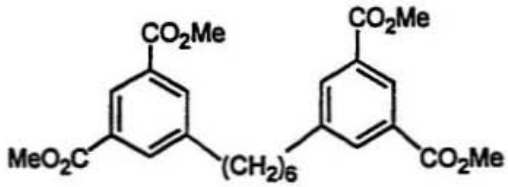
54c: mp 133-133.5 °C (40% toluene/cyclohexane); ^{1}H NMR δ 8.56 (s, 2H), 8.23 (s, 4H), 3.94 (s, 12H), 2.53-2.50 (m, 4H), 1.84-1.79 (m, 4H); ^{13}C NMR δ 165.7, 136.5, 130.7, 129.5, 124.9, 91.9, 79.2, 52.5, 27.6, 19.0; EI-MS *m/z* (%) 491 (31), 490 (100, M^+), 462 (22), 459 (26), 403 (27). Anal. Calc'd for $C_{28}H_{26}O_8$: C, 68.56; H, 5.34. Found: C, 69.03; H, 5.22.



54d

1,9-*Bis*(3,5-*bis*(methoxycarbonyl)-phenyl)-1,8-nonadiyne, 54d: This compound was prepared analogously to **54c**, above, using triflate **52** (7.49 g, 21.9 mmol), 1,8-nonadiyne (1.31 g, 10.9 mmol), DBU (4.12 g, 27.1 mmol), $Pd(PPh_3)_2Cl_2$ (0.30 g, 0.43 mmol) and CuI (0.40 g, 2.1 mmol) in degassed benzene (100 mL) affording **54d** (4.45 g, 8.82 mmol, 81 %) after chromatography (CH_2Cl_2) as a waxy yellowish solid.

54d: mp 80-85 °C (1:1 EtOAc/hexanes, does not crystallize). ^{1}H NMR δ 8.54 (s, 2H), 8.20 (s, 4H), 3.94 (s, 12H), 2.48-2.44 (m, 4H), 1.69-1.66 (m, 6H); ^{13}C NMR δ 165.6, 136.5, 130.6, 129.3, 124.6, 92.3, 79.0, 52.4, 28.0, 27.9, 19.2; EI-MS *m/z* (%) 505 (32), 504 (100, M^+), 473 (17), 413 (16), 385 (27), 231 (20), 221 (37), 115 (20). Anal. Calc'd for $C_{29}H_{28}O_8$: C, 69.04; H, 5.59. Found: C, 69.04; H, 5.64.

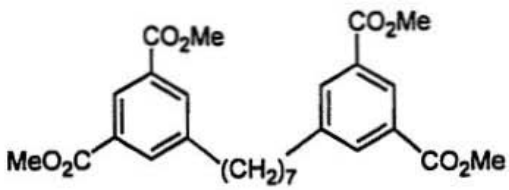


51a

1,6-*Bis*(3,5-*bis*(methoxycarbonyl)phenyl)-hexane, 51a: This compound was prepared analogously to **51c** below, using diynetetraester

54a (0.90 g, 1.9 mmol), 20 % wet palladium hydroxide on C (Pearlman's catalyst) (0.50 g) in ethyl acetate (200 mL) to afford tetraester **51a** (0.90 g, 1.9 mmol, 98 %) as a white solid.

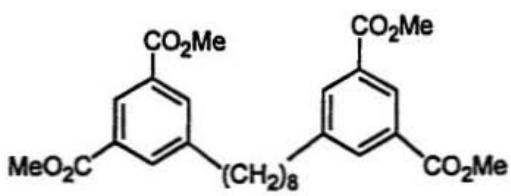
51a: mp 119-121.5 °C (1:1 ether/hexane); ^{1}H NMR δ 8.50 (s, 2H), 8.04 (s, 4H), 3.94 (s, 12H, 2.67 (t, *J*=7.5, 4H), 1.65-1.61 (m, 4H), 1.39-1.35 (m, 4H); ^{13}C NMR δ 166.2, 143.4, 133.6, 130.3, 128.0, 52.1, 35.3, 31.0, 29.3; EI-MS *m/z* (%) 470 (6, M^+), 439 (69), 438 (100), 378 (36), 230 (28), 207 (45), 204 (22), 190 (36), 189 (95), 177 (30), 176 (52), 148 (27). Anal. Calc'd for $C_{26}H_{30}O_8$: C, 66.37; H, 6.43. Found: C, 65.95; H, 6.44.



51b

1,7-*Bis*-(3,5-*bis*(methoxycarbonyl)-phenyl)heptane, 51b: This compound was prepared analogously to **51c** below, using diynetetraester **54b** (4.36 g, 9.15 mmol), 20 % wet palladium hydroxide on C (Pearlman's catalyst) (0.96 g) in ethyl acetate (200 mL) to afford tetraester **51b** (3.95 g, 8.15 mmol, 89 %) as a white solid.

51b: mp 89-91 °C (EtOAc/hexanes); ^{1}H NMR δ 8.50 (s, 2H), 8.04 (s, 4H), 3.94 (s, 12H), 2.70 (t, *J*=7.6, 4H), 1.67-1.63 (m, 6H), 1.35 (br s, 4H); ^{13}C NMR δ 166.3, 143.5, 133.7, 130.4, 128.1, 52.2, 35.4, 31.1, 29.1, 28.9; EI-MS *m/z* (%) 484 (7, M^+), 453 (71), 452 (85), 392 (31), 211 (64), 207 (75), 189 (100), 177 (43), 176 (91), 149 (40), 119 (32), 117 (31). Anal. Calc'd for $C_{27}H_{32}O_8$: C, 66.93; H, 6.66. Found: C, 66.76; H, 6.74.

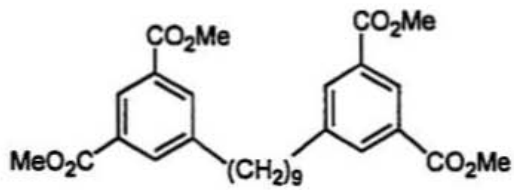


51c

1,8-*Bis*(3,5-*bis*(methoxycarbonyl)-phenyl)octane, 51c: Compound **54c** (3.61g, 7.36 mmol) was dissolved in ethyl acetate (100 mL) and 20 % wet palladium hydroxide on C (Pearlman's catalyst, 0.61 g) was added. The suspension was stirred under 1 atmosphere of

H_2 for 20 min. It was then degassed under reduced pressure and filtered through Celite. The filtrate was concentrated to yield **51c** (3.52 g, 7.06 mmol, 96 %) a white solid.

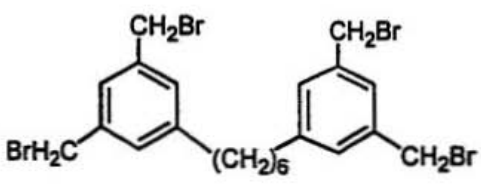
51c: mp 80.5-83 °C (1:1 toluene/hexanes); ^{1}H NMR δ 8.50 (s, 2H), 8.05 (s, 4H), 3.94 (s, 12H), 2.70 (t, *J*=8.0, 4H), 1.64-1.60 (m, 4H), 1.31 (br s, 8 H); ^{13}C NMR δ 165.9, 143.6, 133.3, 130.1, 127.8, 51.8, 35.1, 30.8, 28.9, 28.8; EI-MS *m/z* (%) 498 (2, M^+), 467 (50), 466 (49), 435 (31), 434 (91), 406 (30), 374 (42), 218 (76), 207 (69), 190 (42), 189 (100), 177 (47), 176 (70), 149 (44), 119 (30), 91 (22). Anal. Calc'd for $C_{28}H_{34}O_8$: C, 67.45; H, 6.87. Found: C, 67.58; H, 7.01.



51d

1-9-*Bis*-(3,5-*bis*(methoxycarbonyl)phenyl)-nonane, 51d: This compound was prepared analogously to **51c** above, using diynetetraester **54d** (4.35 g, 8.62 mmol), and 20 % wet palladium hydroxide on C (Pearlman's catalyst) (0.50 g) in ethyl acetate (300 mL) to afford tetraester **51d** (3.60 g, 7.02 mmol, 81 %) as a white solid.

51d: mp 62.5-64 °C (cyclohexane); ^{1}H NMR δ 8.50 (s, 2H), 8.05 (s, 4H), 3.94 (s, 12H), 2.70 (t, *J*=7.1, 4H), 1.67-1.61 (m, 4H), 1.30 (br s, 10H); ^{13}C NMR δ 166.5, 143.7, 133.8, 130.5, 128.2, 52.3, 35.5, 31.2, 29.7, 29.3, 29.1; EI-MS *m/z* (%) 512 (2, M^+), 481 (36), 480 (31), 449 (33), 448 (100), 416 (38), 387 (43), 225 (47), 207 (59), 189 (71), 177 (40), 176 (51), 149 (40). Anal. Calc'd for $C_{29}H_{36}O_8$: C, 67.95; H, 7.08. Found: C, 67.95; H, 7.30.

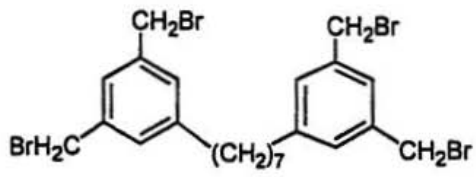


56a

1,6-*Bis*(3,5-*bis*(bromomethyl)phenyl)hexane, 56a: Tetrabromide **56a** was prepared analogously to **56c**, below, using $LiAlH_4$ (1.87 g, 49.3 mmol) and tetraester **51a** (1.90 g, 4.04 mmol) to afford crude **55a** (1.20 g, 3.35 mmol, 83 %). Next, treatment of crude tetraalcohol **55a**

(1.14 g, 3.18 mmol) with HBr/AcOH (5.0 mL, 6.8 g, 25 mmol) yielded tetrabromide **56a** (1.24 g, 2.03 mmol, 53 % from **51a**) as a colorless solid.

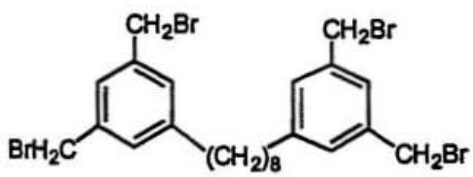
56a: mp 73-74 °C (ether/hexanes); ^{1}H NMR δ 7.23 (s, 2H), 7.13 (s, 4H), 4.44 (s, 8H), 2.58 (t, *J*=7.4, 4H), 1.61-1.57 (m, 4H), 1.38-1.34 (m, 4H); ^{13}C NMR δ 144.0, 138.2, 129.1, 126.9, 35.5, 33.1, 31.0, 29.0; EI-MS *m/z* (%) 531 (39), 529 (38), 277 (32), 237 (30), 226 (46), 225 (73), 224 (30), 199 (95), 197 (100), 159 (39), 145 (41), 119 (93), 117 (51), 115 (47), 91 (49). Anal. Calc'd for $C_{22}H_{26}Br_4$: C, 43.31; H, 4.30. Found: C, 43.49; H, 4.31.



56b

1,7-*Bis*(3,5-*bis*(bromomethyl)phenyl)-heptane, 56b: Tetrabromide **56b** was prepared analogously to **56c**, below, using $LiAlH_4$ (2.35 g, 61.9 mmol) and tetraester **51b** (3.89 g, 8.02 mmol) to afford crude tetraalcohol **55b** (2.83 g, 7.60 mmol, 95 %). Next, treatment of crude tetraalcohol **55b** (2.75 g, 7.38 mmol) with HBr/AcOH (5.0 mL, 6.8 g, 25 mmol) to yielded tetrabromide **56b** (3.13 g, 5.02 mmol, 65 % from **51b**) as a white solid.

56b: mp 59-64 °C (heptane); ^{1}H NMR δ 7.22 (s, 2H), 7.12 (s, 4H), 4.42 (s, 8H), 2.57 (t, *J*=7.5, 4H), 1.61-1.57 (m, 4H), 1.32 (br s, 6H); ^{13}C NMR δ 144.0, 138.1, 129.1, 126.8, 35.4, 33.1, 31.0, 29.1, 29.0; EI-MS *m/z* (%) 201 (19), 199 (19), 120 (21), 97 (33), 95 (20), 91 (25). Anal. Calc'd for $C_{23}H_{28}Br_4$: C, 44.26; H, 4.52. Found: C, 44.33; H, 4.51.

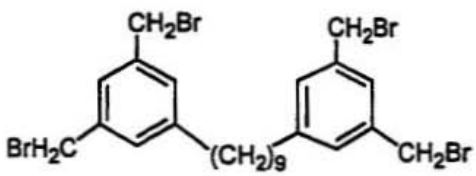


56c

1,8-*Bis*(3,5-*bis*(bromomethyl)phenyl)octane, 56c: $LiAlH_4$ (3.90 g, 103 mmol) was suspended in dry THF (100 ml) and stirred under N_2 for 1 h. Tetraester **51c** (3.50 g, 7.02 mmol) was dissolved in dry THF (100 mL) and added dropwise to the $LiAlH_4$ slurry at 0 °C under N_2. The reaction was

heated to reflux for 15 h, then cooled to 0 °C. The reaction was quenched by the slow addition of ethyl acetate (300 mL) and then aqueous 1M HCl (100 mL). This was stirred for 1 h and separated. The aqueous layer was extracted with ethyl acetate (2 x 50 mL), and the combined organic layers were washed with brine (100 mL), dried ($MgSO_4$), filtered and concentrated to yield crude **55c** (2.65 g, 6.85 mmol, 98 %), a gray-white solid which was used in the next step. Tetraalcohol **55c** (1.69 g, 4.37 mmol) was suspended in glacial acetic acid (50 mL). HBr in acetic acid (30%, 1.0 mL, 1.4 g, 5.0 mmol) was added, and the mixture was heated to reflux overnight. The reaction mixture was cooled, H_2O (50 mL) was added, and the resulting aqueous solution was extracted with CH_2Cl_2 (3 x 50 mL). The organic layer was then washed with H_2O (50 mL), aqueous saturated $NaHCO_3$ (50 mL) and brine (50 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Column chromatography (40 % CH_2Cl_2/hexanes) of the resulting brown oil afforded tetrabromide **56c** (1.34 g, 2.10 mmol, 47 % from tetraester **51c**) as a white solid.

56c: mp 85-86 °C (heptane); ^{1}H NMR δ 7.23 (s, 2H), 7.14 (s, 4H), 4.46 (s, 8H), 2.59 (t, *J*=7.5, 4H), 1.63-1.57 (m, 4H), 1.32 (br s, 8H); ^{13}C NMR δ 144.2, 138.2, 129.2, 126.9, 35.6, 33.1, 31.1, 29.3, 29.2; EI-MS *m/z* (%) 477 (21), 277 (24), 239 (54), 225 (32), 223 (32), 199 (100), 197 (91), 145 (72), 119 (61), 117 (33). Anal. Calc'd for $C_{24}H_{30}Br_4$: C, 45.17; H, 4.74. Found: C, 45.43; H, 4.69.

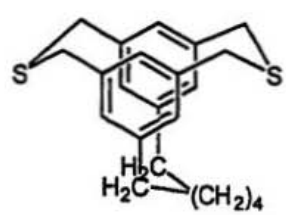


56d

1,9-*Bis*(3,5-*bis*(bromomethyl)phenyl)nonane, 56d: This compound was prepared analogously to **55c** above, using $LiAlH_4$ (1.94 g, 51.1 mmol) and tetraester **51d** (2.32 g, 4.53 mmol) to afford tetraalcohol **55d** (1.53 g, 3.82 mmol, 85 %). Treatment of tetraalcohol **55d** (1.50 g, 3.74 mmol) with HBr/AcOH (7.0 mL, 9.5 g, 35 mmol) yielded tetrabromide **56d** (2.14 g, 3.28 mmol, 88 %) as a white solid.

56d: mp: 69-71.5 °C (toluene/heptane); ^{1}H NMR δ 7.20 (s, 2H), 7.12 (s, 4H), 4.41 (s, 8H), 2.56 (t, *J*=8.0, 4H), 1.63-1.57 (m, 4H), 1.29 (br s, 10H); ^{13}C NMR δ 144.0, 138.0,

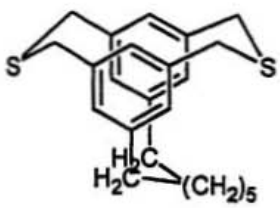
129.0, 126.8, 35.5, 33.1, 31.0, 29.2, 29.1; EI-MS *m/z* (%) 490 (16), 277 (30), 246 (28), 239 (23), 237 (24), 225 (37), 223 (38), 199 (95), 197 (100), 145 (82), 119 (65). Anal. Calc'd for $C_{25}H_{32}Br_4$: C, 46.04; H, 4.95. Found: C, 46.05; H, 4.82.



50a

14,23-Dithia[6.3.3](1,3,5)cyclophane, 50a: : This compound was prepared analogously to **50c**, below, using tetrabromide **56a** (1.12 g, 1.84 mmol) and Na_2S/Al_2O_3 (2.50 g, 6.60 mmol) to afford thiacyclophane **50a** (0.35 g, 0.99 mmol, 53 %) as a white crystalline solid.

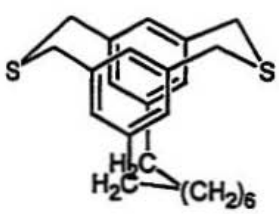
50a: mp 147-149 °C (1:1 ether/hexane); ^{1}H NMR δ 7.04 (s, 2H), 6.59 (s, 4H), 3.77 (d, *J*=15.1, 4H), 3.70 (d, *J*=15.0, 4H), 2.39-2.35 (m, 4H), 1.55-1.51 (m, 4H), 0.99-0.96 (m, 4H); ^{13}C NMR δ 142.3, 136.8, 128.4, 127.1, 38.8, 35.5, 28.7, 28.0; EI-MS *m/z* (%) 355 (23), 354 (100, M^+), 321 (30), 290 (49), 158 (22), 119 (36), 115 (29), 105 (27), 91 (39). Anal. Calc'd for $C_{22}H_{26}S_2$: C, 74.53; H, 7.39. Found: C, 74.06; H, 7.52.



50b

[7.3.3]-15,24-Dithia(1,3,5)cyclophane, 50b: : This compound was prepared analogously to **50c**, below, using tetrabromide **56b** (3.05 g, 4.89 mmol) and Na_2S/Al_2O_3 (6.97 g, 16.7 mmol) to afford thiacyclophane **50b** (0.70 g, 1.90 mmol, 39 %) as a white crystalline solid.

50b: mp 145.5-146.5 °C (1:1 ether/hexane); ^{1}H NMR δ 7.10 (s, 2H), 6.65 (s, 4H), 3.83 (d, *J*=15.3, 4H), 3.77 (d, *J*=15.8, 4H), 2.37-2.33 (m, 4H), 1.56-1.52 (m, 4H), 1.16-1.08 (m, 6H); ^{13}C NMR δ 142.9, 137.0, 128.7, 127.1, 39.2, 34.1, 28.8, 26.5, 26.3; EI-MS *m/z* (%) 369 (26), 368 (100), 335 (27), 304 (51), 158 (31), 145 (30), 119 (55), 115 (38), 105 (35), 91 (52). Anal. Calc'd for $C_{23}H_{28}S_2$: C, 74.95; H, 7.66. Found: C, 75.07; H, 7.86.

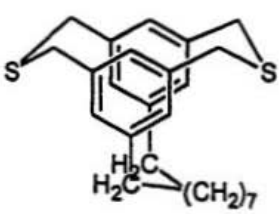


50c

16,25-Dithia[8.3.3](1,3,5)cyclophane, 50c: Tetrabromide **56c** (2.20 g, 3.45 mmol) was dissolved in 10% EtOH/CH_2Cl_2 (500 mL). Na_2S/Al_2O_3 (4.50 g, 11.2 mmol) was added in 4 roughly

equal portions over 1 h. The reaction was stirred at room temperature overnight. The mixture was then suction filtered, and the filtrate was concentrated. The resulting white solid was purified by column chromatography (1:1 CH_2Cl_2/hexanes) affording **50c** (0.78 g, 2.04 mmol, 59 %) as a white solid.

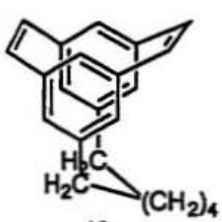
50c: mp 119-121 (heptane); ^{1}H NMR δ 7.20 (s, 2H), 6.66 (s, 4H), 3.84 (s, 8H), 2.42-2.38 (m, 4H), 1.44-1.28 (m, 8H), 1.03-0.98 (m, 4H); ^{13}C NMR δ 137.2, 128.6, 127.4, 120.3, 39.7, 35.5, 29.4, 26.0, 24.5; EI-MS *m/z* (%) 383 (28), 382 (100, M^+), 318 (44), 158 (59), 145 (32), 119 (47), 105 (31), 91 (42). Anal. Calc'd for $C_{24}H_{30}S_2$: C, 75.34; H, 7.90. Found: C, 74.04; H, 8.08.



50d

17,26-Dithia[9.3.3](1,3,5)cyclophane, 50d: : This compound was prepared analogously to **50c**, above, using tetrabromide **56d** (1.76 g, 2.70 mmol) and Na_2S/Al_2O_3 (3.14 g, 7.85 mmol) to afford thiacyclophane **50d** (0.48 g, 1.21 mmol, 45 %) as a white crystalline solid.

50d: mp: 158-159 °C (1:1 toluene/hexane); ^{1}H NMR δ 7.12 (s, 2H), 6.64 (s, 4H), 3.83 (d, *J*=14.9, 4H), 3.77 (d, *J*=15, 4H), 2.39-2.35 (m, 4H), 1.58-1.49 (m, 4H), 1.33-1.28 (s, 10H); ^{13}C NMR δ 142.5, 137.1, 128.7, 126.4, 39.1, 33.9, 27.4, 26.4, 25.4, 24.8; EI-MS *m/z* (%) 397 (23), 396 (80, M^+), 363 (28), 332 (37), 159 (33), 158 (100), 157 (43), 145 (38), 119 (64), 105 (39), 91 (40). Anal. Calc'd for $C_{25}H_{32}S_2$: C, 75.70; H, 8.13. Found: C, 75.76; H, 8.37.

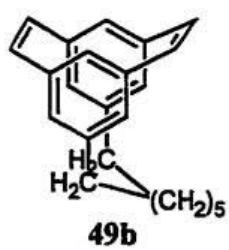


49a

[6.2.2]Cyclophane-13,21-diene, 49a: Thiacyclophane **50a** (0.32 g, 0.90 mmol) was dissolved in CH_2Cl_2 (50 mL). Borch reagent (0.3 mL, 0.5 g, 0.3 mmol) was added under N_2 by syringe, and the reaction mixture was stirred for 1 h. The solvent was then removed under reduced pressure, and the solid residue was quenched by the addition of ethyl acetate (10 mL), stirred for 20 min, then filtered. The solid was washed with cold ethyl acetate (5 mL) and dried *in vacuo* to yield crude

bis(tetrafluoroborate) salt (0.51 g). The *bis*(tetrafluoroborate) salt was suspended in dry THF (50 mL) and ^{t}BuOK (0.43 g, 3.8 mmol) was added. The solution was stirred overnight at room temperature, and the solvent was removed under reduced pressure. The residue was extracted into CH_2Cl_2 (50 mL), washed with aqueous 1 M HCl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 (5 mL) and run through a short plug of silica. The eluate was concentrated to afford the isomeric mixture **57a** (0.31 g, 0.81 mmol, 90 % from thiacyclophane **50a**) as a foamy white solid. No attempt was made to purify this mixture. It was dissolved in CH_2Cl_2 (20 mL) and Borch reagent (0.25 mL, 0.42 mg, 0.25 mmol) was added and the mixture was stirred for 6 h. The solvent was then removed under reduced pressure, and the resulting brown oily solid was suspended in 1:1 ^{t}BuOH/THF (50 mL). ^{t}BuOK (0.40 g, 3.6 mmol) was added and the mixture was stirred under N_2 at room temperature overnight. The solvent was then removed under reduced pressure, and the residue redissolved in CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was washed with aqueous 1 M HCl (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow-brown oil. Column chromatography (35 % CH_2Cl_2/hexanes) afforded cyclophanediene **49a** (0.11 g, 0.38 mmol, 47 % from *bis*(methylthio)cyclophane **57a**) as a colorless crystalline solid.

49a: mp: 60.5-65.5 (sublimed); ^{1}H NMR δ 7.44 (s, 2H), 7.12 (s, 4H), 6.36 (s, 4H), 2.37-2.33 (m, 4H), 1.48-1.42 (m, 4H), 0.72-0.69 (m, 4H); ^{13}C NMR δ 138.7, 136.8, 136.1, 133.8, 126.3, 35.5, 30.1, 28.7; EI-MS *m/z* (%) 287 (19), 286 (82, M^+), 243 (33), 230 (29), 229 (69), 228 (30), 216 (56), 215 (100), 203 (24), 202 (38). Anal. Calc'd for $C_{22}H_{22}$: C, 92.26; H, 7.74. Found: C, 91.98; H, 7.74.

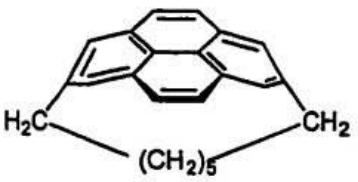


49b

[7.2.2]Cyclophane-14,22-diene, 49b: This compound was prepared analogously to **49a**, above. Thiacyclophane **50b** (0.67 g, 1.8 mmol) and Borch reagent (0.5 mL, 0.8 g, 5 mmol) afforded the crude *bis*(tetrafluoroborate) salt (0.99 g). ^{t}BuOK (0.82 g, 7.3 mmol) then afforded the isomeric mixture **57b** (0.48 g, 1.21 mmol, 67 % from thiacyclophane **50b**) as a foamy white solid. Borch reagent (0.4 mL,

0.6 g, 4 mmol) followed by ^{t}BuOK (0.64 g, 5.7 mmol) and column chromatography (20 % CH_2Cl_2/hexanes) afforded cyclophanediene **49b** (0.16 g, 0.53 mmol, 44 % from *bis*(methylthio)cyclophane **57b**) as a colorless crystalline solid.

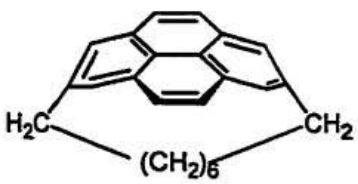
49b: mp: 82-84 °C (hexanes); ^{1}H NMR δ 7.39 (s, 2H), 7.19 (s, 4H), 6.40 (s, 4H), 2.30-2.26 (m, 4H), 1.46-1.43 (m, 4H), 0.86-0.83 (m, 8H); ^{13}C NMR δ 138.4, 136.9, 135.8, 132.8, 125.7, 34.7, 30.7, 27.8, 26.9; EI-MS *m/z* (%) 300 (47, M^+), 243 (28), 230 (33), 229 (56), 228 (24), 217 (41), 216 (75), 215 (100), 202 (34). Anal. Calc'd for $C_{23}H_{24}$: C, 91.95; H, 8.05. Found: C, 91.97; H, 8.08.



48b

[7](2,7)Pyrenophane, 48b: Cyclophanediene **49b** (0.12 g, 0.40 mmol) was dissolved in benzene (20 mL) degassed. DDQ (0.12 g, 0.53 mmol) was added and the reaction mixture was heated to reflux for 1 h. After cooling, the solvent was removed under reduced pressure and the residue was redissolved in CH_2Cl_2 (50 mL) and H_2O (20 mL). The organic layer was washed with aqueous 1 M HCl (2 x 50 mL), aqueous 1 M NaOH (50 mL), and brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure. Column chromatography (25 % CH_2Cl_2/hexanes) of the residue yielded pyrenophane **48b** (0.100 g, 0.335 mmol, 84 %) as a white crystalline solid.

48b: mp 151.5-153 °C (hexanes); ^{1}H NMR δ 7.67 (s, 4H), 7.34 (s, 4H), 2.32-2.28 (m, 4H), 0.47-0.43 (m, 4H), - 1.35 – -1.41 (m, 6H); ^{13}C NMR δ 136.3, 131.7, 130.3, 129.9, 126.4, 35.7, 33.2, 31.4, 23.5; EI-MS *m/z* (%) 298 (36, M^+), 241 (27), 229 (24), 228 (100), 215 (34). Anal. Calc'd for $C_{23}H_{22}$: C, 92.57; H, 7.43. Found: C, 92.29; H, 7.59.

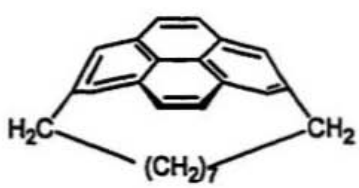


48c

[8](2,7)Pyrenophane, 48c: Thiacyclophane **50c** (0.71 g, 1.9 mmol) was dissolved in CH_2Cl_2 (40 mL). Borch reagent (0.5 mL, 0.8 g, 0.5 mmol) was added under N_2 by syringe, and the mixture was stirred for 1 h. The solvent was then removed under reduced pressure, and the solid

residue was quenched by the addition of ethyl acetate (5 mL), stirred for 20 min, then filtered. The residue was washed with cold ethyl acetate (5 mL) and dried *in vacuo* to yield the crude *bis*(tetrafluoroborate) salt (1.04 g). This was suspended in dry THF (50 mL) and ^{t}BuOK (0.90 g, 8.0 mmol) was added. This was stirred for 2 h at room temperature, and the solvent was removed under reduced pressure. The residue was extracted into CH_2Cl_2 (50 mL), washed with aqueous 1 M HCl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford the isomeric mixture **57c** (0.55 g, 63 % from thiacyclophane **50c**) as a foamy white solid. No attempt was made to purify this mixture, and it was dissolved in CH_2Cl_2 (50 mL). Borch reagent (0.4 mL, 0.6 g, 4 mmol) was added, and the mixture was stirred for 1 h. The solvent was then removed under reduced pressure, and the resulting brown oily solid was suspended in 1:1 ^{t}BuOH/THF (50 mL). ^{t}BuOK (1.10 g, 9.80 mmol) was added and the mixture was stirred under N_2 at room temperature overnight. The solvent was removed under reduced pressure, and the residue was redissolved in CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was washed with aqueous 1 M HCl (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow-brown oil. Column chromatography (hexanes) afforded mixture of diene **49c** and (presumably) pyrenophane **48c**. Treatment of this mixture with DDQ (0.098 g, 0.43 mmol) in refluxing benzene for 3 h, followed by gravity filtration, concentration under reduced pressure, and chromatography (hexanes) afforded pure pyrenophane **48c** (0.120 g, 0.384 mmol, 32 % from *bis*(methylthio)cyclophane **57c**) as colorless crystals.

48c: mp 175.5-176.5 °C (hexanes); ^{1}H NMR δ 7.84 (s, 4H), 7.59 (s, 4H), 2.61-2.57 (m, 4H), 0.92-0.84 (m, 4H), -0.67 – - 0.70 (m, 4H), -1.43 – -1.48 (m, 4H); ^{13}C NMR δ 137.8, 131.3, 128.9, 127.8, 126.6, 35.9, 31.7, 31.1, 23.5; EI-MS *m/z* (%) 312 (41, M^+), 229 (25), 228 (100), 215 (32). Anal. Calc'd for $C_{24}H_{24}$: C, 92.26; H, 7.74. Found: C, 92.01; H, 7.80.

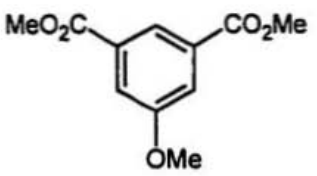


48d

[9](2,7)Pyrenophane, 48d: This compound was prepared analogously to **58c**, above, using thiacyclophane **50d** (0.43 g, 1.1 mmol) and Borch reagent (0.35 mL, 0.58 g, 3.6

mmol) to afford *bis*(tetrafluoroborate) salt (0.60 g). Next, ^{t}BuOK (0.35 g, 3.1 mmol) afforded *bis*(methylthio)cyclophane **57d** (0.40 g, 0.94 mmol, 87 % from thiacyclophane **50d**). Then, Borch reagent (0.3 mL, 0.5 g, 3 mmol), followed by ^{t}BuOK (0.60 g, 5.35 mmol), followed by DDQ (0.60 g, 2.64 mmol) afforded pyrenophane **48d** (0.020 g, 0.061 mmol, 6 % from *bis*(thiomethyl)cyclophane **57d**.) as a white crystalline solid.

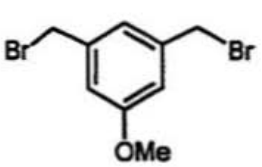
48d: mp 213-215.5 °C (hexanes); ^{1}H NMR δ 7.91 (s, 4H), 7.75 (s, 4H), 2.86-2.82 (m, 4H), 1.14-1.06, (m, 4H), 0.29-0.20 (m, 4H), - 0.90 – -0.97 (m, 2H), -2.03 – -2.14 (m, 4H); ^{13}C NMR δ 136.9, 131.3, 127.6, 126.7, 126.2, 36.3, 30.8, 29.7, 29.3, 25.2; EI-MS *m/z* (%) 327 (26), 326 (97, M^+), 240 (23), 229 (31), 228 (100), 215 (45). Anal. Calc'd for $C_{25}H_{26}$: C, 91.96; H, 8.04. Found: C, 91.81; H, 8.11.



59

Dimethyl 5-methoxyisophthalate, 59. Diester **36** (6.02 g, 28.6 mmol) was dissolved in dry acetone (100 mL). CH_3I (6.15 g, 43.3 mmol) and K_2CO_3 (5.94 g, 43.0 mmol) were added and the resultant slurry was stirred and heated at reflux for 24 h. The solvent was removed under reduced pressure, the oily residue was dissolved in CH_2Cl_2 (100 mL) and washed with H_2O (100 mL), aqueous saturated NH_4Cl (100 mL), and brine (100 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated to yield **59** as a white solid (6.22 g, 27.7 mmol, 97 %).

59: mp 107-108.5 °C (heptane); IR (CH_2Cl_2): 2940 (m), 2840 (m), 1710 (s), 1600 (s), 1110 (s), 1050 (s), 1000 (m); ^{1}H NMR δ 8.28 (t, 2H, *J*=1.4), 7.75 (d, 4H, *J*=1.4), 3.94 (s, 6H), 3.89 (s, 3H); ^{13}C NMR δ 166.1, 159.6, 131.7, 122.9, 119.2, 55.8, 52.4; EI-MS *m/z* (%) 224 (67, M^+), 193 (100), 165 (34), 150 (20), 135 (7), 63 (11); HRMS for $C_{11}H_{12}O_5$: Calc'd 224.0684, Found 224.0688.



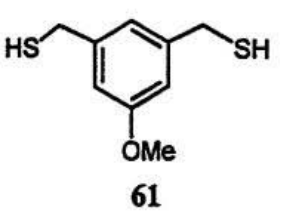
60

3,5-*Bis*(bromomethyl)anisole, 60. $LiAlH_4$ (7.55g, 199 mmol) was placed in dry THF (100 mL) under N_2. To this was added dropwise a solution of **59** (6.02 g, 26.9 mmol) in dry THF (100

75

mL), with cooling in an ice bath. The resultant slurry was stirred at room temperature overnight. The reaction was quenched by slow addition of ethyl acetate (50 mL), with cooling. The solvents were removed under reduced pressure, and the resulting grey powdery residue was redissolved in aqueous 48% HBr (100 mL) and concentrated H_2SO_4 (25 mL) and heated to reflux for 1 h. The clear solution was cooled to room temperature and diluted with H_2O (300 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organic layers were washed with H_2O (2 x 100 mL), aqueous saturated $NaHCO_3$ (2 x 100 mL), and H_2O (100 mL), dried ($MgSO_4$) filtered and concentrated. Flash chromatography (silica, 1:1 CH_2Cl_2/hexanes) followed by crystallization (heptane) yielded a mixture (approx. 10:1) of **60** and **75** (6.08 g). This mixture was carried on without further purification. Compound **60** could also be obtained by reducing **59** with $LiAlH_4$ as before, but working up the reaction with 50 % aqueous H_2SO_4, extracting the product into ethyl acetate (3 x 50 mL), drying ($MgSO_4$) and concentrating to yield crude the diol (0.49 g, 2.9 mmol), which was treated with PBr_3 (0.28 mL, 0.80 g, 2.9 mmol) in CH_2Cl_2 (50 mL), and stirred for 2 h. The solution was then washed with aqueous saturated $NaHCO_3$ (2 x 50 mL), aqueous 1M HCl (50 mL), and H_2O (50mL), dried ($MgSO_4$) filtered and concentrated. Flash chromatography (silica, 1:1 CH_2Cl_2/hexanes) yielded pure **60** (0.645 g, 2.19 mmol, 75 %) as white crystals.

60: mp 107-108.5 °C (heptane); IR ($CHCl_3$) 2840 (w), 1590 (s), 1055 (s); ^{1}H NMR δ 7.00 (s, 1H), 6.86 (s, 2H), 4.43 (s, 4H), 3.82 (s, 3H); ^{13}C NMR δ 159.9, 139.6, 121.8, 114.5, 55.4, 32.9; EI-MS *m/z* (%) 295 (13), 294 (18), 293 (M^+, 26), 292 (12), 291 (13), 215 (92), 214 (16), 133 (13), 91 (13), 65 (27). Anal. Calc'd for $C_9H_{10}Br_2O$: C, 36.77; H, 3.43. Found: C 36.63, H 3.22.

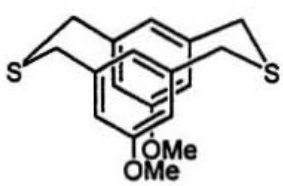


61

3,5-*Bis*(mercaptomethyl)anisole, 61. Dibromide **60** (0.55 g, 1.9 mmol) was dissolved in absolute EtOH (60 mL) and thiourea (0.302 g, 3.97 mmol) was added. The solution was heated at reflux for 4 h, then cooled. The solvents were removed under reduced pressure

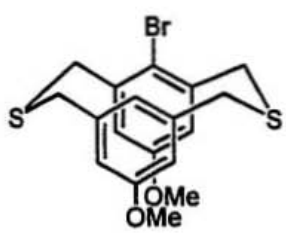
and the residue was suspended in degassed, deionized H_2O (70 mL) to which was added NaOH (2.16 g, 54.0 mmol). The solution was heated to reflux for 18 h under N_2, then cooled and acidified with aqueous 50% H_2SO_4 (30 mL). The resultant aqueous suspension was extracted with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were washed with brine (100 mL), dried ($MgSO_4$), filtered, and concentrated to yield crude **61** as a yellow oil which was carried forward without purification. Column chromatography (CH_2Cl_2) afforded pure **61** (0.320 g, 1.60 mmol, 86 %) as a colorless oil.

61: ^{1}H NMR δ 6.86 (s, 1H), 6.75 (s, 2H), 3.80 (s, 3H), 3.68 (d, *J*=7.6, 4H), 1.77 (t, *J*=7.6, 2H); ^{13}C NMR δ 159.9, 142.9, 119.9, 112.2, 55.2, 28.8; EI-MS *m/z* (%) 200 (58, M^+), 167 (100), 134 (24). Anal. Calc'd for $C_9H_{12}OS_2$: C, 53.96; H, 6.04. Found: C, 54.06; H, 6.25.



62

6,15-Dimethoxy-2,11-dithia[3.3](1,3)cyclophane, 62. Crude dithiol **61** (1.77g, 8.84 mmol) and dibromide **60** (2.60 g, 8.84 mmol) were dissolved in benzene (500 mL), and the solution was degassed with an N_2 flow. This solution was added over 3 days to a vigorously stirred solution of NaOH (1.77 g, 44.3 mmol) in H_2O (75 mL) and 95% EtOH (425 mL). When the addition was complete, the solvents were removed under reduced pressure. The residue was extracted into CH_2Cl_2 (3 x 50 mL), and the organic extracts were washed with aqueous saturated NH_4Cl (50 mL), H_2O (50 mL), dried ($MgSO_4$), filtered and concentrated. Flash chromatography (80% CH_2Cl_2/hexanes) yielded pure **62** (1.50 g, 4.51 mmol, 51 %) as a white solid, and pure **76** (0.185 g, 0.450 mmol, 5 %) as white crystals (Note: if pure **60** were used, **76** would presumably not be formed).

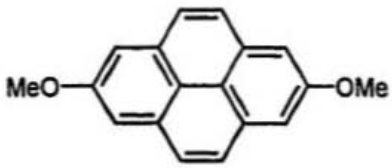


76

62: mp 124-126 °C (heptane); IR (CH_2Cl_2) 2910 (w), 2840 (w), 1590 (w), 1055 (s); ^{1}H NMR δ 6.49 (s, 2H), 6.47 (s, 4H), 3.72 (s, 8H), 3.71 (s, 6H), ^{13}C NMR δ 159.4, 138.3,

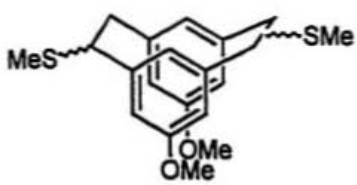
124.6, 112.9, 55.2, 37.9; EI-MS *m/z* (%) 333 (9), 332 (M^+, 41), 167 (12), 166 (29), 136 (100), 135 (22), 91 (12); HRMS Calc'd for $C_{18}H_{20}O_2S_2$: 332.0904, found 332.0888.

76: mp 124-126 °C (heptane); ^{1}H NMR δ 6.79 (s, 1H), 6.47 (s, 2H), 6.44 (s, 2H), 4.43 (d, 2H, *J*=14.2), 3.84 (d, 2H, *J*=15.5, corresponding doublet hidden), 3.72 (s, 3H), 3.65 (d, 2H, *J*=14.5), 3.60 (s, 3H); ^{13}C NMR δ 159.4, 157.7, 139.1, 138.0, 121.0, 118.5, 116.4, 112.0, 61.7, 55.2, 38.4, 37.1; EI-MS *m/z* (%) 412 (79, M^+), 410 (75, M^+), 331 (46), 251 (100), 239 (72), 213 (24), 166 (77), 165 (64), 136 (33), 135 (64), 134 (29), 91 (14). Anal. Calc'd for $C_{18}H_{19}BrO_2S_2$: C, 52.55; H, 4.66. Found: C, 52.53; H, 4.67.



63

2,7-Dimethoxypyrene, 63. Thiacyclophane **62** (1.40 g, 4.21 mmol) was dissolved in dry CH_2Cl_2 (50 mL). Borch reagent (1.6 mL, 2.6 g, 16 mmol) was added by syringe, and the suspension was stirred under N_2 overnight. The solvent was removed, and the residue was quenched with aqueous 80% methanol (100 mL). The resultant white precipitate was isolated by suction filtration, washed with methanol, and dried *in vacuo* to yield the *bis*(tetrafluoroborate) salt as a whitish-beige powder (1.19 g, 2.22 mmol, 53 %). mp >250 °C. This was used without further purification in the next step.



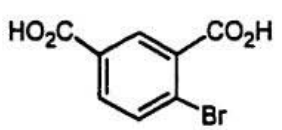
77

The *bis*(tetrafluoroborate) salt (1.14 g, 2.13 mmol) was suspended in dry THF (75 mL) and ^{t}BuOK (0.72 g, 6.4 mmol) was added. The reaction was stirred for 16 h at room temperature under N_2. The reaction was then quenched with aqueous saturated NH_4Cl (10 mL) and the solvents were removed under reduced pressure. The residue was dissolved in CH_2Cl_2 (50 mL), and washed with H_2O (50 mL), aqueous saturated NH_4Cl (50 mL), and brine (50 mL), dried ($MgSO_4$), filtered through a short plug of silica and concentrated to yield the yellowish foamy solid as a mixture of isomers **77** (0.663 g, 2.01 mmol, 94 %). This was carried on without further.

The mixture **77** was dissolved in dry CH_2Cl_2 (50 mL) and Borch reagent (0.6 mL, 1.0 g, 6 mmol) was added by syringe. The mixture was then stirred under N_2 for 1 h.

The solvent was removed under reduced pressure, and the brown oily residue was suspended in a 2:1 THF/^{t}BuOH mixture (75 mL). ^{t}BuOK (0.58 g, 5.2 mmol) was added, and the reaction mixture was stirred under N_2 for 20 h at room temperature. The solvent was removed, the residue was dissolved in CH_2Cl_2 (50 mL) and washed with aqueous saturated NH_4Cl (50 mL) and water (50 mL). The organic layer was dried ($MgSO_4$), filtered and concentrated. The residue was then treated with DDQ (0.30 g, 1.32 mmol) in benzene (25 mL) and refluxed for 3 h. The solvent was removed. Column chromatography (CH_2Cl_2) yielded **63** (0.116 g, 0.44 mmol, 22 % from **70**) as a white solid.

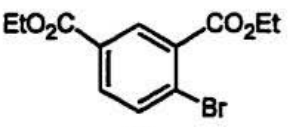
63: mp 198-202 °C (CH_2Cl_2); ^{1}H NMR δ 7.97 (s, 4H), 7.69 (s, 4H). 4.07 (s, 6H); ^{13}C NMR δ 157.1, 131.5, 127.5, 120.1, 110.6, 55.8; EI-MS *m/z* (%) 262 (M^+, 100), 219 (45), 176 (32), 131 (13); HRMS: Calc'd for $C_{18}H_{14}O_2$ 262.0993; found 262.0996.



70

4-Bromoisophthalic acid, 70. 4-Bromoxylene, **69** (25.3 g, 137 mmol) and $KMnO_4$ (100 g, 633 mmol) were placed in 1.5 L H_2O and the mixture was heated under reflux overnight. The mixture was cooled to room temperature and suction filtration removed the black MnO_2. The filtrate was acidified with aqueous 6M HCl (100 ml), and the white precipitate **70** (18.2 g, 74.3 mmol, 54 %, ~100 % based on recovered starting material) was isolated by suction filtration. Starting material **69** (12.2 g) could be isolated from the filtrate by extraction with ether followed by concentration under reduced pressure.

70: mp 286-290 °C, Lit. mp. 287 °C;[49] ^{1}H NMR (DMSO-d_6) 13.56 (br s, 2H), 8.37 (d, *J*=2.1, 1H), 7.00 (dd, *J*=8.1, 2.1, 1H), 7.90 (d, *J*=8.1, 1H); ^{13}C NMR δ 166.8, 166.3, 134.7, 133.8, 133.0, 131.6, 130.5, 125.5.

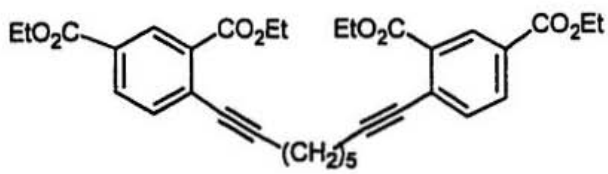


71

Diethyl 4-bromoisophthalate, 71. Diacid **70** (13.03 g, 53.2 mmol) was suspended in absolute EtOH (100 mL) and concentrated sulfuric acid (4 mL) was added. The solution was heated under reflux overnight. The mixture was cooled and the

solvent was removed under reduced pressure. The residue was redissolved in diethyl ether (50 mL) and washed with water (2 x 50 mL), aqueous saturated $NaHCO_3$ (3 x 50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography in 20 % ether/hexanes afforded pure diester **71** (12.8 g, 42.5 mmol, 80 %) as a colorless oil.[49]

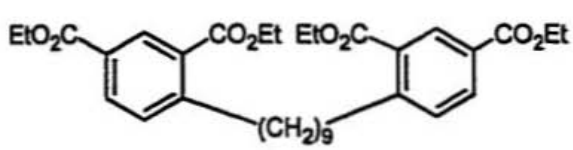
71: ^{1}H NMR δ 8.40 (d, *J*=2.1, 1H), 7.95 (dd, *J*=8.4, 2.2, 1H), 7.73 (d, *J*=8.4, 2H), 4.43 (q, *J*=7.2, 2H), 4.39 (q, *J*=7.1, 2H), 1.43 (t, *J*=7.2, 3H), 1.41 (t, *J*=7.1, 3H); ^{13}C NMR δ 165.4, 165.0, 134.4, 132.7, 132.0, 129.6, 126.6, 61.9, 61.5, 14.2, 14.1.



72

1,9-*Bis*(2,4-*bis*(ethoxycarbonyl)-phenyl)nona-1,8-diyne, 72. A solution of diester **71** (10.8 g, 35.9 mmol) and nonadiyne (2.16 g, 18.0 mmol) in Et_3N (80 mL) was degassed. $Pd(PPh_3)_2Cl_2$ (0.50 g, 0.71 mmol) and CuI (0.60 g, 3.2 mmol) were added, and the solution was heated under reflux under N_2 for 18 h. The mixture was then cooled, filtered, rinsed with ether, and concentrated under reduced pressure. Column chromatography (35 % Et_2O/hexanes) afforded pure **72** (8.00 g, 12.5 mmol, 70 %) as a colorless solid.

72: mp 63-64 °C (ether/hexanes); ^{1}H NMR δ 8.53 (d, *J*=1.7, 2H), 8.03 (dd, *J*=8.1, 1.8, 2H), 7.55 (d, *J*=8.1, 2H), 4.41 (q, *J*=7.2, 4H), 4.39 (q, *J*=7.1, 4H), 2.55-2.53 (m, 4H), 1.74-1.71 (m, 6H), 1.42 (t, *J*=7.1, 6H), 1.41 (t, *J*=7.2, 6H); ^{13}C NMR δ 165.6, 165.2, 134.2, 132.3, 131.7, 131.1, 129.0, 128.5, 99.1, 79.2, 61.2, 28.1, 27.9, 19.7, 14.2; EI-MS *m/z* (%) 531 (38), 485 (35), 441 (40), 271 (26), 269 (24), 221 (73), 190 (36), 103 (26), 82 (87), 80 (87), 79 (44). Anal. Calc'd for $C_{33}H_{36}O_8$: C, 70.69; H, 6.41. Found: C, 70.74; H, 6.60.

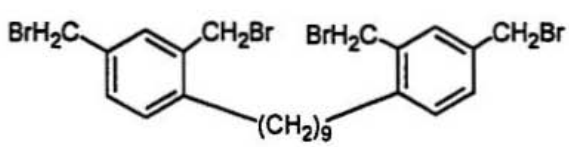


73

1,9-*Bis*(2,4-*bis*(ethoxycarbonyl)-phenyl)nonane, 73. Diynetetraester **72**

(4.19 g, 7.47 mmol) was dissolved in ethyl acetate (200 mL) and 20 % wet palladium hydroxide on C (Pearlman's catalyst) (0.80 g) was added. This was stirred under 1 atm. H_2 for 3 h, until uptake of H_2 ceased. The mixture was then filtered through Celite and concentrated to afford pure tetraester **73** (4.21 g, 7.40 mmol, 99 %) as an oily white solid.

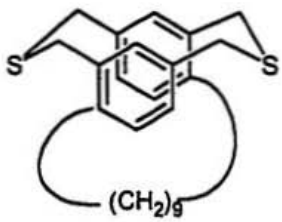
73: mp 47-49 °C (EtOAc/heptane); ^{1}H NMR δ 8.50 (d, *J*=1.8, 2H), 8.05 (dd, *J*=8.0, 1.9, 2H), 7.32 (d, *J*=8.1, 2H), 4.39 (q, *J*=7.1, 8H), 2.98 (t, *J*=7.7, 4H), 1.62-1.54 (m, 4H), 1.41 (t, *J*=7.1, 6H), 1.40 (t, *J*=7.1, 6H), 1.34-1.25 (m, 10H); ^{13}C NMR δ 166.9, 165.7, 149.4, 132.1, 131.6, 130.9, 130.1, 128.0, 60.9, 34.4, 31.5, 29.5, 29.3, 14.2; EI-MS *m/z* (%) 523 (40), 522 (19), 494 (19), 207 (21), 204 (24), 203 (100), 179 (37), 175 (22), 131 (24), 117 (19), 91 (21). Anal. Calc'd for $C_{29}H_{36}O_8$: C, 69.70; H, 7.78. Found: C, 69.44; H, 7.99



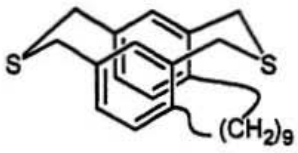
66

1,9-*Bis*(2,4-*bis*(bromomethyl)-phenyl)nonane, 66. Tetraester **73** (2.20 g, 3.87 mmol) was dissolved in dry THF (75 mL). This was added dropwise to a slurry of $LiAlH_4$ (0.81 g, 21 mmol) in dry THF (75 mL), then stirred at room temperature under N_2. After 6 h, the reaction was quenched by the cautious addition of ethyl acetate (10 mL). It was then poured into aqueous 1M HCl (100 mL) and extracted into ethyl acetate (2 x 100 mL). The organic layer was washed with brine and concentrated to afford tetraalcohol **74** (1.40 g, 3.49 mmol, 90 %). This compound was not purified but used directly in the next step. Tetraalcohol **74** (0.83 g, 2.1 mmol) was slurried in glacial AcOH (30 mL) and 30% HBr in AcOH (3.5 mL, 4.7 g, 17 mmol) was added. The solution was stirred and heated under reflux overnight. The reaction was cooled and water (50 mL) was added. This was extracted with ether (3 x 50 mL), washed with H_2O (3 x 50 mL), aqueous saturated $NaHCO_3$ (3 x 50 mL), and brine (50 mL). It was then dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Chromatography (25% CH_2Cl_2/hexanes) afforded pure tetrabromide **66** (1.24 g, 1.90 mmol, 83 % from tetraester **73**) as a white solid.

66: mp 112-114 °C (CH_2Cl_2/hexanes); ^{1}H NMR δ 7.35 (d, *J*=1.7, 2H), 7.27 (dd, *J*=7.8, 1.7, 2H), 7.18 (d, *J*=7.8, 2H), 4.51 (s, 4H), 4.46 (s, 4H), 2.70 (t, *J*=7.7, 4H), 1.66-1.60 (m, 4H), 1.39-1.33 (m, 10H); ^{13}C NMR δ 142.2, 135.8, 131.0, 130.2, 129.5, 119.9, 33.0, 32.1, 31.1, 30.8, 29.6, 29.4; EI-MS *m/z* (%) 492 (6), 411 (5), 277 (7), 237 (14), 199 (56), 197 (60), 119 (68), 118 (55), 117 (31), 82 (95), 80 (100), 79 (37). Anal. Calc'd for $C_{25}H_{32}Br_4$: C, 46.04; H, 4.95. Found: C, 46.03; H, 4.89.



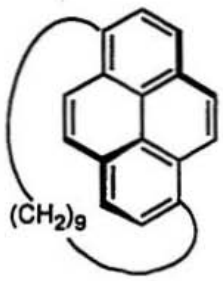
65



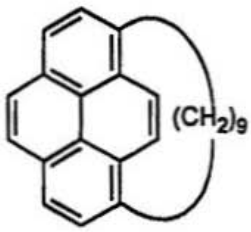
67

(±)-17,26-Dithia[9.3.3](1,2,4)cyclophane, 65, and 17,26-dithia[9.3.3](1,2,4)cyclophane, 67: Tetrabromide **66** (0.57 g, 0.87 mmol) was dissolved in 10 % absolute EtOH/CH_2Cl_2 (400 mL). Na_2S/Al_2O_3 (1.4 g, 3.5 mmol) was added in portions and the mixture was stirred vigorously for 2 h. It was then suction filtered through Celite and concentrated. Column chromatography (40 % CH_2Cl_2/hexanes) afforded a single spot (by tlc), which consisted of at least two components by ^{1}H NMR. Tlc analysis in a number of solvent mixtures (toluene, 20% ether/hexanes, 10% ether/cyclohexane, 25% toluene/cyclohexanes) resulted in, at best, very slight separation. Attempted chromatography in a very nonpolar solvent (5 % ether/hexanes) resulted in decomposition, with only a small amount of product recovered from the column, and no separation of the recovered product. Recrystallization (toluene/hexanes) appeared to result in some enrichment of the major product (whose structure is uncertain), but it was still not pure. Subsequent steps were carried out on the impure mixture.

Impure **65** and **67**: ^{1}H NMR 7.13 (s), 6.84 (s), 3.98 (d, *J*=14.8), 3.85 (s?), 3.80 (s), 2.84-2.75 (m), 2.22-2.12 (m), 1.52-1.26 (m); ^{13}C NMR δ (obvious signals only) 132.3, 127.5, 127.1, 39.2, 29.2, 26.2, 25.3, 24.3, 22.7; EI-MS *m/z* (%) 396 (34, M^+). Anal. Calc'd for $C_{25}H_{32}S_2$: C, 75.70; H, 8.13. Found: C, 75.93; H, 8.46.



64



68

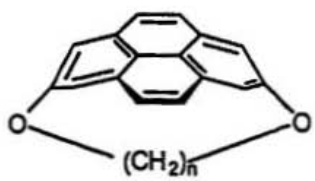
[9](1,6)pyrenophane, 64 and [9](1,8)pyrenophane, 68. This synthesis was conducted analogously to that of the [9](2,7)pyrenophane **50d**. The crude product mixture from the previous step (0.25 g, 0.63 mmol) was dissolved in CH_2Cl_2 (15 mL). Borch reagent (0.3 mL, 0.5 g, 3 mmol) was added under N_2 by syringe, and the mixture was stirred for 1 h. The solvent was then removed under reduced pressure. The oily residue was quenched with aqueous 80 % MeOH (2 mL), forming an oily solid. This could not be isolated by filtration, so it was just dried *in vacuo*. This was suspended in dry THF (20 mL), and ^{t}BuOK (0.60 g, 5.3 mmol) was added. This was stirred overnight at room temperature, then quenched with H_2O (1 mL). The solvent was removed under reduced pressure. The residue was extracted into CH_2Cl_2 (60 mL), washed with aqueous 1 M HCl (50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure to afford a complex isomeric mixture (0.101 g, 38 % from thiacyclophanes **64/66**) as a foamy white solid. No attempt was made to purify this mixture, and 0.60 g of this solid was dissolved in CH_2Cl_2 (5 mL) and Borch reagent (0.2 mL, 0.4 g, 2 mmol) was added. The mixture was stirred for 1 h. The solvent was then removed under reduced pressure, and the resulting brown oily solid was suspended in 1:1 ^{t}BuOH/THF (40 mL). ^{t}BuOK (0.51 g, 4.5 mmol) was added, and the mixture was stirred under N_2 at room temperature overnight. The solvent was then removed under reduced pressure, and the residue redissolved in CH_2Cl_2 (50 mL) and H_2O (50 mL). The organic layer was washed with aqueous 1 M HCl (2 x 50 mL), H_2O (50 mL), brine (50 mL), dried ($MgSO_4$), and concentrated under reduced pressure to afford a yellow-brown oil. Treatment of this mixture with DDQ (0.100 g, 0.441 mmol) in refluxing benzene for 1 h, followed by concentration under reduced pressure, and chromatography (10 % CH_2Cl_2/hexanes) afforded a mixture of pyrenophanes **64** and **68** (0.026 g, 0.080 mmol, 22 % from thiacyclophanes **65** and **67**) as a white solid. Recrystallization from hexanes yielded colorless needles consisting of impure **68**, while the mother liquor was enriched in **64**.

Impure **64** and **68**: mp 186-188 °C (hexanes); ^{1}H NMR δ (**64**, obvious peaks only) 8.20 (d, *J*=9.1 Hz), 8.00 (d, *J*=7.7 Hz), 7.98 (d, *J*=9.3 Hz), 7.71 (d, *J*=7.9 Hz), 3.79-3.65 (m), 2.96-2.86 (m), -1.20 – -1.40 (m), -1.65 – -1.78 (m); EI-MS *m/z* (%) 326 (79, M^+), 228 (100).

Chapter 6 – Pyrenophane Spectroscopy, Chemistry, and Applications

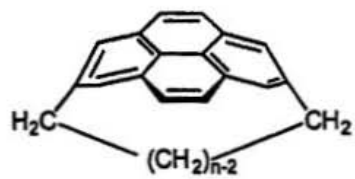
6.1 - Introduction

In the last chapter, the preparation of a series of 1,n-dioxa[n](2,7)pyrenophanes **1a-f** (referred to here as the dioxa series), and a number of [n](2,7)pyrenophanes **2a-c** (the hydrocarbon series) was described. Also prepared was 2,7-dimethoxypyrene **3**. In this chapter, the physical, spectroscopic, and chemical behavior of these compounds shall be examined, and attempts to correlate any trends observed with the distortion of the pyrene unit and the magnitude of strain present in the molecule will be made. Their physical properties and X-ray crystallographic studies of their structure, shall be considered first, followed by spectroscopic properties. Finally, studies of the chemical reactivity of the pyrenophanes, including attempts to generate functionalized derivatives thereof, will be presented.



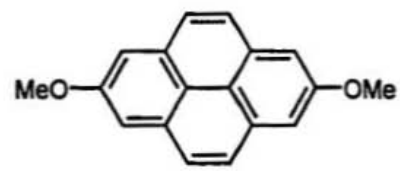
1

a: n=5 **d:** n=8
b: n=6 **e:** n=9
c: n=7 **f:** n=10



2

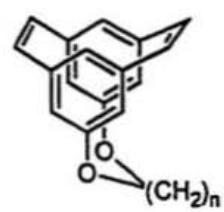
a: n=7
b: n=8
c: n=9



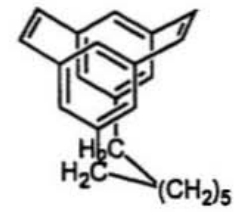
3

6.2 - Physical Properties

All pyrenophanes isolated (**1** and **2**), as well as the pyrene **3**, were colorless, crystalline solids. Although the crystals tended to turn yellow after prolonged (~1 week) exposure to air, pyrenophanes were found to be stable indefinitely in the solid state. In solution, the pyrenophanes decomposed slowly (over several weeks; shorter tethers appeared to decompose more rapidly) to produce a black tarry substance. The dioxapyrenophanes **1** were soluble in ethyl acetate, dichloromethane and chloroform, but were insoluble in hydrocarbon solvents like hot hexane and heptane. X-ray quality crystals could be obtained from boiling xylenes. In contrast, hydrocarbons of the



4, a: n=5
b: n=6



5

pyrenophane series **2** were soluble in hexanes at room temperature. Crystals could only be obtained by cooling a solution of **2** in hexanes to -20 °C. The melting points of **1** (excluding **1a** and **1b**, which darkened, and presumably decomposed, prior to melting at about 155 and 190 °C, respectively) ranged from 171-173 °C for **1f** to > 250 °C for **1d**. For the hydrocarbon series, melting points increased from 153.3-155 °C for **2a** to 213-215 °C for **2c**. In general, the melting points appear to increase to a maximum at a tether length of around 10 atoms, at which point they start to drop. This might result from two, opposing, trends. On the one hand, as the tether lengthens, the pyrene unit becomes flatter and less "hemispherical" in shape, which probably results in better crystal packing and a consequently higher melting point. Beyond a ten-atom tether length, however, the tether becomes less strained and consequently more conformationally mobile. "Floppy" appendages on a molecule reduce its ability to pack into an orderly crystal structure, which would result in a drop in the melting point. This "floppy tether" hypothesis would also explain the substantial increase in melting point on going, for example, from cyclophanediene **5** ($C_{23}H_{24}$, mp 82-84 °C) to pyrenophane **2a** ($C_{23}H_{22}$, mp 153-155 °C).

6.3 - X-Ray Crystallography

One of the most useful properties of the dioxa[n]pyrenophanes, **1**, when compared to, for example, the [n]paracyclophanes, is that the former are solids of which crystals, suitable for X-ray analysis, could be obtained. The X-ray structures of **1a-f** and **2b** were determined at the Memorial University X-Ray Diffraction Facility by Dr. J. Bridson and Mr. D. Miller, who made available the results examined here. This allowed a quantitative determination, for each member of the dioxa series, of the degree of bending of the pyrene unit imposed by the tether, at least in the solid state. The hydrocarbon series was

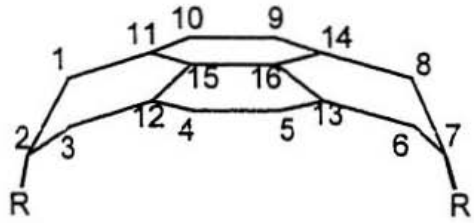
also crystalline, but crystals of **2a** and **2c**, although they diffracted, produced diffraction data that could not be refined effectively. Therefore, only the crystallographic data for **2b** are reported.

The X-ray analyses of **1** reveal, not surprisingly, that the pyrene unit becomes increasingly distorted from planarity as the tether length shortens (see structures in Appendix A). Deviation of the tether from ideal bond angles is also evident, as demonstrated in Table 6-1. In the smaller pyrenophanes (**1a, 1b, 1c**), the bridge C-C-C bond angles display considerable distortion from the ideal tetrahedral (109.5°) bond angle. For **1a**, the range of angles is 114.3 to 117.6 °, and the average is 116.5 °. In **1b**, the angles range from 115.0 to 119.4 °, with an average of 117.2 °. For **1c**, the range is 115.3 to 120.3 °, with an average of 118.6 °. It is somewhat surprising that the tether of **1c** displays more distorted bond angles that the presumably more strained **1b**, which in turn has larger bond angles than **1a**. Data on bond angles of the longer tethers are more difficult to obtain, as increasing disorder of the tether in the crystals is evident. Cases where the bond angle data were unavailable due to disorder are denoted by an asterisk in the table. This disorder probably results from increased conformational mobility as the tether becomes less strained, and supports the floppy tether hypothesis, presented in the previous section, to explain the decreasing melting point trend of the larger pyrenophanes.

Table 6-1: Tether Bond Angles

Compound	C_I-O-C_α (av.)	C-C-C_{max}	C-C-C_{min}	C-C-C_{av}
1a	110.5	117.6	114.3	116.4
1b	110.6	119.4	117.2	117.9
1c	111.8	120.3	115.4	118.6
1d	112.5	*	*	*
1e	113.7	116.1	112.9	114.5
1f	115	*	*	*
2b	(C_I-C_α-C_β) 109.2	*	*	*

To quantify the extent of the distortion of the pyrene moieties in **1**, it was decided to measure the angles formed between adjacent planes of C atoms, in a method analogous



Plane	Defined By
A	1,2,3
B	1,3,11,12
C	11,12,15
D	4,5,9,10
E	13,14,16
F	6,8,13,14
G	6,7,8

Figure 6-1: Planes For Bend Measurement of Pyrenophanes

to that used to determine the angles α and β in the [n]paracyclophanes (see Chapter 2). A series of planes were defined, A to G, using sets of three or four atoms, as illustrated in Fig. 6-1. In cases where four atoms were used, the "least squares" plane was determined mathematically. The angles between these planes were then measured and compared, the results of which are in Table 6-2. For molecules **1c**, **1d**, and **1e**, C_2 symmetry results in the planes at one end of the molecule being equal to the corresponding angle at the other end, for example angle AB = angle FG. The angles between the C_2-O bond and planes AB and FG was also measured for **1a**, giving values of 8.2° and 8.7°. This is markedly lower than the analogous β angle of 18.8° observed in a [6]paracyclophane derivative, as described in Chapter 2.

Table 6-2: Angles Between Least Squares Planes (°)

Compound	AB	BC	CD	DE	EF	FG	AG
1a	18.2	16.0	20.5	20.5	16.1	17.9	109.1
1b	16.3	13.2	16.1	14.8	13.1	14.3	87.8
1c	13.1	9.9	13.5	13.5	9.9	13.1	72.9
1d	11.5	8.4	9.0	9.0	8.4	11.5	57.7
1e	7.5	5.9	6.6	6.6	5.9	7.5	39.9
1f	6.6	7.9	3.7	5.3	3.5	7.9	34.6
2b	14.3	12.3	13.8	13.8	12.3	14.3	80.8

Examination of the data in Table 6-2 shows that the bend in the pyrenophanes is spread quite evenly over the entire "aromatic" surface. Comparison of the dioxapyrenophane **1b** (with eight atoms in the tether) with the corresponding hydrocarbon [8]pyrenophane (also eight atoms in the tether) **2b** reveals that the former is considerably more curved, as measured by the angle between planes A and G. The reason for this is unclear. One possibility is that the benzylic CH_2 groups in **2** are more easily deformed to smaller bond angles than the aryl oxygens in **1**, perhaps because of the tendency of the lone pairs on the latter to delocalize into the aromatic rings. The O atoms may remain in a hybridization state (closer to sp^2, with 120 ° ideal bond angles) that permits "partial" delocalization of one of the lone pairs into the aromatic system. This larger bond angle would result in greater strain being imposed on the pyrene unit, which

6a

6b

results in a larger bend angle. The C_1-C_α-C_β bond angle is indeed slightly smaller in **2b** than the C_1-O-C_α **1b** (by 1.4 °) but it is hard to say whether this small difference could account for the 7.8 ° difference in the overall bend of the pyrene units. Another possibility is that the increased deformation is simply the result of C-O bonds being slightly shorter than C-C bonds, which would result in the dioxa tethers being somewhat shorter than the all-carbon tethers.[1]

As pyrene is a fullerene fragment, it was of interest to compare the bend of the pyrene moiety of the pyrenophanes with the bend of the pyrene unit of D_{5h} C_{70} buckminsterfullerene, **6b**. If the pyrene subunits of **6b** are divided into planes defined as in Fig. 6-1, it was found that, in the full circle of the C_{70} equator (360 °), where there are twenty intersections between adjacent planes, the average value of each intersection angle

[1] For Bond length data, see: March, J. *Advanced Organic Chemistry, 4th Ed.* J. Wiley and Sons, New York, **1992**. p. 21.

must mathematically be 18 °. The average bend of a single pyrene subunit, with six such intersections, must be 108 °. Comparison of this angle with the corresponding angle (AG) of the most distorted pyrenophane **1a** shows that **1a** is slightly *more bent* (by 1.1°) than the pyrene unit of D_{5h} C_{70}. This indicates that the pyrene moiety in **1a** displays a larger end-to-end bend than the pyrenes in **6b**. However, this does not necessarily imply that the pyrene in **1a** is more strained than that in **6b**.

Another method to compare the pyrenes in **1a** and **6b** is to use Haddon's POAV analysis, described in Chapter 2.[2] Because the hydrogen atoms in the crystal structure of **1a** are calculated, not actually observed, only the pyrene C atoms not bearing hydrogens can be considered by this method. Applying the POAV analysis to the quaternary carbons of **1a** and comparing these results to the analogous values obtained from both experimental[3] and theoretical[4] structures of the C_{70} fullerene **6b** (Table 6-3) clearly demonstrates that the magnitude of the pyramidalization of the pyrene atoms in **1a** is much smaller than that observed in **6b**. Only the two carbons in the middle of the pyrenophane (C15 and C16) approach the degree of pyramidalization observed in **6b**.

Table 6-3: POAV Pyramidalization Angles (°) for **1a** and D_{5h} C_{70}.

atom (Fig. 6-1)	**1a**	D_{5h} C_{70} (calc.)[4]	D_{5h} C_{70} (exp.)[3]
2	2.9	8.8	8.7
7	2.7	8.8	8.7
11	5.3	10.1	10.3
12	6.0	10.1	10.3
13	5.7	10.1	10.3
14	5.3	10.1	10.3
15	6.9	8.8	8.7
16	6.8	8.8	8.7

[2] a) Haddon, R.C.; Scott, L.T. *Pure Appl. Chem.* **1986**, *58*, 137-142. b) Haddon, R.C. *Acc. Chem. Res.* **1988**, *21*, 243-249.
[3] Nikolaev, A.V.; Dennis, T.J.S.; Prassides, K.; Soper, A.K. *Chem. Phys. Lett.* **1994**, *223*, 143-148.
[4] Raghavachari, K.; Rohlfing, C.M. *J. Phys. Chem.* **1991**, *95*, 5768-5773.

by subscripts – the aromatic protons H_A and H_B, the tether protons H_α, H_β and so forth with increasing distance from the oxygens in **1**, or from the pyrene in **2**. The H_α protons in **1** and **2** have therefore been assigned. Starting with this, the other peaks might be assigned. The first question was which of the two aromatic singlets corresponded to the four protons, H_A, at either end of the pyrenophane (on carbons 1,3,6, and 8), proximal to the tether, and which resulted from the four "central" protons H_B (on carbons 4, 5, 9, and 10). This was established by NOED experiments, in which the methyl signal of the 2,7-dimethoxypyrene **3**, and the (already assigned) first tether methylene protons (H_α) of 1,10-dioxa[10](2,7)pyrenophane, **1d**, were saturated. Saturation of the methyl signal of **3** at δ 4.07 ppm resulted in an 8.5 % enhancement of the higher field aromatic singlet at δ 7.69 ppm. In the case of pyrenophane **1d**, saturation of the methylene signal at δ 4.02 ppm resulted in a 4.8 % enhancement of the δ 7.72 ppm singlet. In both cases, no significant enhancement (< 0.5 %) was observed for the lower field aromatic singlet. Although this assignment has not been made rigorously (i.e., through NOED experiments) for all the pyrenophanes, it seems reasonable to surmise that, in all the pyrenophanes studied, the upfield aromatic signal corresponds to the protons adjacent to the tether H_A, while the four "central" protons H_B resonate further downfield.

The NOED experiment conducted on **1d** also resulted in the enhancement of some of the tether signals. Saturation at δ 4.02 ppm produced an enhancement of 4.5 % of the multiplet at δ 0.93 ppm. It also produced an enhancement (2.5 %) at the *highest field signal* at δ –1.17 ppm, and *no enhancement* of the signal at - 0.67 ppm. This curious result suggested that the simple assignment of the tether signals to protons by relating highest-field shifts with the "central" tether protons (i.e. δ H_α > δ H_β > δ H_γ > etc...) might not be correct. The central protons of the tether, at least in the larger pyrenophanes, do not necessarily produce the highest field signals.

A ^1H-^1H-COSY analysis of the $-O(CH_2)_6O-$ pyrenophane **1b** revealed that the signal at δ 3.59 ppm is coupled to the δ 0.10 multiplet, which is in turn coupled to the -1.46 ppm signal. So in this compound, at least, the chemical shift of the tether protons does increase with distance from the pyrene unit – the highest field protons are indeed those in the middle of the tether (H_γ). For **1c** and **1d**, however, ^1H-^1H-COSY experiments

revealed that the highest field signal resulted from the γ-Hs, while the δ H's were observed further downfield. Possibly, the tether adopts a conformation which results in the H_γ protons being held in the shielding cone of the aromatic system more so than the C_δ protons. The assignment[6] of all pyrenophane protons is given in Table 6-4. Signals not assigned unambiguously are given *in italics*.

Table 6-4: ^{1}H Chemical Shifts

Compound	H_B	H_A	H_α	H_β	H_γ	H_δ	H_ε
1a	7.72	7.22	3.31	-0.04	-2.10		
1b	7.84	7.44	3.59	0.10	-1.46		
1c	7.91	7.64	3.76	0.71	-1.89	-0.73	
1d	7.92	7.72	4.02	0.93	-1.17	-0.67	
1e	7.98	7.83	4.19	1.22	-0.27	-0.64	-1.04
1f	7.96	7.85	4.31	1.41	-0.14	*-0.14*	*-0.63*
3	7.97	7.69	4.07				
2a	7.67	7.34	2.30	*0.45*	*-1.38*	*-1.38*	
2b	7.84	7.59	2.59	0.88	-0.69	-1.45	
2c	7.91	7.75	2.84	*1.10*	*0.25*	*-0.94*	*-2.08*

6.4.2 - ^{1}H NMR – Trends

Consideration of the proton NMR spectra of all the pyrenophanes revealed a number of intriguing trends in terms of chemical shift. The most obvious is the extreme upfield shifting of many of the tether protons which are situated in the shielding cone of the aromatic rings. In the dioxa series, the highest field protons range from δ -0.63 in the $-O(CH_2)_{10}O-$ pyrenophane **1f**, to δ -2.10 for the $-O(CH_2)_5O-$ pyrenophane **1a**. For the hydrocarbon series, the highest field protons range from -1.38, in **2a** to -2.08 in **2c**. First of all, it can be stated conclusively that considerable ring current is present even in the most distorted pyrenophanes. The chemical shifts of the tether protons of the smaller

[6] These assignments are unambiguous only as long as our assignment of the H_A protons (by analogy with

pyrenophanes are much further upfield than the highest observed chemical shift of [7]paracyclophane, which has the highest field tether chemical shift (-0.6 ppm) of any [n]paracyclophane.[7] Secondly, the chemical shifts of the highest field signals do not always increase with decreasing tether length: **1c** has higher field protons than **1b**, and the **2c** highest-field signal is at a higher field than either of its smaller analogues **2a** or **2b**.

The second pattern discernible as the tether shortens, also observed in the [n]paracyclophanes (see Chapter 2), is the upfield shifting of both of the aromatic proton signals, especially the signals of the protons adjacent to the tether H_A which go from δ 7.85 in **1f** to δ 7.22 in **1a**, and from 7.75 in **2c** to 7.34 in **2a**. It seems unlikely that these shifts are due to a decrease in the magnitude of the ring current, as the deshielding of the "central" tether protons demonstrates that the ring current remains strong even in the highly distorted pyrenophanes. Other effects, such as the rehybridization of the aromatic C atoms presumably affects these chemical shifts. Another observable trend in the ^1H NMR spectra is the remarkable upfield shift in the first methylene proton signals in the dioxa-series. This ranges from δ 4.41 in **1f** to δ 3.31 in **1a**. The upfield shifting of the tether methylenes might be simply due to their being held close to the shielding cone of the aromatic rings. The reason for the high-field shifting of the aromatic protons remains unclear.

6.4.3 - ^{13}C Assignment and Patterns

In molecules such as those being discussed here, the assignment of all the carbon resonances (as identified in Fig. 6-3) can be very challenging. In the dioxa series, the first tether methylenes (C_α) are relatively easy to assign to the signals at 74-78 ppm. Assignment of the other peaks is more difficult. Analysis of the HETCORR spectrum of compound **1b** revealed that the upfield aromatic proton resonance H_A (δ 7.44) showed a cross-peak with the upfield C resonance at δ 123.2 ppm, and the latter signal must therefore correspond to C_A in Fig. 6-3. A crosspeak is also visible between the downfield proton resonance H_B and the C resonance at δ 127.4, which can therefore be assigned to

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the NOED data of **1d** and **3**) and of the C_α protons (by their chemical shift) are accepted as being correct.
[7] Wolf, A.D.; Kane, V.V.; Levin, R.H.; Jones Jr., M. *J. Am. Chem. Soc.* **1973**, *95*, 1680.

C_B. The *ipso* carbon C_I can be easily assigned in **1** because of its markedly deshielded position relative to the other Cs, a result of its being bonded to the highly electronegative

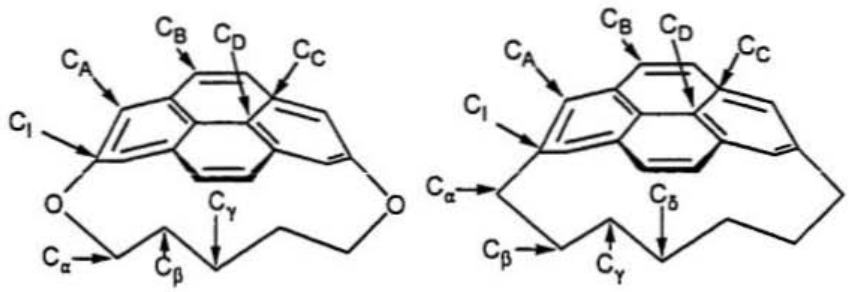


Figure 6-3: Carbon Nomenclature for NMR Assignment

O atom. The other two quaternary signals in **1**, C_C and C_D, have not been rigorously distinguished, although based on relative peak heights, the downfield quaternary signal is much larger than the upfield ones. This *might* suggest that the four C_C atoms are represented by the downfield signal, and the two C_Ds by the upfield one. HETCORR analysis also permitted the assignment of many of the tether Cs, except in cases where the signals were so close in chemical shift that their crosspeaks were indistinguishable in the 2D NMR spectra. The results of the ^{13}C assignments are given in Tables 6-5 and 6-6. Again, resonances that have not been assigned with certainty are given in *italics*.

Unlike the proton spectra, the carbon spectra of the pyrenophanes do not appear to change a great deal as the tether shortens. Small trends are visible in the shifts of the aromatic carbons as the tether shortens, but since some of these signals have not been assigned with certainty, little can be deduced from this.

Table 6-5: ^{13}C Chemical Shifts of Pyrene Moiety

Compound	C_I	C_C	C_B	C_D	C_A
1a	152.0	*133.4*	*126.7*	*126.3*	123.1
1b	153.6	*132.7*	126.9	*127.4*	123.2
1c	153.6	*132.7*	127.0	*125.3*	122.0
1d	154.8	*132.3*	127.1	*123.6*	121.0
1e	155.1	*132.0*	127.2	*122.5*	120.3
1f	156.9	*131.9*	127.2	*121.8*	118.7

3	157.1	*131.5*	127.5	*120.1*	110.6
2a	*136.3*	*131.7*	*130.3*	*129.9*	*126.4*
2b	*137.8*	*131.3*	*128.9*	*127.8*	*126.6*
2c	*136.9*	*131.3*	*127.6*	*126.7*	*126.2*

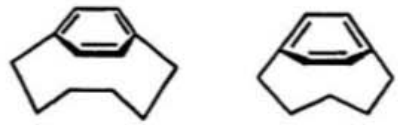
Table 6-6: ^{13}C Chemical Shifts of Tethers

Compound	C_α	C_β	C_γ	C_δ	C_ε
1a	76.3	*27.9*	*26.9*		
1b	77.7	26.7	27.9		
1c	75.8	*28.9*	*28.8*	*28.3*	
1d	76.3	*30.1*	*30.0*	28.3	
1e	75.3	*29.2*	*29.0*	*28.9*	31.3
1f	74.2	31.0	*29.8*	*29.0*	*27.8*
3	55.8				
2a	35.7	*33.2*	*31.4*	*23.5*	
2b	35.9	*31.7*	*31.1*	*23.5*	
2c	36.3	*30.8*	*29.7*	*29.3*	*25.2*

6.4.4 - Other NMR Experiments

In Chapter 2, it was described how, at low temperatures (- 80 °C), the highest field tether proton signal of [6]paracyclophane **7a** (δ + 0.33 ppm) splits to produce two new multiplets, one downfield, the other upfield at δ – 0.6 ppm.[8] Similarly, at -72°C, [5]paracyclophane **7b** displays C_s symmetry in the ^1H NMR, with each pair of geminal protons displaying two signals – one (higher field) signal for the proton being forced towards the benzene, the other (lower field) one corresponding to the proton pointing away from the aromatic ring.[9] These results indicate that, at low temperatures, the rigid tether in such molecules "freezes" into one conformation on the NMR timescale, so that on any given tether carbon, one proton is being forced towards the benzene ring and into

[8] Kane, V.V.; Wolf, A.D.; Jones Jr., M. *J. Am. Chem. Soc.* **1974**, *96*, 2643-2644.
[9] Jenneskens, L.W.; de Kanter, F.J.J.; Kraakman, P.A.; Turkenburg, L.A.M.; Koolhaas, W.E.; de Wolf, W. H.; Bickelhaupt, F.; Tobe, Y.; Kakiuchi, K.; Odaira, Y. *J. Am. Chem. Soc.* **1985**, *107*, 3716-3717.



7a **7b**

its shielding cone while the other is pointing away. The activation barrier to this flipping in **7a** and **7b** have been estimated at, respectively, 11.7 and 14.3 kcal/mol at -49 °C.[9] Since the tethers of the pyrenophane **1a** are clearly highly strained, an attempt to reproduce this "freezing" behavior of the tether in pyrenophane **1a** was made through low temperature NMR.

For this experiment, **1a** was dissolved in deuterated dichloromethane (CD_2Cl_2), which was chosen for its low freezing point. VT-NMR ^1H spectra were taken at 20 °C intervals from 0 ° to -80 ° C. Surprisingly, even at -80 °C, there was no sign of any of the tether signals splitting to form two new signals. The fine structure of the tether proton signals disappeared as the temperature dropped, which might hint at the beginning of tether freezing. On the other hand, this might just be an effect of increasing solvent viscosity with lowered temperature. No attempt to study **1a** at temperatures below -80 ° C was made, but it can be conclusively stated that in **1a**, unlike the [5] and [6]paracyclophanes, no tether freezing could be conclusively observed at -72 °C.

One final NMR technique that was briefly explored was the use of $^1J_{13C\text{-}1H}$ coupling constants to determine the percentage of s character in the C atom's bonding orbital.[10] There is a linear relationship between the percent s character of a bonding orbital and the magnitude of the coupling constant between the two bonded atoms, as given in the equation:

$$\%s_{C\text{-}H} = 0.2(^1J_{C\text{-}H})$$

For example, the $^1J_{C\text{-}H}$ for methane, which is sp^3, is 125 Hz, which works out to 25 % s character. For sp^2-hybridized benzene, the coupling constant is 159 Hz, which equals 32 % s character. It has already been discussed how pyramidalization of (normally planar)

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[10] Lambert, J.B.; Shurvell, H.F.; Lightner, D.; Cooks, R.G. *Introduction to Organic Spectroscopy* MacMillan, New York, 1987, p. 73.

sp^2 C atoms is believed to result in rehybridization – an increase in the p character (and hence a decrease in the s character) of the bonding orbitals of the atom being deformed. In the case of the tether carbons, a deformation from an ideal tetrahedral angle of 109° to a larger angle should also result in a rehybridization, which should again decrease the percentage of s character in the C-H bonds of the tether. ^{13}C NMR spectra of selected pyrenophanes (**1b,c,d**) were therefore collected, with the proton noise decoupler turned off, to provide non-^1H-broadband-decoupled ^{13}C spectra, from which the $^1J_{C\text{-}H}$ values could be obtained.

Table 6-7: ^1J C-H Coupling Constants and Calculated Hybridization (^1J; % s char.)

Compound	C_A	C_B	C_α	C_β	C_γ
-OC_6O-, **1b**	161.0; 32.2 %	162.7; 32.5 %	146.3; 29.3 %	128.0; 25.6 %	125.3; 25.1 %
-OC_7O-, **1c**	163.7; 32.7 %	161.9; 32.4 %	145.8; 29.2 %	124.3; 24.9 %	124.9; 25.0 %
-OC_8O-, **1d**	160.5; 32.1 %	161.1; 32.2 %	146.4; 29.3 %	123.8; 24.8 %	128.8; 25.8 %

The results of this experiment are summarized in Table 6-7, where the $^1J_{C\text{-}H}$ values and the resulting calculated % s characters are listed. Due to overlapping signals, not all the tether carbon signals could be discerned. Unfortunately, there is no easily discernable pattern in either the aromatic or the tether carbons in terms of s character in the bonding orbitals. In many cases, the percentage of s character appears to *increase* as the tether is shortened. These results appear to contradict the rehybridization hypothesis described earlier. At the very least, they suggest that rehybridization of the carbon atoms might be overwhelmed by other factors as the pyrenophane becomes more strained. Most likely, as indicated by the POAV data (Table 6-3), the greatest carbon pyramidalization in **1** occurs in the quaternary carbons of the pyrene unit, which cannot be observed by $^1J_{C\text{-}H}$ coupling constants.

Figure 6-4
Dioxapyrenophane UV Spectra in Ether

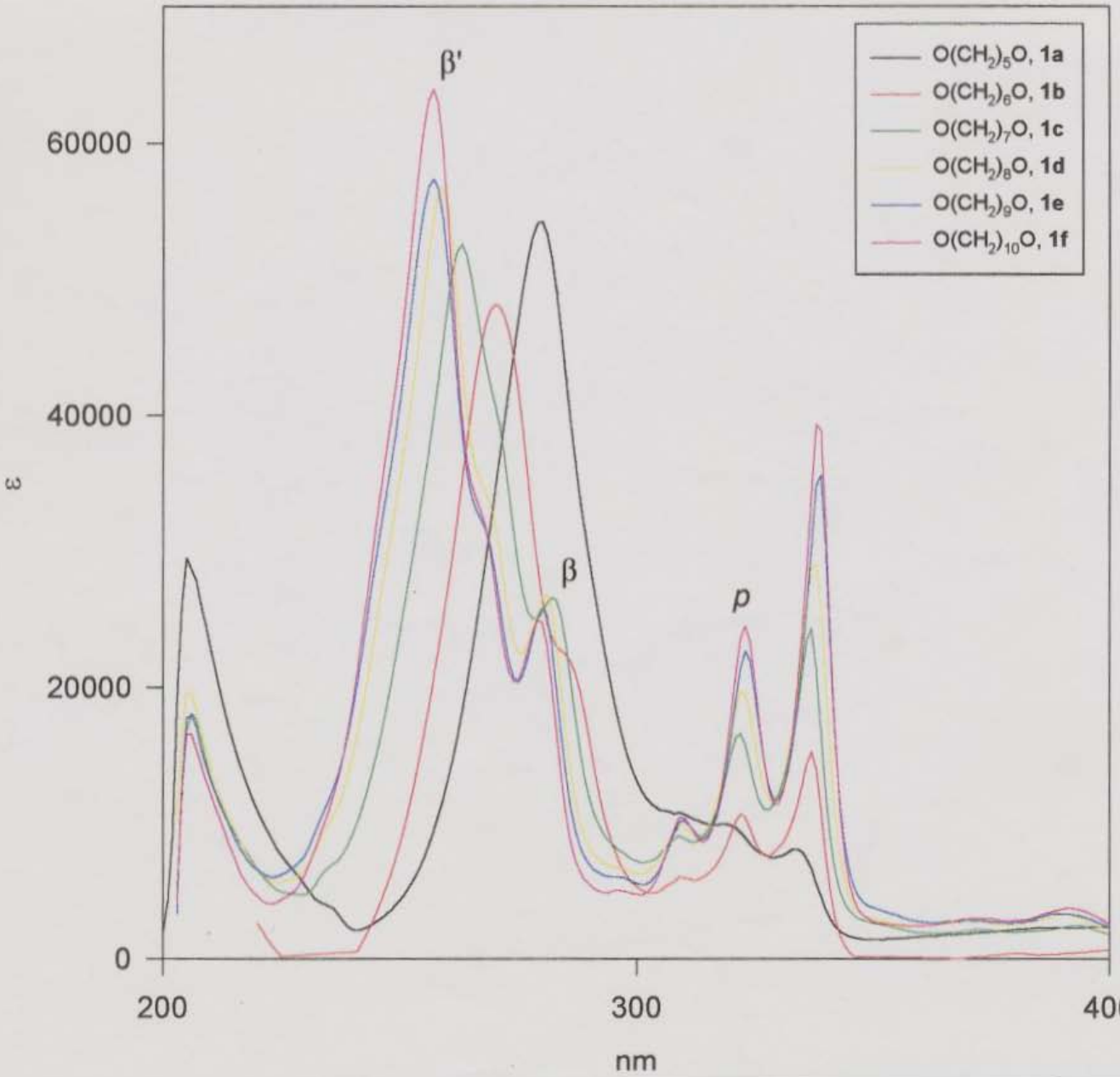
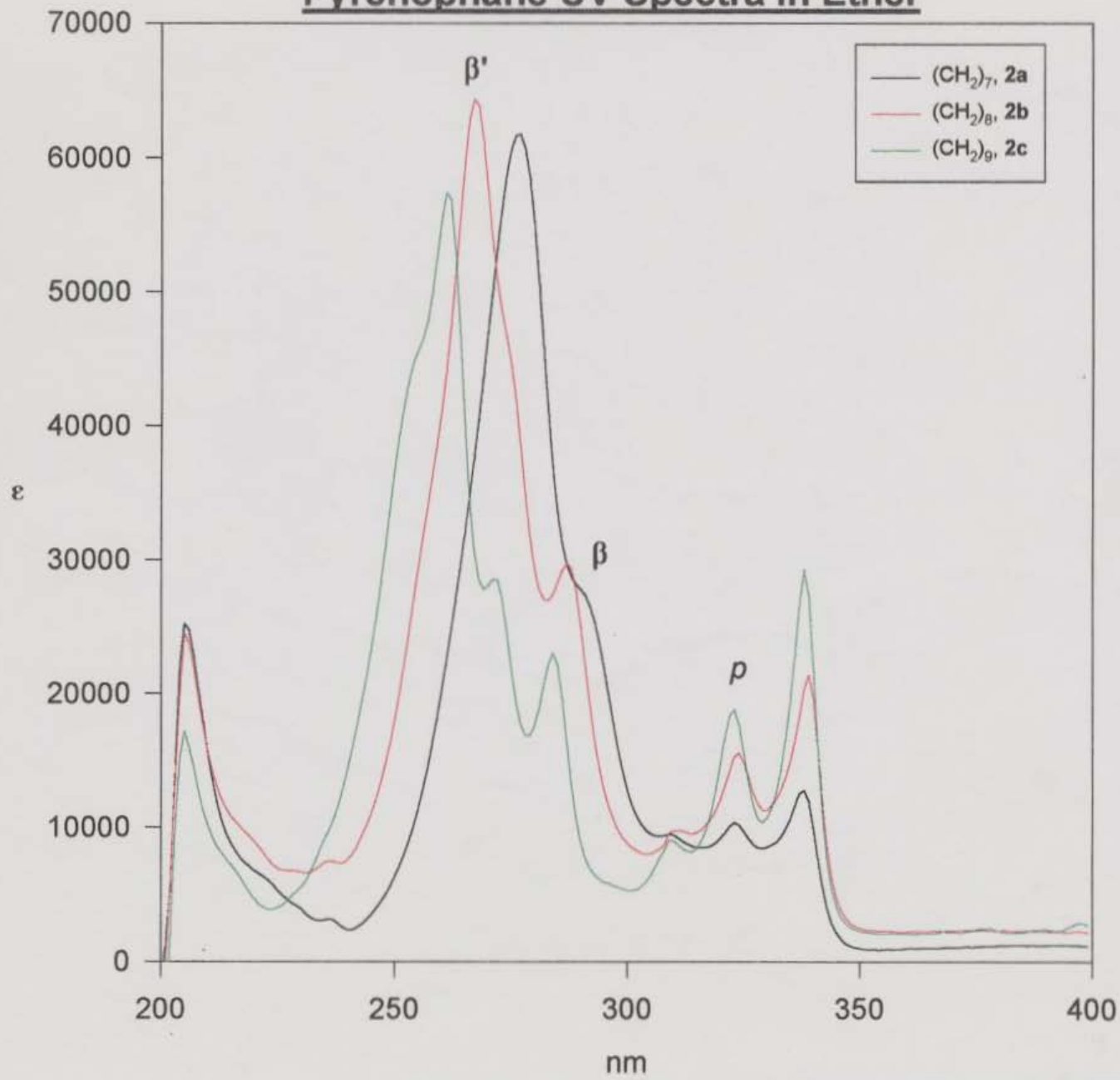


Figure 6-5:
Pyrenophane UV Spectra in Ether



6.5 - Ultraviolet-Visible Spectroscopy

In Chapter 2, the ultraviolet spectra of [n]paracyclophanes were discussed, and it was shown that increasing the distortion of the benzene ring resulted in the marked red-shifting of the major α, β, and *p* absorption bands. Before considering the UV spectrum of the pyrenophanes, the spectrum of pyrene itself might be considered.

Like benzene, Clar has classified the absorption bands of pyrene according to their behavior with changes in temperature and solvent.[11] A strong absorption at 242 nm (ε_{max} 8.84 x 10^4) is called the β′ band. A second band with a maximum at 273 nm (ε_{max} 5.36 x 10^4) is the β. Finally, a series of three bands (ε_{max} 1.25, 3.23, 5.58 x 10^4) at 306, 320, and 336 nm are termed the *p* bands. Due to their extremely low extinction coefficients, the α bands (at 352-372 nm) are very difficult to see in the UV spectrum of pyrene.

The UV spectra (Table 6-8, Figs. 6-4, 6-5, observed in diethyl ether) of the pyrenophanes, at least the less strained ones, bear a reasonable resemblance to that of pyrene itself. For the $O(CH_2)_{10}O$ tether (**1f**), the β′ band at 257 nm, the β band at 279 nm, and the *p* "triplet" at 309-338 nm are clearly visible. As with benzene, substitution of the aromatic hydrocarbon has just resulted in a slight red-shift of all the bands. As the tether is shortened and the aromatic nucleus is more distorted, however, systematic

Table 6-8: Major Pyrenophane UV/Vis Absorbance Bands

Band:	β′		β		*p*					
Cpd.	λ_{max}	ε	λ_{max}	ε	λ_{max}	ε	λ_{max}	ε	λ_{max}	ε
1a	280	54000	n/o	n/o	n/o	n/o	318	10000	334	8100
1b	270	48000	n/o	n/o	309	6000	322	11000	337	15000
1c	263	53000	282	27000	309	9000	322	17000	337	24000
1d	259	57000	280	26000	310	10000	323	23000	339	36000
1e	257	57000	280	26000	310	10000	323	23000	339	36000
1f	257	64000	279	25000	309	10000	323	25000	338	39000
2a	277	62000	n/o	n/o	309	9000	323	10000	338	13000

[11] Clar, E. *Spectrochimica Acta* **1950**, *4*, 116-121.

2b	267	64000	287	30000	311	10000	324	16000	339	21000
2c	261	57000	284	23000	309	9500	323	19000	338	29000
Pyrene (Ref. 10)	242	88400	273	53600	306	12500	320	32300	336	55800

changes in the spectra are observed. First of all, the β′ band is markedly red-shifted, more so than the β band, which becomes a mere shoulder on the larger β′ band in the $O(CH_2)_6O$ pyrenophane **1b**, then disappears altogether in the $O(CH_2)_5O$ **1a** spectrum. In the latter compound, the β′ band is more than 20 nm red-shifted relative to the $O(CH_2)_{10}O$ spectrum. Unlike the β and β′ bands, the *p* bands show little red-shift with increasing distortion; indeed they show a slight blue-shift. There is also a clear decrease in the intensity of the absorptions of the *p* bands as the pyrene moiety is more distorted so that, in the spectrum of **1a**, they appear as little more than slight humps on the baseline.

These observations are difficult to explain without a detailed knowledge of the electronic and molecular orbital structure of pyrene, and the effects of a nonplanar distortion on this structure. The red-shift of the β and β′ bands can be, in a very general sense, attributed to the lowered gap between the occupied and unoccupied orbitals in the pyrene moiety. It *cannot* be attributed to a reduced HOMO-LUMO gap itself, as the bands do not represent the lowest energy transition observed for pyrene. The forbidden α band, not observed here due to its extremely low extinction coefficient, corresponds to that transition. More interesting, and more difficult to explain, is the blue-shift and decrease in intensity of the *p* bands. The blue-shift implies that the energy difference between the orbitals corresponding to the ground and excited states is *increasing*. The intensity decrease of the absorption indicates that the transition is becoming "less allowed" – in other words, more forbidden. But without knowing the exact properties of the ground and excited state orbitals involved in this transition, it is impossible to guess which UV transition selection rule (forbidden due to spin, orbital symmetry, or angular momentum)[12] is being increasingly enforced as the pyrene unit becomes more deformed. These uncertainties might be resolved by performing a high level calculation of the MO structure of pyrene in increasingly distorted geometries and thereby predicting the

frequencies of the electronic transitions in the molecule. These values could then be compared to the experimental UV data. It would be interesting to see which computational method provide the best correlation with the empirical data. The use of UV in chemistry, however, has been declining in recent decades. Although very popular for applications like structural elucidation in the middle of the century, it has since been supplanted in this area by more powerful techniques such as NMR and x-ray crystallography. The use of UV spectroscopy in chemistry over the past twenty years has faded considerably (except, perhaps, in the study of small, reactive species), and while the latest *ab initio* techniques are frequently used to predict molecular geometry, NMR and (less frequently) IR spectra, the author is aware of no recent instance (at least in this field) where computational chemistry has been used to predict or interpret a UV spectrum. This might be due to the inability of most *ab initio* methods to calculate accurately excited states of large molecules. The interpretation of the results presented here presents an opportunity for the revival of the "lost art" of ultraviolet spectroscopy.

6.6 – Cyclic Voltammetry

6.6.1 – Introduction to CV

To investigate the redox properties of pyrenophanes and to determine the effects, if any, that bend has on the redox potentials of aromatic systems, compounds **1** and **2** were studied by cyclic voltammetry (CV). CV is an electroanalytical technique that allows the observation of the redox behavior of a compound over a wide potential range.[13] It involves cycling the potential of an electrode immersed in an (unstirred) solution and observing the current generated. The results of a cyclic voltammetry are usually displayed as a cyclic voltammogram, an idealized example of which is illustrated in Fig. **6-4**. The cycle starts, for example, at a negative potential (*a*) and sweeps towards the positive – the forward scan. When the applied voltage becomes sufficiently high to oxidize the substance being analyzed, an *anodic current* results, reaching a maximum (*b*) called the *anodic peak potential* (P_a). Because the solution is unstirred, the concentration of the substrate at the electrode becomes depleted, resulting in the decay of the magnitude

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[12] Ref. 10, p. 260-261.
[13] For an introduction to CV, see: Kissinger, P.T.; Heineman, W.R. *J. Chem. Ed.* **1983**, *60*, 702-706.

of the current. When the potential reaches its maximum, called the *switching potential* (*c*), the direction of the sweep reverses, and the applied voltage now sweeps towards the negative – the reverse scan. When the potential becomes low enough to reduce the oxidized substrate generated by the forward scan, a cathodic current is produced, with a maximum (*d*) called the *cathodic peak potential* (P_c). The sweep then returns to its initial potential (*a*).

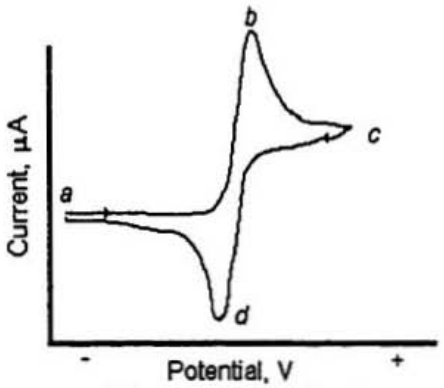


Figure 6-6: Stylized CV

From such studies, such information as the first (and subsequent) oxidation and reduction potentials of a compound can be obtained, which allows the determination of the size of the HOMO – LUMO gap. The number of electrons transferred in a reduction step can also be determined. To the best of our knowledge, neither [n]paracyclophanes nor any other cyclophanes have ever been studied systematically by CV. CV was therefore chosen to study the redox behavior of pyrenophanes.

6.6.2 - Cyclic Voltammetry – Experimental

Solution samples (0.6-2.9 mmol/L) were prepared by dissolving pyrenophanes **1** and **2** in CH_3CN, which was distilled from CaH_2 prior to use. To each solution was added recrystallized tetraethylammonium perchlorate as an electrolyte to produce a concentration of approx. 0.1 M. These solutions were degassed with an Ar flow and placed in a three-electrode cell with an 0.0052 cm^2 Pt electrode attached to a Pine RDE 4 potentiostat. Polarograms were obtained using Colin's Wacky Cyclic Voltammetry Acquisition Program V. 3.1[14] at a scan rate of 100 mV/sec with a saturated sodium chloride/Calomel (SSCE) reference electrode.

[14] Cameron, C. Memorial University of Newfoundland. 1997.

Figure 6-7:
Dioxapyrenophane Cyclic Voltammetry, Normalized to 1 mM

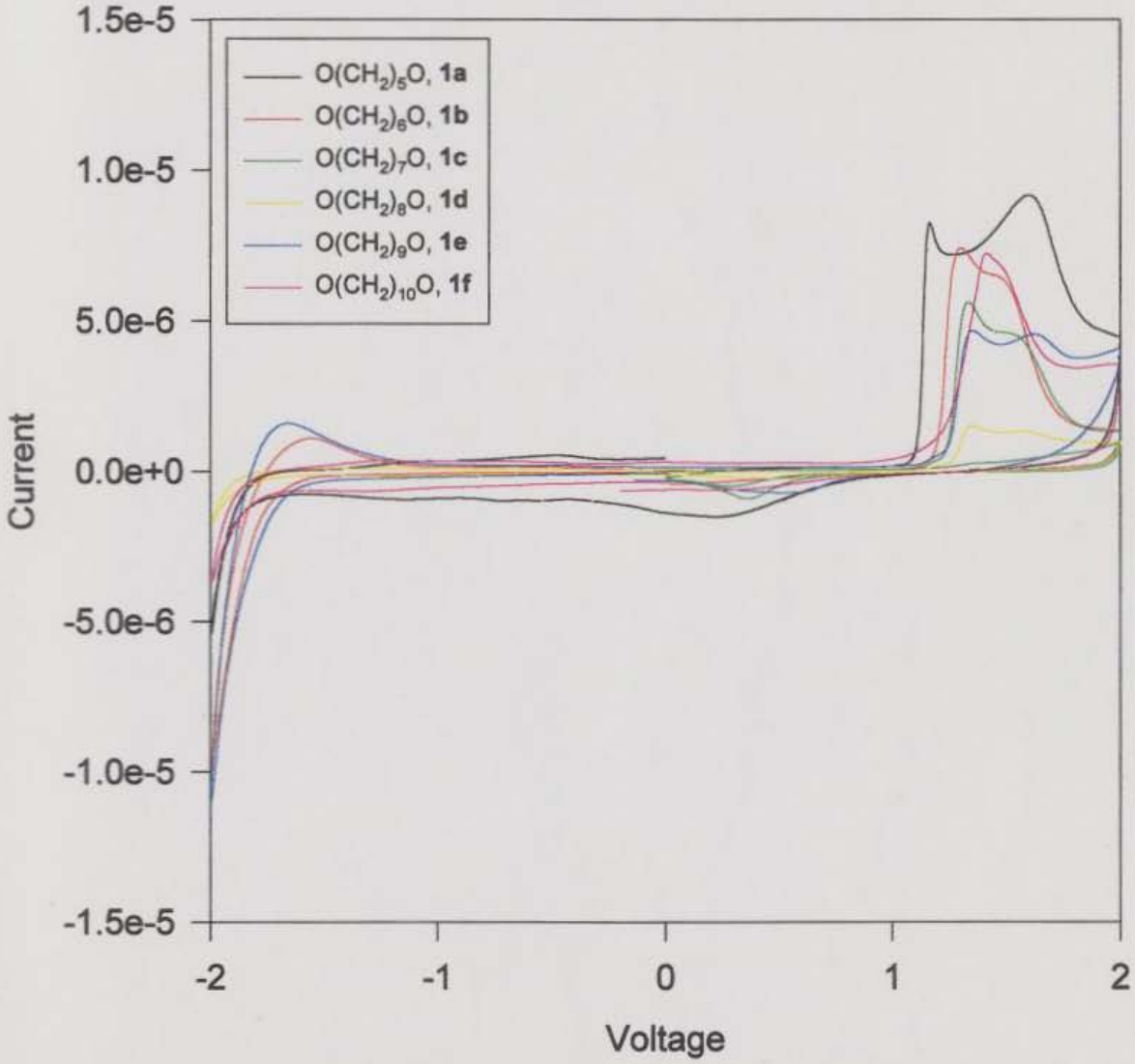
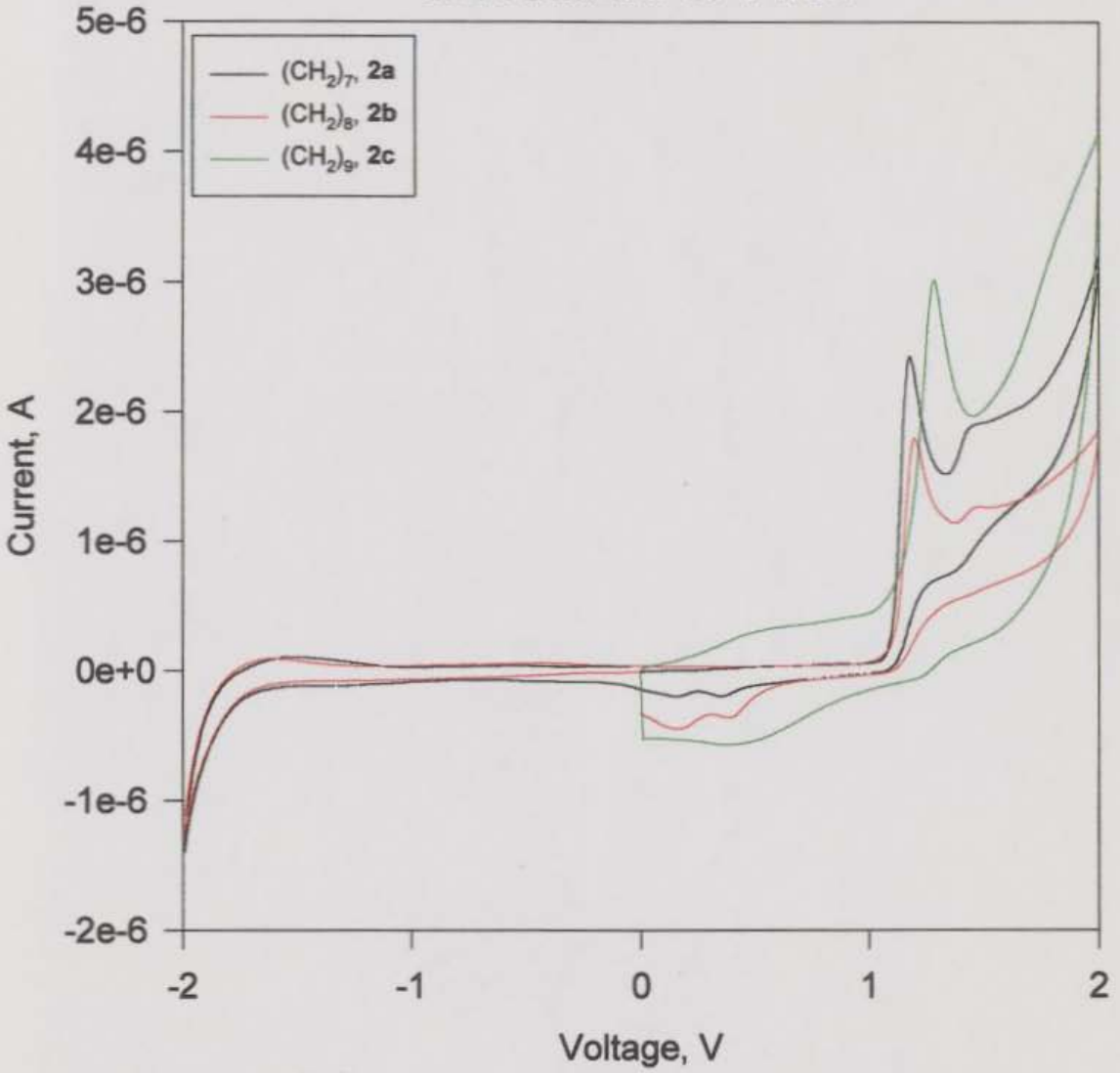


Figure 6-8:
Hydrocarbon Pyrenophane Cyclic Voltammetry, Normalized to 1 mM



6.6.3 - Cyclic Voltammetry – Results and Discussion

Table 6-9: Cyclic Voltammetry Oxidation Potentials

Compound	V	A (x 10^{-6})
1a	1.17	8.26
1b	1.30	7.45
1c	1.33	5.65
1d	1.35	1.54
1e	1.35	4.70
1f	1.41	7.27
2a	1.18	2.43
2b	1.20	1.81
2c	1.28	3.02

The pyrenophane cyclic voltammograms (Figs. 6-7, 6-8; Table 6-9) bear little similarity to the ideal CV curves illustrated earlier. The positive scans (0 to +2 V) show a clear anodic peak potential between 1.17 V (for **1a**, the OC_5O tether) and 1.41 V (**1f**, the $OC_{10}O$ tether). The hydrocarbon-tethered pyrenophanes **2** also fall within this range. There was a clear trend for this initial oxidation: as the pyrenophanes became more distorted, their P_a became less positive. In other words, greater distortion renders the pyrenophanes easier to oxidize. This is consistent with the (already mentioned) rule of thumb that distortion results in the raising of the HOMO. However, instead of decaying, the anodic current remains high as the potential increases to 2 V. In some cases (especially, **1a**) a second, broad peak potential can be discerned around 1.6 V. In others (e.g. **1b**), this second oxidation is only evidenced by a shoulder on the first anodic peak.

During the reverse sweep, no cathodic peak potential whatsoever is observed. This means that the oxidation product from the forward sweep is unstable and decomposes before it can be reduced. This behavior is identical with that reported for pyrene itself (P_a 1.54 V vs. SCE),[15] which undergoes an irreversible oxidation due to the

[15] Peover, M.E.; White, B.S. *J. Electroanal. Chem.* **1967**, *13*, 93-99.

instability of the resultant radical cation, and produces an insulating film on the electrode. This is observed with the pyrenophanes: a second cycle of forward and reverse scans from 0 to 2 V results in a P_a of much lower intensity than the first sweep, and by the third cycle, the peak is barely noticeable. All this implies that the electrochemical oxidation of **1** or **2** results in the generation of an unstable radical cation which rapidly decomposes to some insoluble by-product, which coats the electrode and prevents it from interacting further with the solution.

The negative scan region (0 to -2 V) is much less interesting. No cathodic peak potential whatsoever is visible except for a marked increase in current very close to the switching potential at -2 V. Since this potential is outside the useful electrochemical window of acetonitrile anyway, little significance can be attached to this observation. What is significant is that neither **1** nor **2** is reduced at potentials above about -1.8 V. This is significant when contrasted with fullerenes, curved aromatic systems whose electrochemistry has been investigated extensively.[16] As discussed in Chapter 3, fullerenes were predicted to be electron deficient – easy to reduce, but hard to oxidize. This has been demonstrated with CV, where the reduction of both C_{60}, **6a**, and C_{70}, **6b**, to their hexaanions, C_{60}^{6-} and C_{70}^{6-} respectively, has been demonstrated. The reduction potentials for the sequential addition of electrons to C_{60} are -0.52, -0.91, -1.41, -1.89, -2.39, -2.80 V (vs. SCE), and all these reductions are reversible. The values for the reduction of C_{70} are almost identical.[16d] In other words, fullerenes are very easily reduced to stable anionic compounds. By contrast, at potentials as low as -1.9 V, at which C_{60} would have been reduced *four times*, the pyrenophanes have still not been reduced at all. This is an instance where, although they are fullerene fragments and are clearly bent, the pyrenophanes differ markedly from the fullerenes themselves. In terms of oxidation chemistry, the pyrenophanes and the fullerenes are quite similar. C_{60} and C_{70} undergo single electron oxidation at 1.72 and 1.66 V, respectively.[16e] These

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[16] a) Allemand, P.-M.; Koch, A.; Wudl, F.; Rubin, Y.; Diederich, F.; Alvarez, M.M.; Anz, S.J.; Whetten, R.L. *J. Am. Chem. Soc.* **1991**, *113*, 1050-1051. b) DuBois, D.; Kadish, K.M.; Flanagan, S.; Haufler, R.E.; Chibante, L.P.F.; Wilson, L.J. *J. Am. Chem. Soc.* **1991**, *113*, 4364-4366. c) DuBois, D.; Kadish, K.M.; Flanagan, S.; Wilson, L.J. *J. Am. Chem. Soc.* **1991**, *113*, 7773-7774. d) Xie, Q.; Perez-Cordero, E.; Echegoyen, L. *J. Am. Chem. Soc.*, **1992**, *114*, 3978-3980 e) Xie, Q.; Arias, F.; Echegoyen, L. *J. Am. Chem. Soc.* **1993**, *115*, 9818-9819 f) Echegoyen, L; Echegoyen, L.E. *Acc. Chem. Res.* **1998**, *31*, 593-601.

oxidations are irreversible under some conditions,[16c] but reversible in others.[16e] The pyrenophanes therefore appear to be slightly more easily oxidized than the fullerenes.

It was originally thought that, due to strain relief on reduction (and resultant pyramidalization) of the bridgehead carbons in the pyrenophanes, these compounds might display interesting electrochemical behavior. Unfortunately, under the conditions described here, the oxidation product was shown to be unstable, and no reduction of pyrenophanes could be conclusively observed. The work done on the fullerenes, which involved the measurement of potentials as low as -3 V vs. SCE, shows that the methodology exists to allow the electrochemical reduction of compounds with very low reduction potentials. Unfortunately, our group lacks both the instrumentation and the expertise to carry out these studies on our own. The collaboration of cyclic voltammetry specialists would be essential to extend and refine these preliminary studies, and such collaborations are currently being organized.

6.7 - Chemistry of Pyrenophanes

Having successfully prepared a number of [n](2,7)pyrenophanes, the possibility of extending the synthesis to form true buckybowls by annellating five membered rings onto the pyrene moiety, as illustrated in Fig. 6-9, was now considered. It was hoped that

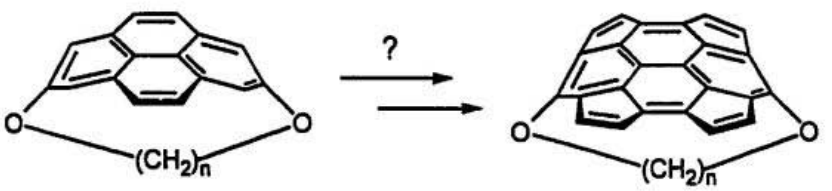

Figure 6-9: Annellation of 5-membered Rings onto Pyrenophanes

the considerable bend already present in the polycyclic aromatic system would reduce the energetic barrier to the introduction of five membered rings, perhaps allowing such rings to be formed at non-pyrolytic temperatures. To test the feasibility of this idea and to determine the optimal conditions (if any) for the introduction of two-carbon fragments and the subsequent closure of the desired five membered rings onto the pyrene moiety,

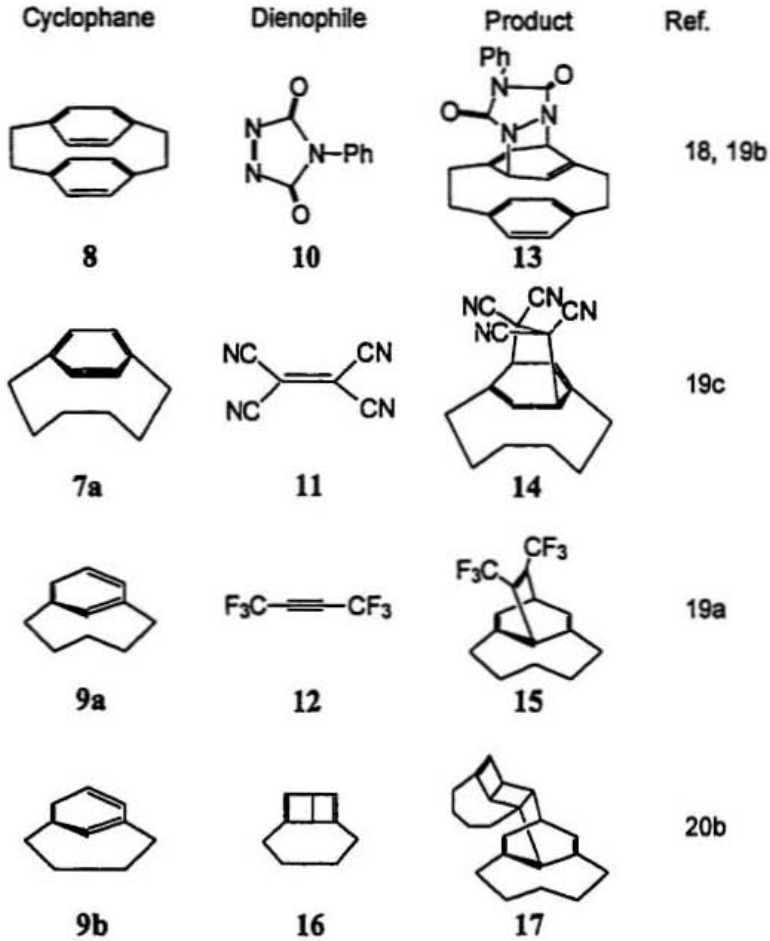

Figure 6-10: Diels-Alder Adducts of Cyclophanes

experiments were conducted to explore the chemical behavior of [n](2,7)pyrenophanes. The results of these experiments will be discussed here.

6.7.1 – Diels-Alder Reactions - Introduction

Whereas most 1,3-dienes readily undergo [4+2] cycloadditions (Diels-Alder reactions) with reactive dienophiles, aromatic compounds such as benzene, although they contain formal 1,3-diene groups, are notoriously unreactive to dienophiles except under exceptionally forcing conditions.[17] However, when the benzene ring is strained (for example, in cyclophanes), and when pyramidalization of two of the sp^2 carbon atoms in

[17] a) Sauer, J. *Angew. Chem., Int. Ed. Engl.* **1966**, *5*, 211-230. b) Ciganek, E. *Tetrahedron Lett.* **1967**, 3321-3325.

the benzene ring would result in strain relief, the reactivity of the arene ring markedly increases.[18] Examples of this can be seen in the work of Hopf,[19] Bickelhaupt,[20] and Gassmann,[21] (Fig. 6-10) who have demonstrated that [6]paracyclophane **7a**, [2.2]paracyclophane **8**, and [5]metacyclophane **9a** were reactive to a number of strong dienophiles, such as 4-phenyl-1,2,4-triazolin-3,5-dione (PTAD) **10**, tetracyanoethylene (TCNE) **11**, and hexafluoro-2-butyne **12**, to afford **13**, **14**, and **15**, respectively. Extremely reactive species, such as [4]metacyclophane **9b**, have been observed to undergo Diels-Alder reactions with their own Dewar benzene isomer **16** to form dimers such as **17**.[20b] Rate studies have demonstrated that [4+2] cycloadditions with cyclophanes as dienes belong to the class of normal electron demand reactions, in which the diene HOMO interacts with the dienophile LUMO.[22]

Less work has been done on the reactivity of strained polycyclic aromatic hydrocarbons in Diels-Alder reactions, although they are expected to be slightly more reactive than simple cyclophanes due to the higher HOMO energies inherent in fused aromatic systems. Wiberg has reported the reaction of [n](1,4)naphthalenophanes **18** with dicyanoacetylene **19**,[23] and Vögtle[24] and others have described the addition of a number of dienophiles to [n](9,10)anthracenophanes.[23]

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[18] For a review of cycloaddition reactions of cyclophanes, see: Misumi, S. *Pure Appl. Chem.* **1987**, *59*, 1627-1636.

[19] a) Noble, K.-L.; Hopf, H.; Jones, Jr., M.; Kammula, S.L. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 602. b) Murad, A.F.; Kleinschroth, J.; Hopf, H. *Angew. Chem., Int. Ed. Engl.* **1980**, *19*, 389-390. c) Hopf, H.; Witulski, B.; Jones, P.G.; Schomberg, D. *Liebigs Ann.* **1995**, 609-612.

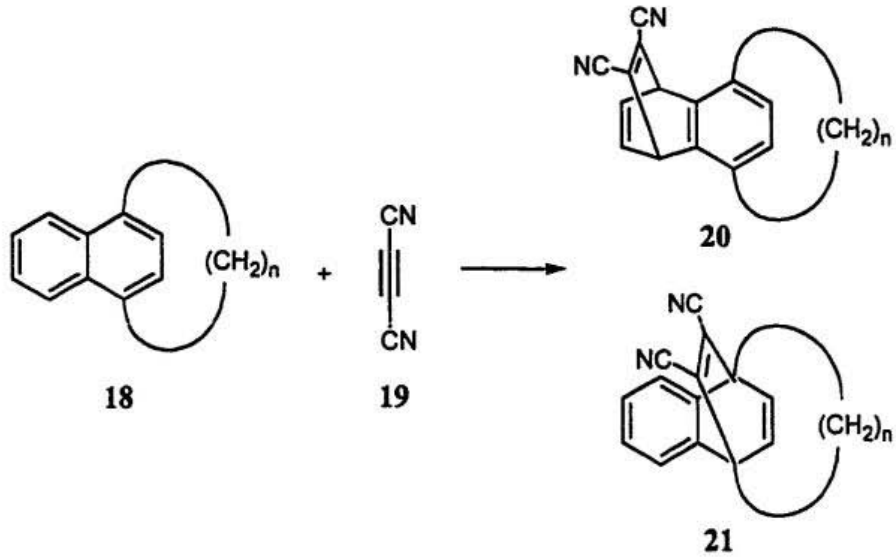
[20] a) Turkenburg, L.A.M.; Blok, P.M.L.; de Wolf, W.H.; Bickelhaupt, F. *Angew. Chem., Int. Ed. Engl.* **1982**, *21*, 298. b) Kostermans, G.B.M.; van Dansik, P.; de Wolf, W.H.; Bickelhaupt, F. *J. Am. Chem. Soc.* **1987**, *109*, 7887-7888.

[21] Gassmann, P.G.; Bailey, T.F.; Hoye, R.C. *J. Org. Chem.* **1980**, *45*, 2923.

[22] Bickelhaupt, F.; de Wolf, W.H. *J. Phys. Org. Chem.* **1998**, *11*, 362-376 and references therein.

[23] Wiberg, K.; O'Donnell, M. *J. Am. Chem. Soc.* **1979**, *101*, 6660 -6666.

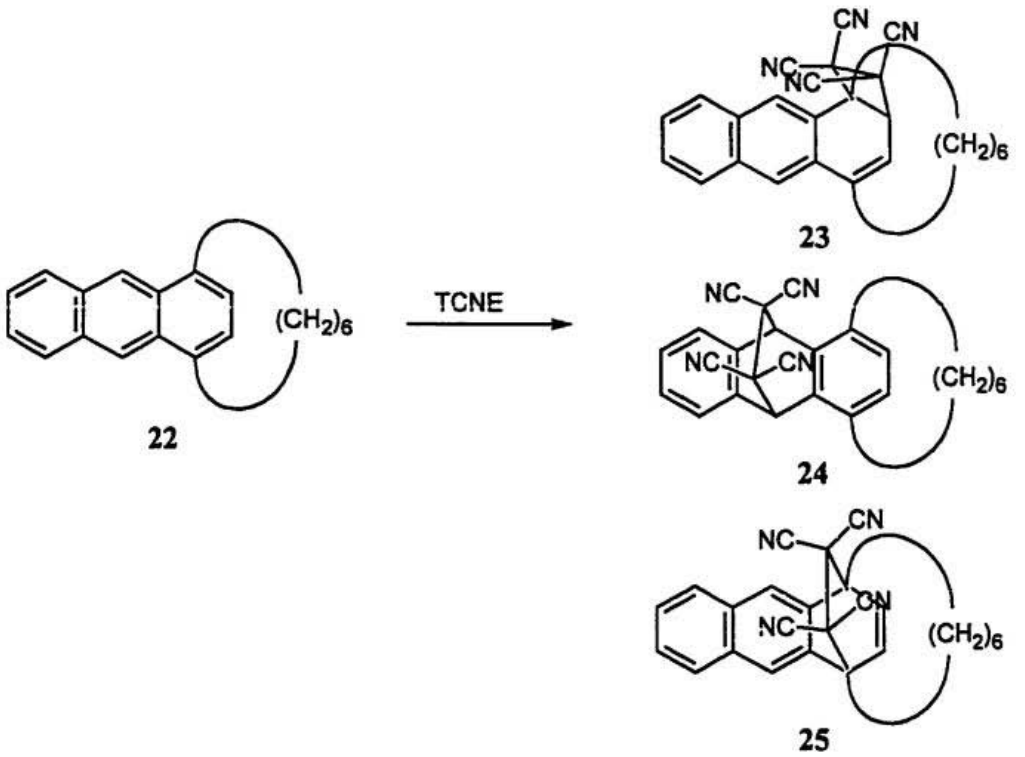
[24] Vögtle, F.; Koo Tze Mew, P. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 60-62.



Scheme 6-1: Products of Addition to (1,4)[n]Naphthalenophane.

Although, generally speaking, strain does appear to increase the reactivity of arenes to Diels-Alder reactions, many unexpected results have been obtained from these cycloaddition reactions. For instance, Wiberg and O'Donnell's [n](1,4)naphthalenophane work (Scheme 6-1) showed that, for the shorter tethers (n=8,9), only addition (of dicyanoacetylene) at the *unsubstituted* ring occurred (**20**), while for longer tethers (n=10,14) products corresponding to addition at *both* the unsubstituted and the substituted (**20** and **21**) rings were formed. This bizarre result is the opposite of what would be expected if these reactions were driven by the relief of strain, as only in addition at the substituted ring should substantial relief occur, by allowing the arene ring to relax from its strained, near-planar conformation Tobe's work has shown that, in many instances, thermal [2+2] additions occur in preference to [4+2] Diels-Alder reactions in many cyclophanes.[25] For example (Scheme 6-2), [6](1,4)anthracenophane **22** reacts with TCNE in CH_2Cl_2 to form [2+2] adduct **23** solely, while in benzene, a mixture of **23** (82 %) and [4+2] adduct **24** (13 %) were formed.[25b] Despite the considerable strain undoubtedly imposed by the six-atom tether, no strain-relieving [4+2] addition across carbons 1 and 4, as in **25**, was observed. **25** may, in fact, be considerably

[25] a) Tobe, Y.; Sorori, T.; Kobiro, K.; Kakiuchi, K.; Odaira, Y. *Tetrahedron Lett.* **1987**, *28*, 2861-2862. b) Tobe, Y.; Takemura, A.; Jimbo, M.; Takahashi, T.; Kobiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1992**, *114*, 3479-3491.



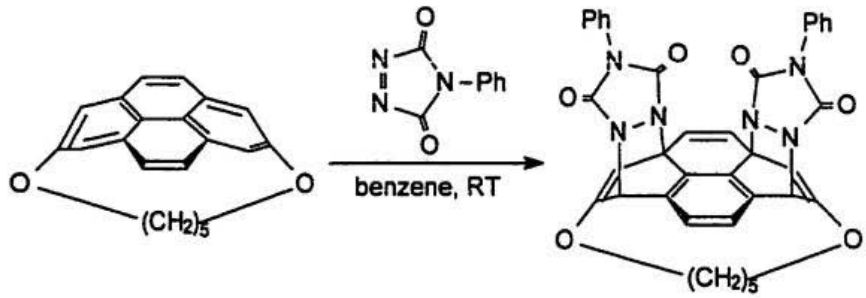
Scheme 6-2: Products of Diels-Alder Reaction of **22** and TCNE

strained itself. Clearly, other factors, besides the relief of tether-induced strain, control the reactivity of aromatic hydrocarbons in Diels-Alder reactions and other cycloadditions.

6.7.2 - Diels-Alder Reactions - Results and Discussion

To study the reactivity of (2,7)pyrenophanes with Diels-Alder dienophiles, it was chosen to work first with the "super-dienophile" 4-phenyl-1,2,4-triazolin-3,5-dione, **10**, abbreviated as PTAD. One advantage of this dienophile is that its red color, which decolorizes as it reacts, can serve as an indicator of the rate and the completeness of the reaction. Treatment of 1,7-dioxa[7](2,7)-pyrenophane **1a** with two equivalents of PTAD in benzene at room temperature, resulted in rapid fading (< 1 hour) of the red color and formation of a white precipitate. The white powder could be isolated by filtration, and its mass corresponded to a 1:2 pyrenophane/PTAD adduct. Attempts to purify and characterize the product were frustrated by its near-total insolubility in all organic solvents and its propensity to bind irreversibly to silica. A very poor ^{1}H NMR spectrum could be obtained in DMSO-d_6, but this was insufficient to determine the structure of the

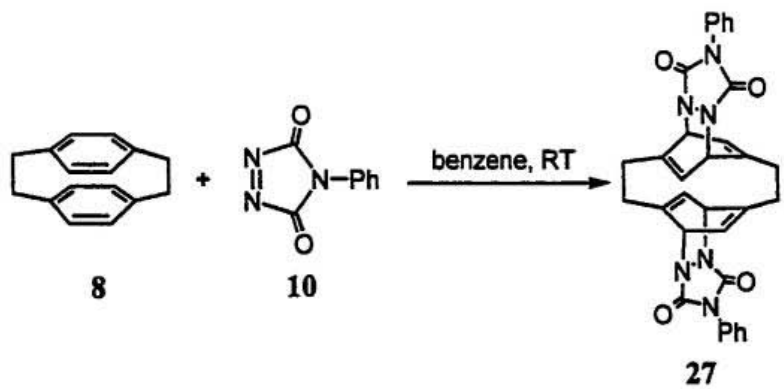
product. A "wild guess" at the structure might be **26** (Scheme 6-3), as this is one of the few bis-adducts which retains any aromatic stabilization and might correspond to the ^{1}H NMR obtained, but in the absence of any more concrete data this must be considered completely speculative.



Scheme 6-3: Diels-Alder Reaction of **1a** and PTAD

There is a literature precedent for the formation of a double-PTAD adduct with a cyclophane. Recently, Matsumoto reported the result of the Diels-Alder reaction between [2.2]paracyclophane and excess PTAD (Scheme 6-4), and obtained a crystal structure of 2:1 adduct **27**.[26] PTAD is evidently a strong enough dienophile to react with even the slightly strained benzene ring of the monoadduct **13**.

Despite the unknown structure of the mysterious PTAD adduct, it was possible to

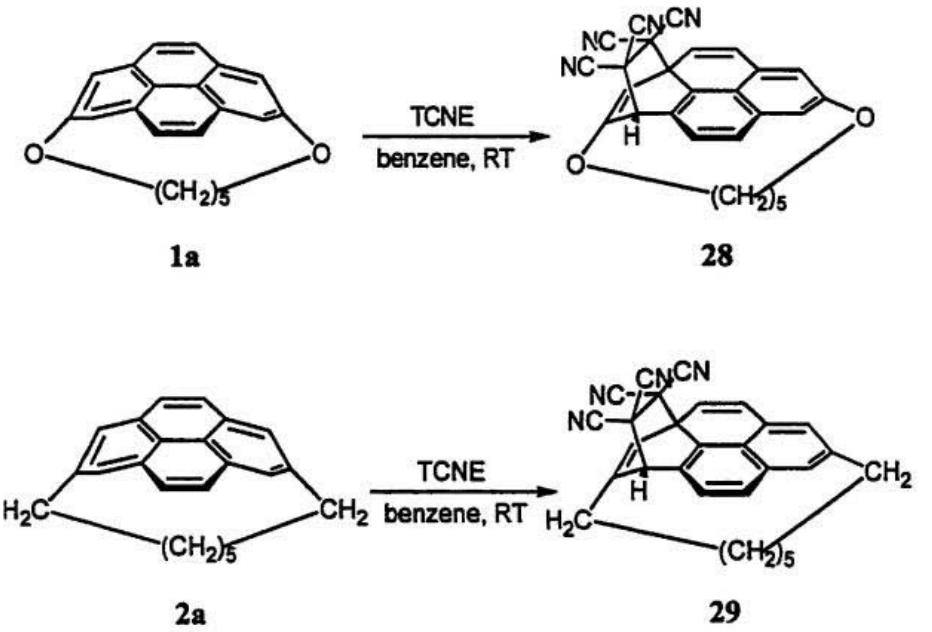


Scheme 6-4: Matsumoto's Bis-Adduct of **8** and PTAD

[26] Matsumoto, K.; Toda, M.; Kakehi, A. *Heterocycles* **1995**, *41*, 471-476.

examine the effect of tether length on its formation. For an 8-atom tether (1,8-dioxa[8](2,7)-pyrenophane, **1b**) decolorization of the PTAD took over 3 hours (vs. less than 1 hour for the 7-atom tethered **1a**), and isolation afforded a white precipitate with intractable properties identical to those of its previously-described analogue. With a 10-atom tether **1c**, however, the PTAD had not been consumed even after 5 days, and only a small amount of white precipitate had formed. According to these observations, the reactivity of pyrenophanes to PTAD increases with decreasing tether length, and is presumably an effect of increasing strain.

Our goal was now to generate an isolable, characterizable pyrenophane Diels-Alder adduct. A reaction of **1a** with *N*-phenylmaleimide in refluxing xylenes yielded no isolable products. A reaction with TCNE (**11**), however, was more productive (Scheme 6-5). Reacting **1a** and **11** in benzene at room temperature afforded, after chromatography, **28** as a white, crystalline solid in quantitative yield.[27] ^{1}H and ^{13}C NMR



1a **28**

2a **29**

Scheme 6-5: Diels-Alder Adducts of Pyrenophanes and TCNE

data could be collected for this compound, and X-ray crystallography proved the structure to be the [4+2] adduct **28**. The product was unstable in air, gradually

decomposing to a brown sludge, which prevented an accurate elemental analysis. The homologous pyrenophane **1b** failed to react with TCNE under identical conditions, or in refluxing benzene. The hydrocarbon pyrenophane **2a** also reacted to give TCNE adduct **29**. These results were encouraging (although, ultimately misleading) examples of a pyrenophane reacting under mild conditions to form a single product in high yield.

6.7.3 - Electrophilic Substitution – Halogenation and Friedel Crafts Acylation

To be useful as a precursor for larger bowl-shaped polycyclic aromatic hydrocarbons, the pyrenophanes **1** and **2** had to be functionalized: the arene – H bonds replaced with either an organic group (such as acetyl) or a halide, which could subsequently be transformed into a C-C bond using, for example, Pd-catalyzed couplings. Both acyl and halide groups are normally introduced into aromatic compounds by electrophilic substitution reactions – the former *via* Friedel-Crafts acylation, the latter by electrophilic halogenation. The feasibility of electrophilic substitution on highly strained pyrenophanes was therefore explored.

6.7.3.1 - Bromination

An examination of the literature revealed some successful electrophilic halogenations of paracyclophanes. A functionalized [10]paracyclophane derivative had been monochlorinated using iodobenzene dichloride,[28] and [10]paracyclophane derivatives were brominated using Br_2/I_2 in CCl_4.[29] The results of attempted halogenation of more strained cyclophanes were, however, less encouraging. While a successful bromination of a [6](1,3)naphthalenophane (**30** to **31**, Scheme 6-6) was reported,[30] treatment of [6]paracyclophane **7a** with Br_2 in CCl_4 at 0 °C afforded the 1,4-Br_2 *addition* product **32** quantitatively (Scheme 6-7). This product was unstable in the solid state, decomposing to produce a mixture of tether cleavage products and rearranged,

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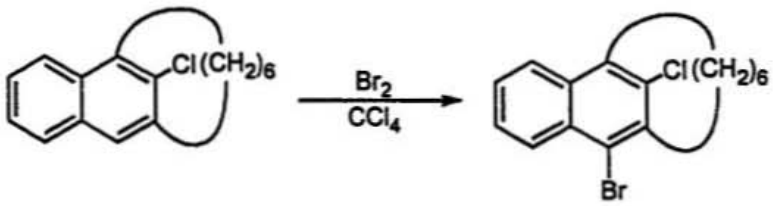
[27] Bodwell, G.J.; Bridson J.N.; Houghton T.J.; Kennedy J.W.J.; Mannion, M.R. *Chem. Eur. J.* **1999**, *5*, 1823-1827.
[28] Keefer, R.M.; Andrews, L.J. *J. Am. Chem. Soc.* **1957**, *79*, 4348-4353.
[29] Smith, B.H. Ph. D. Thesis, Cornell University, Ithaca, New York, **1960**. Cited in: Smith, B.H. *Bridged Aromatic Compounds* Academic Press, New York, **1964**. p. 211.
[30] Parham, W.E.; Johnson, D.R.; Hughes, C.T.; Meilahn, M.K.; Rinehart, J.K. *J. Org. Chem.* **1970**, *35*, 4048-4552.

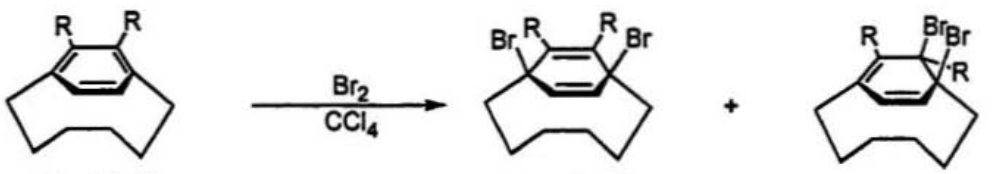


30 **31**

Scheme 6-6: Bromination of (1,3)Naphthalenophane

brominated cyclophanes.[31] The paracyclophane diester **33** also underwent addition instead of substitution to afford a 3:2 mixture of the 1,4- and 1,2-addition products **34** and **35**.[32] The stabilies of these compounds were not discussed, but **35** was stable enough to afford an X-ray crystal structure. These results suggest that aromatic hydrocarbons, if sufficiently strained, will undergo strain-relieving addition reactions, despite the loss of aromatic stabilization that such reactions involve.

Given the considerable strain present in [n](2,7)pyrenophanes, where n is less than 10, it was anticipated that addition reactions might be favored over substitution. It was indeed observed that treatment of (1,10)dioxa[10](2,7)pyrenophane **1d** with bromine in CH_2Cl_2 at 0 ° C produced a dark, intractable precipitate from which no products could be isolated. Test-tube tests indicated that other, milder brominating agents, such as Br_2/dioxane,[33] pyridinium hydrobromide perbromide,[33b,34] and NBS, when reacted with



7a, R=H
33 , R=CO_2Et

32, R=H
34, R=CO_2Et

35, R=CO_2Et

Scheme 6-7: Addition of Br_2 to [6]Paracyclophane Derivatives.

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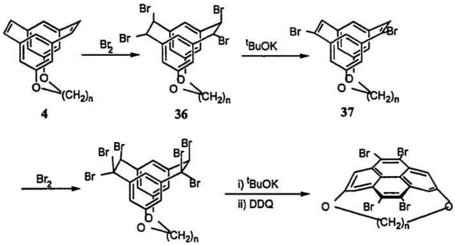
[31] Tobe, Y.; Ueda, K-I.; Kakiuchi, K.; Odaira, Y.; Kai, Y.; Kasai, N. *Tetrahedron* **1986**, *62*, 1851-1858.
[32] Liebe, J.; Tochtermann, W. *Tetrahedron Lett.* **1983**, *24*, 2549-2552.
[33] a) Fieser, L.F.; Fieser, M. Reagents for Organic Synthesis J. Wiley & Sons, New York, 1967. pp. 333-334. b) Buehler, C.A.; Pearson, D.E. Survey of Organic Syntheses Wiley Interscience, New York, 1970. p. 360.
[34] Husstedt, U.; Schafer, H.J. *Tetrahedron Lett.* **1981**, *22*, 623-624.



4 36 37 38 39

Scheme 6-8 : Route to Brominated Pyrenophane **39**

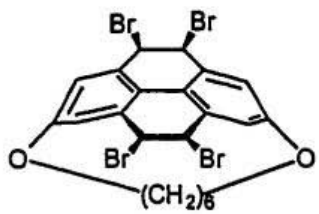
1d or **1b**, failed to generate products that could be observed by tlc analysis. Strained pyrenophanes appeared to resist undergoing simple substitution reactions with brominating agents.

It was therefore decided to concentrate on an alternate route to brominated pyrenophanes. Illustrated in Scheme 6-8, this involved the treatment of a cyclophanediene **4** with bromine, to afford the tetrabromide **36**. Treatment of this with base should yield a mixture of dibromocyclophanedienes such as **37** by elimination of HBr, which after a second sequence of bromine/base, should generate a tetrabromocyclophanediene, which should allow tetrabromopyrenophane **39** by reaction with DDQ. The results of the treatment of 1,8-dioxa-[8.2.2](1,3,5)cyclophane-15,23-diene, **4b**, with a variety of brominating agents by this approach are outlined in the following section.

i) *Br_2/CH_2Cl_2, 0 °C*: Addition of 2 eq. of Br_2 to a solution of cyclophanediene **4b** resulted in instantaneous discoloration of the Br_2 solution and formation of a dark precipitate, which was isolated by filtration. Mass spectral analysis confirmed the addition of at least three bromine atoms to **4b**. This product was sparingly soluble in $CDCl_3$, and ^{1}H NMR spectral data displayed a complex aromatic/alkene

region, and a tether that had been desymmetrized along the long axis of the molecule, but where the geminal protons on each tether carbon appeared to be equivalent. The $CDCl_3$ solution was too dilute for a useful ^{13}C NMR spectrum to be obtained, but the peaks observed in its ^{13}C NMR spectrum obtained definitively ruled out the desired tetrabromide **36** (n=6) as the product obtained. It was therefore elected to pursue less harsh bromination methods.

ii) Br_2/dioxane/CH_2Cl_2, 0 °C: Treatment of **4b** with Br_2/dioxane in CH_2Cl_2 resulted in the immediate formation of a gray precipitate. This was isolated by filtration, but was found to be insoluble in most organic solvents and immobile on tlc. The filtrate was shown to contain a complex mixture of products by tlc, of which the least polar was isolated by column chromatography (~20 % yield). At first glance, the NMR data for this compound suggested it was tetrabromotetrahydropyrenophane **40**, but treatment of this compound with DDQ in toluene at reflux resulted in no reaction, with the starting



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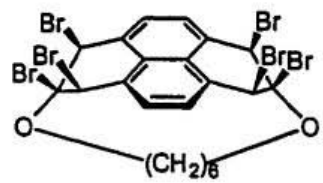
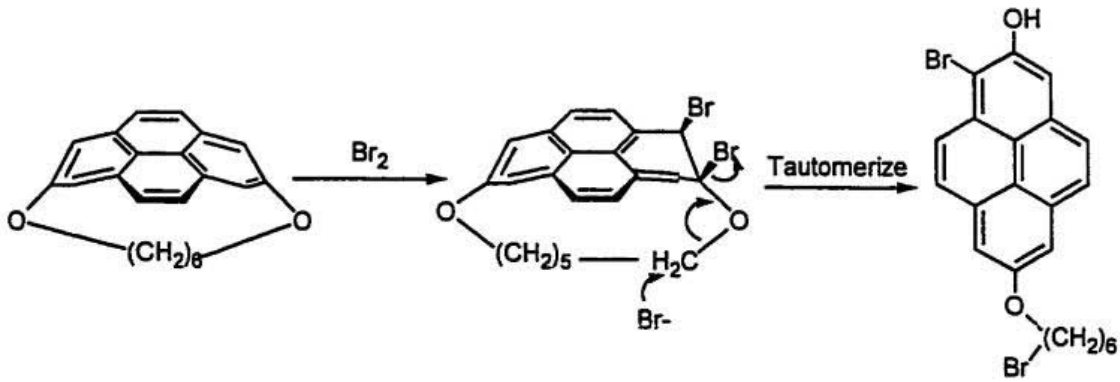


41

material recovered quantitatively. This was perhaps not surprising, as the benzylic Hs in **40** would be sterically very hindered by the tether. Treatment with base (^{t}BuOK/THF) immediately produced intractable, baseline material by tlc. Closer examination of the spectral data of the bromination product led to the proposal of structure **41**, a hexabromohexahydropyrenophane, as being more consistent with the NMR data – particularly the signal at δ 98.9 in the ^{13}C NMR spectrum, which was hard to reconcile with an aryl ring in **40**, but is attributable to the bromohydrin ether carbon in **41**. Unfortunately, the compound proved unstable in the solid state, decomposing to a brown tarry substance before any x-ray crystallographic or elemental composition analysis data could be obtained. These results suggested that oxidation to the pyrenophane seemed to occur in preference to bromine addition to the alkenes, but once the pyrenophane was



1b **42** **43**

Scheme 6-9: Mechanism for Tether Cleavage of **1b** by Br_2

formed, strain-relieving addition reactions did occur. It was then decided to reduce the temperature of the reaction, in the hopes that any pyrenophane generation could be suppressed.

iii) *Br_2/dioxane/CH_2Cl_2, -78 °C*: Once again, addition of the bromine complex resulted in the consumption of the starting material, and the generation of both baseline and mobile spots by tlc. A single product was isolated by chromatography, although again in low yield (19 %, based on product MW =555). Mass spectra indicated the addition of three Br atoms, and the loss of 2 or 3 hydrogens. The ^1H NMR (due to insufficient sample, a ^{13}C spectrum was not obtained) of this product revealed that the aromatic region had been completely desymmetrized (four AB doublets, presumably corresponding to the four protons on the diene bridges). A peak at δ 6.05 suggested a phenolic proton. The tether protons, specifically the two terminal CH_2s (those attached to the O atoms) appeared as simple triplets, showing that the geminal tether protons were magnetically equivalent. Since the aromatic region was clearly desymmetrized, the only way the tether could be symmetrical was if it had cleaved. A plausible mechanism for a bromination of pyrenophane **1b**, with tether cleavage, can be drawn (Scheme 6-8) to yield the brominated hydroxypyrene **43**. This structure corresponds to the proton spectrum obtained. The mass spectral data suggested the product contained *three* bromines, although this most likely corresponds to a minor, tribrominated impurity. Attempts to grow crystals of this compound were unsuccessful, and as with all of the

bromination products described here, it rapidly turned black in the solid state, preventing further structural analysis.

These results implied that many unforeseen reactions competed with – or completely overwhelmed – the desired addition of Br_2 to the alkene units of cyclophanediene **4b**. Although no structures could be rigorously assigned to the mixtures of products obtained from these bromination reactions, it was clear from the NMR spectra that tether cleavage had occurred in most of the major products isolated. Tether cleavage is presumably a secondary reaction of a strained intermediate – perhaps a pyrenophane. The formation of tetrahydropyrenes from metacyclophanes by treatment with bromine was known,[35] and if Br_2 was indeed promoting the formation of pyrenophanes from **4b**, the generation of products like **43** might be expected. If pyrenophanes were generated in this system, a number of other reactions could be envisaged as subsequently occurring. If any electrophilic substitution took place, the HBr produced could induce rearrangements, polymerization, and tether cleavage (see the section on protonation experiments, below, for more on this). As the mechanism in Scheme 6-8 indicates, plausible tether cleavage pathways can be proposed that do not require HBr to be present. The fact that the isolated products never amounted to more than about 20 % of the starting material consumed in the reactions demonstrates the products that were isolated represent only a small fraction of the total amount of products formed. A large amount of the cyclophanediene **4b** was converted to insoluble material for which no structural data whatsoever was obtained.

From all this, it was concluded that the treatment of **4b** with bromine or some other brominating agent probably results in the rapid generation of a pyrenophane, which can subsequently undergo bromine addition, substitution, and/or tether cleavage (or combinations thereof) to yield the complex mixture of products observed. Since this was observed at temperatures as low as -78 ° C, it did not seem practical to attempt these reactions at even lower temperatures, in the hopes that a single product might predominate. Since it was impossible to make any rigorous structural assignment of the products, nothing had really been proven about the reactivity of cyclophanedienes or pyrenophanes. What had been proven was that, in our hands, a variety of mild

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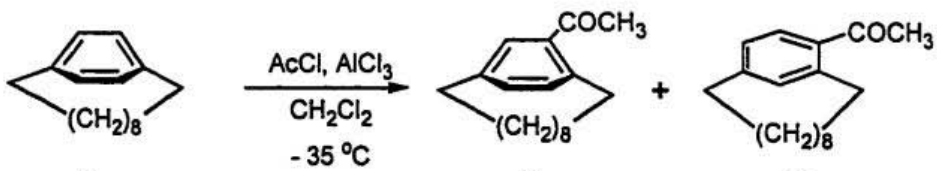
[35] Umemoto, T.; Satani, S.; Sakata, Y.; Misumi, S. *Tetrahedron Lett.* **1975**, 3159-3162.

bromination methods failed to provide any of the desired tetrabromocyclophane **36**. Although only a few of the large arsenal of methodologies available for aromatic halogenation had been utilized, it was decided to explore other methods for the selective functionalization of pyrenophanes.

6.7.3.2 - Friedel Crafts Acylation

Very little research has investigated the Friedel-Crafts acylation of strained aromatic compounds. It has long been known that [2.2]paracyclophane **8** can be acetylated under extremely mild conditions (-35 °C), with rupture of the bridge occurring at higher temperatures. Similar conditions were used in the acetylation of [10]paracyclophane **7c** (Scheme 6-9), affording a mixture of 12-



7c **46** **47**

Scheme 6-10: Friedel-Crafts Acetylation of [10]Paracyclophane

acetyl[10]paracyclophane **46** and the rearranged 12-acetyl[10]metacyclophane **47**. If the minimally strained [10]paracyclophane rearranges under Friedel-Crafts conditions, prospects for the successful functionalization of highly strained pyrenophanes such as **1a** and **2a** using this method seemed bleak. Nevertheless, an attempt was made.

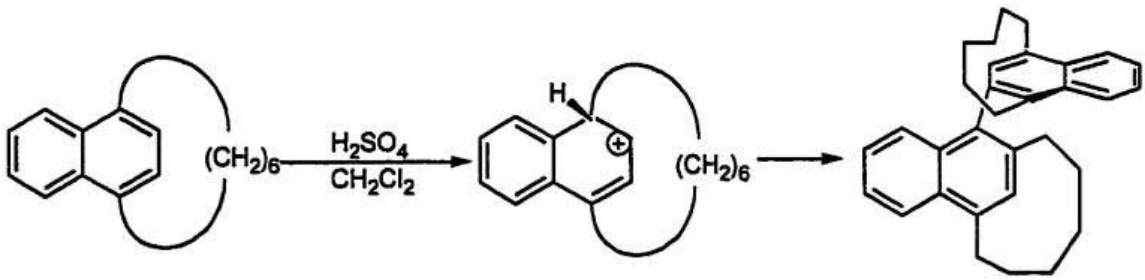
Since the dioxapyrenophane series contained Lewis-basic oxygen atoms that might further complicate their reactivity, it was elected not to attempt any Friedel-Crafts reactions on these compounds. The hydrocarbon pyrenophane [7](2,7)pyrenophane **2a** was selected as the substrate. Treatment of **2a** with acetyl chloride and $AlCl_3$ in CH_2Cl_2 at 0 °C resulted in a deep red solution, which rapidly turned brown. Quenching and extraction isolated a brown oily solid that resulted in an unbroken streak on tlc analysis. No further isolation was attempted.

As a control experiment, the above conditions were reproduced except that the acetyl chloride was left out. This mixture turned blood red, and tlc after five minutes revealed a number of spots clustered around the pyrenophane spot. This meant that the

$AlCl_3$ induced a rapid reaction (possibly the rearrangement of the tether?) in [n](2,7)pyrenophanes. Lewis-Acid induced tether rearrangement was well known in the [n]paracyclophanes,[8,21] so this phenomenon was explored in greater detail in the pyrenophanes.

6.7.3.3 - Reaction with Lewis Acids

To explore the reactivity of pyrenophanes with Lewis acids, and in the hope of perhaps observing a pyrenophane-Lewis acid complex, [7](2,7)pyrenophane **2a** was placed in an NMR tube and dissolved in CD_2Cl_2. $AlCl_3$ was added, and ^1H NMR spectra were acquired at increasing time intervals. What was observed was the gradual disappearance (complete in 2 hours) of the pyrenophane signals, and the appearance of a forest of new signals. The most significant aspect about these new signals is the absence of any significant peaks below δ 0 ppm. This means that the tethers are no longer held in the shielding cone of the aromatic system. Since it is not plausible for dearomatization of the pyrene ring to have occurred, the tether must either have cleaved, or else have rearranged to positions in which it is no longer forced to lie beneath the aromatic rings. Quenching the NMR-tube reaction, followed by tlc analysis, revealed a very complex mixture of spots, as well as an intense baseline spot. No further isolation of products was



18 **45** **44**

Scheme 6-11: Electrophilic Telomerization of Naphthalenophane **18**

attempted. However, mass spectral analysis of the crude product mixture provided an intriguing result. The starting material, **2a**, gives a strong M^+ mass peak at 298. Lewis-acid induced *rearrangement* of the tether, therefore, should still never result in a mass over 298. The crude product shows peaks clustered around 596, which would imply a

dimer of **2a**. This was the first evidence that a process, called telomerization, was occurring, of which there was some literature precedent.

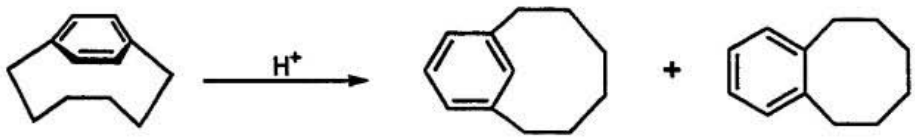
It was well known that treatment of strained cyclophanes, such as [n]paracyclophanes, with Lewis acids resulted in isomerization of the tether to generate less strained isomers. However, dimerization had never been reported until Tobe demonstrated (Scheme 6-10) that treatment of [6](1,4)naphthalenophane **18** and [6](1,4)anthracenophane **22** with acid resulted in dimerization and trimerization to yield structures such as **44**, a dimer of **18**.[36] This was postulated to involve strain-relieving *ipso* protonation of the bridgehead carbon to form an arenium ion **45**, which, after tether rearrangement, acts as an electrophile in a Friedel-Crafts-like reaction with another cyclophane. This tendency to telomerize, while it has been observed, is much less pronounced in simple mononuclear cyclophanes such as [6]paracyclophane.[18] This is believed to stem from the higher HOMO levels present in PAHs and their consequently increased tendency to react with electrophiles.

Once again, the inability to isolate the products of the reaction of **2a** with $AlCl_3$ precluded definitive statements about the chemical processes taking place. However, the presence of signals corresponding to "dimer-sized" molecules in the mass spectrum of the crude product strongly suggests that, as with the linear acene series of cyclophanes, pyrenophanes were undergoing telomerization reactions under Lewis acidic conditions.

6.7.3.4 - Protonation

Having observed considerable reactivity of the pyrenophanes under Lewis acidic conditions, it was decided to investigate the behavior of pyrenophanes when treated with Brønsted-Lowry acids. It was well documented that, when treated with CF_3CO_2H, [6]paracyclophane isomerized to a mixture of [6]meta- **48** and [6]orthocyclophane **49**. When a stronger acid, such as triflic acid, was used, only [6]orthocyclophane **49** was obtained (Scheme 6-12). The previous section described the telomerization observed when PAH cyclophanes were treated with catalytic amounts of H_2SO_4. Furthermore, one of Tobe's papers[34] described computational work (MNDO/PM3) on the proton affinity of

[36] a)Tobe, Y.; Jimbo, M.; Kobiro, K.; Kakiuchi, K. *J. Org. Chem.* **1991**, *56*, 5241-5243. b) Tobe, Y.; Takemura, A.; Jimbo,. M.; Takahashi, T.; Kobiro, K.; Kakiuchi, K. *J. Am. Chem. Soc.* **1992**, *114*, 3479-3491.

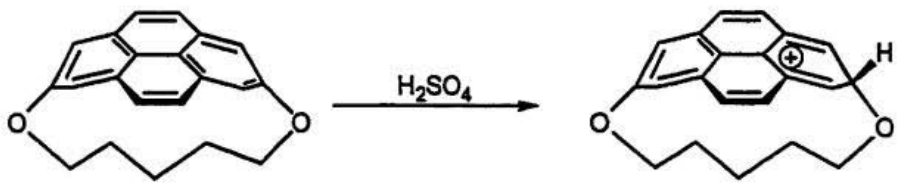


7a **48** **49**

Scheme 6-12: Acid-Catalyzed Rearrangement of [6]Paracyclophane

the *ipso* carbons of paracyclophane **7a** and PAH cyclophanes **18** and **22**. These calculations suggested that the PAH cyclophanes are more strained, and therefore possess a higher proton affinity, than simple paracyclophanes. It was decided to investigate the chemistry of pyrenophanes under strongly acidic conditions using NMR spectroscopy.

It was observed that the treatment of dioxapyrenophane **1a** or pyrenophane **2a** with concentrated sulfuric acid led to the immediate generation of an intense blood-red color, presumably indicating the presence of a protonated pyrenophane species. An immediate quench with water, followed by extraction, allows the recovery of the starting pyrenophane. If, as all preceeding research appears to imply, the Lewis basic centers in cyclophanes are the *ipso* carbons, this protonated intermediate must have the structure **50** (Scheme 6-12). An attempt to confirm this by ^{1}H NMR spectroscopy was foiled by the apparent insolubility of this species in the SO_2/D_2SO_4 solvent used to acquire the spectra. The structure of the postulated protonation product could therefore not be ascertained. In any event, the red color faded to black in about 10 minutes at room temperature, and an intractable black tarry substance was deposited.

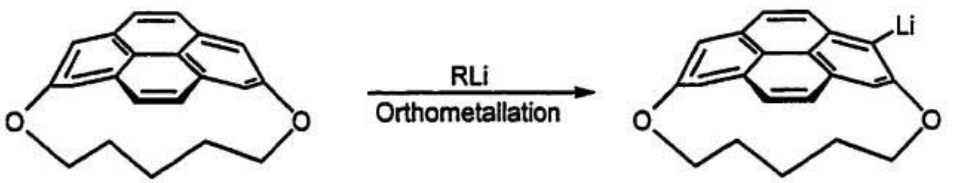


1a **50**

Scheme 6-13: Possible Structure of Protonated Pyrenophane **1a**

6.7.4 - Reactions with Organometallic Compounds

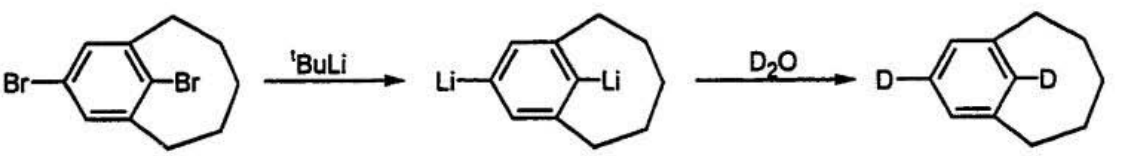
Our attempts to generate reliably functionalized pyrenophanes using various electrophilic/Lewis acidic reagents having failed, attention was now turned to using basic reagents to activate pyrenophane C-H bonds. Specifically, it was hoped to use the oxygens in dioxa[n]pyrenophanes as directing groups in a directed orthometalation reaction (Scheme 6-14),[37] to generate metalated pyrenophane **51**, which could subsequently be quenched with some electrophile. There was little precedent in the literature for such a transformation. In fact, the chemistry of cyclophanes under basic



1a **51**

Scheme 6-14: Directed Orthometallation of Pyrenophane **1a**

conditions appears to have received far less attention than electrophilic cyclophane chemistry. Most of the reported work examined the reaction of bases with metacyclophanes,[22,38] in some cases causing tether cleavage or rearrangement, but in several instances successfully achieving a halogen-metal exchange (e.g. **52** to **53**, Scheme 6-15) to generate lithiated [5]metacyclophanes such as **53**. The successful metalation of highly strained cyclophanes made us hopeful that a directed orthometalation of



52 **53** **54**

Scheme 6-15: Metalation of Strained Metacyclophane **52**

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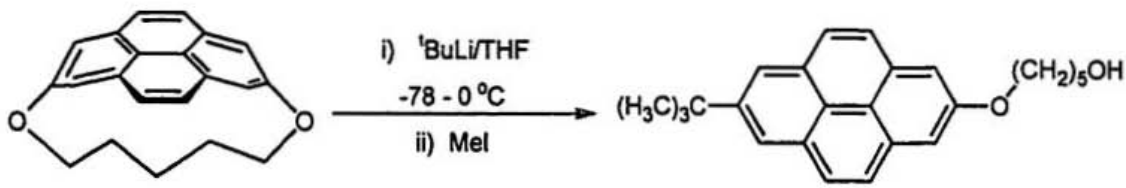
[37] a) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879-933. b) Snieckus, V. *Pure Appl. Chem.* **1990**, *62*, 2047-2056.
[38] Jenneskens, L.W.; de Boer, H.J.R.; de Wolf, W.H.; Bickelhaupt. F. *J. Am. Chem. Soc.* **1990**, *112*, 8941-8949.

pyrenophanes might be feasible.

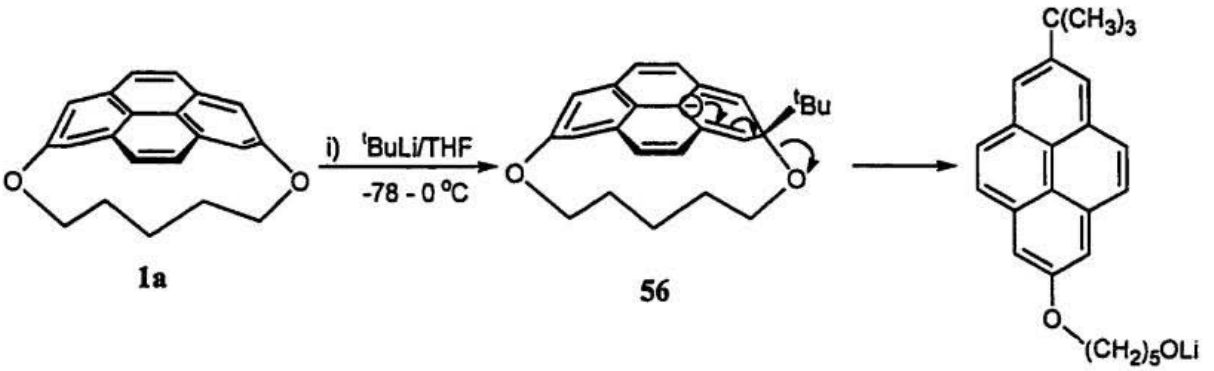
The first experiment in this area involved the treatment of 1,7-dioxa[7](2,7)pyrenophane **1a** with *n*-butyllithium in THF at -78 °C, followed by a quench with CH_3I. This base was not expected to be reactive enough to effect transmetalation, and as expected, the starting material was recovered quantitatively. This experiment was conducted to ensure that no unforeseen, base-induced reactions might be competing with



1a **55a**

Scheme 6-16: Product of Reaction of Pyrenophane **1a** with ^{t}BuLi

orthometalation. A similar reaction, with tetramethylethylenediamine (TMEDA) as an additive to increase the basicity of the *n*-BuLi, also resulted in the recovery of the starting material. However, replacement of the *n*-BuLi with *t*-BuLi resulted in the formation of a deep red-orange solution, which faded on the addition of excess CH_3I. Tlc revealed the formation of a relatively polar product, which was isolated by column chromatography. NMR and mass spectral data revealed this product to be the tether-cleaved alcohol **55a**. Presumably, this product is produced in an S_NAr mechanism via the "Meisenheimer-like" intermediate **56**, followed by ring cleavage to generate alkoxide **57**. One puzzle is why the lithium alkoxide **57** was not methylated in the presence of methyl iodide. Most likely, **57** is a "tight ion pair," which alkylates very slowly in THF. The addition of a tight ion pair disruptor, such as TBAI, might have resulted in the formation of the methyl ether of **55a**, but this experiment was not attempted.



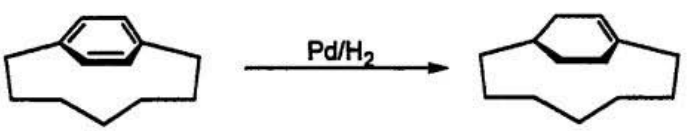
1a **56** **57**

Scheme 6-17: Mechanism of Ring-opening by ^{t}BuLi

An analogous result was obtained for the homologous pyrenophane **1b**, generating the homologous alcohol **55b**. With the longer tether of **1c**, the development of a reddish color was observed, but the starting material was recovered nearly quantitatively after the CH_3I quench. No tether-cleaved alcohol was isolated. From this it was concluded that this tether cleavage reaction is a result of strain relief.

6.7.5 - Hydrogenation

A final aspect of pyrenophane chemistry that was investigated was its behavior under hydrogenation conditions. Both paracyclophanes[39] and metacyclophanes[22] had been observed to rapidly take up hydrogen under mild conditions to form hyperstable,



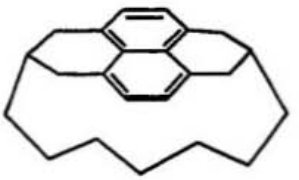
7d **58**

Scheme 6-18: Hydrogenation of Paracyclophane

nonaromatic olefins such as **58** (Scheme 6-17). The susceptibility of pyrenophane **2a** to hydrogenation was studied by placing it under 1 atm H_2 in the presence of Pearlman's catalyst. This resulted in the uptake of hydrogen and the disappearance of the fluorescent

[39] Li, Z-H.; Jones Jr., M. *Tetrahedron Lett.* **1978**, *28*, 753-754.

pyrenophane spot on tlc anaylsis. Work-up and chromatography resulted in the isolation of a single spot (by tlc) which turned out (by ^{1}H NMR) to be a mixture of products. However, a spectrum corresponding to a symmetrical major product could be discerned in the ^{1}H and ^{13}C NMR spectrum, and the structure **59** has been tentatively assigned to this major product on the basis of MS and NMR evidence. The identity of the minor product, which appears to be far less symmetrical, has not been determined.



59

6.8 - Collaborative Work

The unusual structural characteristics and chemical properties of the pyrenophanes make them of considerable interest to chemists with a very diverse range of scientific specialities. One of the most satisfying aspects of this project was the number of collaborative ventures it has spawned, many in areas of chemistry that are far removed from organic synthesis. Such multidisciplinary work ensures that the pyrenophanes presented here do not remain simple lab curiosities but allows them to serve as useful tools in the examination of questions in other areas of science. Although a detailed description of all these projects is far beyond the scope of this thesis, a brief description of a few of these collaborative projects will be presented.

i) *HOMA Analysis of Pyrenophane Structure* - In Chapter 1, the concept of the Harmonic Oscillator Model of Aromaticity (HOMA) index was described,[40] which quantifies the aromaticity of a ring or rings by measuring the extent of variation of the bond lengths (geometric index GEO) and the deviation of the

[40] a) Kruszewski, J.; Krygowski, T.M. *Tetrahedron Lett.* **1972**, *36*, 3839-3842. b) Krygowski, T.M.; Cyranski, M. *Tetrahedron* **1996**, *52*, 1713-1722.

bond lengths from an ideal value (energetic index EN). This index has been developed by Krygowski and co-workers at the University of Warsaw, and his group are now analyzing the crystallographic data of the pyrenophanes to determine the effect that nonplanar distortions have on the "aromaticity" (as defined by the HOMA model, see Chapter 1) of PAHs. At the time of writing, these studies are reportedly at an advanced stage, and have demonstrated that very little loss of aromaticity (as measured by HOMA) is observed as the pyrene moiety becomes more distorted. When published, these will provide a quantitative answer to the question of "how aromatic are the pyrenophanes?"[41]

ii) *Functionalization of Pyrenophane Organometallic π-Complexes* – One aspect of aromatic chemistry that was not pursued in our research program was the coordination chemistry of the aromatic system. It has long been known that transition metal complexes of the π-system of aromatic molecules like benzene can be prepared. Such complexes often display reactivity not observed in the free aromatic molecule itself. Prof. Abd-El-Aziz at the University of Winnipeg has developed methodologies for the functionalization of arenes coordinated to an $FeCp^+$ moiety.[42] He has been provided with samples of pyrenophane **2a** and **2b** to allow him to attempt to prepare metal complexes and subject them to his methodologies. It will be interesting to see if a pyrenophane-$FeCp^+$ complex might be more amenable to functionalization than the pyrenophane itself. This work has just been initiated, so no results, positive or otherwise, have been reported yet.

iii) *Spectroscopic Examination of Pyrenophane Radical Anions* – Prof. F. Gerson, of the Universitat Basel, has specialized in the study of the radical ions of organic molecules using electron spin resonance spectroscopy (ESR).[43] ESR is a technique in which unpaired electrons in a molecule, in the presence of a

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[41] At least, if you accept the validity of the HOMA model of aromaticity. See Chapter 1 for a full discussion.

[42] For examples of Prof. Abd-El-Aziz' work, see: a) Abd-El-Aziz, Schriemer, D.C.; de Denus, C.R; A.S. *Organometallics* **1994**, *13*, 374-384. b) Abd-El-Aziz, A.S.; Epp, K.M.; de Denus, C.R; Fisher-Smith, G. *Organometallics* **1994**, *13*, 2299-2308.

[43] Recent papers include: a) Gerson, F.; Lamprecht, A.; Scholz, M.; Troxler, H.; Lenoir, D. *Helv. Chim. Acta* **1996**, *79*, 307-318. b) Bachmann, R.; Gerson, F.; Merstetter, P; Vogel, E. *Helv. Chim. Acta* **1996**, *79*, 1627-1634.

magnetic field, resonate at a specific frequency.[44] Because they can interact with nuclear magnetic dipoles (e.g. ^1H) the electron resonance displays splittings that reflect the position and the intensity of electron spin in the molecule. From this, information about the geometry and the extent of delocalization of the radical anion can be obtained. Prof. Gerson's group has conducted ESR and ENDOR (electron-nuclear double resonance, in which the nuclei are also irradiated) studies of **1b** reduced with potassium, and have thereby deduced structural information about the radical anion of **1b**, **1b**$^{\cdot-}$. The replacement of H with D in a radical anion alters the ESR spectrum and confirms the assignment of various coupling constants. To assist Prof. Gerson in his assignment of the ESR coupling constants of **1b**$^{\cdot-}$, the synthesis of deuterated derivatives of **1** is being undertaken in our laboratories.

iv) *Spectroscopic Examination of Pyrenophane-Muonium Radicals*– Interest in the electrochemical properties of the fullerenes has sparked considerable research into the structure and properties of reduced fullerene species and fullerene radicals, as was briefly discussed above in the section on cyclic voltammetry. The analogous examination of fullerene fragments allows their comparison to fullerenes themselves. A novel method for the study of organic radical species involves bombarding the compound with a beam of muonium, a "novel atom" consisting of an electron and a muon (Mu), a positively charged subatomic particle with a weight one ninth that of hydrogen. This bombardment generates a muonated radical species (imagine adding H$^{\cdot}$ to a molecule, except Mu$^{\cdot}$ is added). The muonated species can then be studied by an assortment of novel spectroscopic methods. The TRIUMF accelerator facility at Simon Fraser University is one of the only places in the world where such muon research can be carried out, and Prof. P. Percival has conducted investigations of muonium-C_{60} and other fullerene adducts there.[45] To complement this research, he has been provided with samples

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[44] Ebsworth, E.A.V.; Rankin, D.W.H.; Cradock, S. *Structural Methods in Inorganic Chemistry* Blackwell Scientific Publications, Oxford, 1987, pp 105-119.

[45] a) Percival, P.W.; Wlodek, S. *Chem. Phys. Lett.* 1992, *196*, 317-320. b) Percival, P.W.; Addison-Jones, B.; Brodovitch, J.-C.; Ji, F.; Horoyski, P.J.; Thewalt, M.L.W.; Anthony, T.R. *Chem. Phys. Lett.* 1995, *245*, 90-94.

of **1a** and **1b** on which to perform analogous experiments. At the time of writing, results from this research are still being analyzed.

The brief descriptions of these collaborative efforts provided here are not intended to provide even a basic introduction to the science involved. They are simply included to demonstrate that even interest-driven basic science, which was what initially inspired us to attempt the synthesis of the pyrenophanes, can ultimately result in practical applications in totally unrelated fields. The above paragraphs describe the interaction of synthetic organic chemistry with theoretical chemistry, organometallic chemistry, and even particle physics. Through such multidisciplinary endeavors, our work allows others to pursue research in their own fields and, in return, potentially new directions for synthetic work are provided. Hopefully, these and other collaborative ventures will result in the identification of other novel properties and uses for the pyrenophanes long into the future.

6.9 - Conclusions

This chapter has described studies of the spectroscopic and chemical properties of the pyrenophanes whose synthesis was described in Chapter 5. This is, to our knowledge, the first systematic study of the effects of increasing nonplanar distortion on a polycyclic aromatic hydrocarbon. This allowed the identification of trends in, for example, NMR chemical shifts, UV absorption bands, and redox potentials, as the pyrene unit became more distorted. Consideration of the question of the aromaticity of these compounds was also possible. Magnetically, the extremely high shifts of the tether protons confirms the presence of a strong ring current, and crystallography revealed that the bond lengths of the pyrene moieties were little affected by distortion. Preliminary HOMA analysis also suggests little loss of aromaticity as the pyrenes become more bent. So geometrically and magnetically, the nonplanar distortion appears to have had little influence on aromaticity. Chemically, however, the behavior of the pyrenophanes was very different from what would be expected of a "normal" aromatic compound. Like [n]paracyclophanes, they were extremely reactive, undergoing addition reactions easily, and resisting attempts at functionalization, which generally resulted in tether cleavage.

Chemically, therefore, the pyrenophanes were not very aromatic. This enhanced reactivity also resulted in the failure of attempts to add five membered rings onto the pyrenophane moiety, and thereby generate true buckybowls.

As fullerene fragments, it was of interest to compare the properties of the pyrenophanes to those of D_{5h} C_{70} buckminsterfullerene, **6b**. The differences between the two classes of compounds were pronounced. Although the bend along the long axis of the pyrenophane **1a** was greater than that expected in the fullerene **6b**, the ability of the pyrenophane to assume a saddle-shaped conformation reduced the pyramidalization of the aromatic carbons, which is probably a more accurate measurement of the strain present in the molecule. The absence of five-membered rings probably results in marked differences in the chemistry of **1a** and **6b**; for example, **1a** displays little of the redox chemistry observed in **6b**. The structural relationship between **1a** and **6b** is, therefore, perhaps not as close as was first hoped. **1** and **2** might be best considered as comparison compounds for fullerenes, which demonstrate the effects of the *absence* of 5-membered rings in curved aromatic compounds.

Numerous avenues of pyrenophane research remain to be explored. For synthetic chemists, although the attempts described here were all failures, effective methodologies for the functionalization of the pyrenophanes might still merit exploration. For theoretical chemists, reproducing and rationalizing the experimental data presented here will test the ability of computational chemistry to accurately model curved aromatic systems. Finally, the application of pyrenophanes to the study of problems in other areas of chemistry will hopefully continue. All this makes it likely that the study of these fascinating molecules will continue for many years.

6.10 - Experimental

Experimental details are identical with those outlined in Chapter 5. Selected NMR spectra from this Chapter are reproduced in Appendix D.

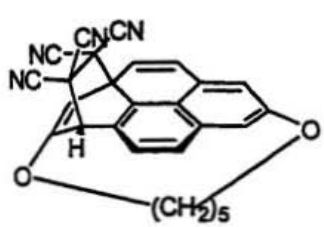
Diels-Alder Reaction: 1a + PTAD: Pyrenophane **1a** (0.024 g, 0.078 mmol) was dissolved in benzene (6 mL). PTAD (0.016 g, 0.089 mmol) was added. This was stirred at room temperature for 1 h, after which the red color had completely faded and a white

precipitate had formed. Tlc revealed unreacted **1a** was still present, so more PTAD (0.023 g, 0.13 mmol) was dissolved in benzene (5 mL) and added. After 2 h, starting material had disappeared by tlc, so the mixture was filtered and the solid colorless residue (0.043 g) was washed with pentane. Attempts to purify this sparingly soluble compound by column chromatography resulted in apparent decomposition, as the silica turned yellow and no products were eluted.

Diels-Alder Reaction: 1b + PTAD: This reaction was performed analogously to that described above, using **1b** (0.029 g, 0.092 mmol) and PTAD (0.043 g, 0.25 mmol) affording a white solid (0.062 g). Attempts to crystallize this product from CH_2Cl_2, $CHCl_3$, CCl_4, xylenes, and DMSO all failed.

Attempted Diels-Alder Reaction: 1a + *N*-Phenylmaleimide: Pyrenophane **1a** (0.020 g, 0.066 mmol) was dissolved in xylenes (5 mL) and NPM (0.012 g, 0.069 mmol) dissolved in xylenes (2 mL) was added. This was stirred at room temperature for 2 h, then refluxed for 24 h. A brown precipitate had formed, which was isolated by filtration. This solid (3.0 mg) turned out to be intractable. The filtrate contained unreacted **1a** and *N*-phenylmaleimide.

Diels-Alder Reaction: 1b + N-Phenylmaleimide: 1b (0.087 g, 0.28 mmol) was dissolved in toluene (15 mL), and N-phenylmaleimide (0.048 g, 0.28 mmol) dissolved in toluene (5 mL) was added dropwise. The reaction was stirred at room temperature for 1 h, then refluxed for 12 h under N_2. No reaction was discernable by tlc in either case.

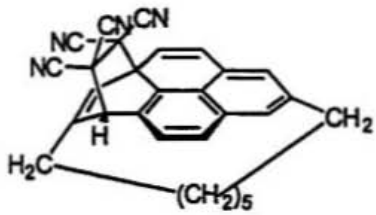


28

Diels-Alder Reaction: Pyrenophane 1a + TCNE: Adduct 28: Pyrenophane **1a** (15 mg, 0.050 mmol) was dissolved in benzene (5 mL), and TCNE (22.5 mg, 0.176 mmol) in benzene (2 mL) were mixed and stirred overnight at room temperature. The reaction mixture was then concentrated under reduced pressure. Column chromatography in neat CH_2Cl_2 to yield a white crystalline solid, **28** (22 mg, ~100 %).

28: mp 160 °C (dec.); ^{1}H NMR: δ 7.66 (d, *J*=8.8, 1H), 7.53 (d, *J*=8.6, 1H), 7.32 (d, *J*=1.9, 1H), 7.22 (d, *J*= 9.9, 1H), 7.07 (d, *J*=1.9, 1H), 6.67 (d, *J*=9.9, 1H), 5.04 (d, *J*=1.9, 1H), 4.26 (dd, *J*=12.2, 6.8, 1H), 4.17 (d, *J*=1.9, 1H), 3.85 (ddd, *J*=12.8, 7.1, 1.8, 1H), 3.60-3.53 (m, 2H), 1.14-1.02 (m, 1H), 0.96-0.72 (m, 2H), 0.20-0.00 (m, 2H), -1.69 - -1.78 (m, 1H); ^{13}C NMR: (some quaternary carbons not observed) δ 171.5 (0), 156.6 (0), 147.5 (0), 136.6 (0), 132.9 (1), 132.7 (0), 129.9 (0), 127.3 (1), 127.2 (1), 126.3 (0), 124.8 (1), 123.5 (1), 121.6 (1), 111.4 (0), 111.3 (0), 111.2 (0), 111.0 (0), 106.6 (1), 76.3 (2), 71.9 (2), 54.0 (1), 32.6 (2), 30.2 (2), 28.2 (2); EI-MS *m/z* (%) 430 (7, M^+), 303 (15), 302 (71), 234 (26), 218 (15), 216 (13), 206 (35), 205 (45), 189 (28), 188 (69), 187 (23), 176 (53), 128 (100), 94 (31), 76 (74), 69 (41); good analytical data for this compound could not be obtained.

Attempted Diels-Alder Reaction: Pyrenophane 1b + TCNE. This reaction was carried out analogously to the one above, with **1b** (0.027 g, 0.086 mmol) and TCNE (0.0220 g, 0.17 mmol) in benzene (15 mL). After 24 h at room temperature and 48 h at reflux, no product could be observed by tlc and starting material could be recovered quantitatively.



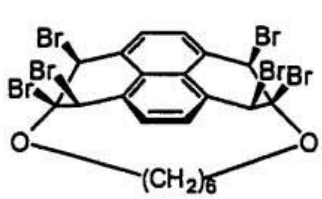
29

Diels-Alder Reaction: Pyrenophane 2a + TCNE: Adduct 29. This reaction was carried out analogously to the one above, with **2a** (0.130 g, 0.436 mmol) and TCNE (0.056 g, 0.43 mmol) in benzene (20 mL) which was stirred for 1 h. Cooling the reaction in a water bath resulted in the formation of colorless crystals which were isolated by filtration (0.041 g, 0.097 mmol, 22 %). Concentration of the filtrate afforded more product (0.10 g, 0.24 mmol, 55 %) for a total yield of 77 %. NMR and X-ray crystallographic analysis proved the product to have the structure **29**.

29: mp: 110 °C (dec., benzene); ^{1}H NMR: δ 7.69 (d, *J*=8.5, 1H), 7.59 (s, 1H), 7.49 (d, *J*=8.4, 1H), 7.28 (d, *J*=9.9, 1H), 7.15 (s, 1H), 6.70 (d, *J*=9.9, 2H), 5.99 (s, 1H), 4.43 (s, 1H), 3.11-3.04 (m, 1H), 2.39-2.23 (m, 2H), 1.94-1.72 (m, 2H), 1.09-0.80 (m, 2H), 0.42-

0.28 (m, 1H), 0.20-0.00 (m, 1H), -0.29 - -0.36 (m, 1H), -0.48 - -0.62 (m, 1H), -0.86 - -0.96 (m, 2H), -1.37 - -1.43 (m, 2H); ^{13}C NMR δ (decomposition apparent) 153.3, 141.5, 135.1, 133.9, 130.3, 130.1, 128.0, 124.6, 122.8, 120.3, 111.8, 54.6, 53.7, 35.3, 34.8, 31.6, 30.6, 26.3, 24.5.

Cyclophanediene 4b + Br_2. Compound **4b** (0.0534 g, 0.17 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0°C. To this was added a solution of Br_2 in CH_2Cl_2 (5.1 mL, 0.075 mol/L, 0.37 mmol) dropwise. The Br_2 was instantly decolorized as it was added, and a dark precipitate was formed. The reaction was filtered to isolate a gray solid that was only marginally soluble in CH_2Cl_2. Treatment of this solid (or the residue from the filtrate) with ^{t}BuOK (0.080 g, 0.71 mmol) resulted in a complex mixture of products by tlc. No purification was attempted.



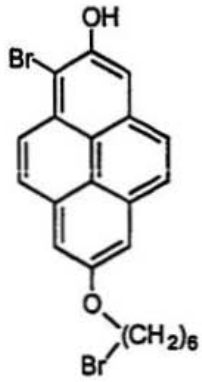
41

Cyclophanediene 4b + Br_2/dioxane: Compound **4b** (0.150 g, 0.47 mmol) was dissolved in CH_2Cl_2 (20 mL) and cooled to 0 °C. Br_2·dioxane complex (0.250 g, 1.03 mmol) was added and a gray precipitate formed instantly. Filtration afforded a brown solid (0.045 g), and a filtrate which was concentrated to afford an oily brown solid consisting of a number of mobile spots on tlc. Column chromatography allowed the isolation of a colorless, crystalline solid (0.060 g, 20 %) to which has been tentatively assigned the structure **41**.

Treatment of **41** (0.030 g, 0.05 mmol) with DDQ (0.023 g, 0.10 mmol) in refluxing toluene (5 mL) for 12 h resulted in no reaction. The starting material was recovered nearly quantitatively (0.029 g). Treatment of **41** with ^{t}BuOK (0.070 g, 0.6 mmol) in THF (20 mL) resulted in only baseline material by tlc.

41: mp 190 °C (dec., CH_2Cl_2); ^{1}H NMR: δ 7.63 (s, 4H), 5.48 (s, 4H), 3.38 (t, *J*=5.0, 4H), 1.10-1.06 (m, 4H), - 0.02 – -0.06 (m, 4H); ^{13}C NMR δ 134.3, 128.5, 125.9, 98.9, 65.6, 51.0, 29.2, 24.4; EI-MS *m/z* (%) 316 (11), 234 (14), 206 (19), 205 (18), 188 (18), 176 (19), 82 (99), 81 (46), 80 (100).

Cyclophanediene 4b + Br_2/dioxane, -78 °C. Cyclophanediene **4b** (0.059 g, 0.19 mmol) was dissolved in CH_2Cl_2 (10 mL) and cooled to -78 °C. Br_2/dioxane (0.046 g, 0.19 mmol) was dissolved in CH_2Cl_2 (10 mL) and added to the cooled solution dropwise. A solution of 5% aqueous $Na_2S_2O_3$ (10 mL) was added, and the solution was allowed to warm to room temperature. The organic layer was washed with brine, dried ($MgSO_4$), filtered and concentrated. Tlc analysis indicated the presence of at least one mobile spot and a strong baseline spot. Column chromatography of the residue (40 % CH_2Cl_2/60-80 petroleum ether) afforded an unstable brown film (20 mg) whose ^1H NMR suggests structure **43**.



43

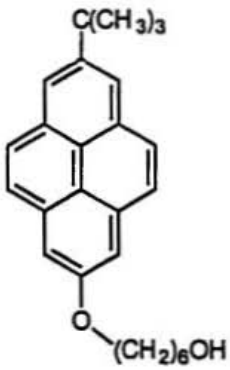
43: mp 92-94 °C (CH_2Cl_2); ^1H NMR: δ 8.28 (d, *J*=9.2, 1H), 8.08 (d, *J*=9.2, 1H), 7.96 (d, *J*=9.0, 1H), 7.90 (d, *J*=9.0, 1H), 7.80 (s, 1H), 7.72 (s, 2H), 6.05 (s, 1H), 4.25 (t, *J*=6.4, 2H), 3.46 (t, *J*=6.8, 2H), 1.99-1.91 (m, 4H), 1.62-1.56 (m, 4H); EI-MS *m/z* (%) 556 (9), 478 (43, M^+), 476 (84, M^+), 474 (40, M^+), 314 (98), 312 (100), 234 (46), 205 (36), 176 (28).

55a

7-*Tert*-butyl-2-(6-hydroxy-1-oxahexyl)pyrene, 55a: Pyrenophane **1a** (0.025 g, 0.083 mmol) was dissolved in dry THF (20 mL) and cooled to - 78 °C under N_2. ^{t}BuLi (0.2 mL, 0.2 mmol) was then added and the reaction was stirred at - 78 °C under N_2 for 1 h. dry CH_3I (1 mL) was added and the reaction was allowed to warm to room temperature. It was then quenched with H_2O (1 mL), extracted into CH_2Cl_2 (2 x 25 mL), which was washed with brine (25 mL), dried ($MgSO_4$), filtered, and concentrated under reduced pressure. Column chromatography (CH_2Cl_2) afforded 15 mg (51 %) of **55a** as a brownish solid.

55a: mp 108-112 °C (CH_2Cl_2); IR ($CHCl_3$) 3620 (w), 2960 (s), 2890 (m), 1615 (s), 1455 (s), 1305 (s); ^1H NMR: δ 8.18 (s, 2H), 8.02 (d, *J*=9.0, 2H), 7.94 (d, *J*=9.0, 2H), 7.67 (s,

2H), 4.25 (t, *J*=6.2, 2H), 3.73-3.69 (m, 2H), 1.98-1.93 (m, 2H), 1.73-1.65 (m, 4H), 1.57 (s, 9H); ^{13}C NMR δ 157.0, 147.9, 132.4, 130.0, 128.2, 126.7, 122.9, 122.4, 120.0, 110.7, 68.2, 62.9, 35.1, 32.5, 31.9, 29.2, 22.5; EI-MS *m/z* (%) 361 (27), 360 (93, M^+), 345 (35), 274 (61), 259 (100), 231 (29), 189 (32).



55b

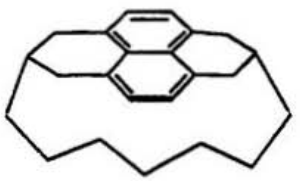
7-*Tert*-butyl-2-(7-hydroxy-1-oxaheptyl)pyrene, 55b: Prepared analogously to **55a**, above, using pyrenophane **1b** (0.040 g, 0.17 mmol) and ^{t}BuLi (0.2 mL, 0.2 mmol), and yielding **55b** (0.055 g, 94 %) as a brownish solid.

55b: mp 95-97 °C (CH_2Cl_2); ^{1}H NMR: δ 8.18 (s, 2H), 8.02 (d, *J*=9.0, 2H), 7.95 (d, *J*=9.0, 2H), 7.67 (s, 2H), 4.25 (t, *J*=6.5, 2H), 3.71-3.67 (m, 2H), 1.95-1.91 (m, 2H), 1.67-1.50 (m, 6H), 1.57 (s, 9H); ^{13}C NMR δ 157.1, 147.9, 132.4, 130.0, 128.1, 127.8, 126.7, 125.4, 122.9, 122.4, 120.0, 110.7, 68.3, 63.0, 35.1, 32.7, 32.0, 29.7, 29.4, 26.0, 25.6; EI-MS *m/z* (%) 375 (29), 374 (100, M^+), 359 (26), 274 (57), 259 (95), 245 (33), 231 (43), 219 (29), 218 (45), 189 (41). Anal. Calc'd for $C_{26}H_{30}O_2$: C, 83.38; H, 8.07. Found: C, 83.07; H, 8.08.

Attempted Friedel-Crafts Acylation, 2a + AcCl: $AlCl_3$ (0.190 g, 1.42 mmol) was dissolved in CH_2Cl_2 (50 mL). This was cooled to 0 °C and acetyl chloride (0.08 mL, 0.09 g, 1 mmol) was added by syringe. Pyrenophane **2a** (0.25 g, 0.84 mmol) was dissolved in CH_2Cl_2 (4 mL) and added dropwise. The colorless solution turned blood red. After 10 min, the reaction had turned brown. It was then quenched with aqueous 20 % HCl (50 mL) and stirred for 12 h. The organic layer was washed with aqueous saturated $NaHCO_3$ (50 mL) and brine (40 mL), dried ($MgSO_4$), filtered, and concentrated to afford a yellow-brown oil. This was an extremely complex mixture of products from which no pure compoud was isolated by chromatography (25% ethyl acetate/hexanes).

Protonation Experiment. Pyrenophane **1b** (0.010 g) was dissolved in SO_2 (with 1 drop CH_2Cl_2 for a lock signal) at -78 °C in an NMR tube. After acquiring a ^{1}H NMR spectrum, D_2SO_4 (0.1 mL) was added and the solution was mixed, generating a deep red

liquid. Acquisition of a ^{1}H NMR spectrum resulted in very little signal (receiver gain went very high), presumably due to the species of interest having precipitated out.



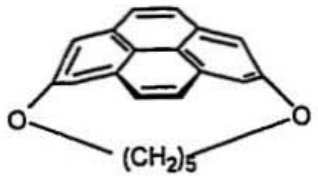
59

Hydrogenation of 2a: Pyrenophane **2a** (0.146 g, 0.490 mmol) was dissolved in ethyl acetate (20 mL) and Pearlman's catalyst (0.025 g) was added. This was stirred under 1 atm. H_2 for 6 h, then filtered through Celite and concentrated under reduced pressure. Chromatography of the residue (10 % CH_2Cl_2/hexanes) afforded a colorless oil (0.122 g) that consisted of an inseparable mixture of major and a minor product. The major product appears to have the structure **59**. The identity of the minor product is unknown.

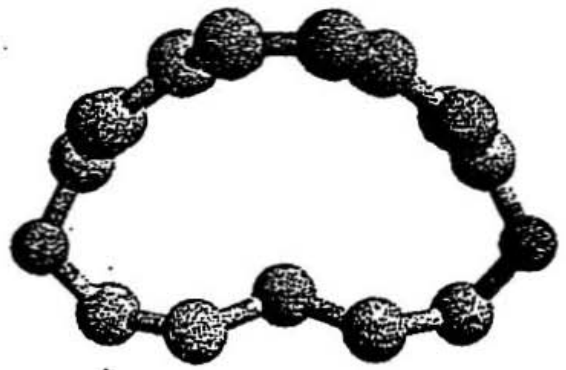
59: ^{1}H NMR: δ (obvious peaks only) 7.08 (s), 3.34 (dd, *J*=14.4, 3.5), 2.81 (dd, *J*=14.7, 1.8); ^{13}C NMR δ (obvious peaks only) 130.7, 124.7, 122.5, 34.5, 28.0, 27.8, 25.7, 24.6, 21.8; EI-MS *m/z* (%) 304 (100, M^+), 178 (37).

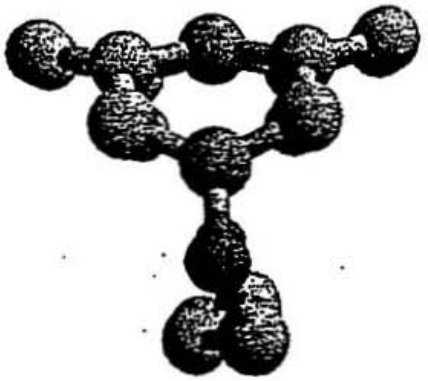
Appendix A – X-Ray Crystal Structures of Selected Compounds

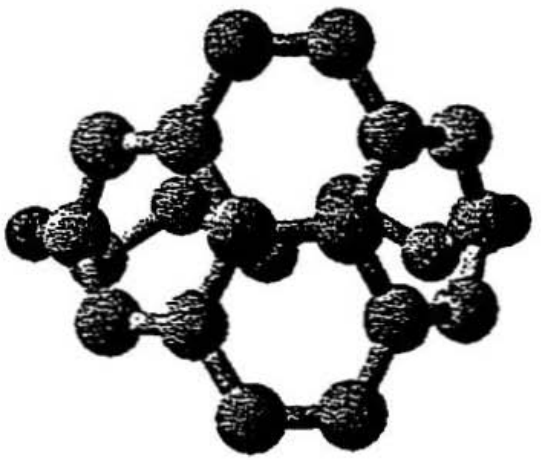
(Compounds as numbered in Chapter 6)

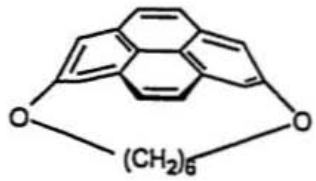


1,7-Dioxa[7](2,7)pyrenopha

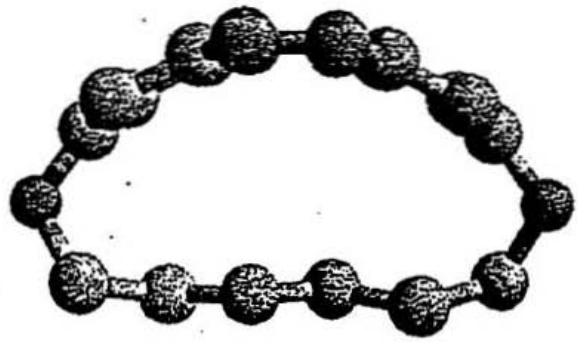


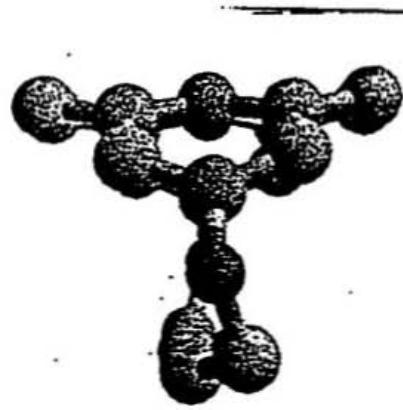


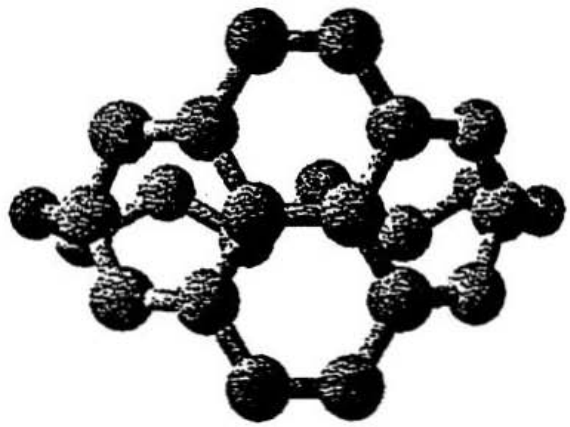


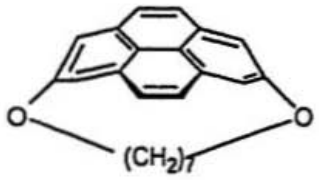


1,8-Dioxa[8](2,7)pyrenophane, 1b

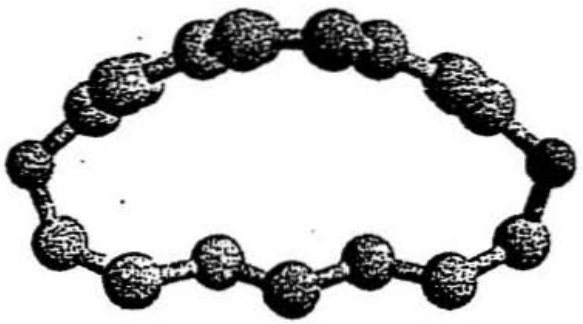


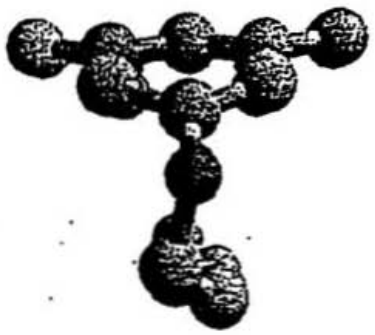


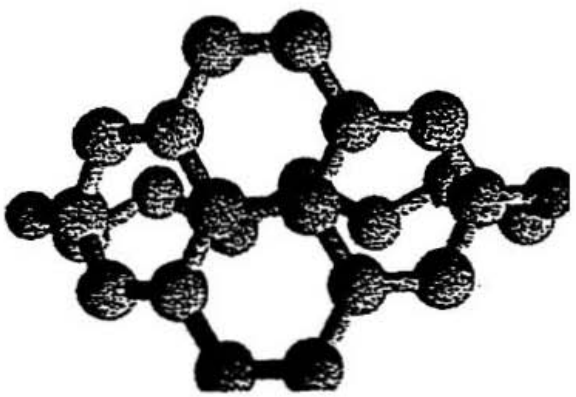


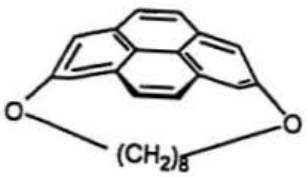


1,9-Dioxa[9](2,7)pyrenop

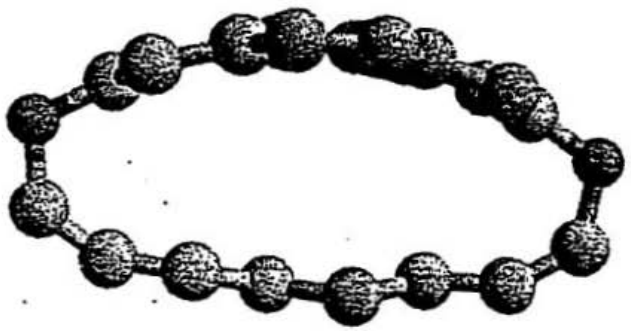


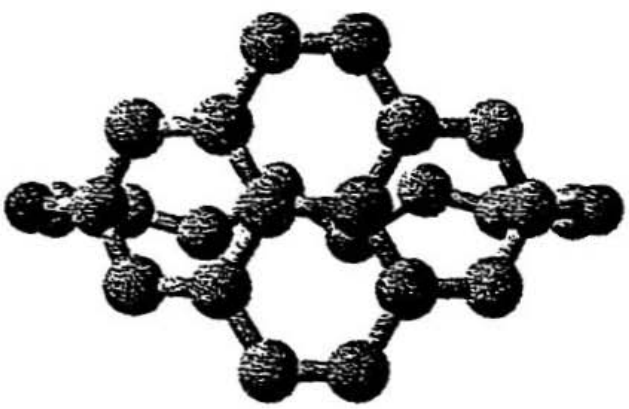


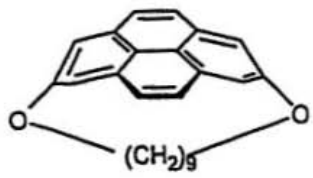




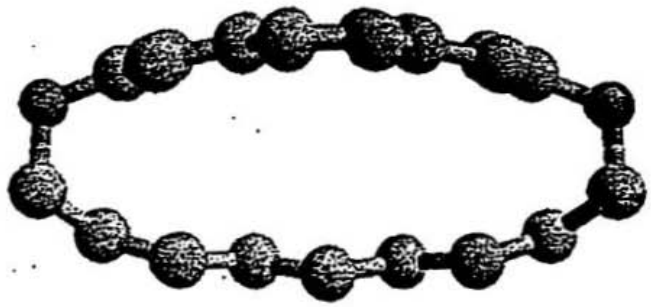
1,10-Dioxa[10](2,7)pyrenop

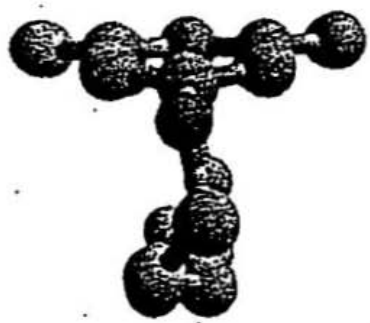


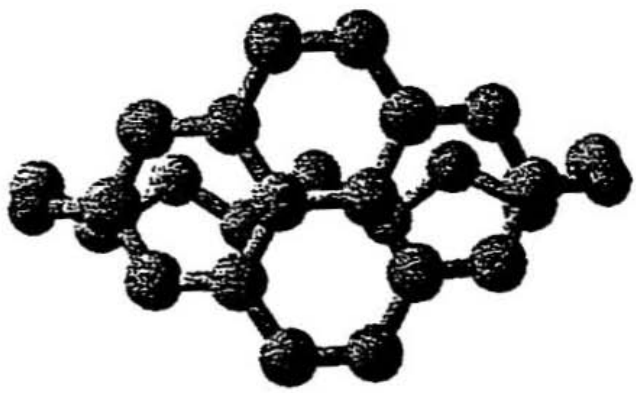


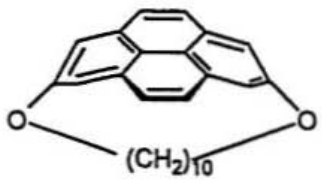


1,11-Dioxa[11](2,7)pyrenophane, 1e

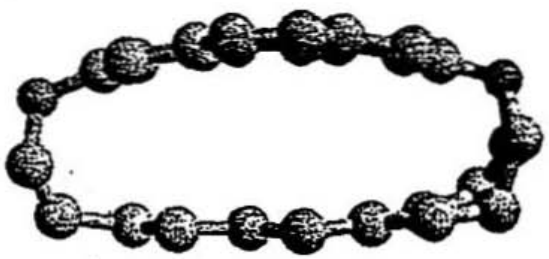


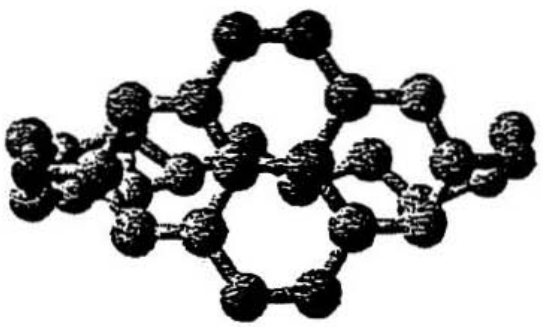


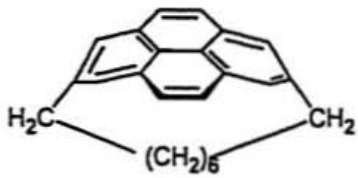




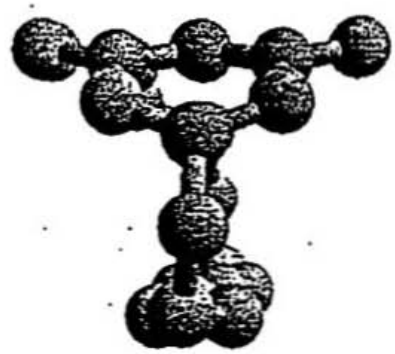
1,12-Dioxa[12](2,7)pyrenophane, 1f

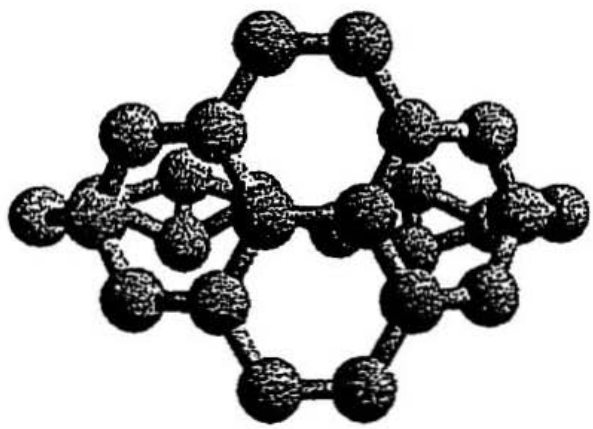


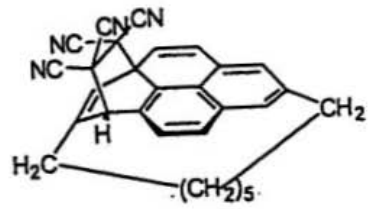




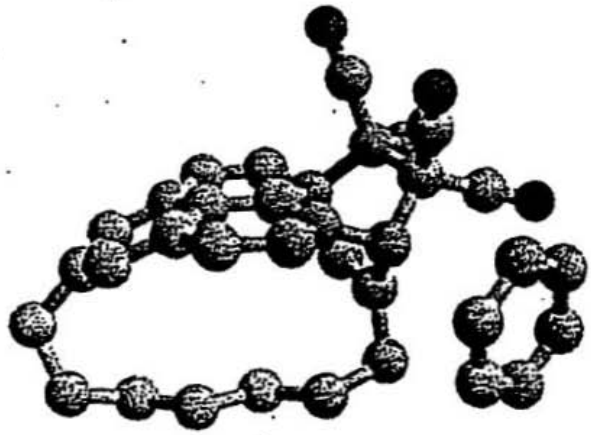
[8](2,7)Pyrenophane, 2b





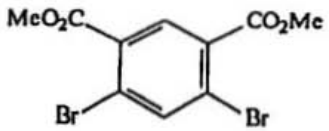


29



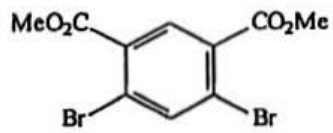
Appendix B – Selected NMR Spectra from Chapter 4

Compounds appear in the order in which they are described in the Experimental section of the text.

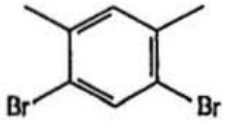


28

10 8 6 4 2 0 ppm



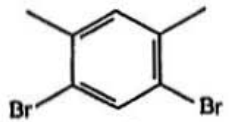
28



33

283

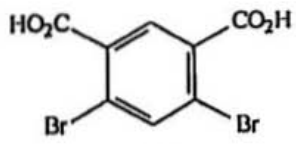
8 6 4 2 0 ppm



33

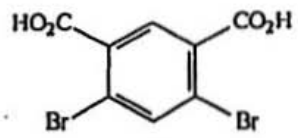
284

250 200 150 100 50 0 ppm



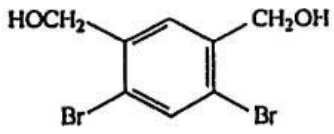
34

10 5 0 ppm

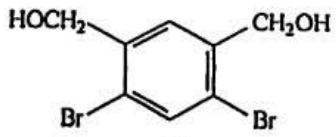


34

200 150 100 50 0 ppm

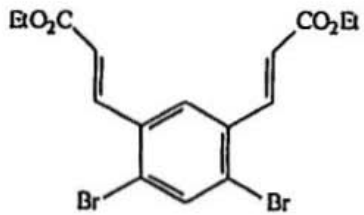


35

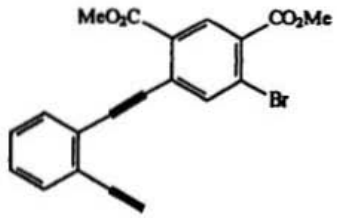


35

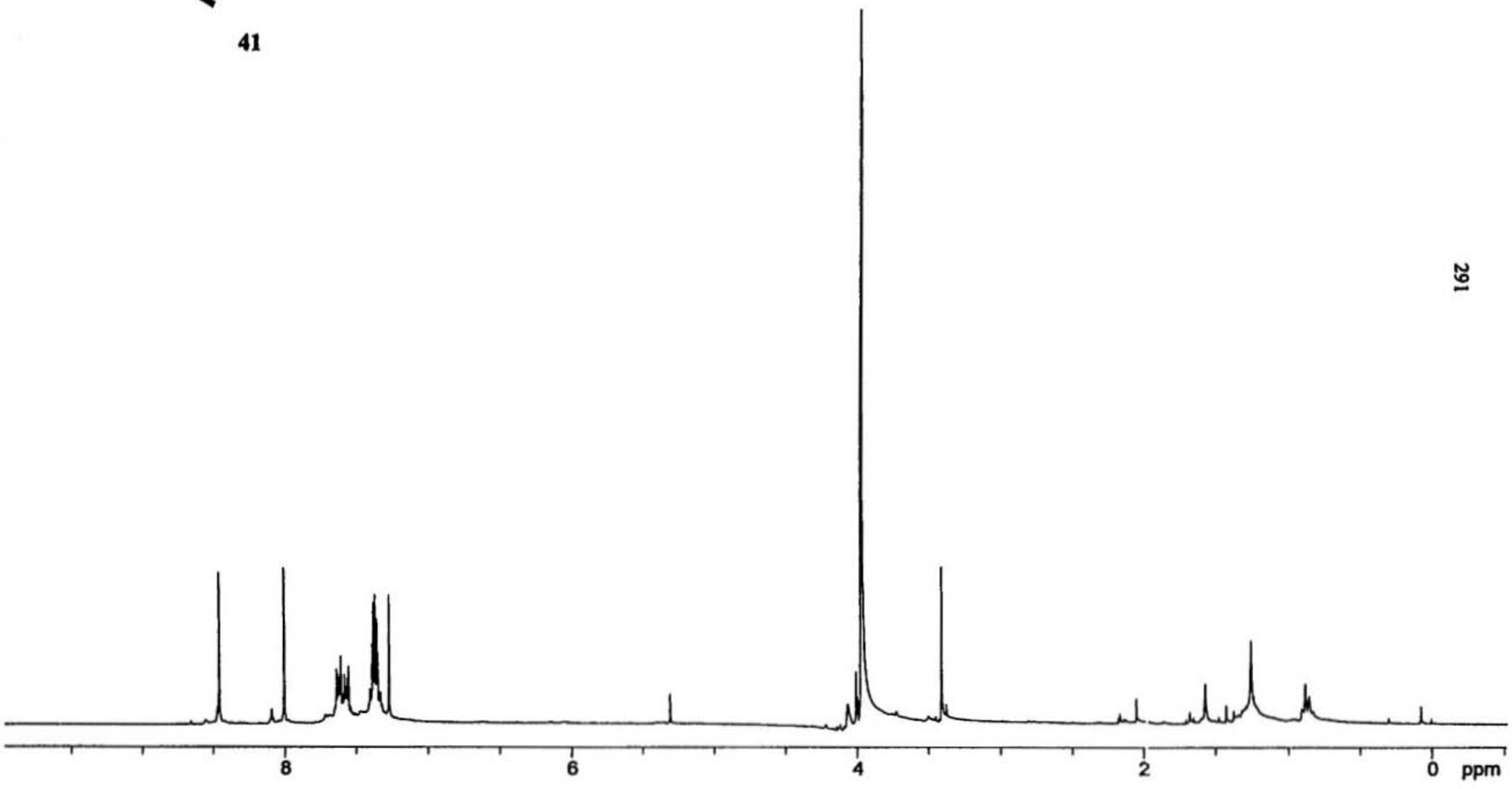
37

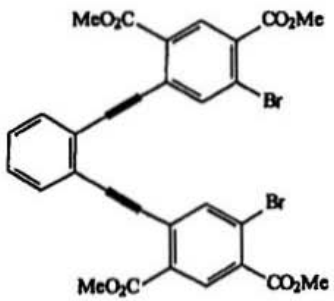


37



41





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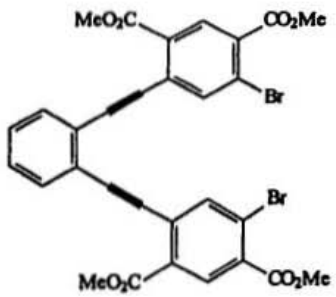

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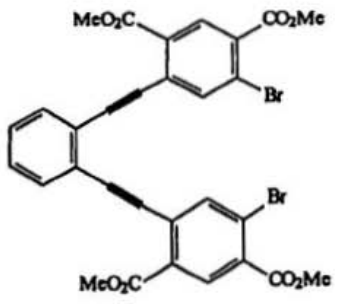
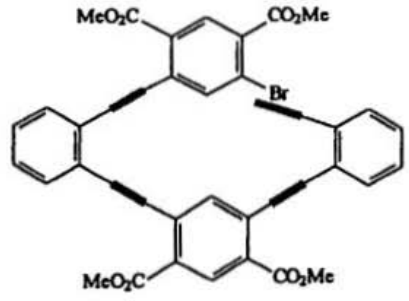
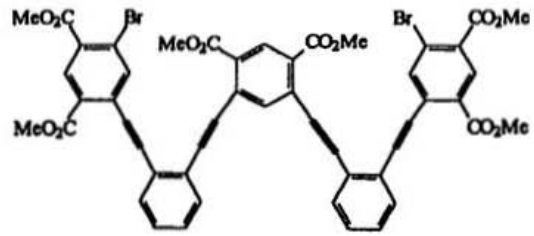

MeO2C
CO2Me
Br
Br
MeO2C
CO2Me

42

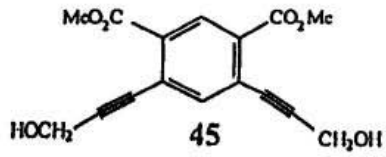

MeO2C
CO2Me
Br
MeO2C
CO2Me

43

294
8
6
4
2
0
ppm



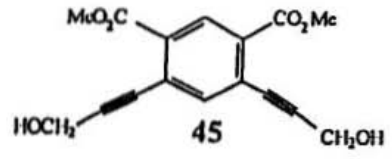
44



45

296

8 6 4 2 0 ppm



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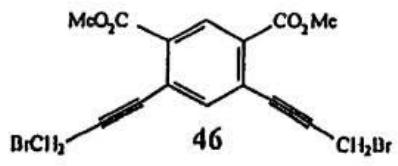
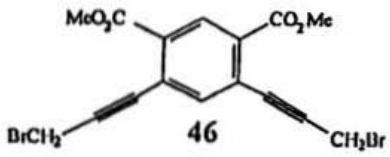


46

8 6 4 2 0 ppm



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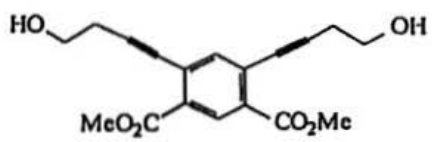

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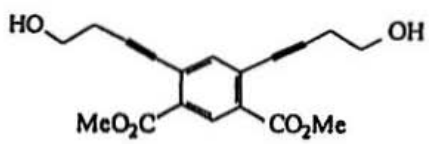

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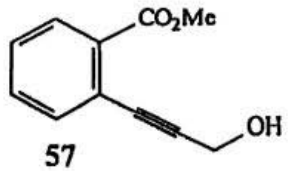
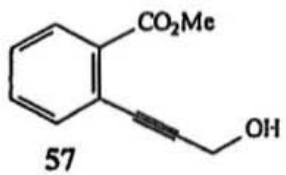


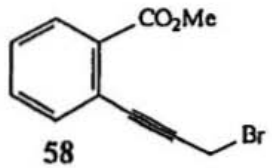
57



57

303

250 200 150 100 50 0 ppm



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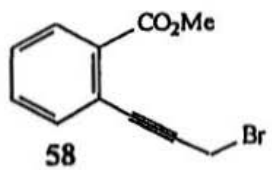

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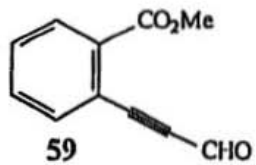

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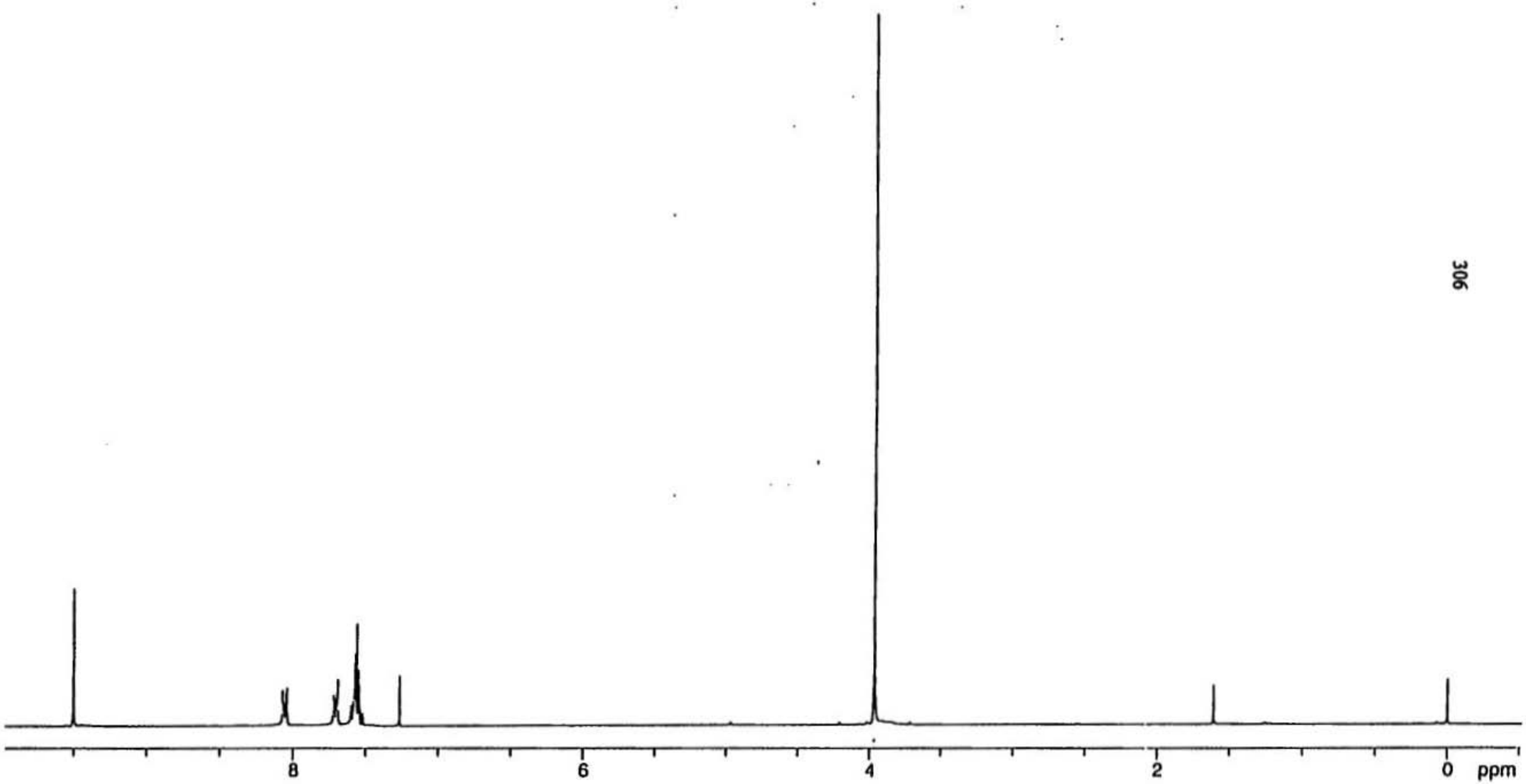

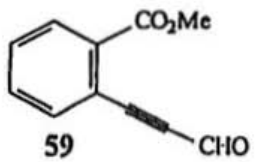

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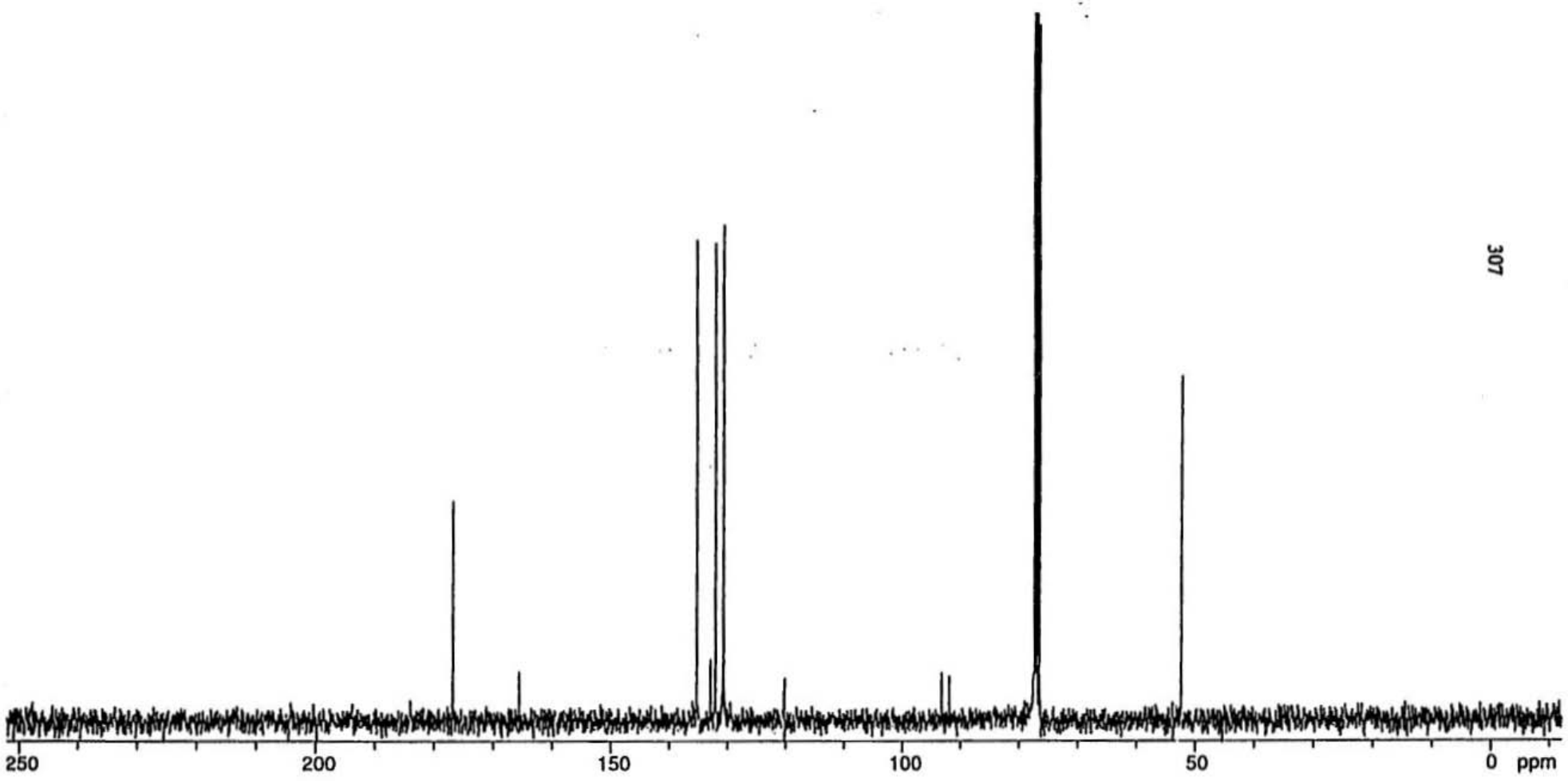

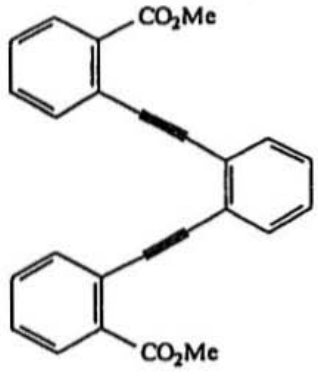

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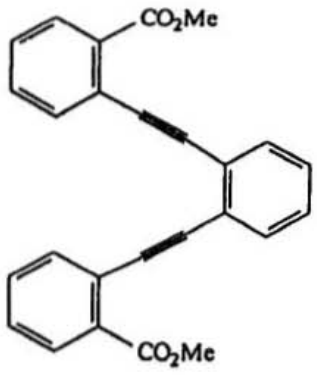
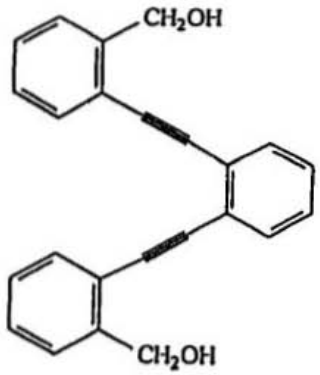


62

200 150 100 50 0 ppm



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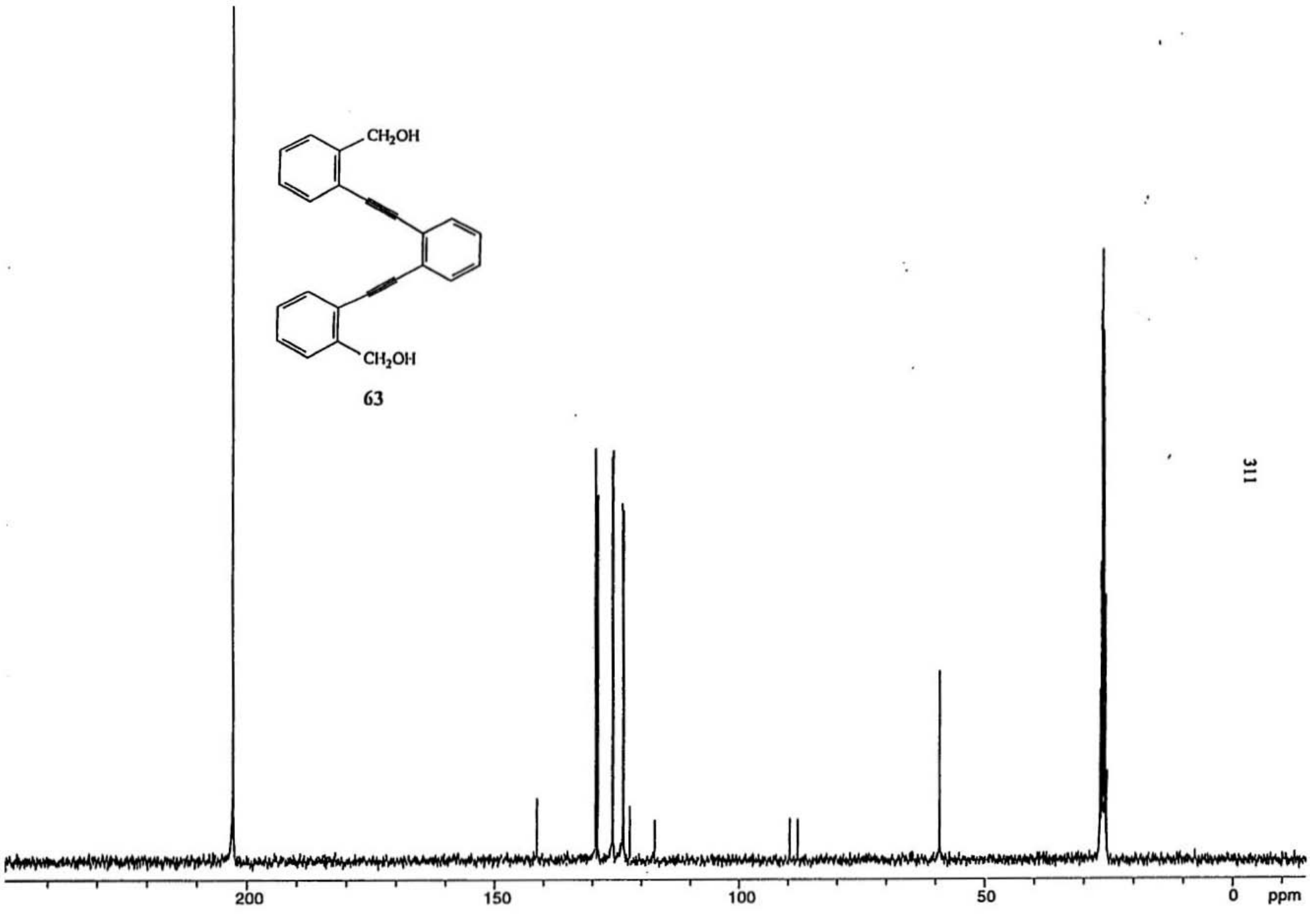

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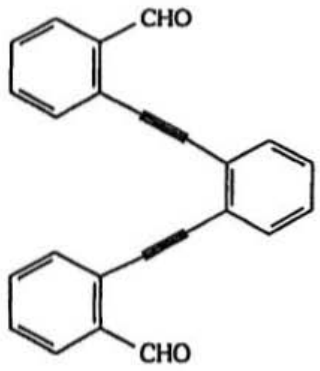

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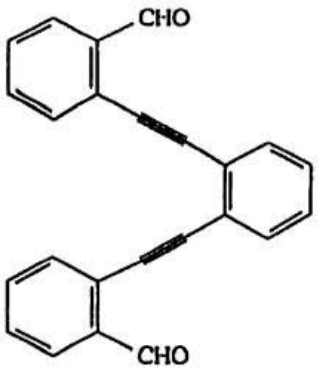

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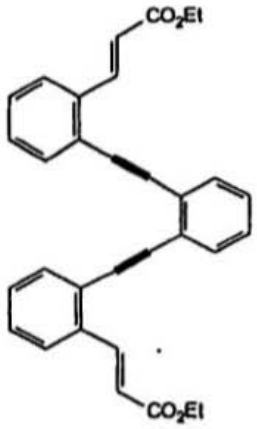

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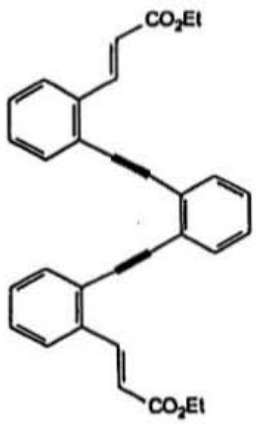
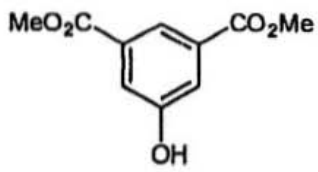


65

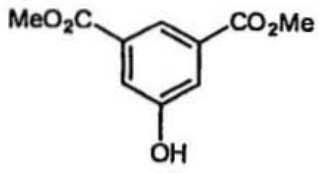
200 150 100 50 0 ppm

Appendix C – Selected NMR Spectra from Chapter 5

(Compounds as numbered in Chapter 5; compounds appear in the order in which they are described in the Experimental section of the text.)

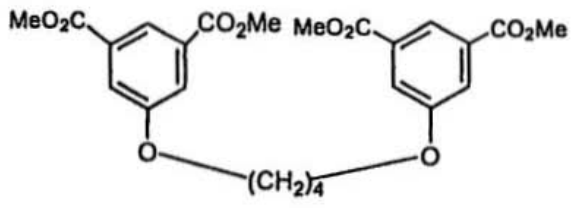


36

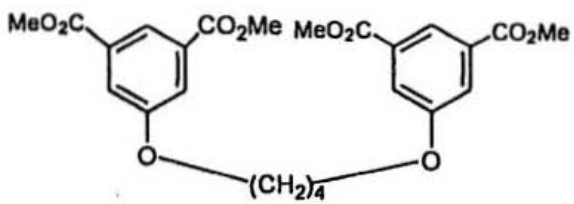


36

250 200 150 100 50 0 ppm



38a



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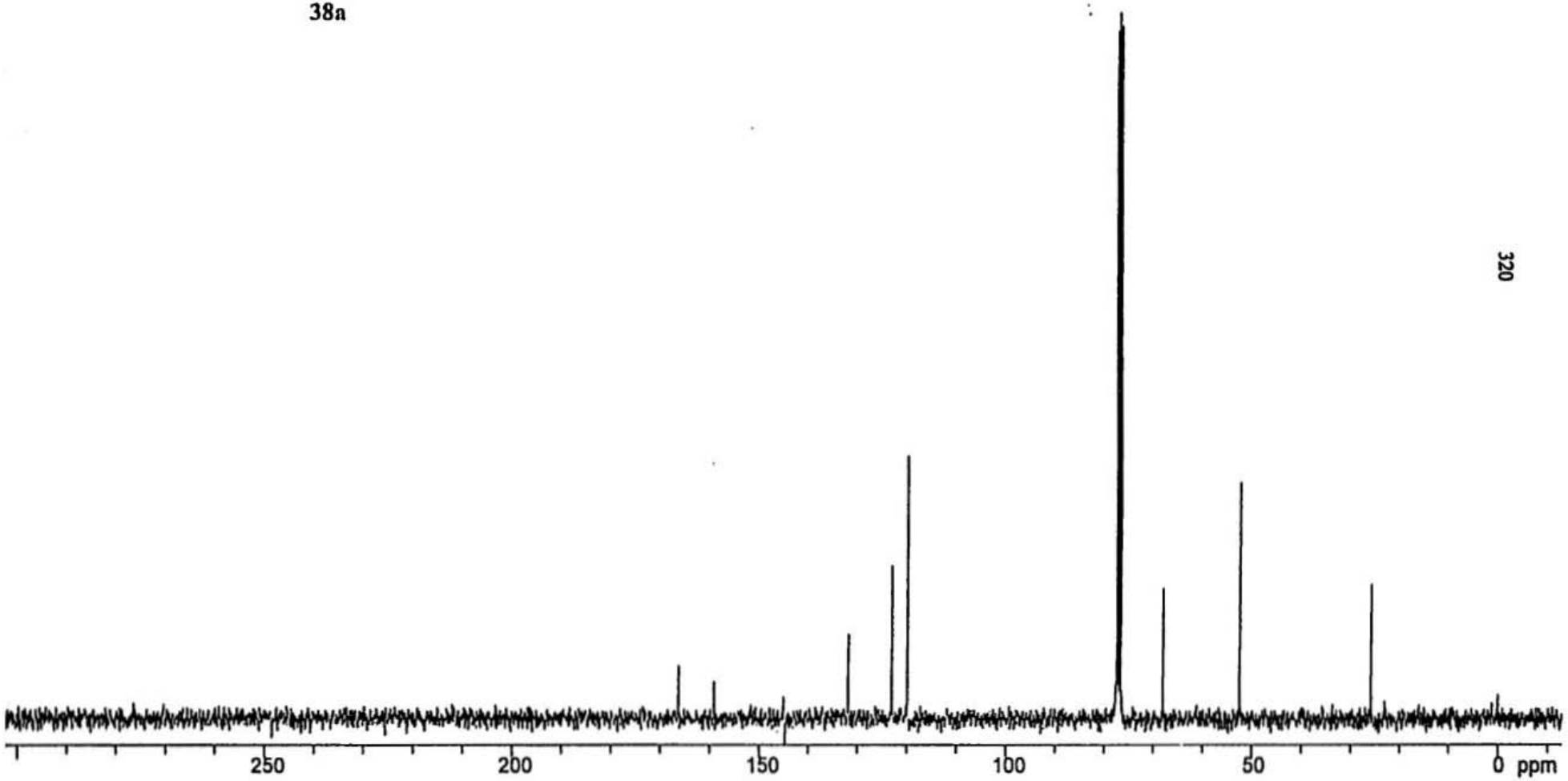
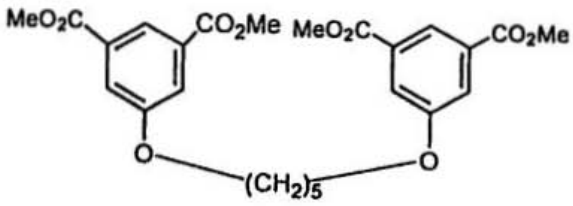
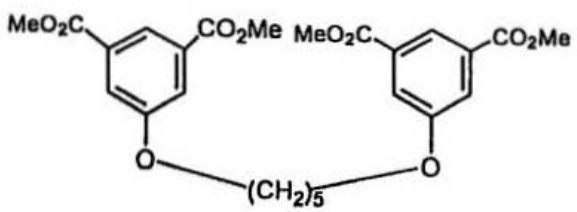


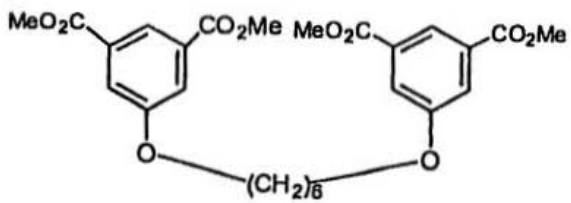


38b



38b

250 200 150 100 50 0 ppm



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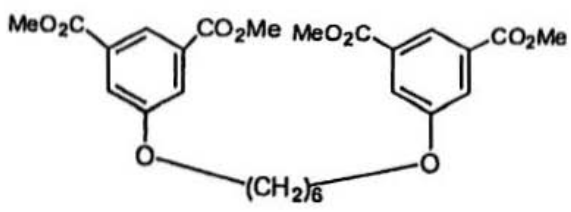
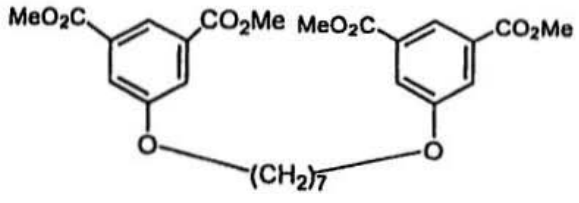


38c

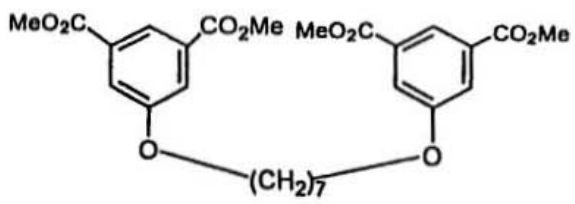
200 150 100 50 0 ppm



38d

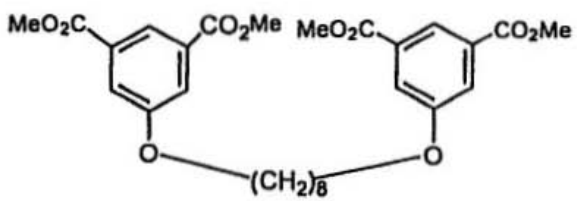
325

8 6 4 2 ppm

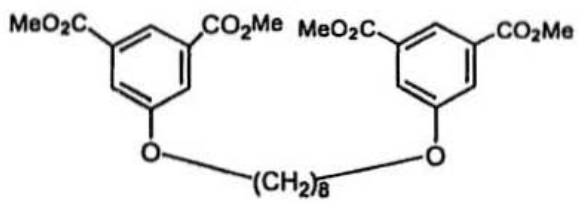


38d

250 200 150 100 50 0 ppm



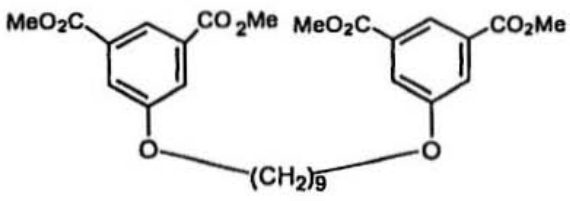
38e



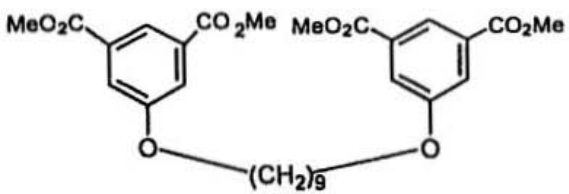
38c

328

150 100 50 0 ppm



38f



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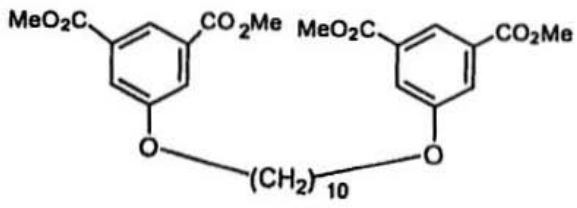
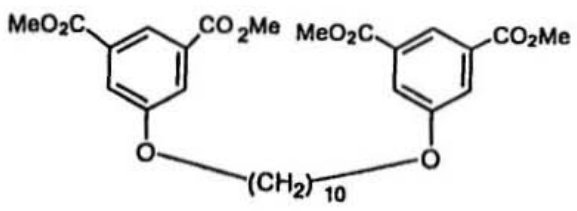


38g



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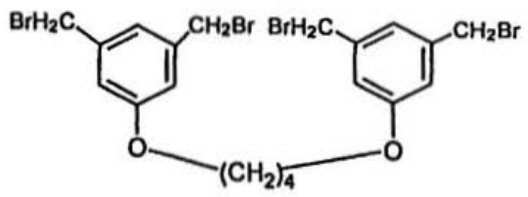

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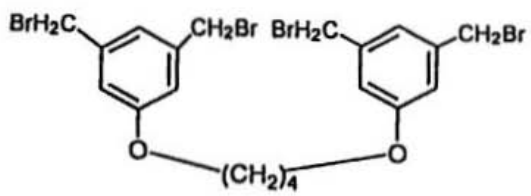

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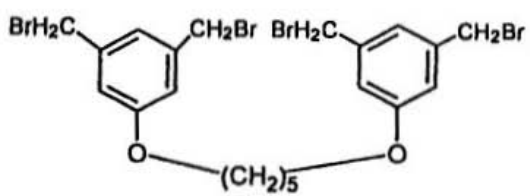

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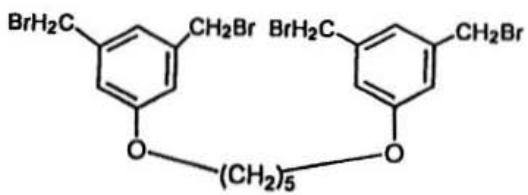

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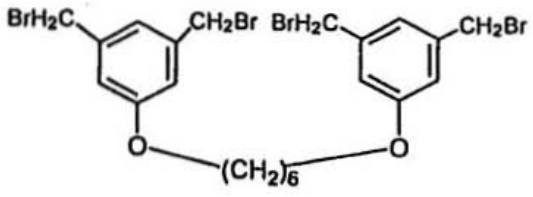

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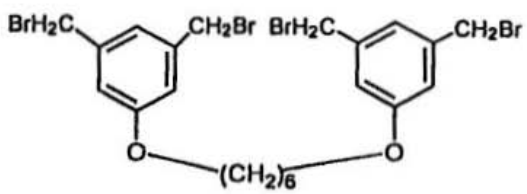

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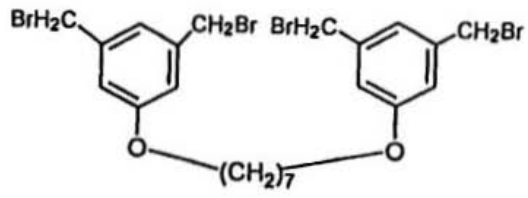

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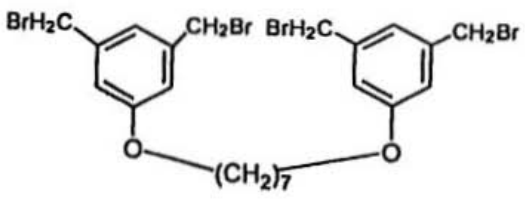

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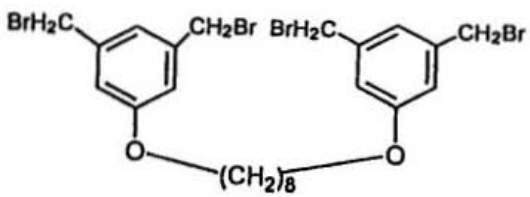

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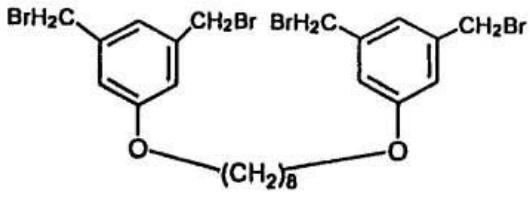

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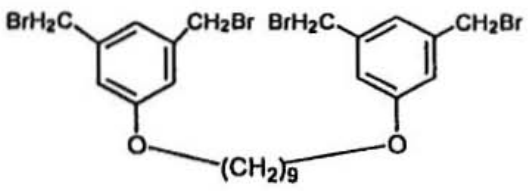

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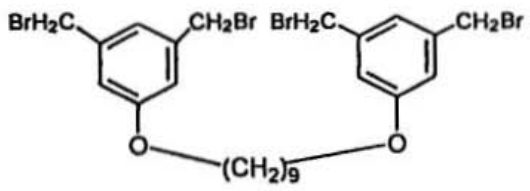

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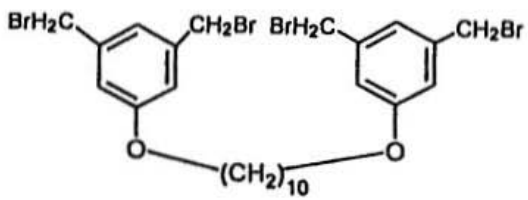

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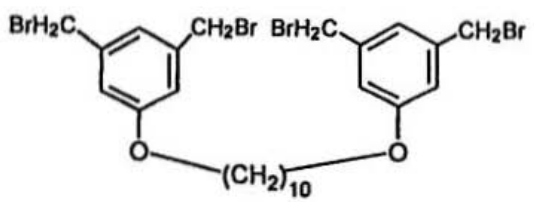
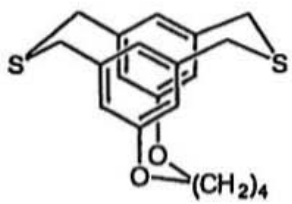


34g

150 100 50 0 ppm



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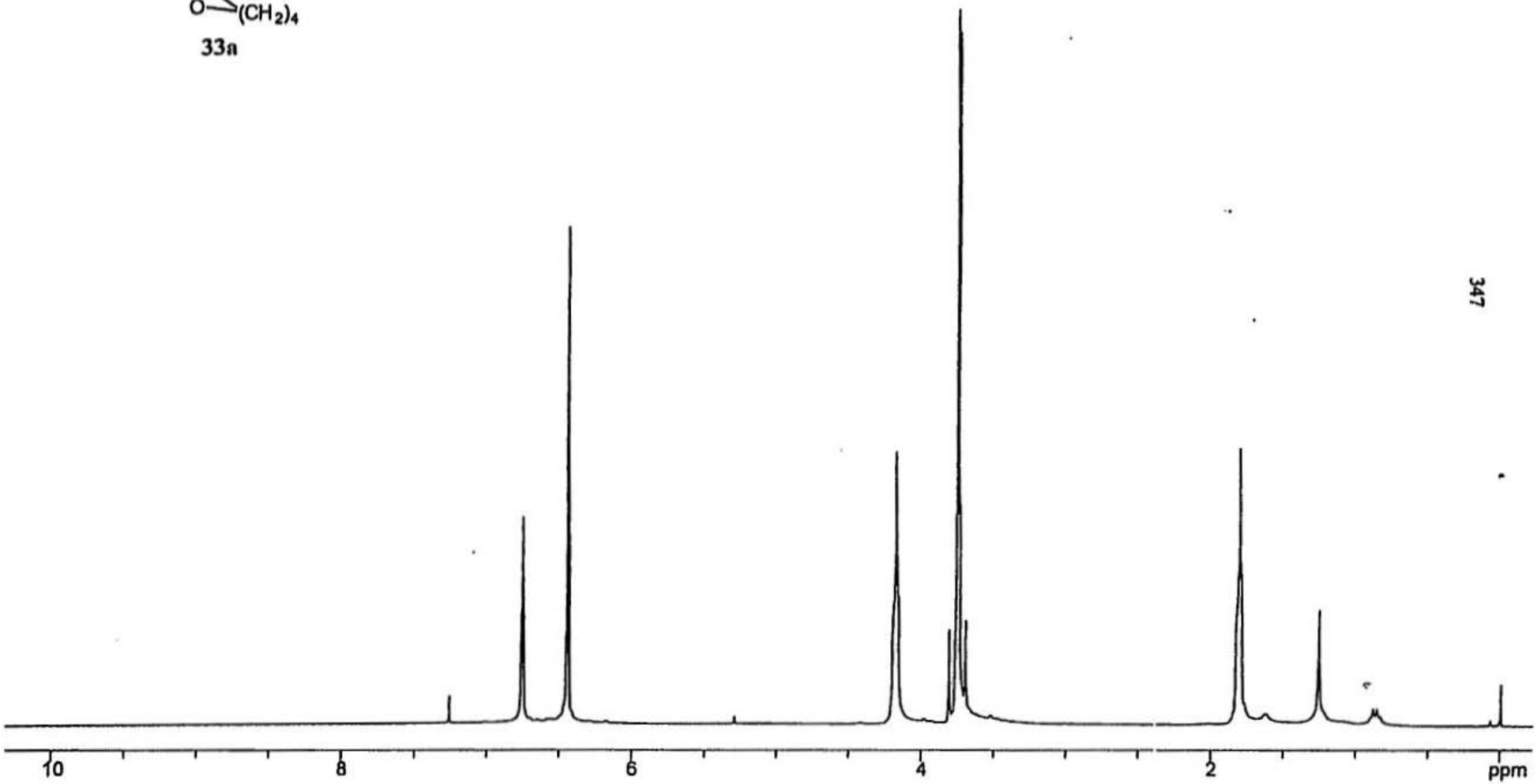
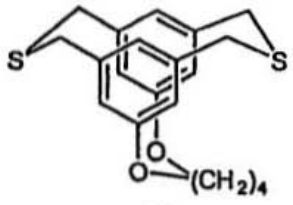
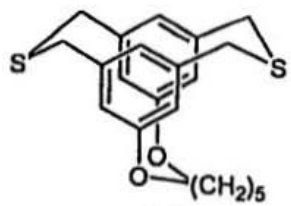




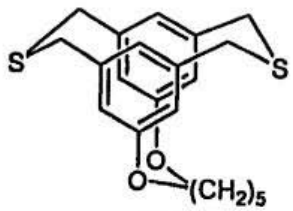
33a

348

200 150 100 50 ppm



33b



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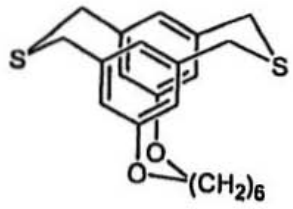
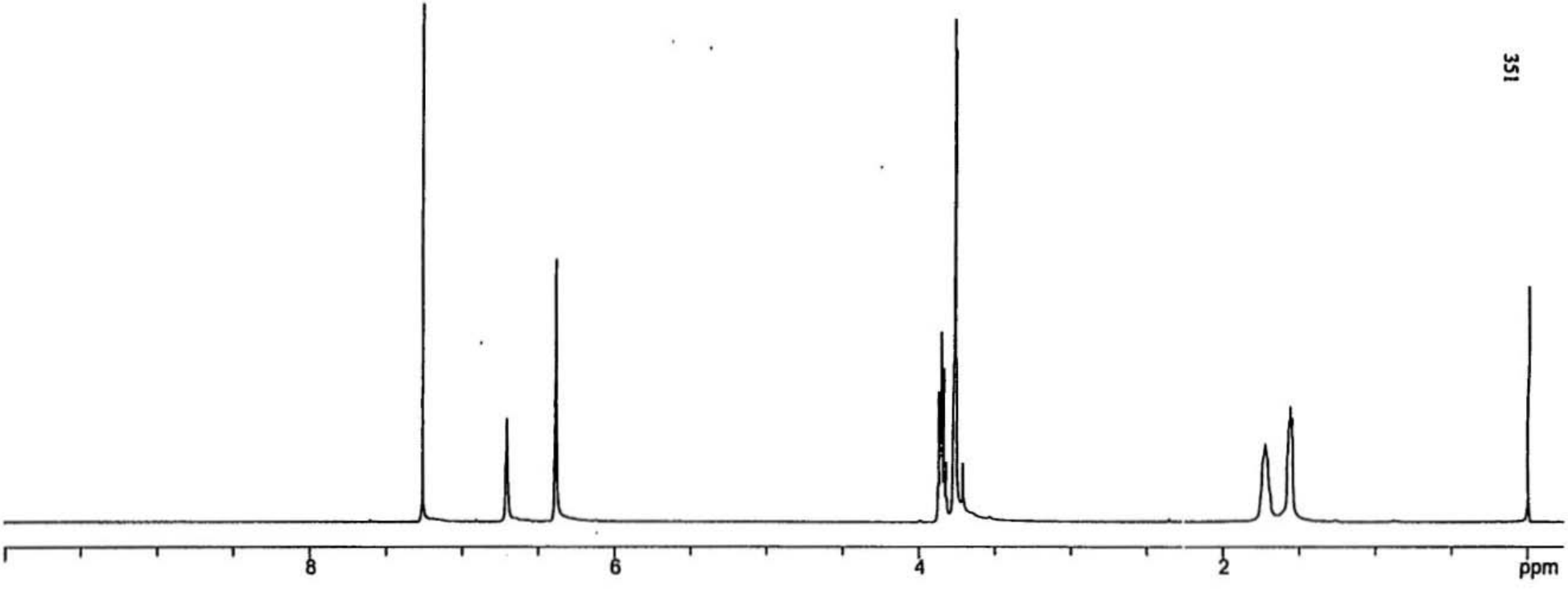
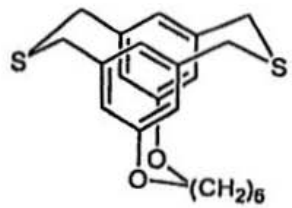
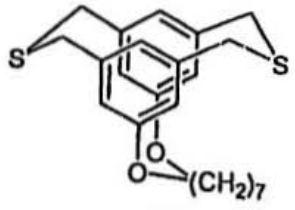


33c





33c



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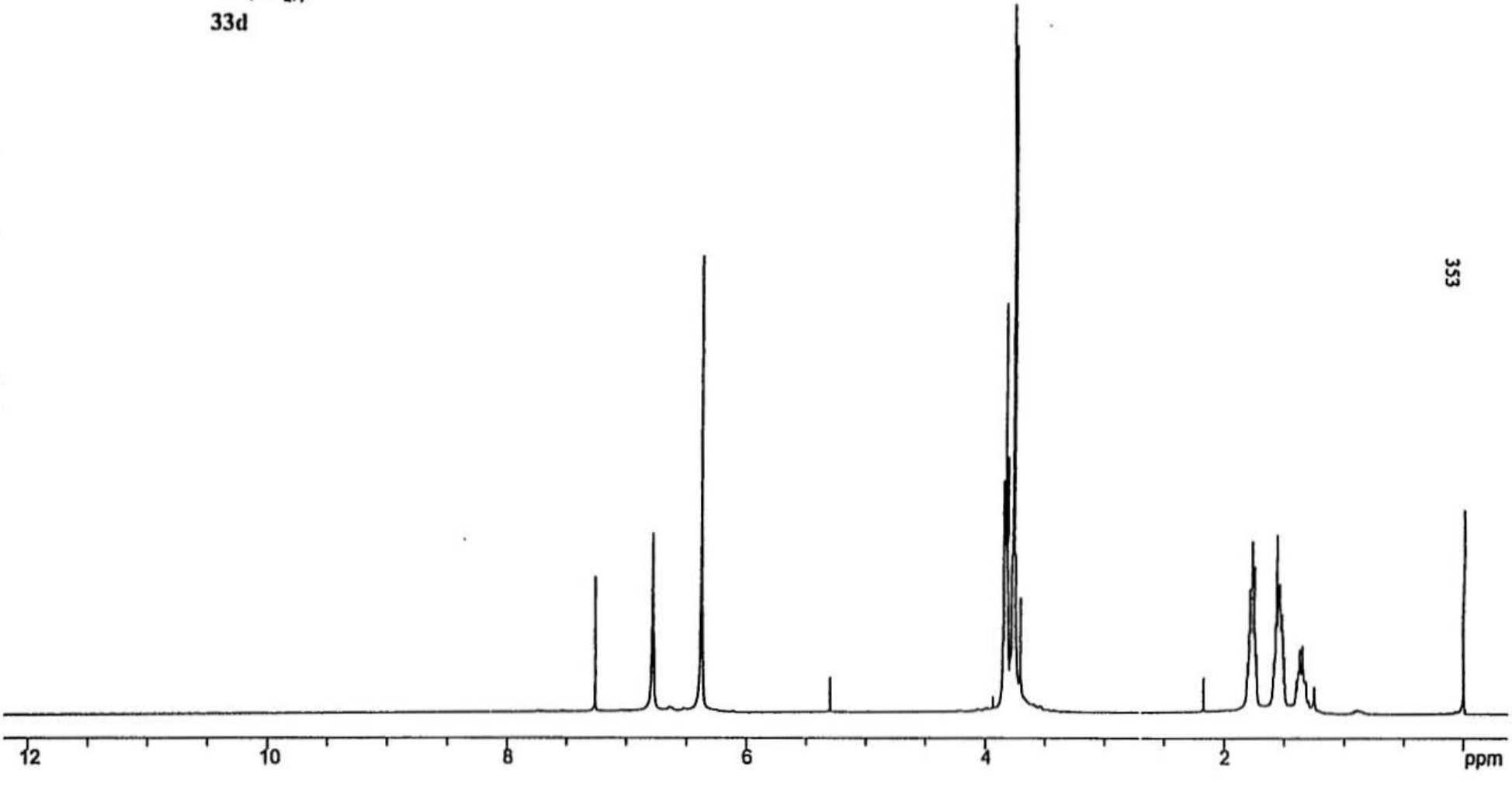

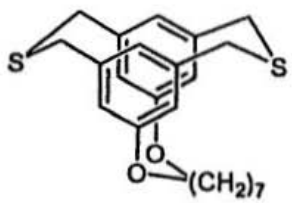

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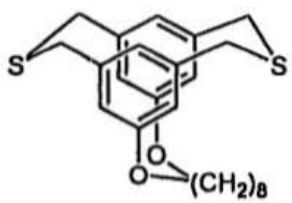

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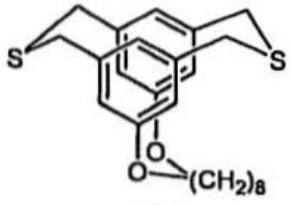
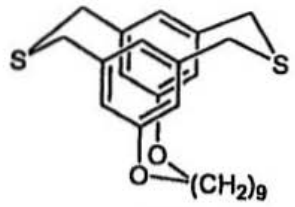


33c

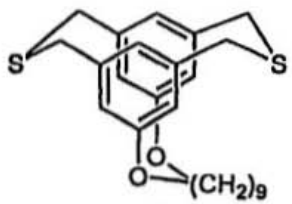
150 100 50 0 ppm



33f

357

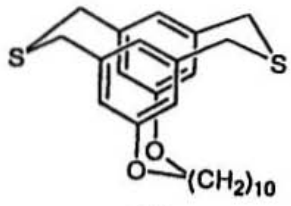
8 6 4 2 0 ppm



33f

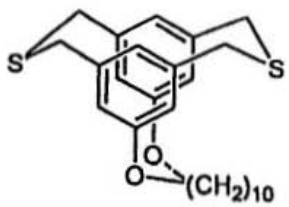
358

250 200 150 100 50 0 ppm



33g

12 10 8 6 4 2 ppm



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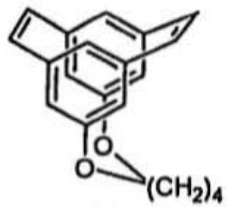
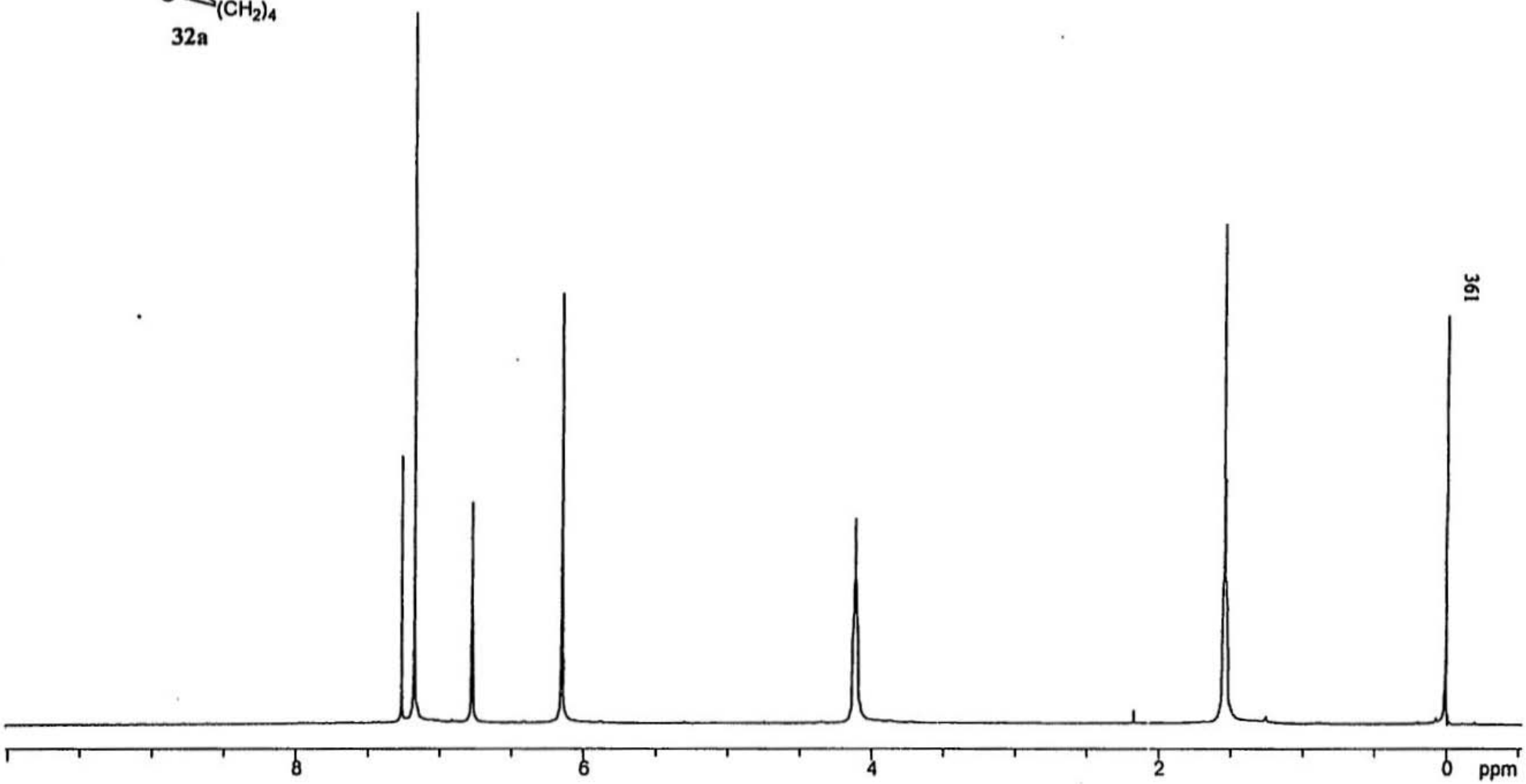
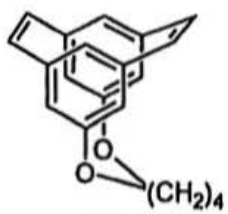


32a





32a

362

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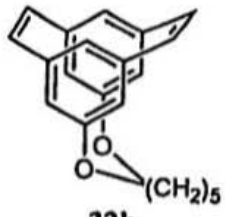
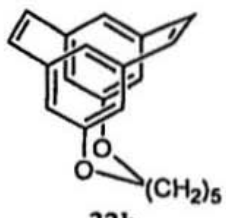


32b



32b

364

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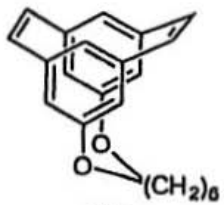
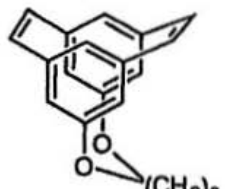


32c

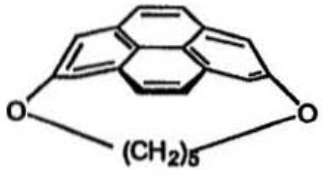
10 8 6 4 2 0 ppm



32c

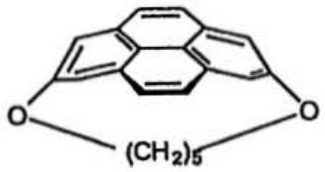
366

200 150 100 50 0 ppm



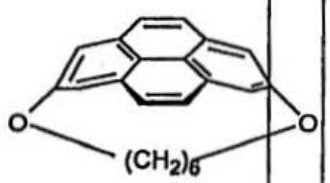
31b

2 10 8 6 4 2 0 -2 ppm



31b

250 200 150 100 50 0 ppm



31c

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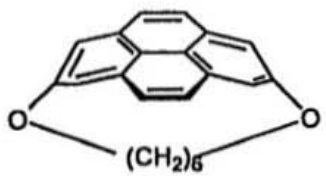
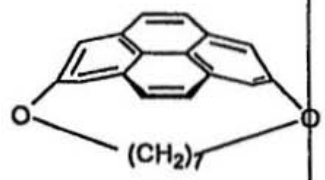
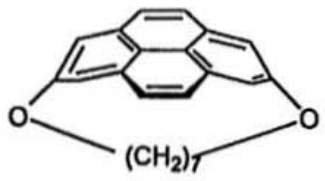


31c



31d

10 8 6 4 2 0 -2 ppm



31d

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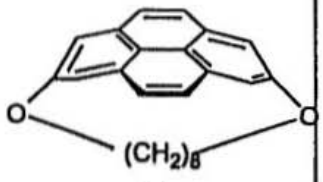
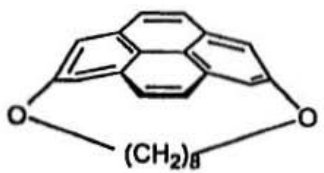
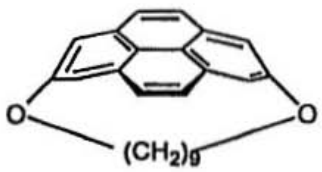


31e

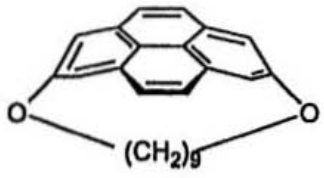


31c

200 150 100 50 0 ppm



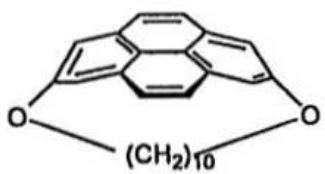
31f



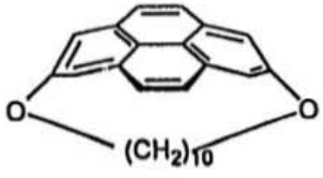
31f

376

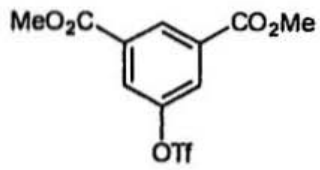
250 200 150 100 50 0 ppm



31g

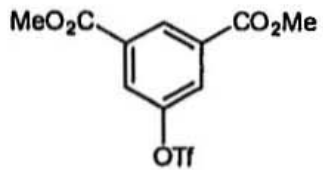


31g

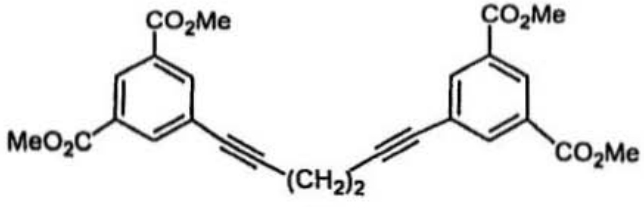


52

8 6 4 2 0 ppm

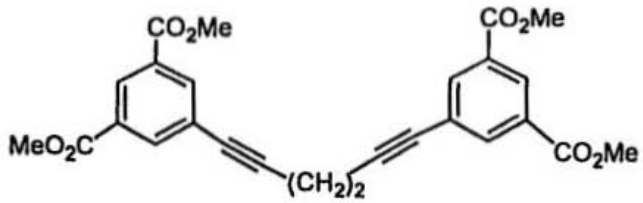


52

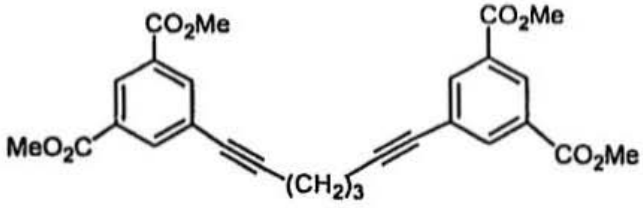


54a

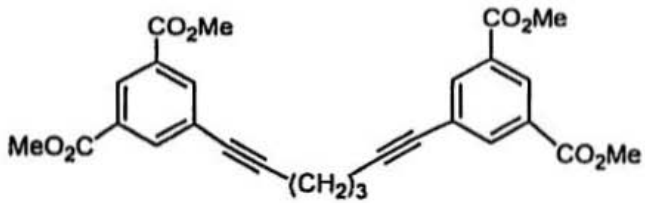
8 6 4 2 0 ppm



54a



54b



54b

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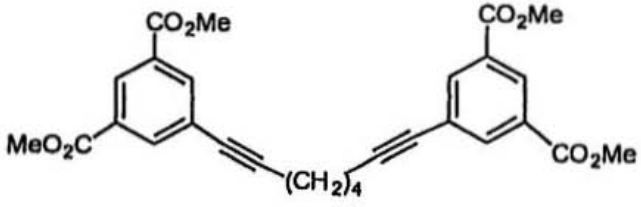
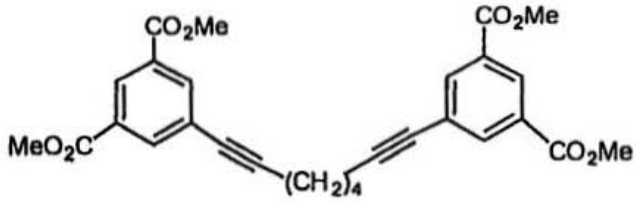


54c

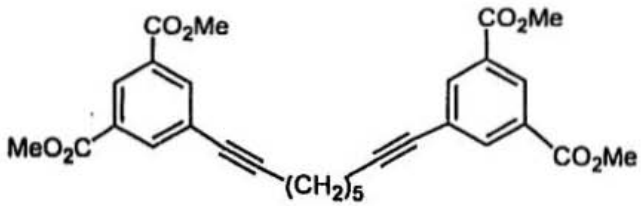
8 6 4 2 0 ppm



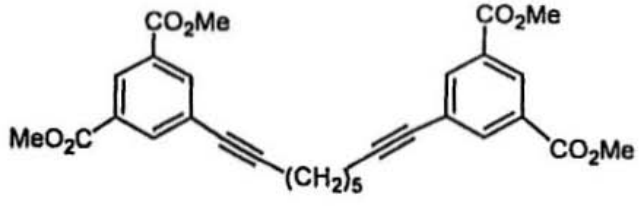
54c

386

200 150 100 50 0 ppm



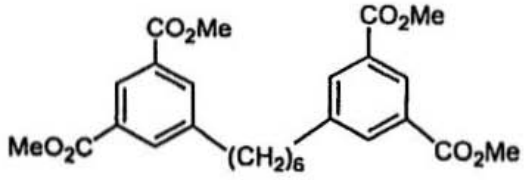
54d



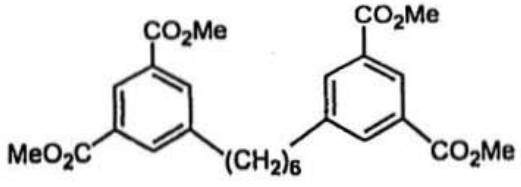
54d

388

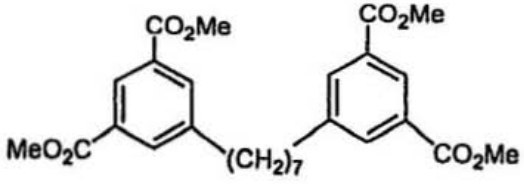
250 200 150 100 50 0 ppm



51a

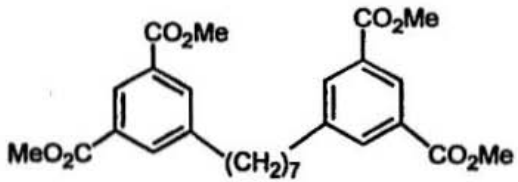


51a



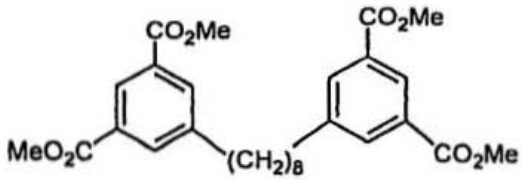
51b

8 6 4 2 0 ppm

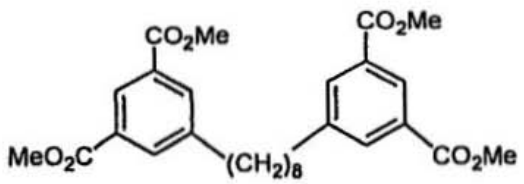


51b

200 150 100 50 0 ppm



51c



51c

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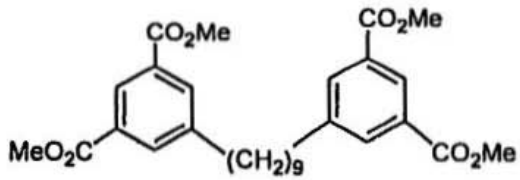
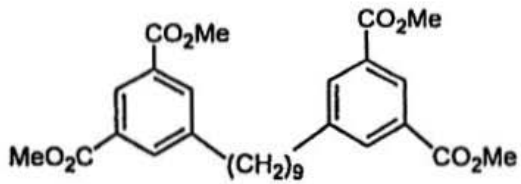


51d

8 6 4 2 0 ppm



51d

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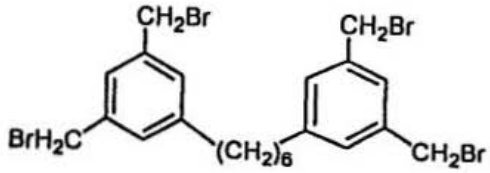
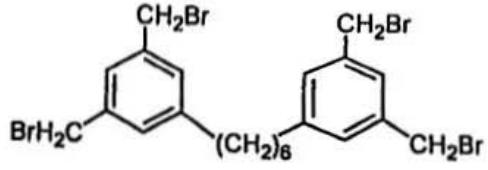
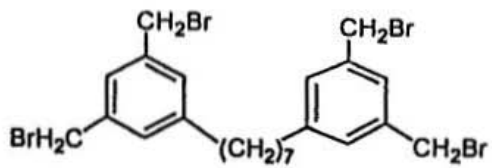


56a



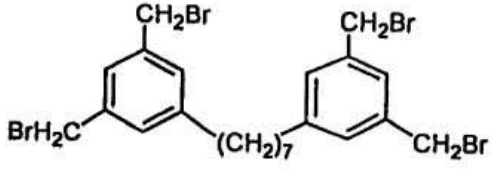
56a

200 150 100 50 0 ppm

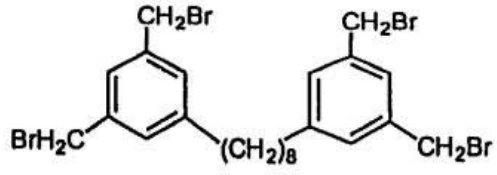


56b

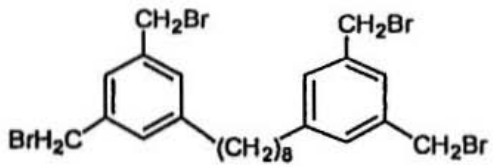
8 6 4 2 0 ppm



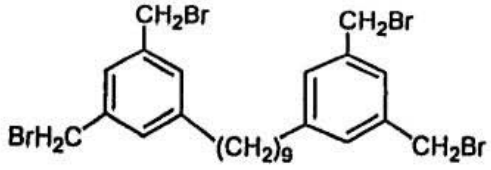
56b



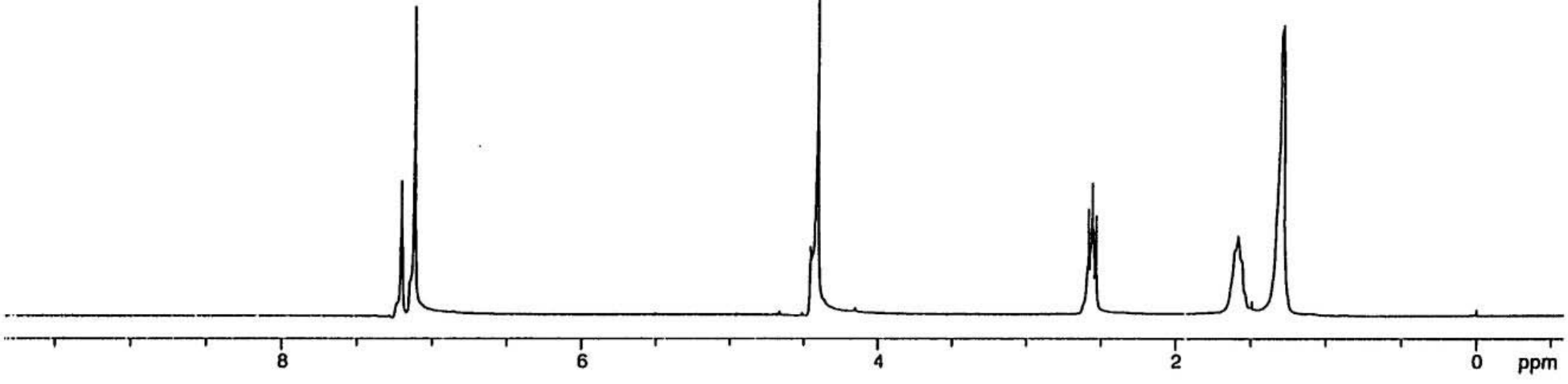
56c

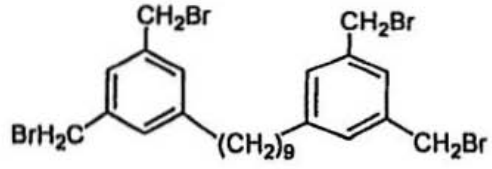


56c



56d

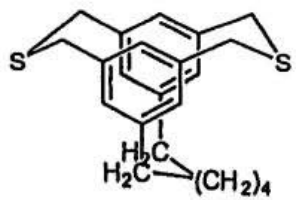




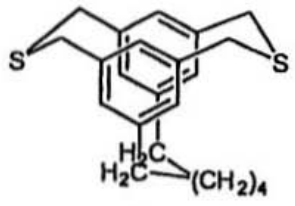
56d

404

200 150 100 50 0 ppm



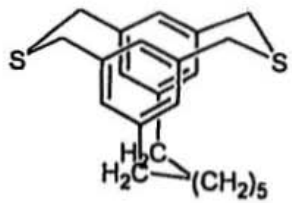
50a



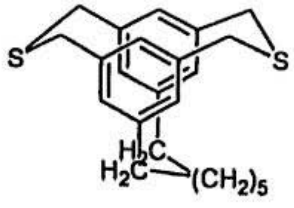
50a

406

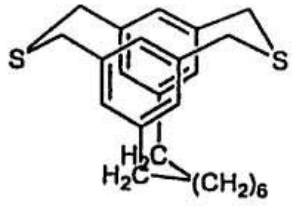
200 150 100 50 0 ppm



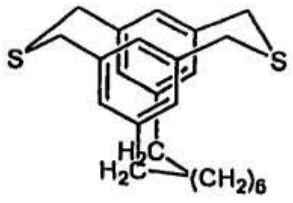
50b



50b



50c



50c

410

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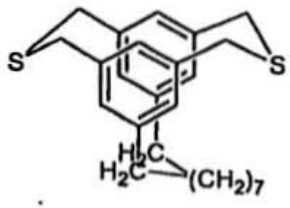
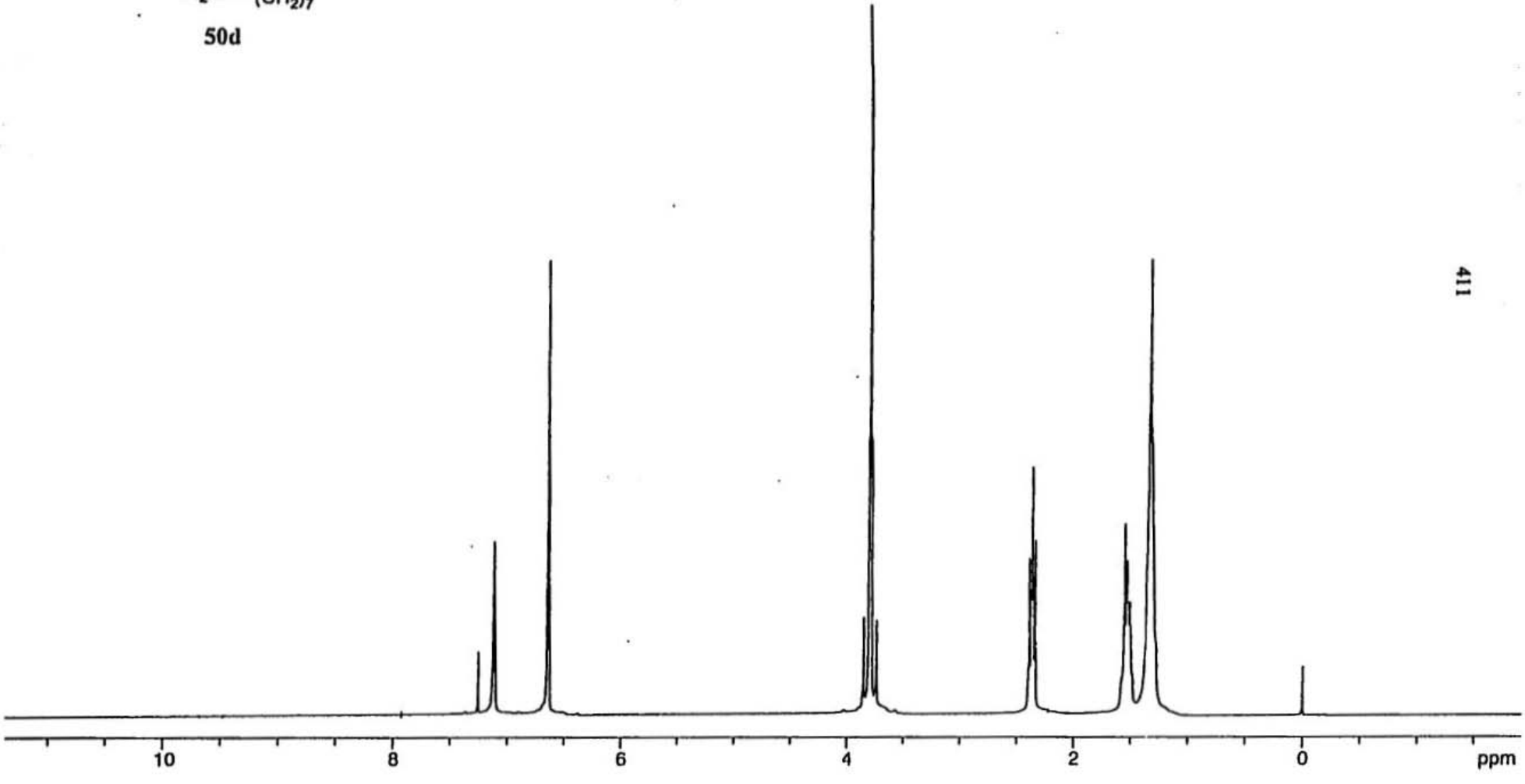
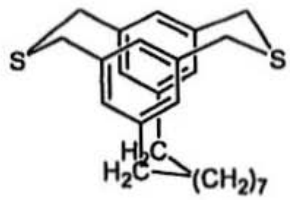


50d





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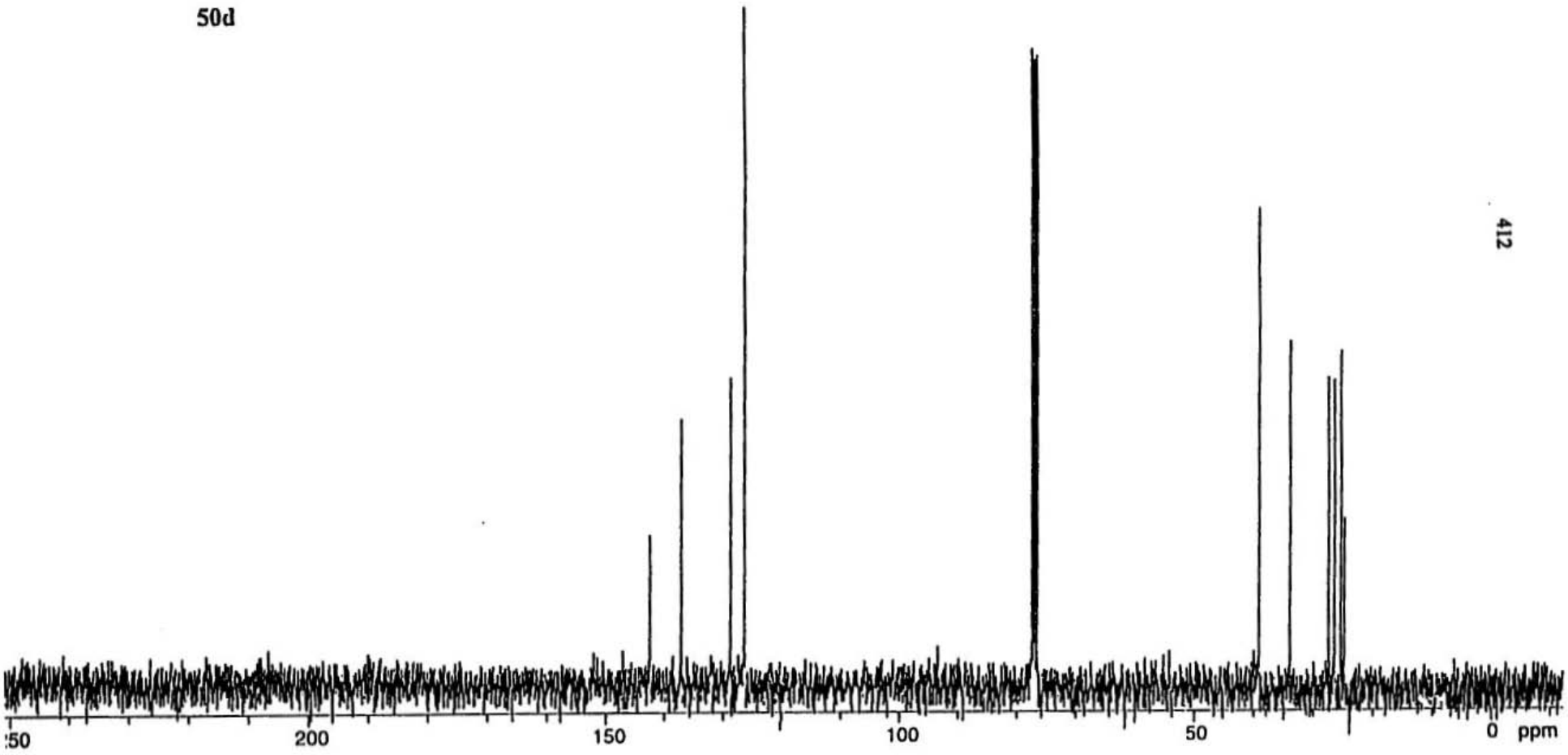
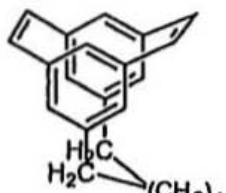
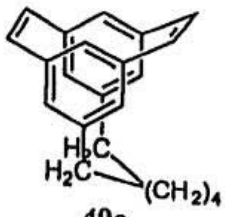




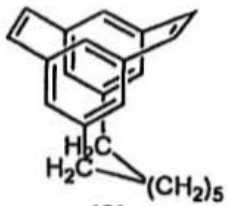
49a

10 8 6 4 2 0 ppm

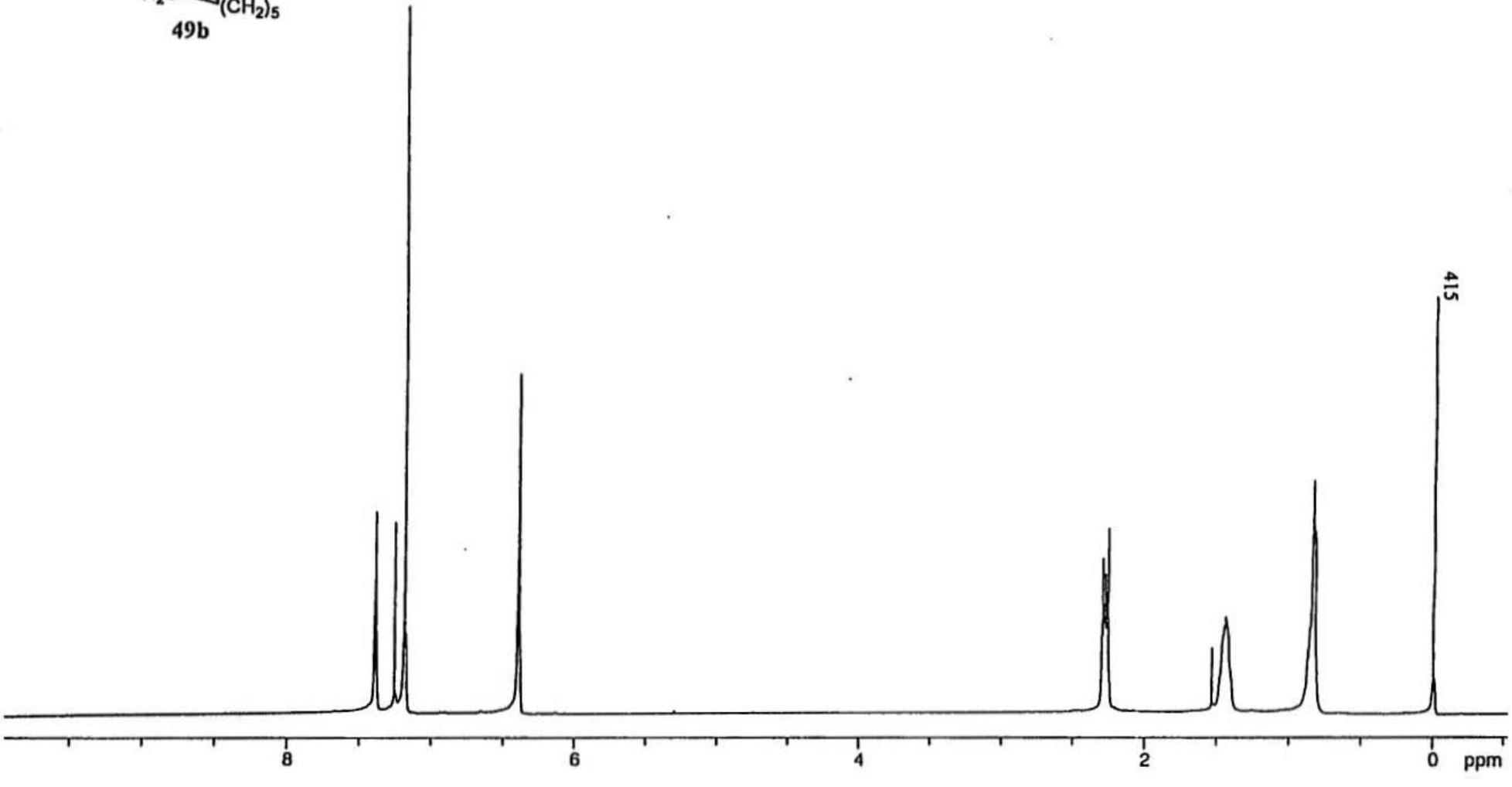


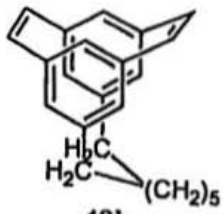
49a

200 150 100 50 0 ppm



49b





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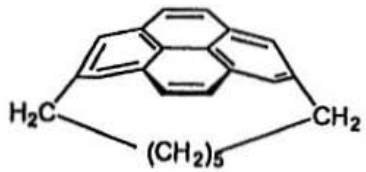

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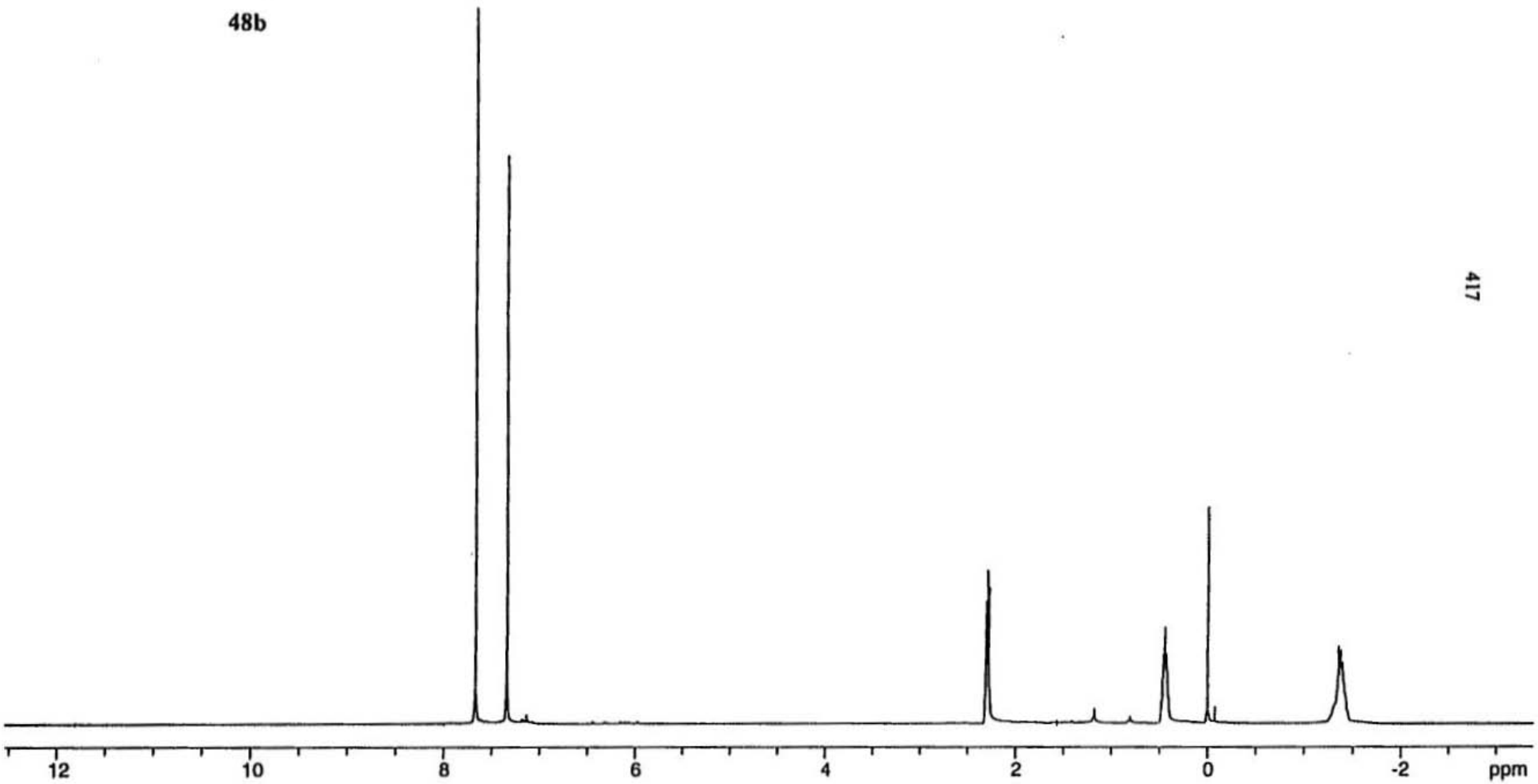

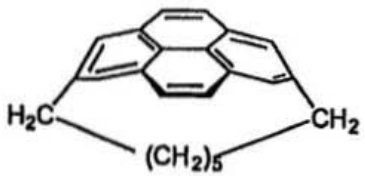

48b

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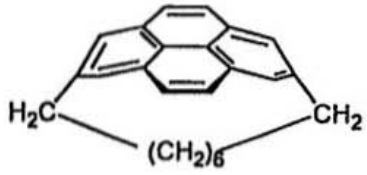
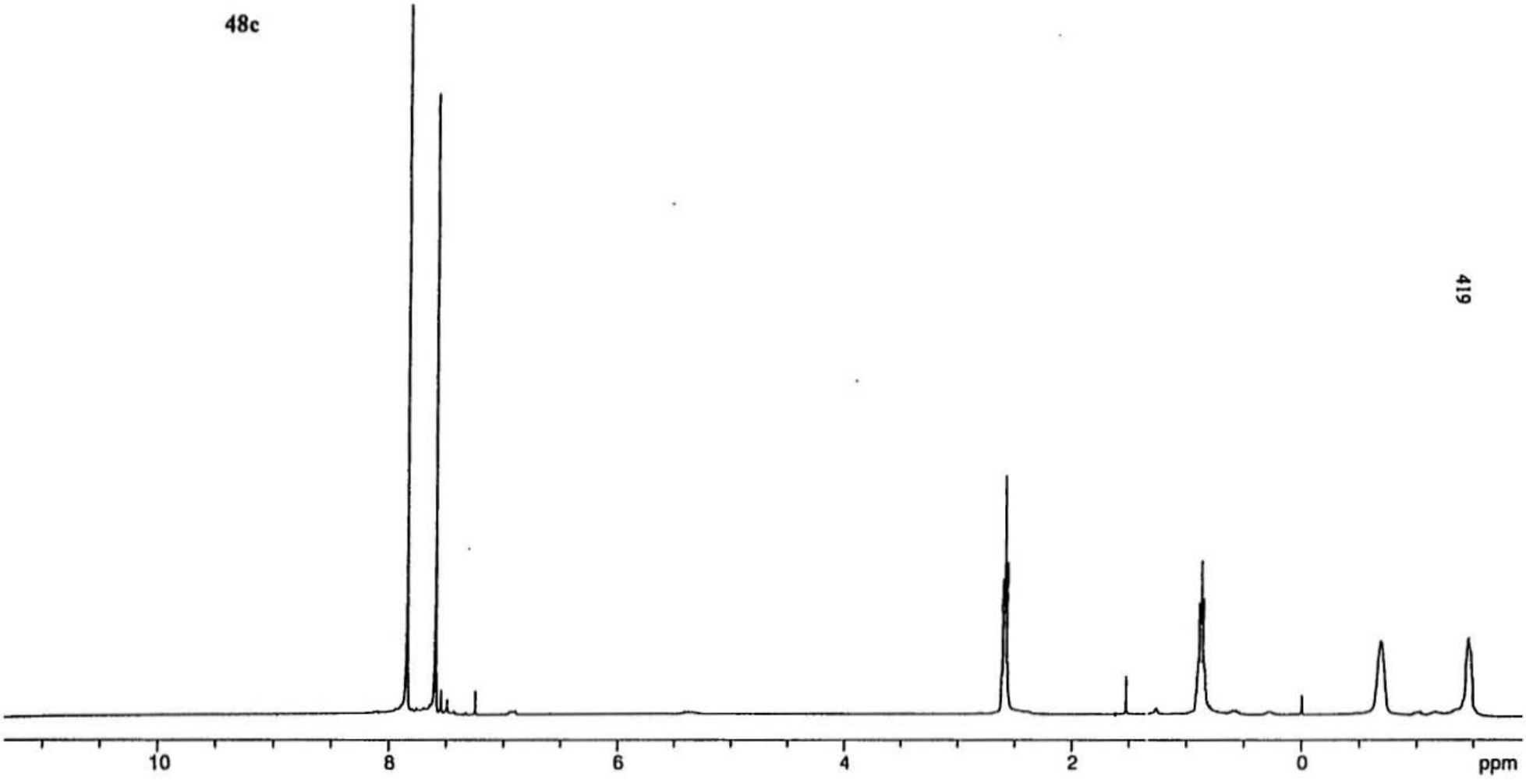
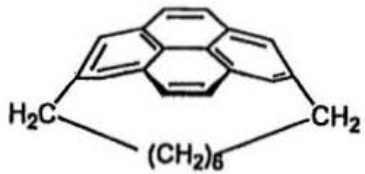


48c





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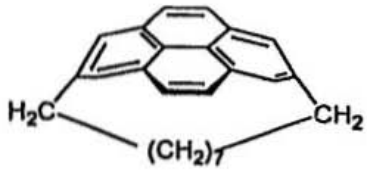
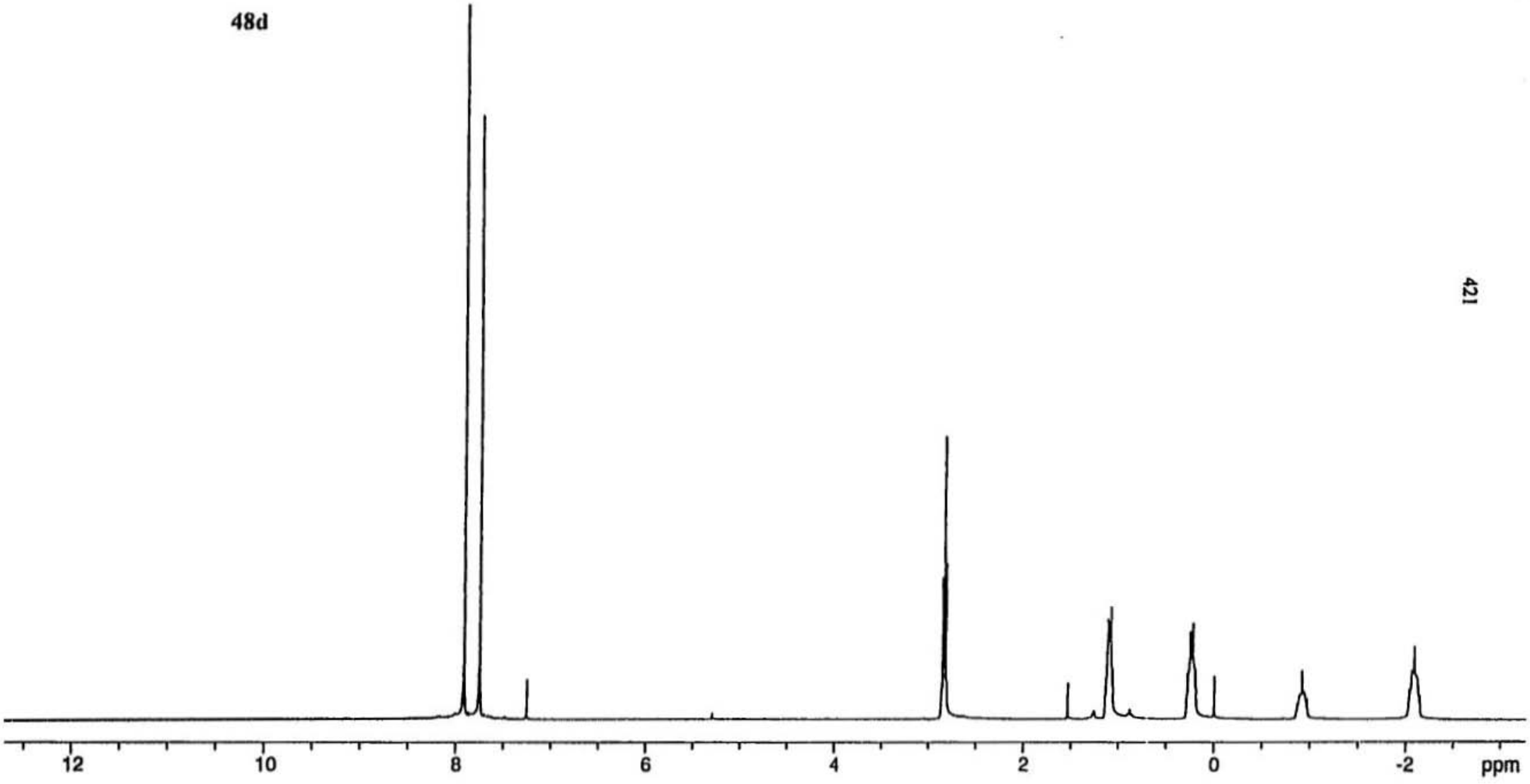
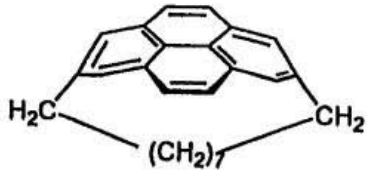


48d





48d

422

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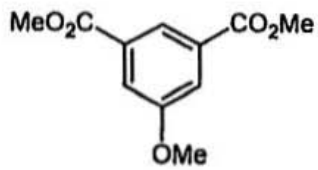
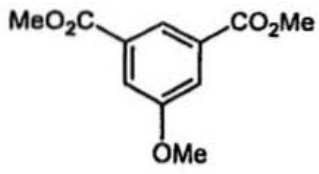


59



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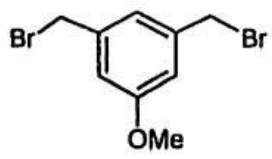

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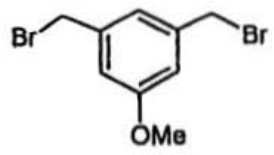

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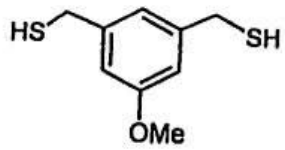

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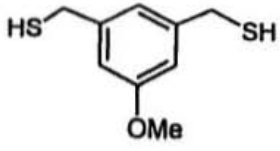

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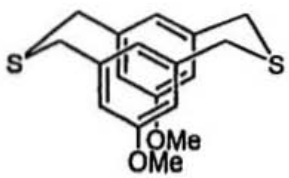

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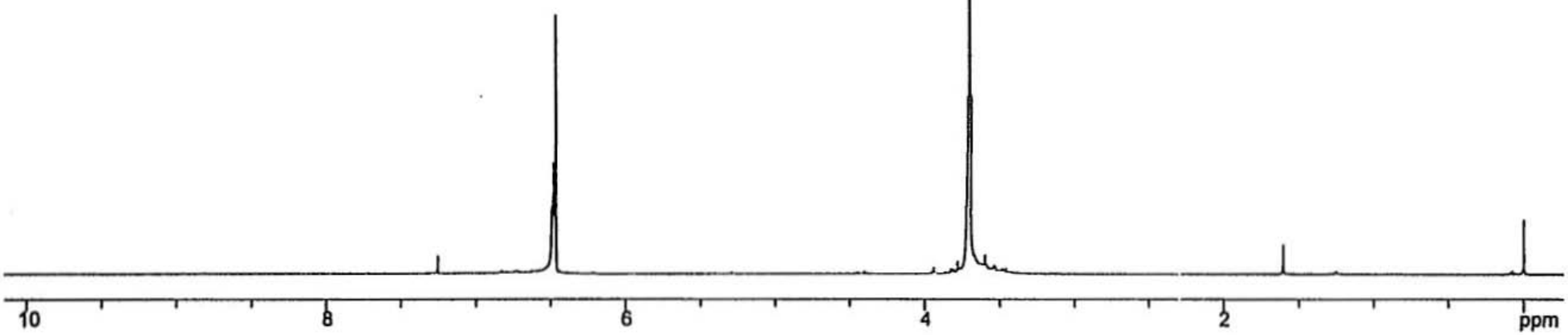
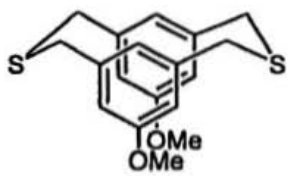
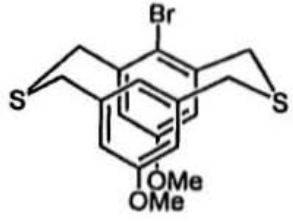
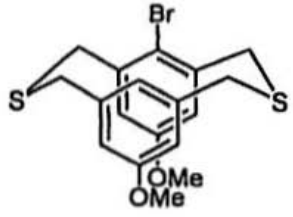




62



76



76

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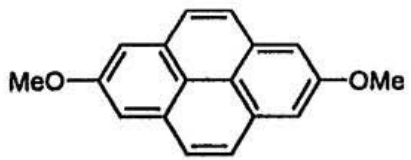

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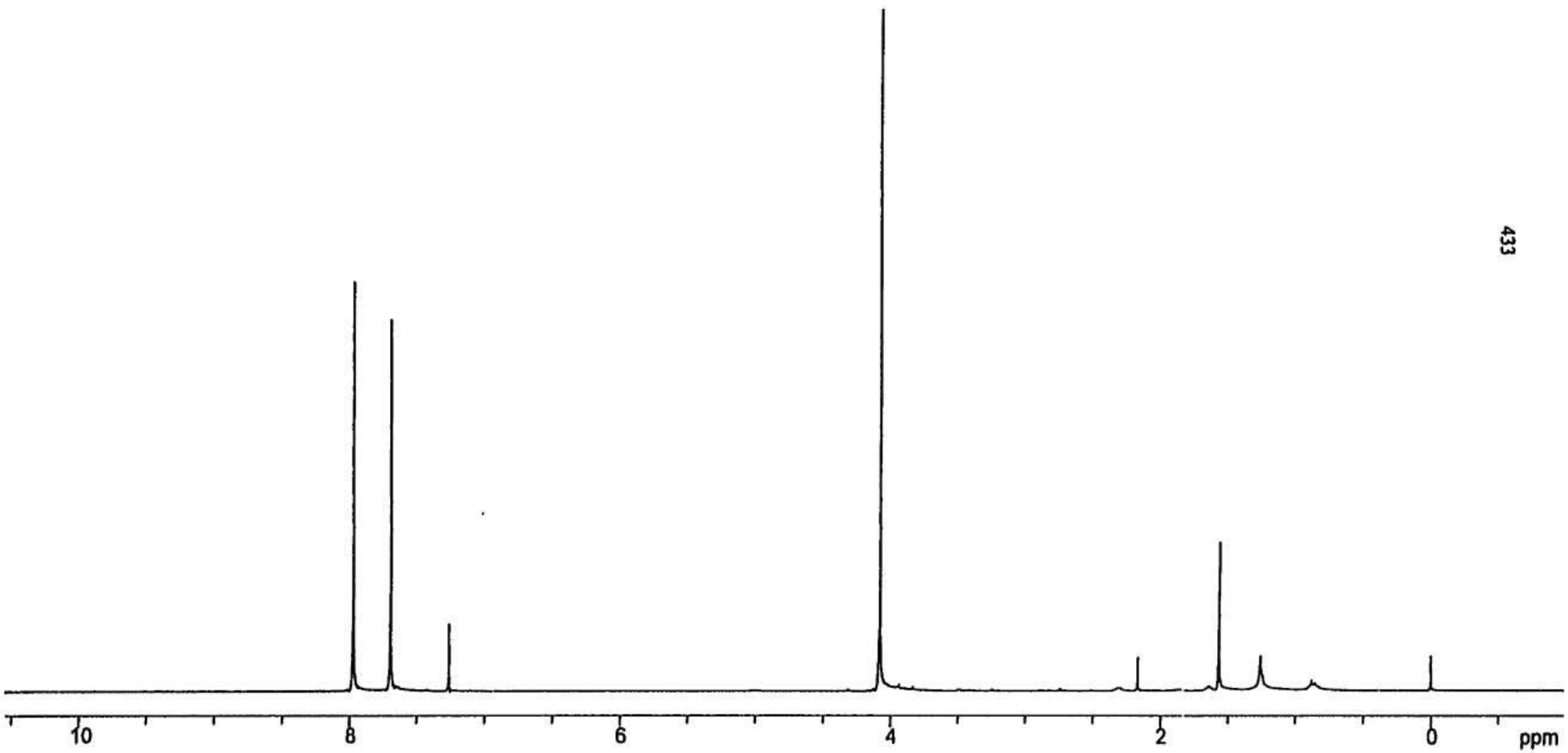

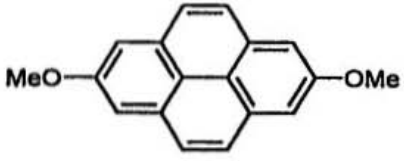

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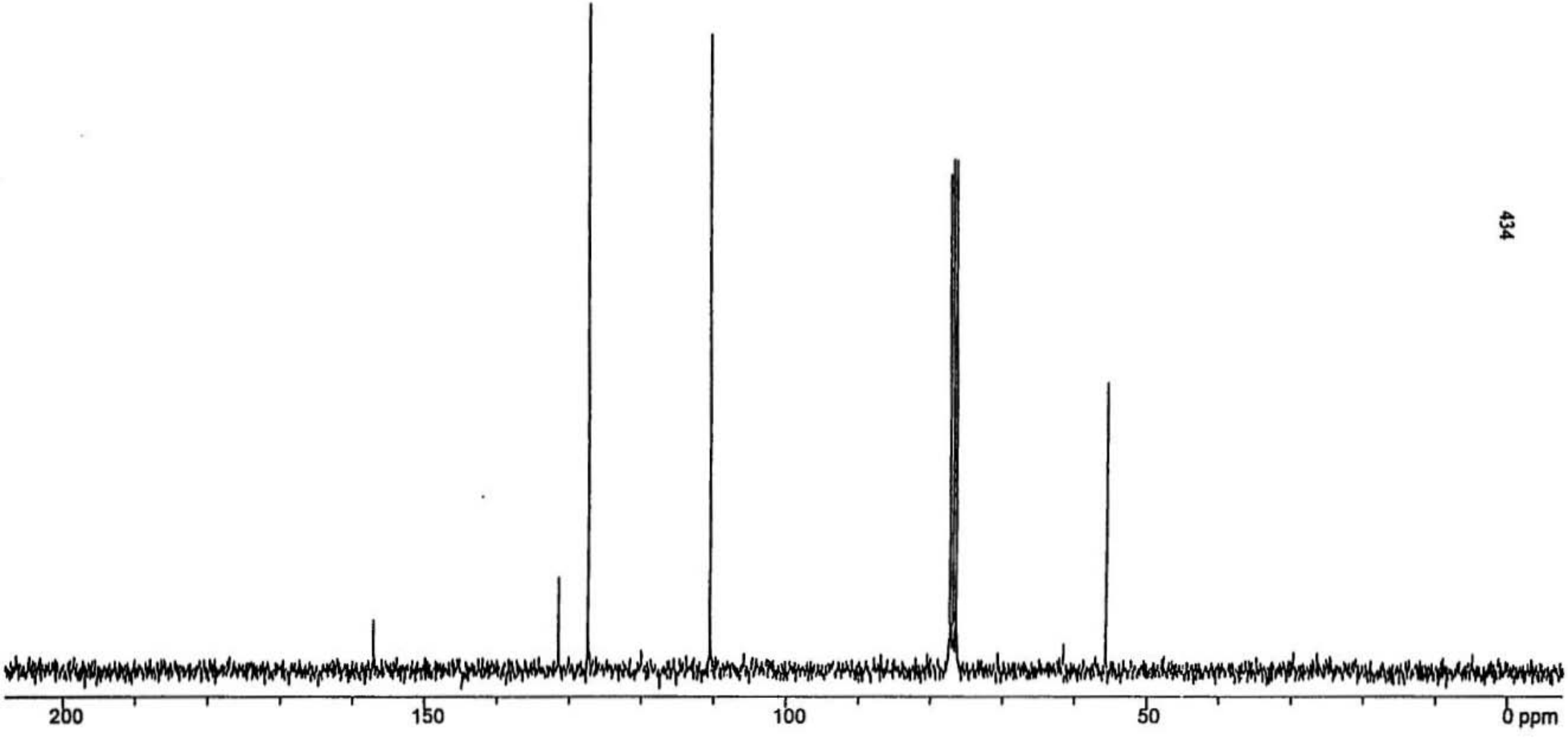

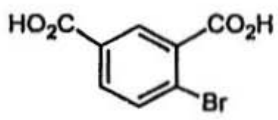

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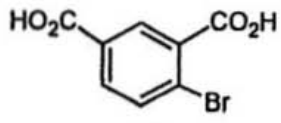

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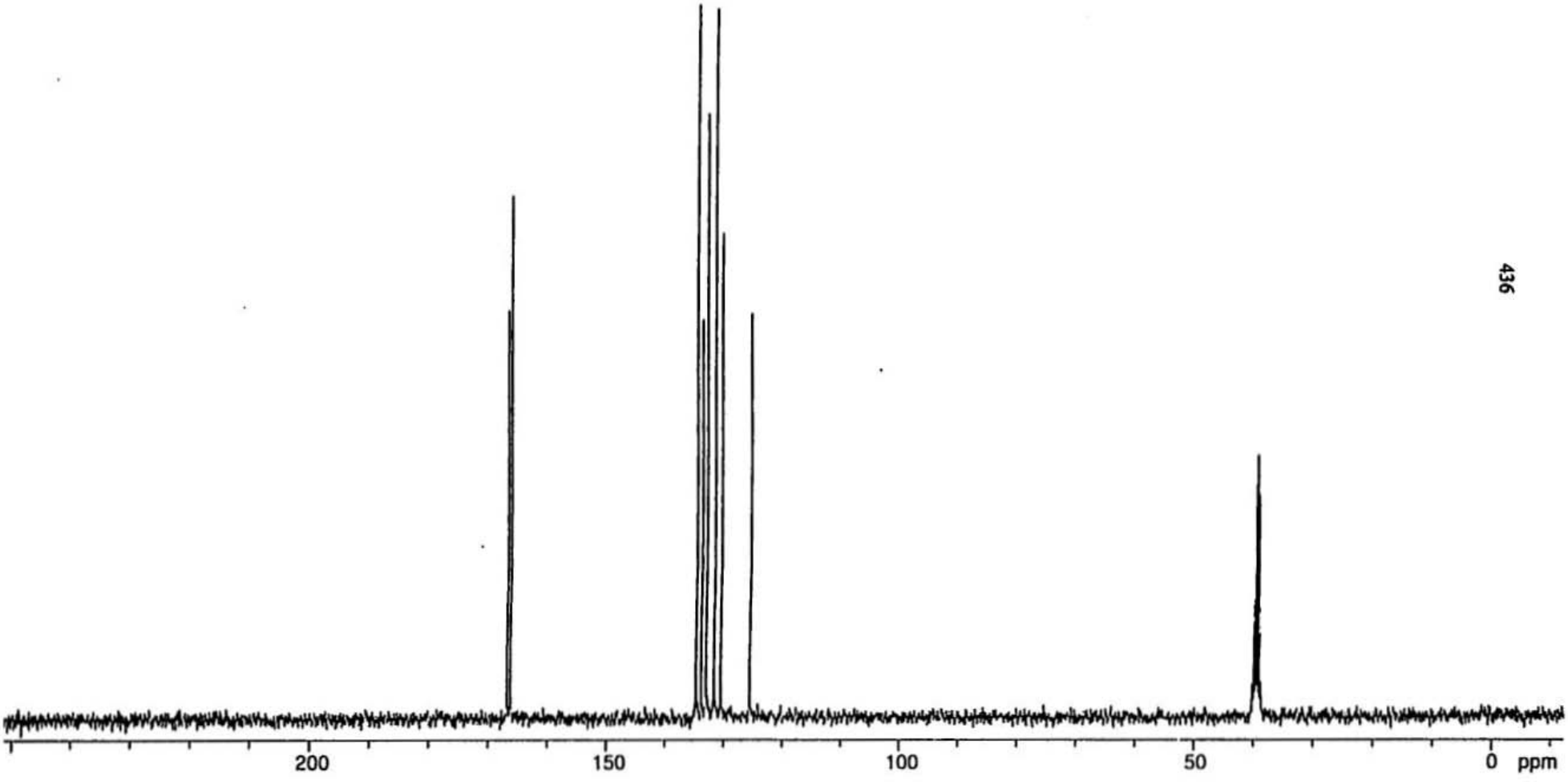

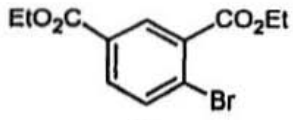

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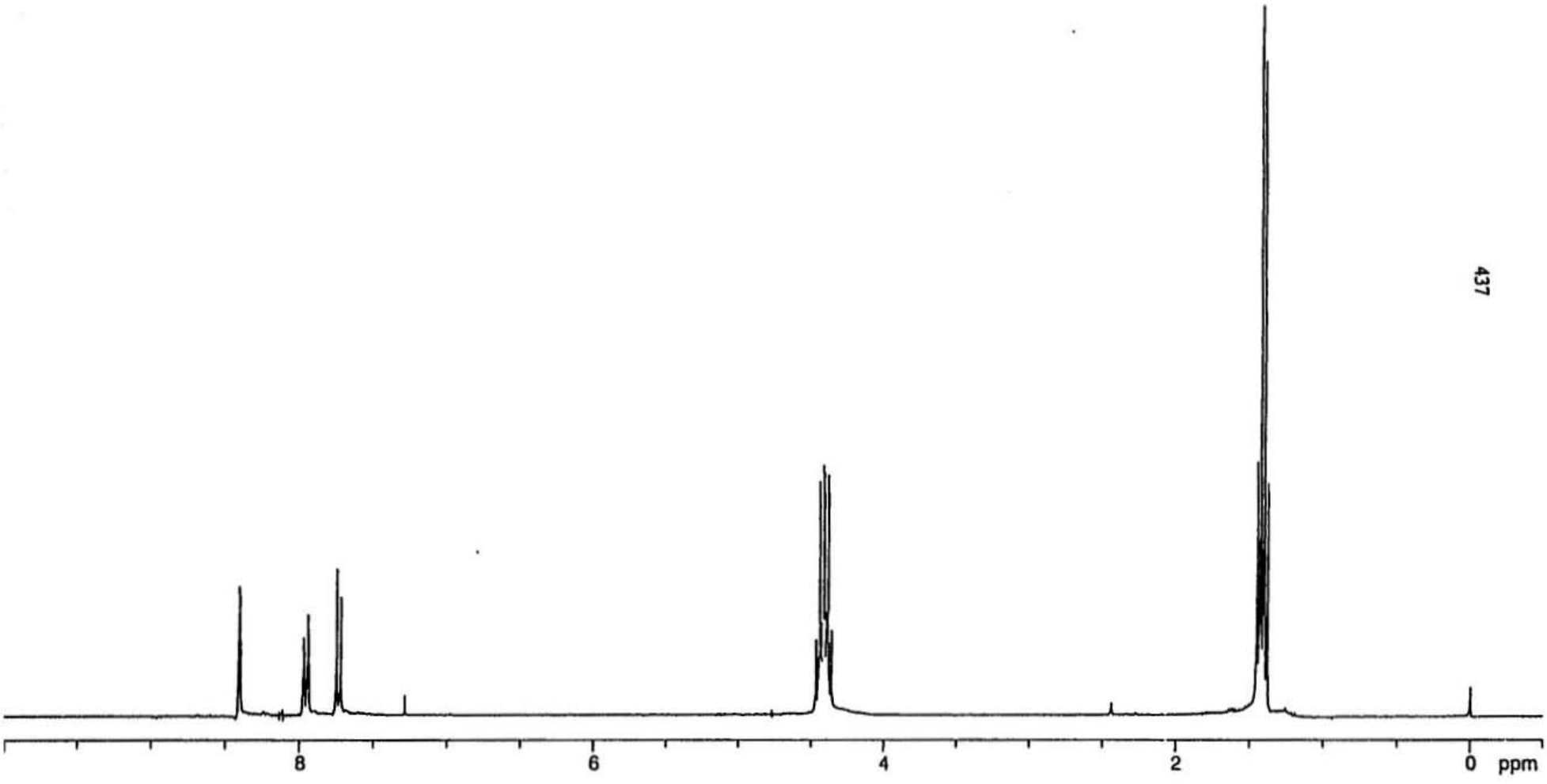

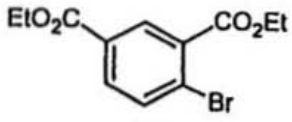

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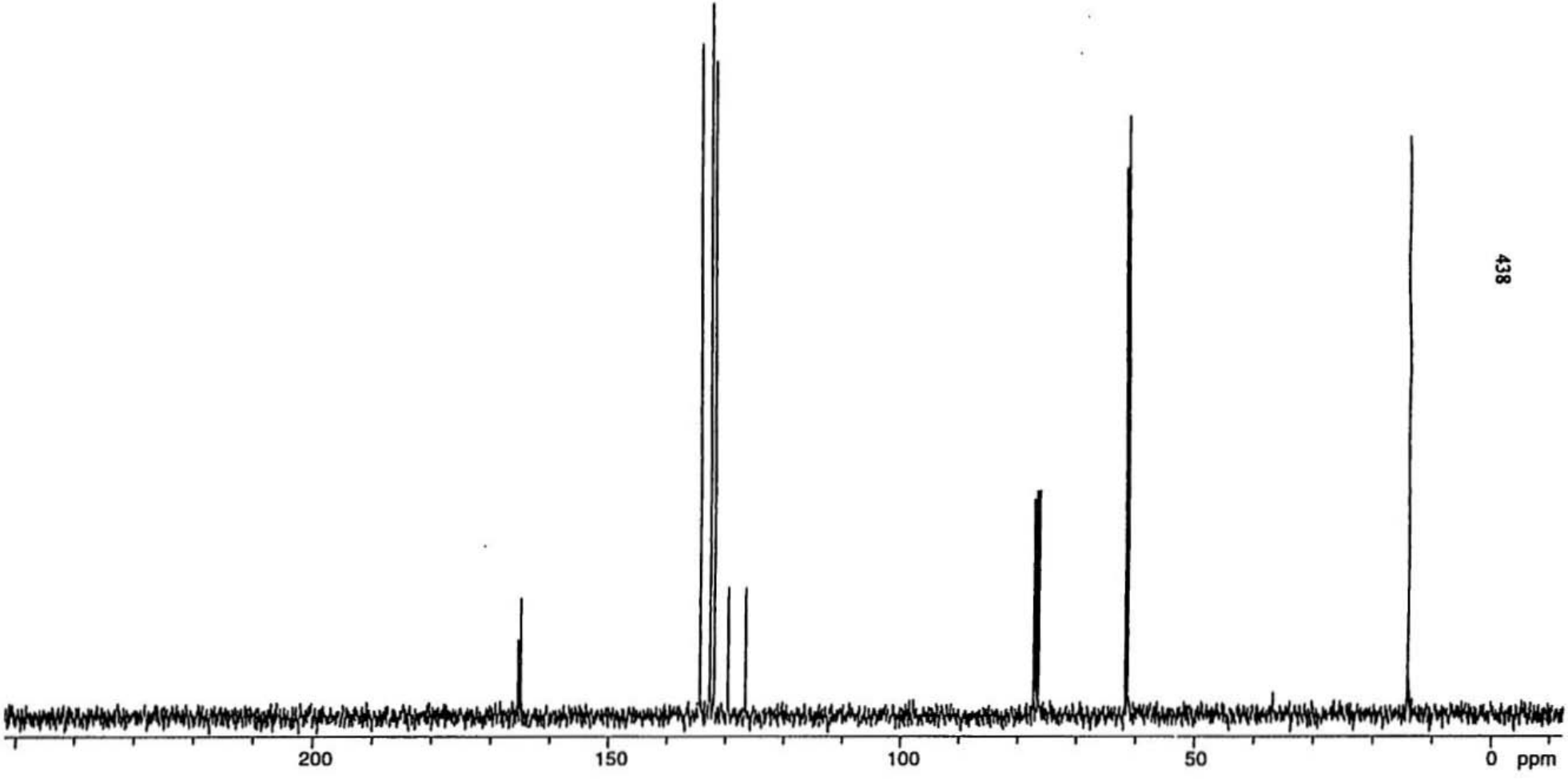

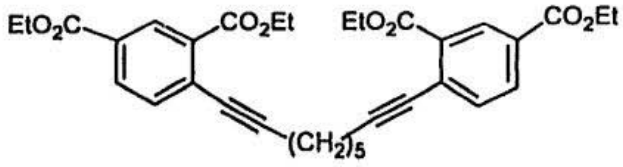

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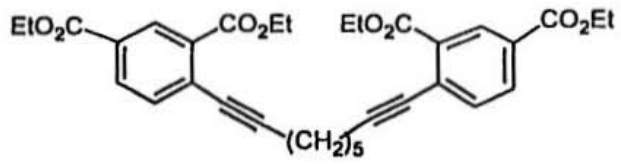

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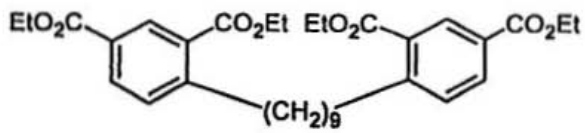

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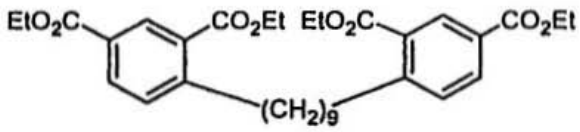

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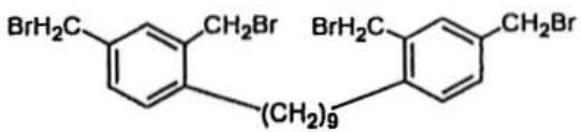
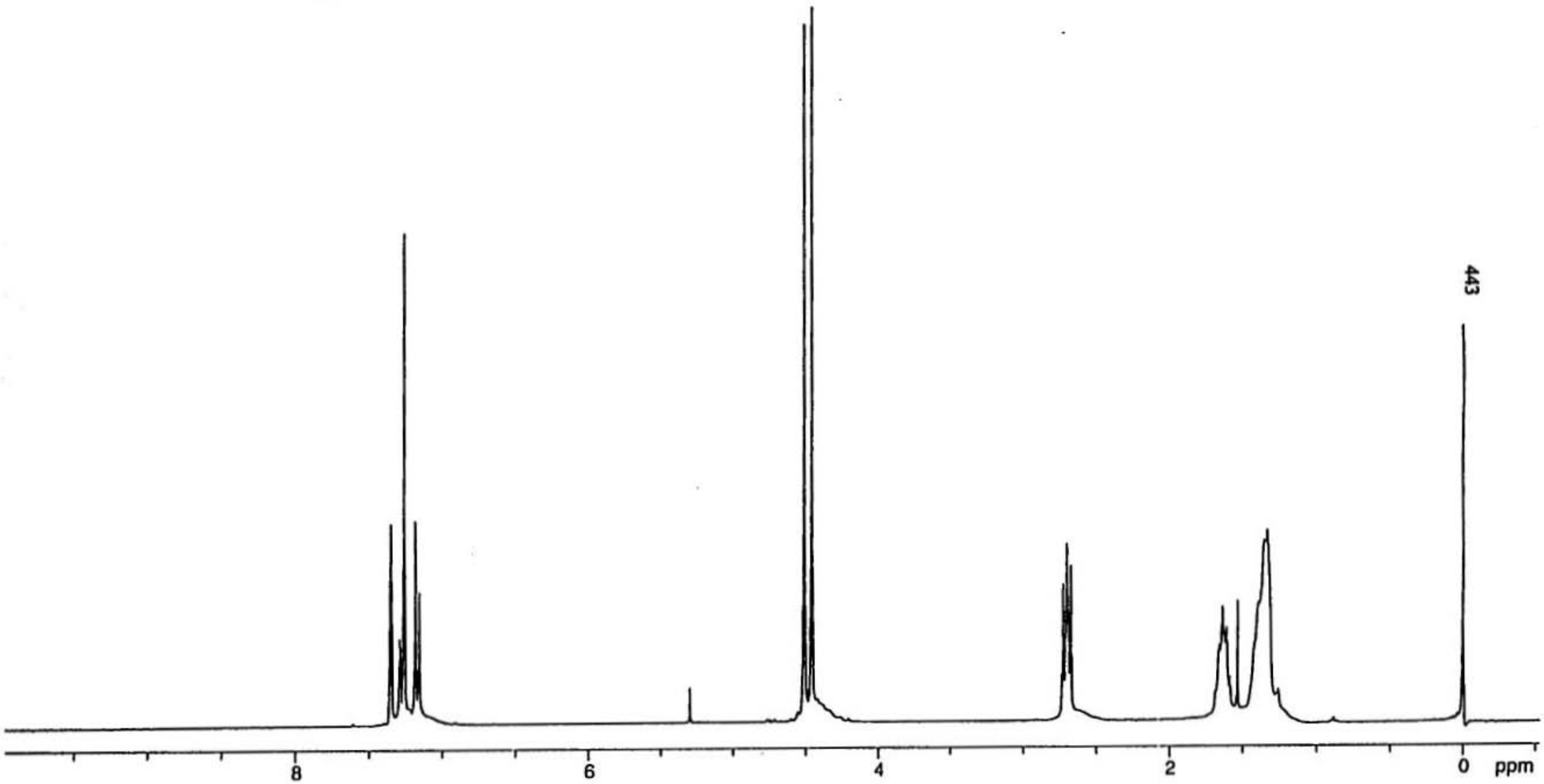
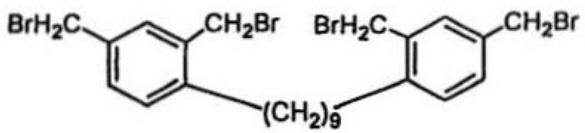


66





66

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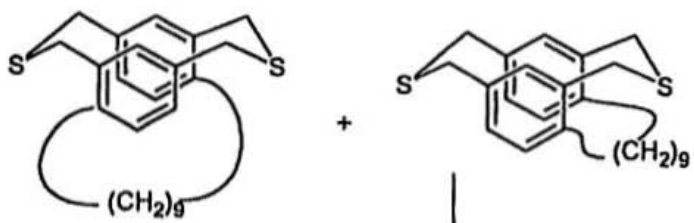
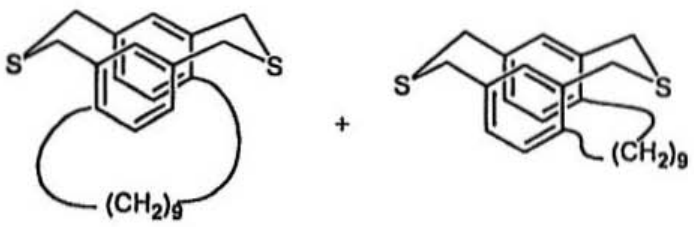


65

+

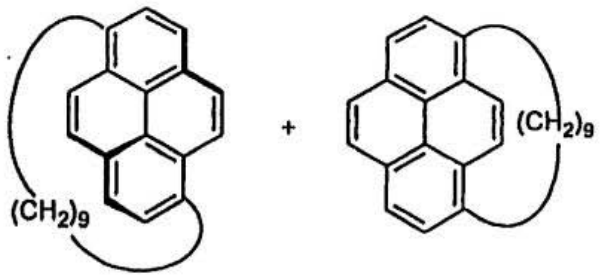
67



65

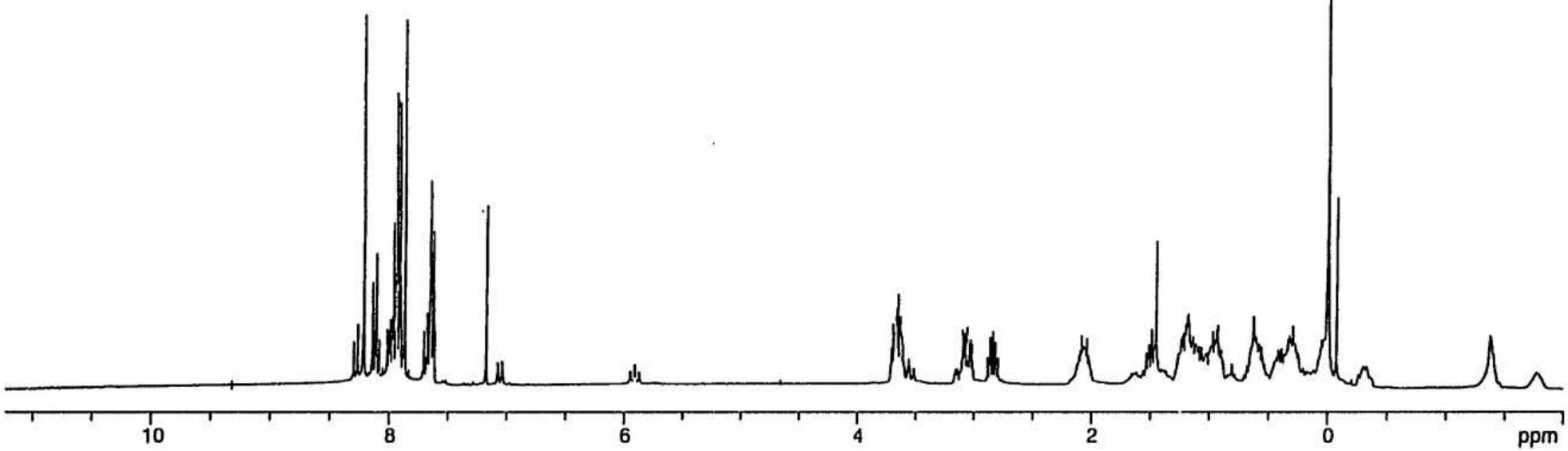
+

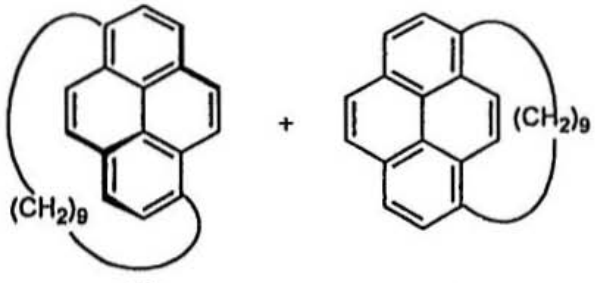
67



64 68

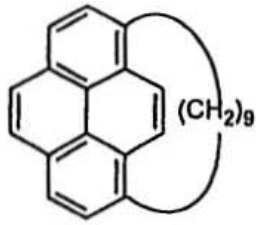
(Crude Product Mixture)





64 68

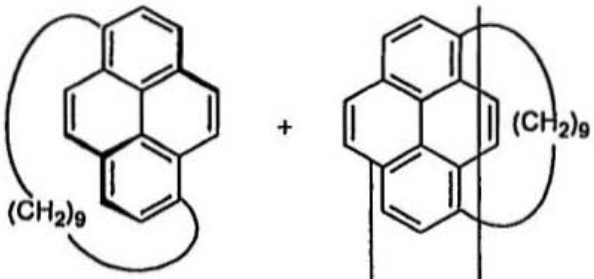
(Crude Product Mixture)



68

(Hexane Crystalline Fraction)

10 8 6 4 2 0 ppm

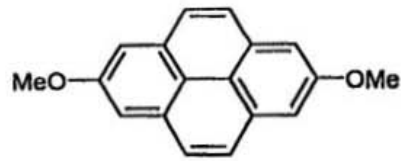


64 68

(Hexane-Soluble Fraction)

Appendix D – Selected Spectra from Chapter 6

(Compounds as numbered in Chapter 6; compounds appear in the order in which they are described in the Experimental section of the text.)



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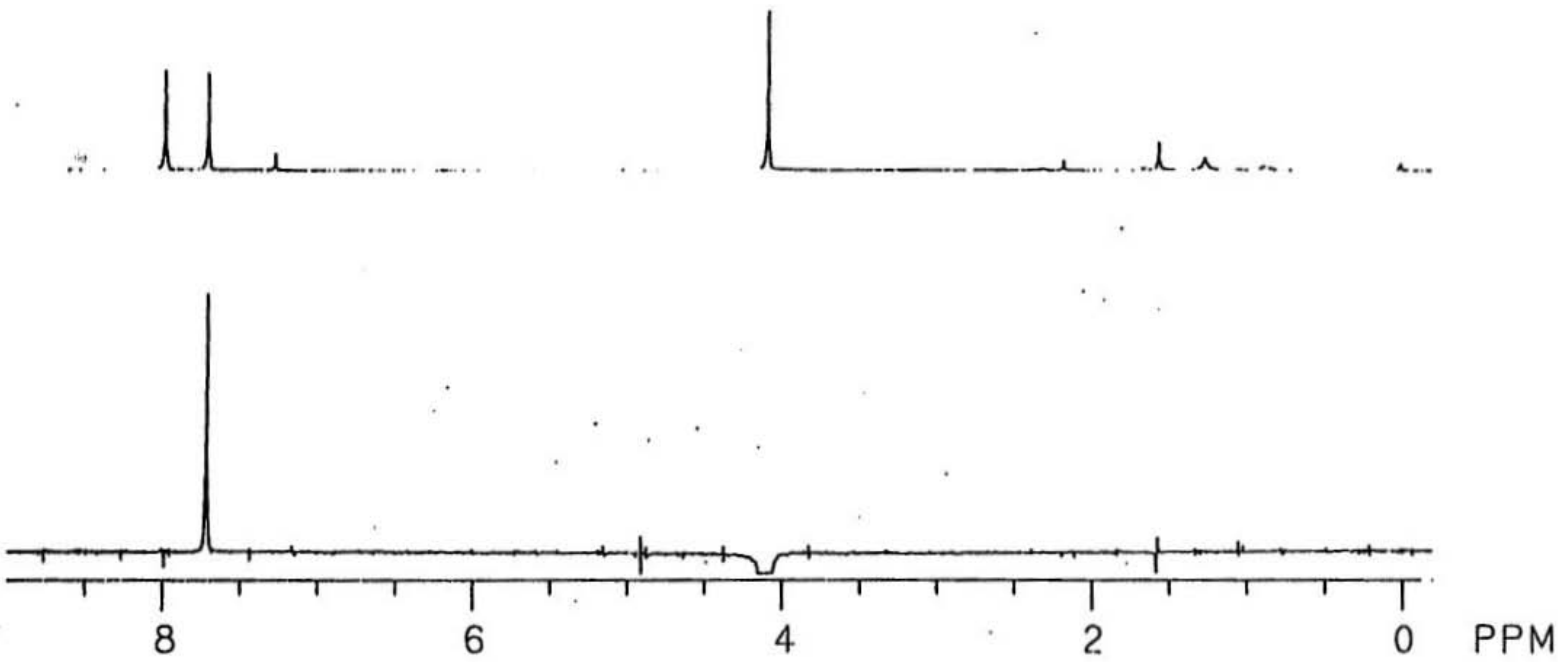
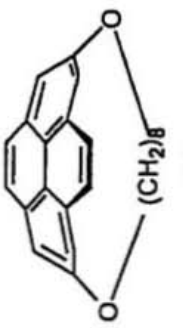
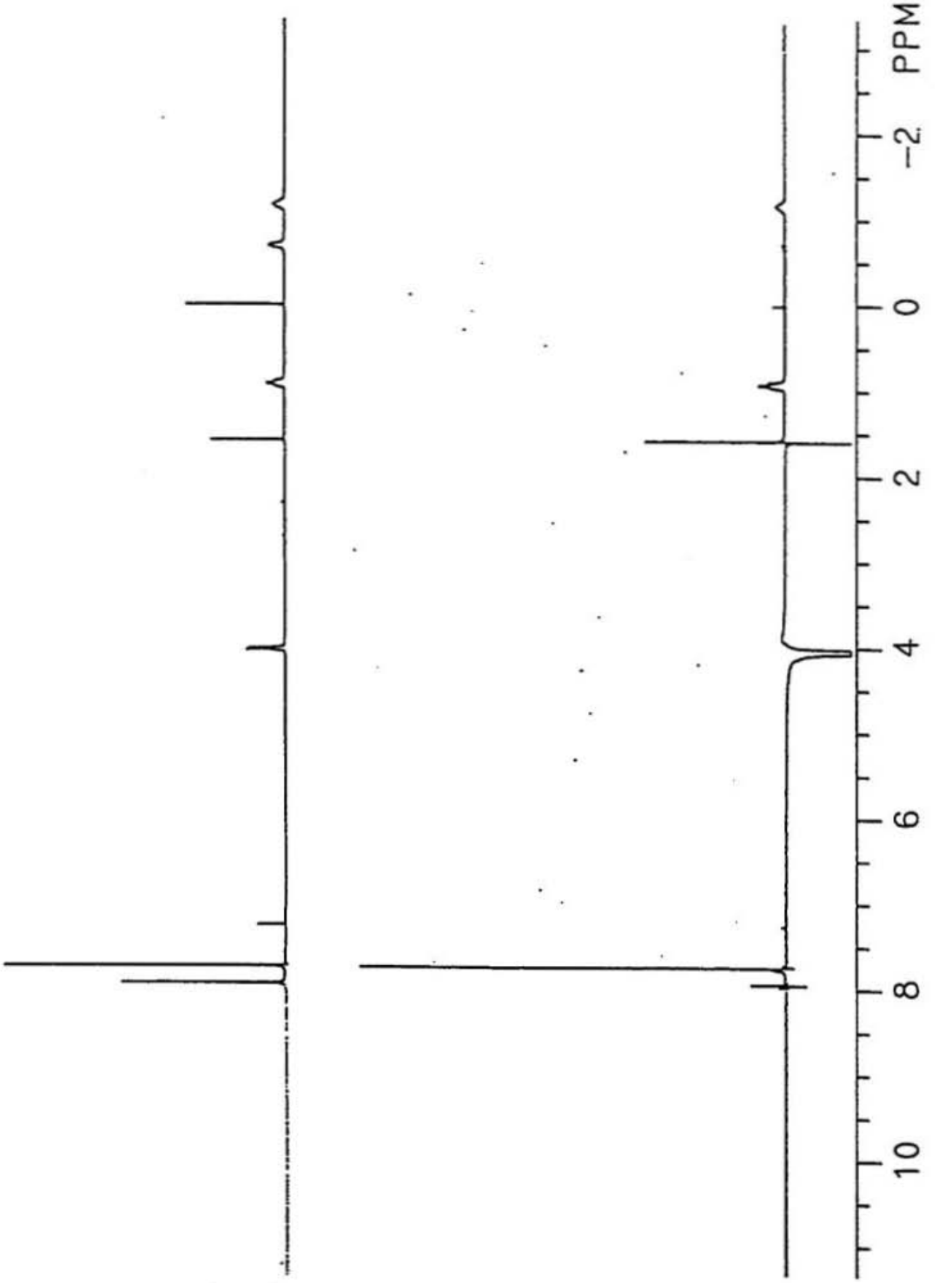
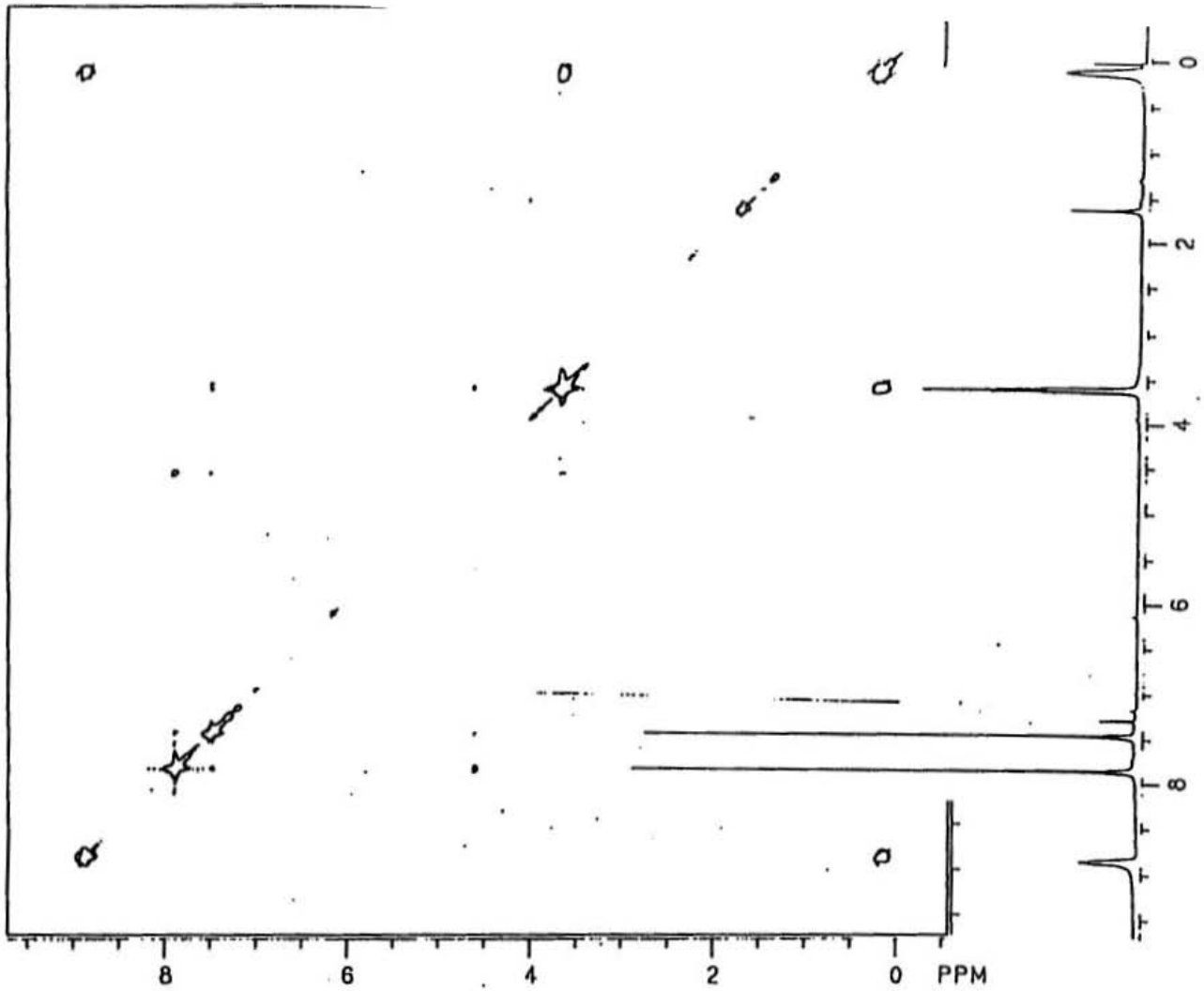


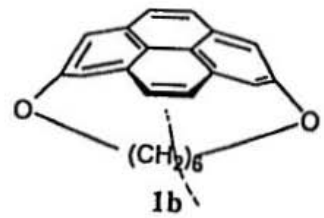


1d

NOED







1b

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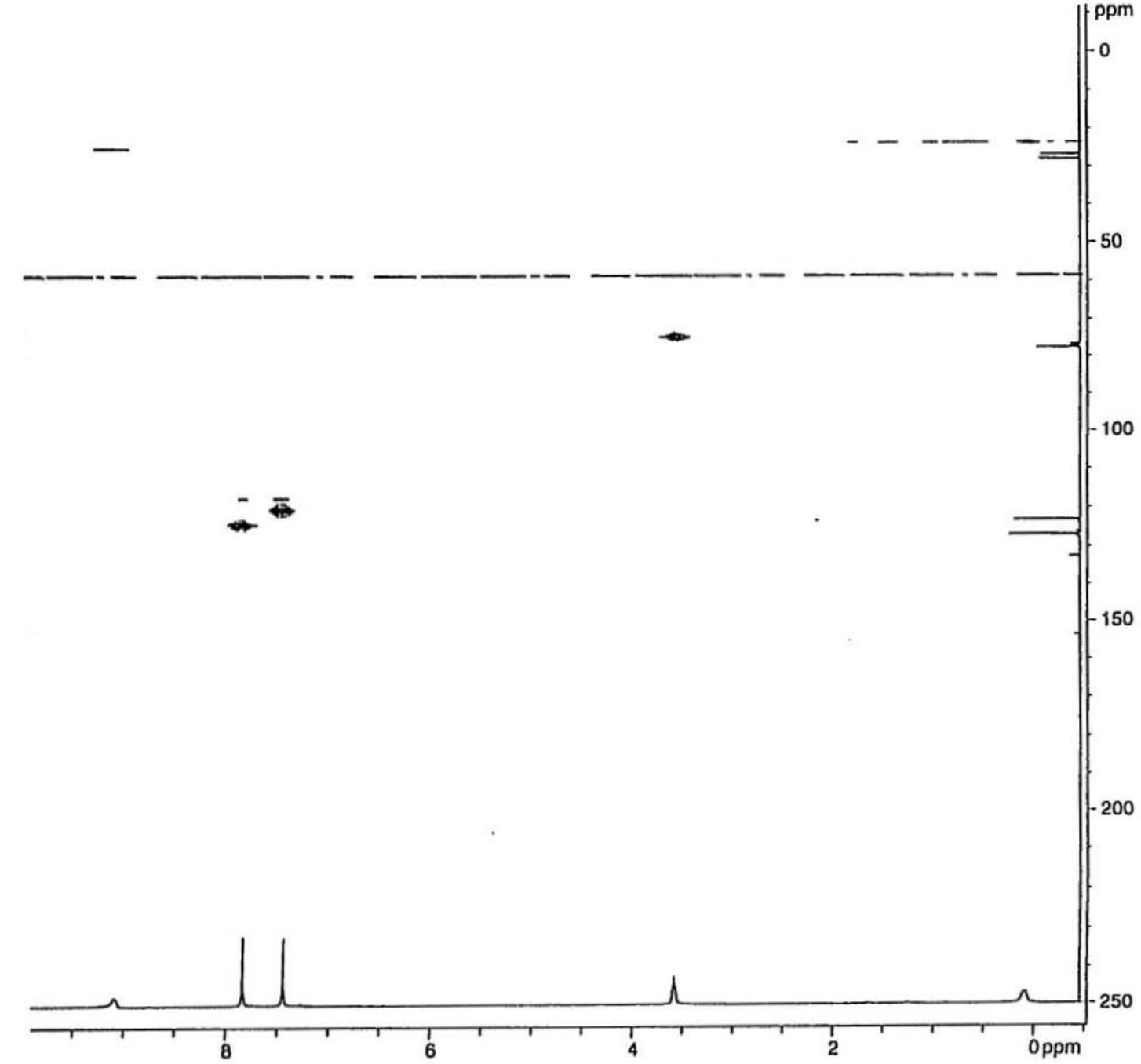

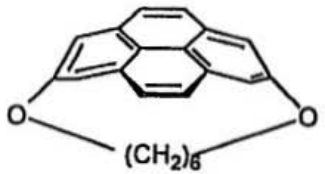

1b

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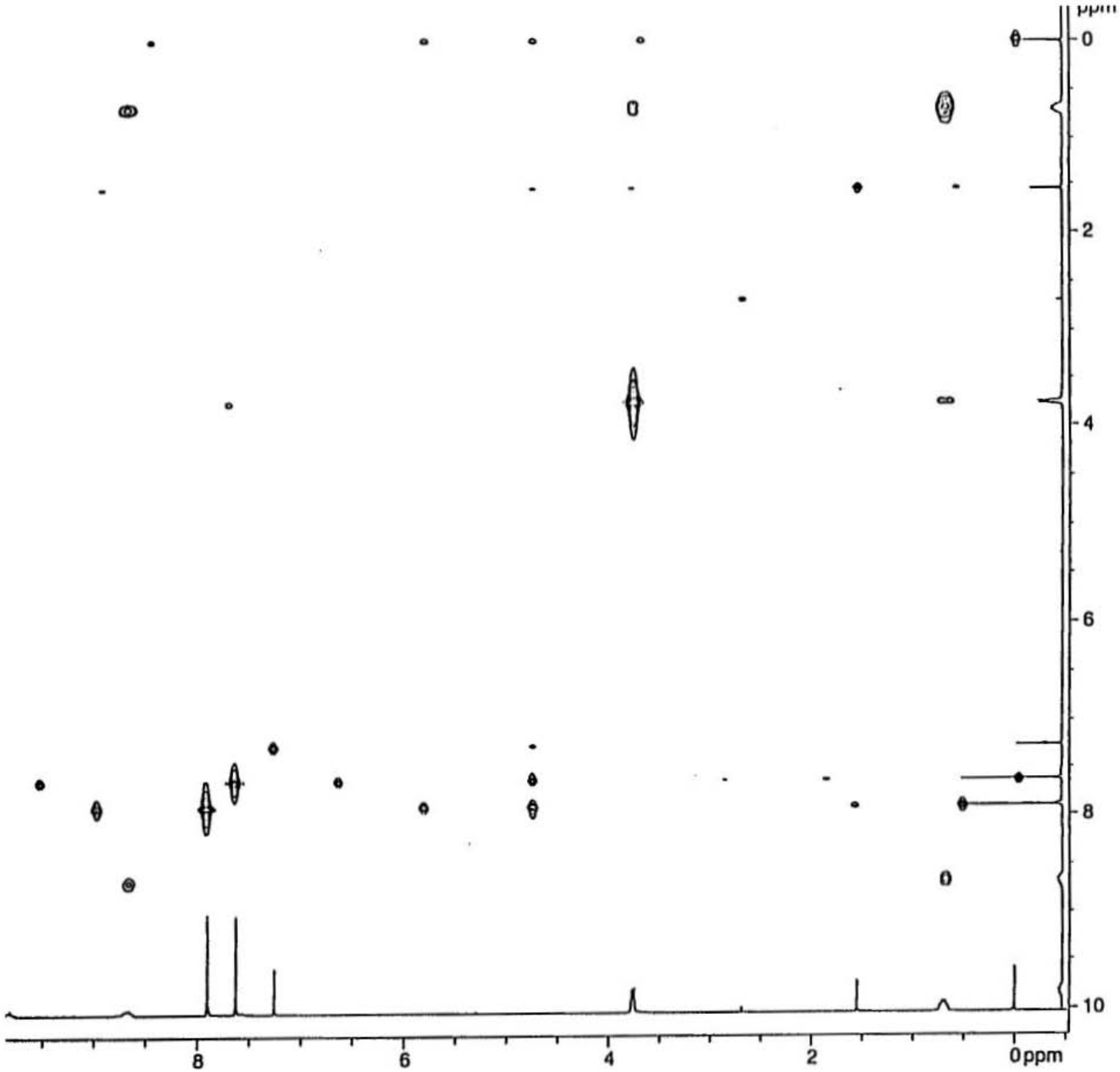
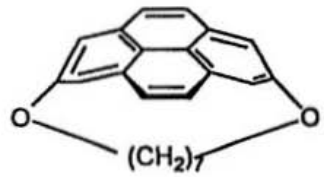
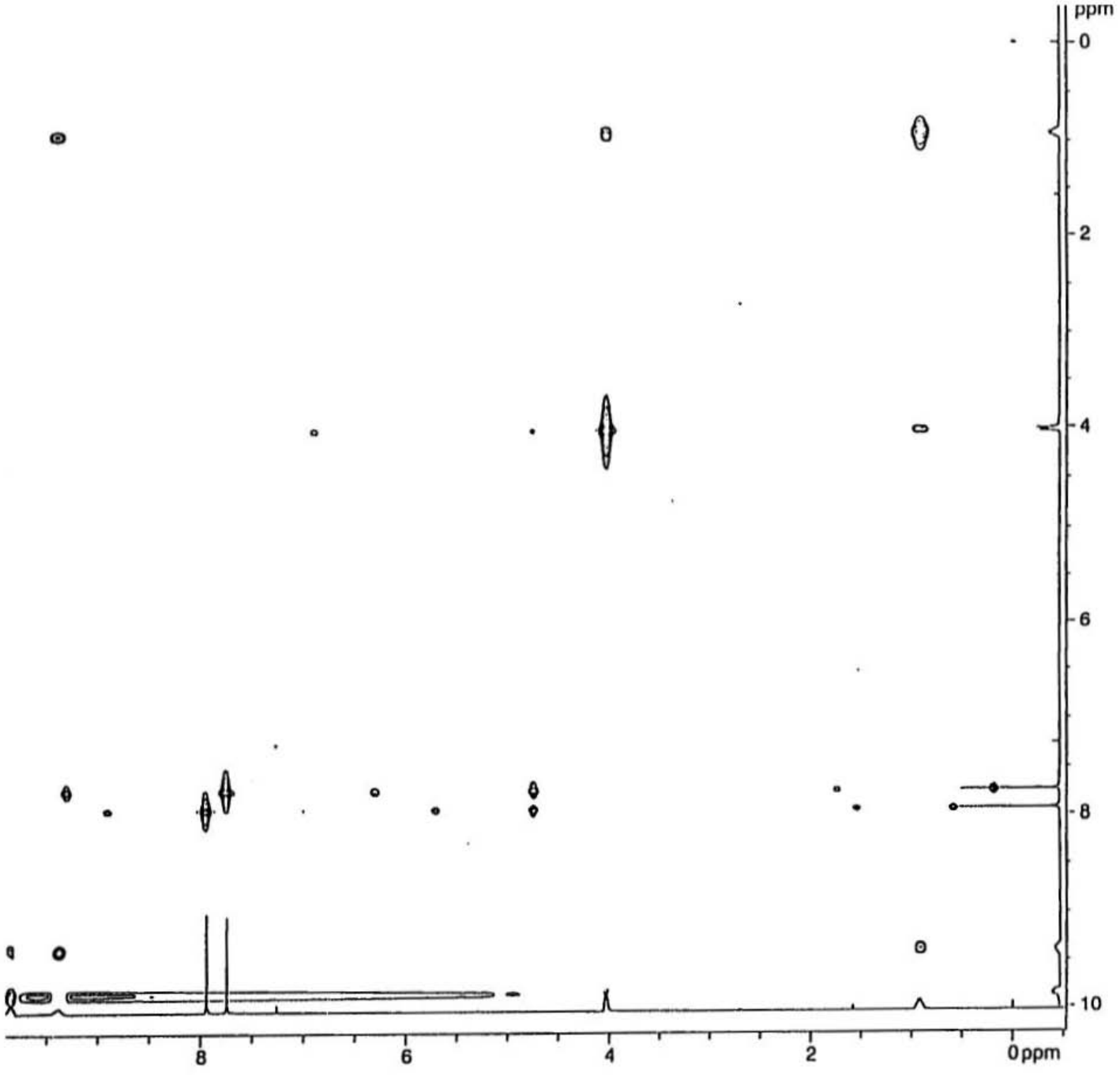
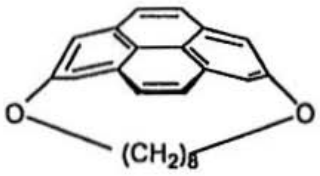




1c

^1H-^1H COSY





1d

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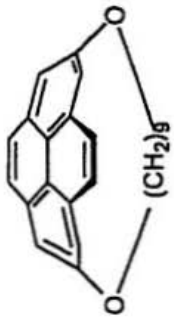

1c

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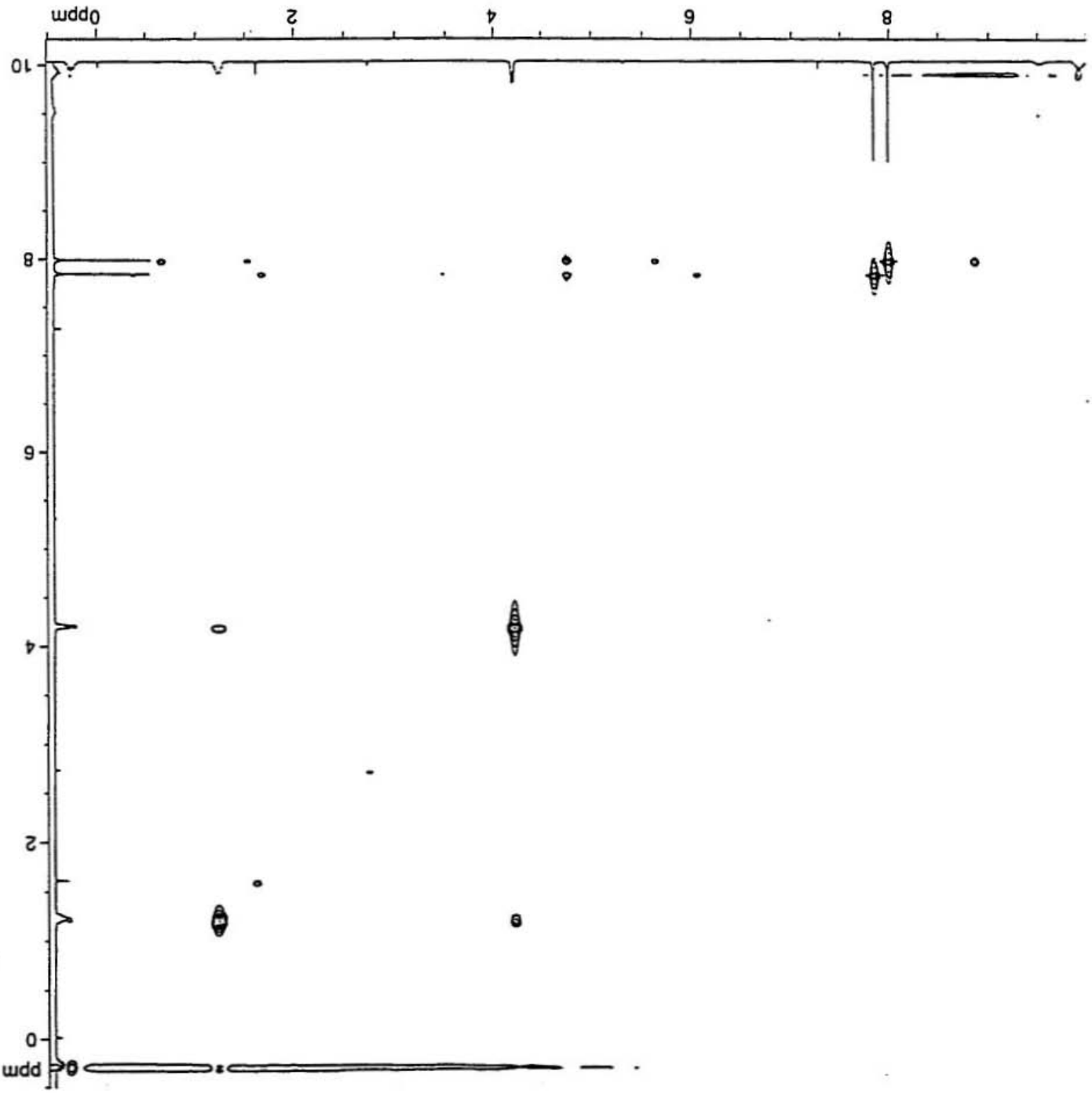

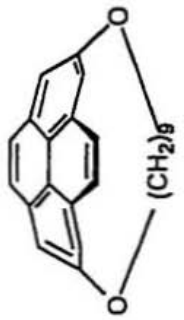

1e

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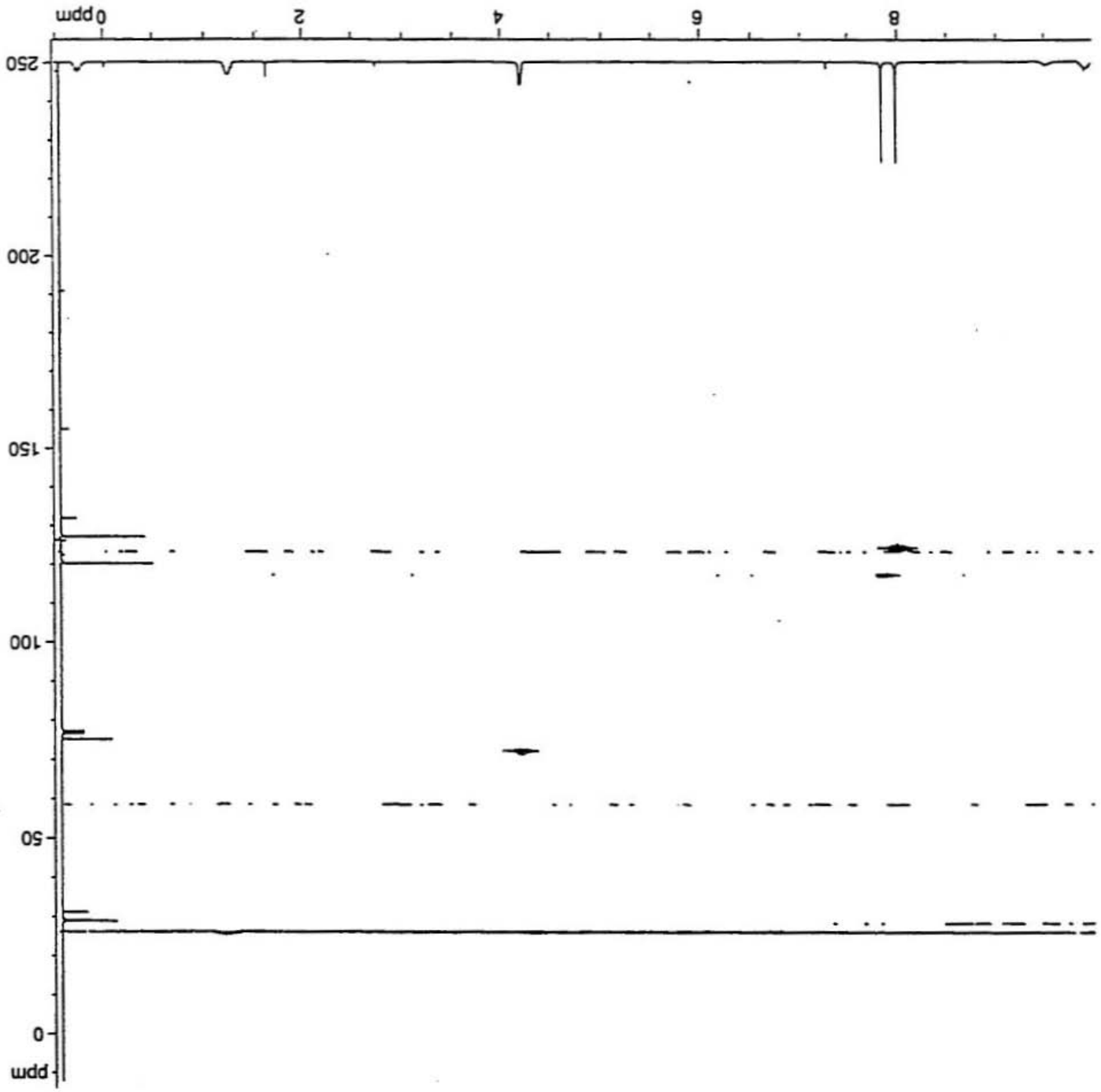

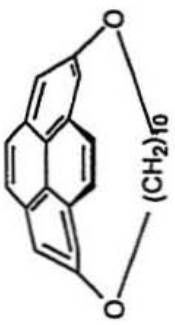

1f

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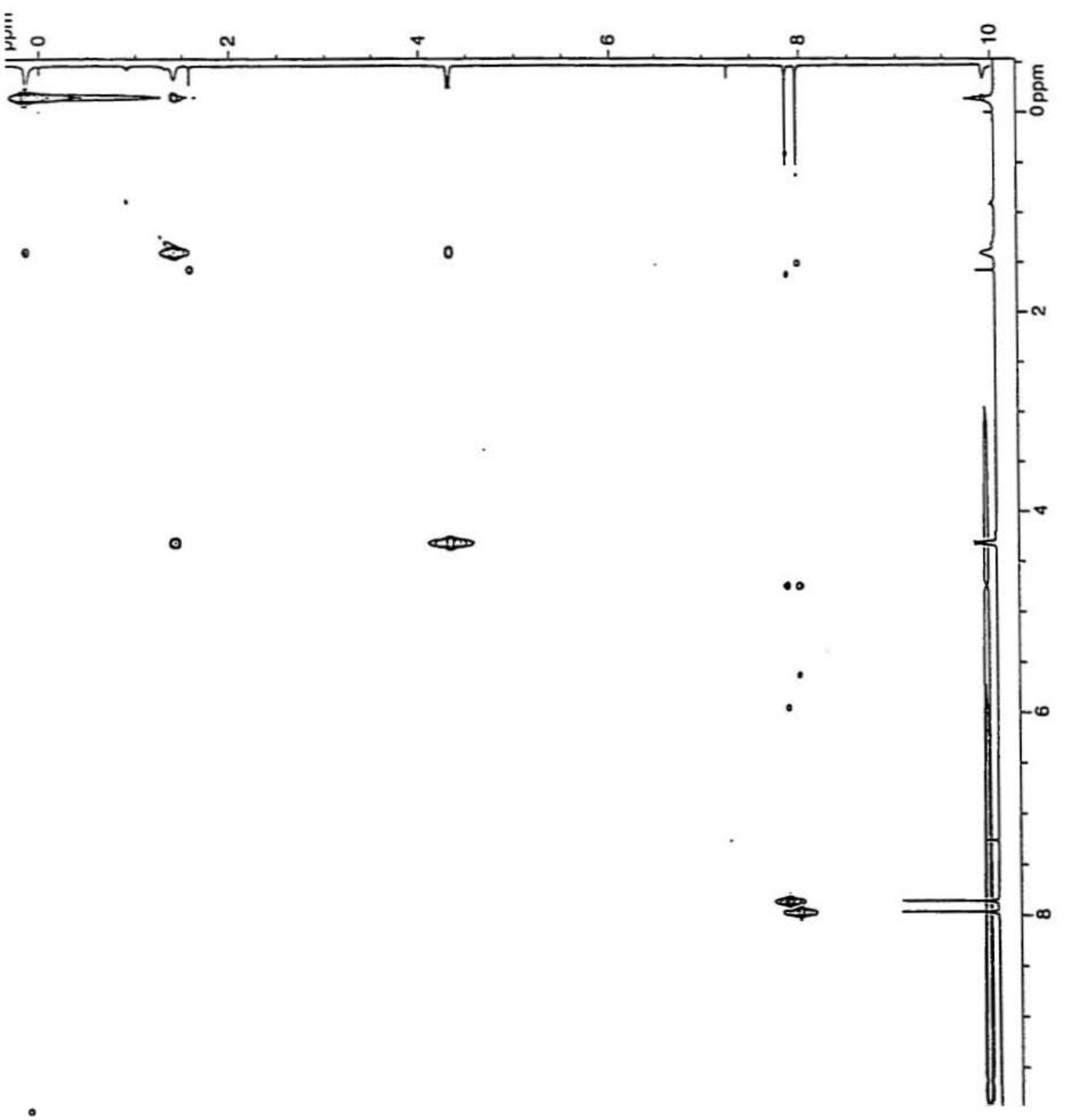

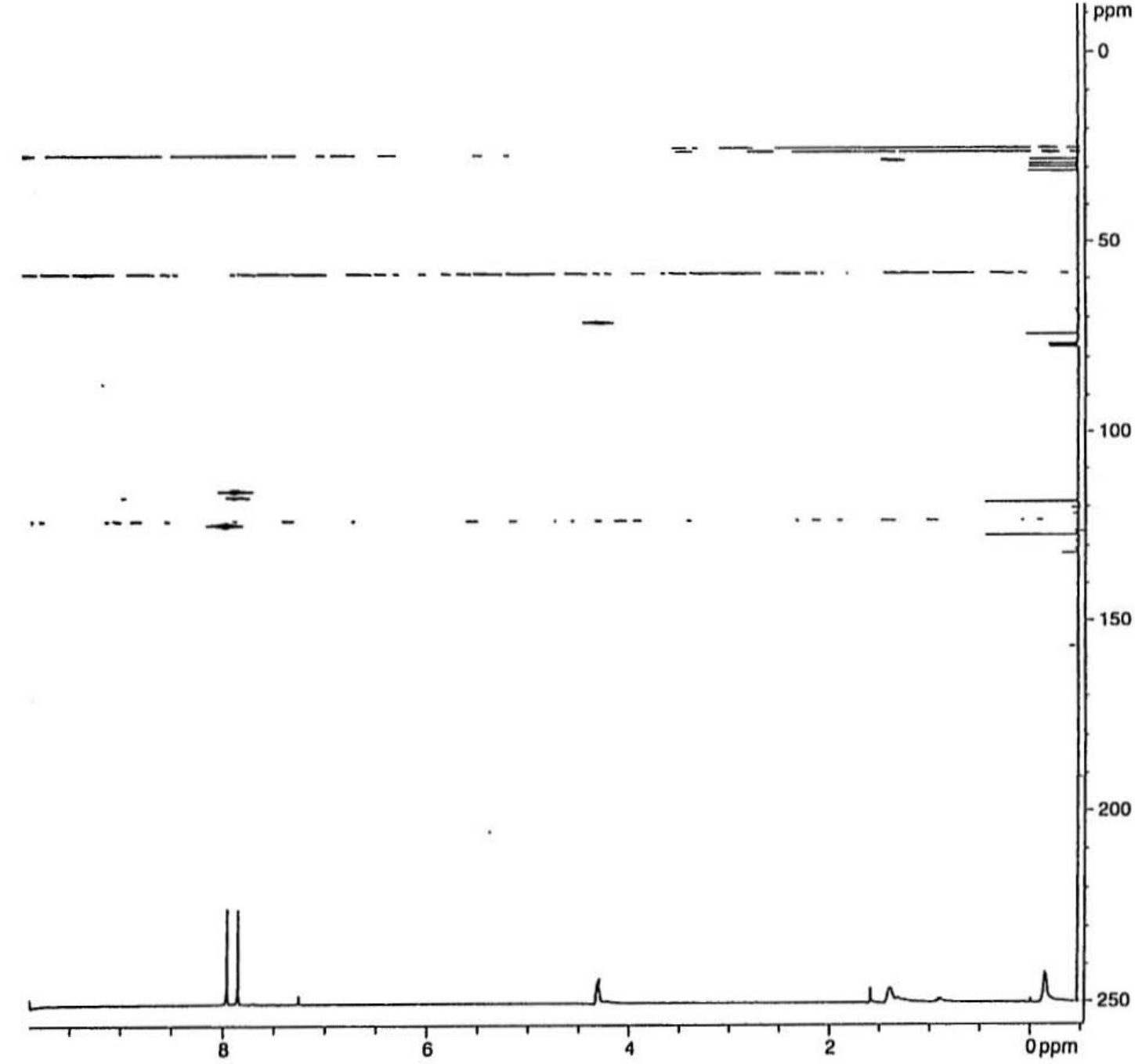

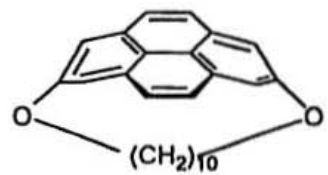

1f

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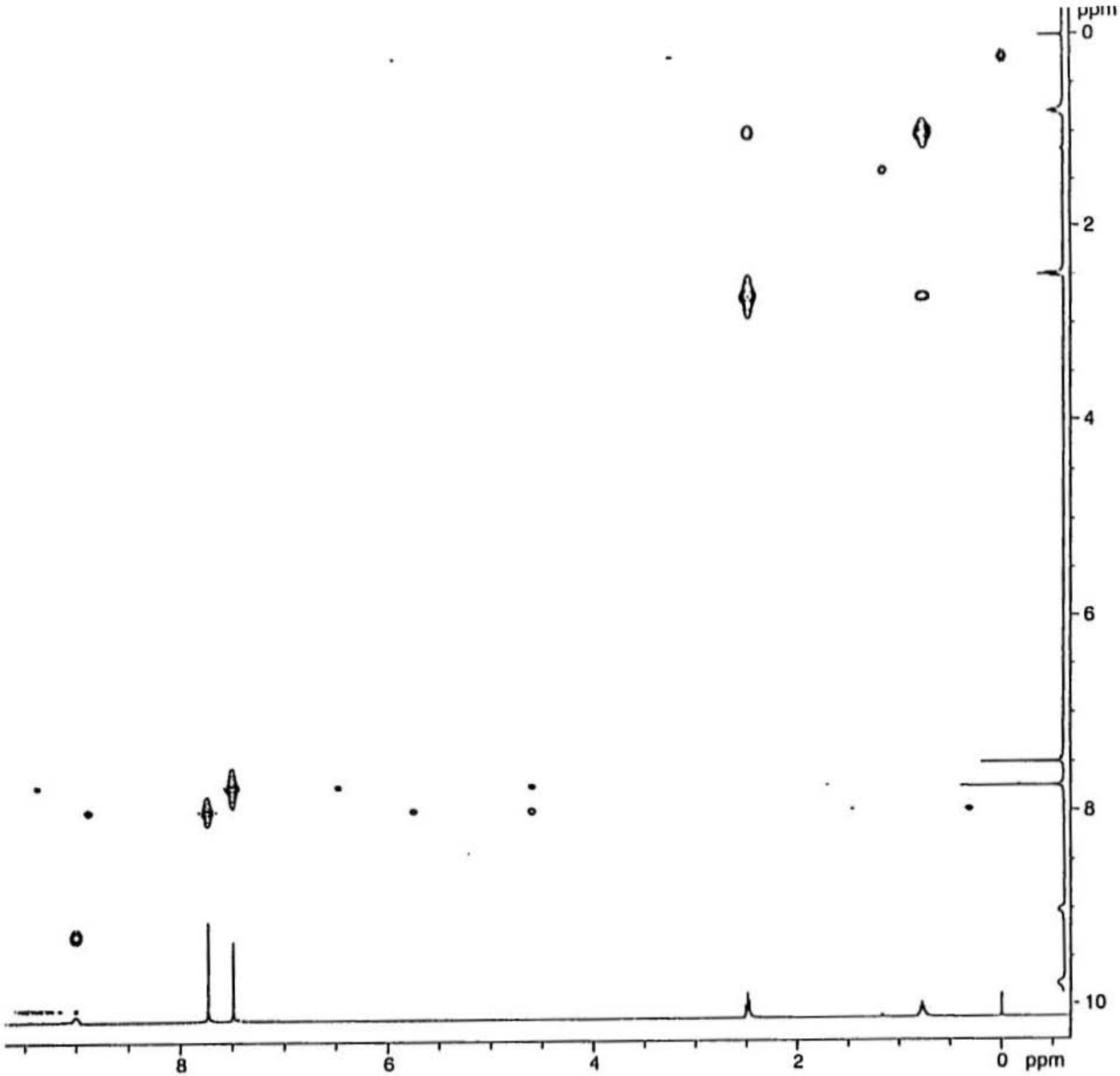

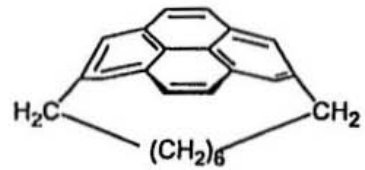

2b

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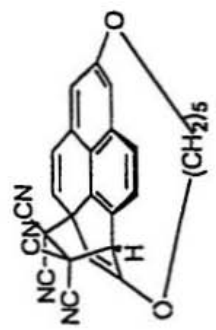

28

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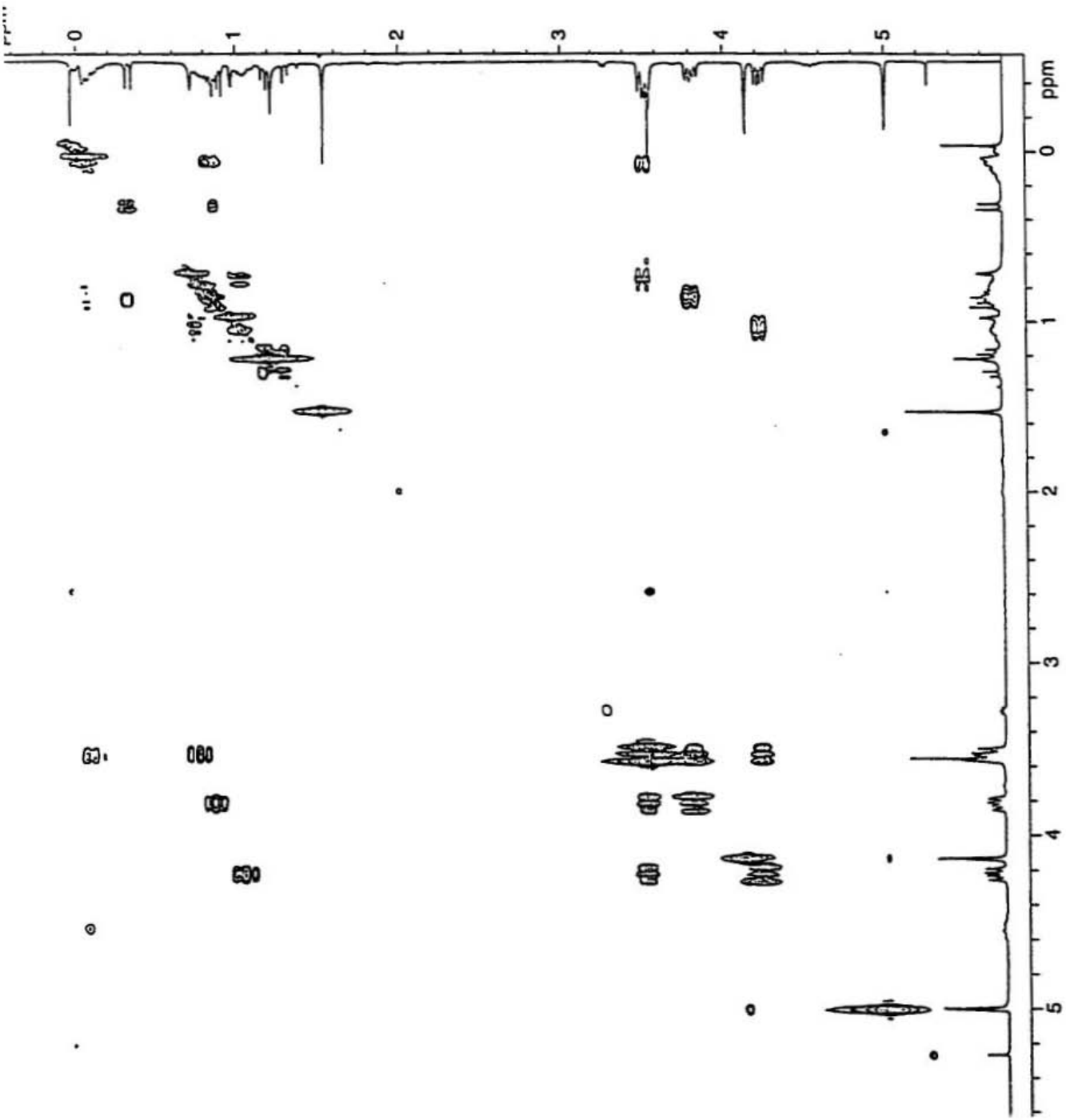

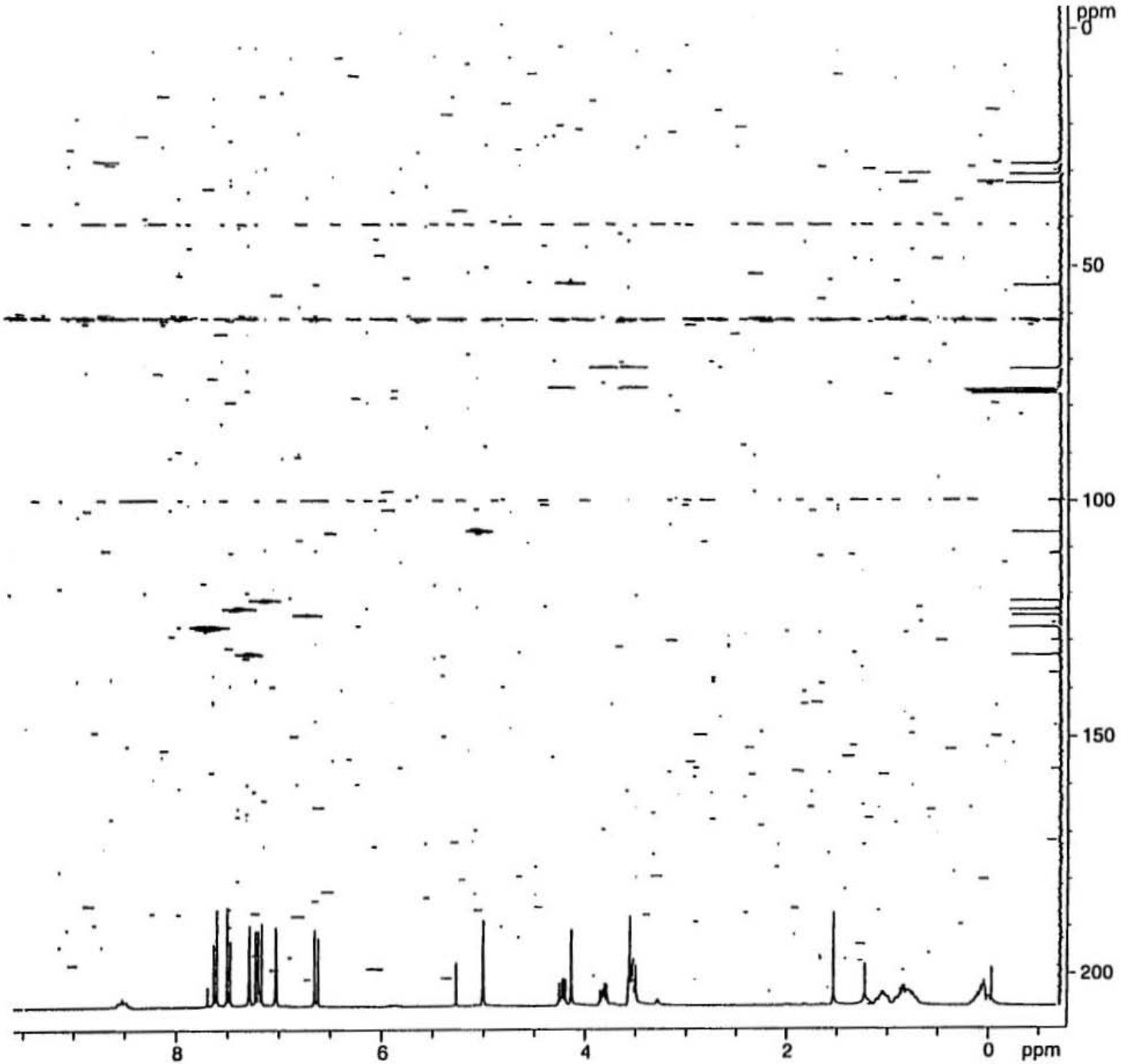

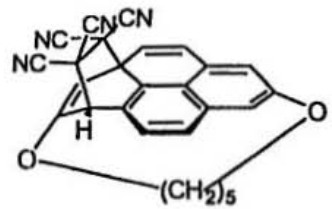

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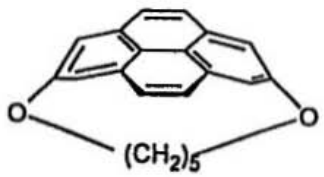
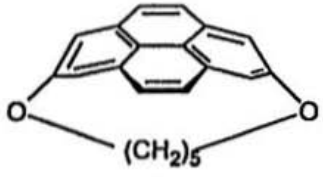


1a

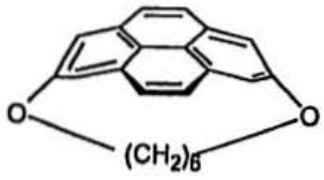
In CD_2Cl_2, at 0 °C

10 8 6 4 2 0 -2 ppm



1a

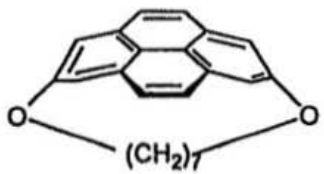
In CD_2Cl_2, at - 80 °C



1b

BB ^{1}H Decoupler OFF

200 150 100 50 0 ppm

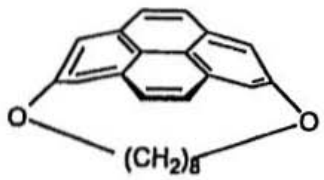


1c

BB ^{1}H Decoupler OFF

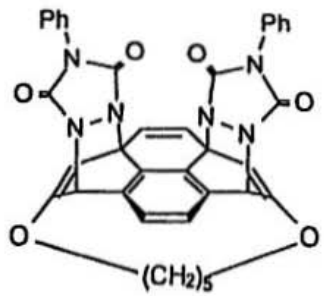
469

200 150 100 50 0 ppm

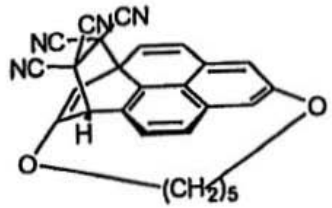


1d

BB ^{1}H Decoupler OFF



26 (?)



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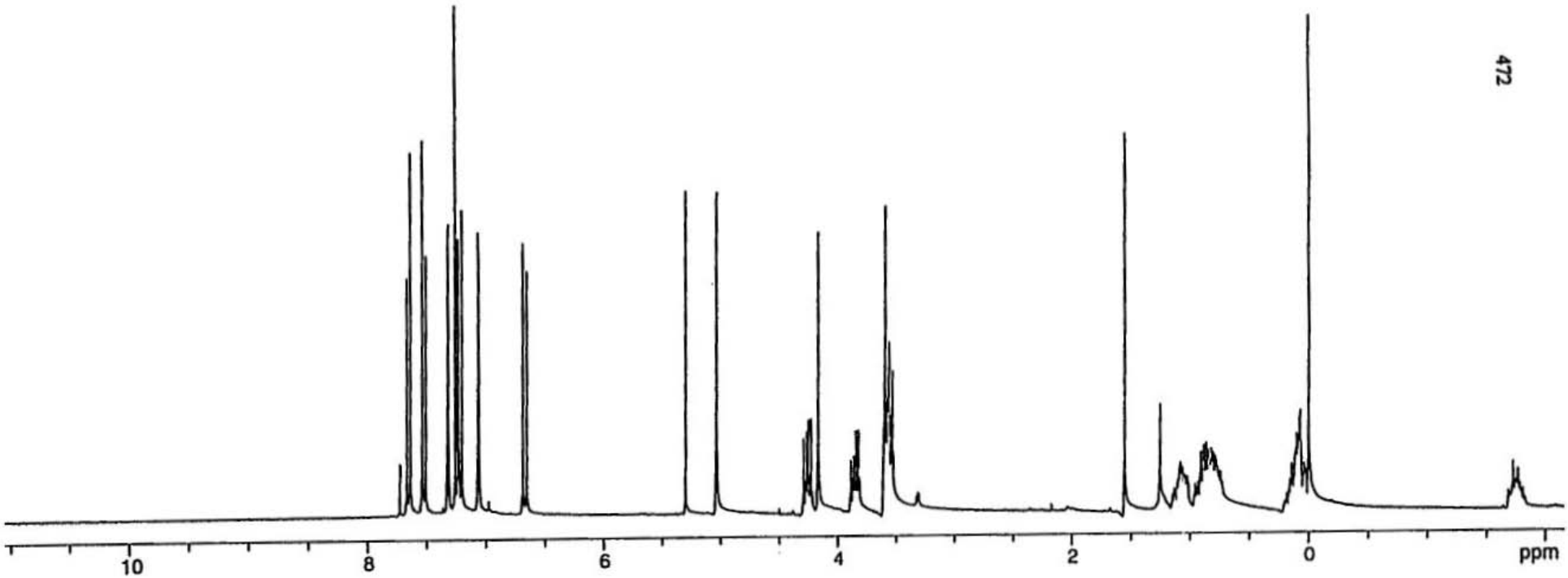

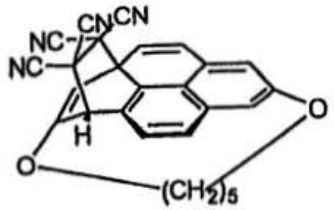

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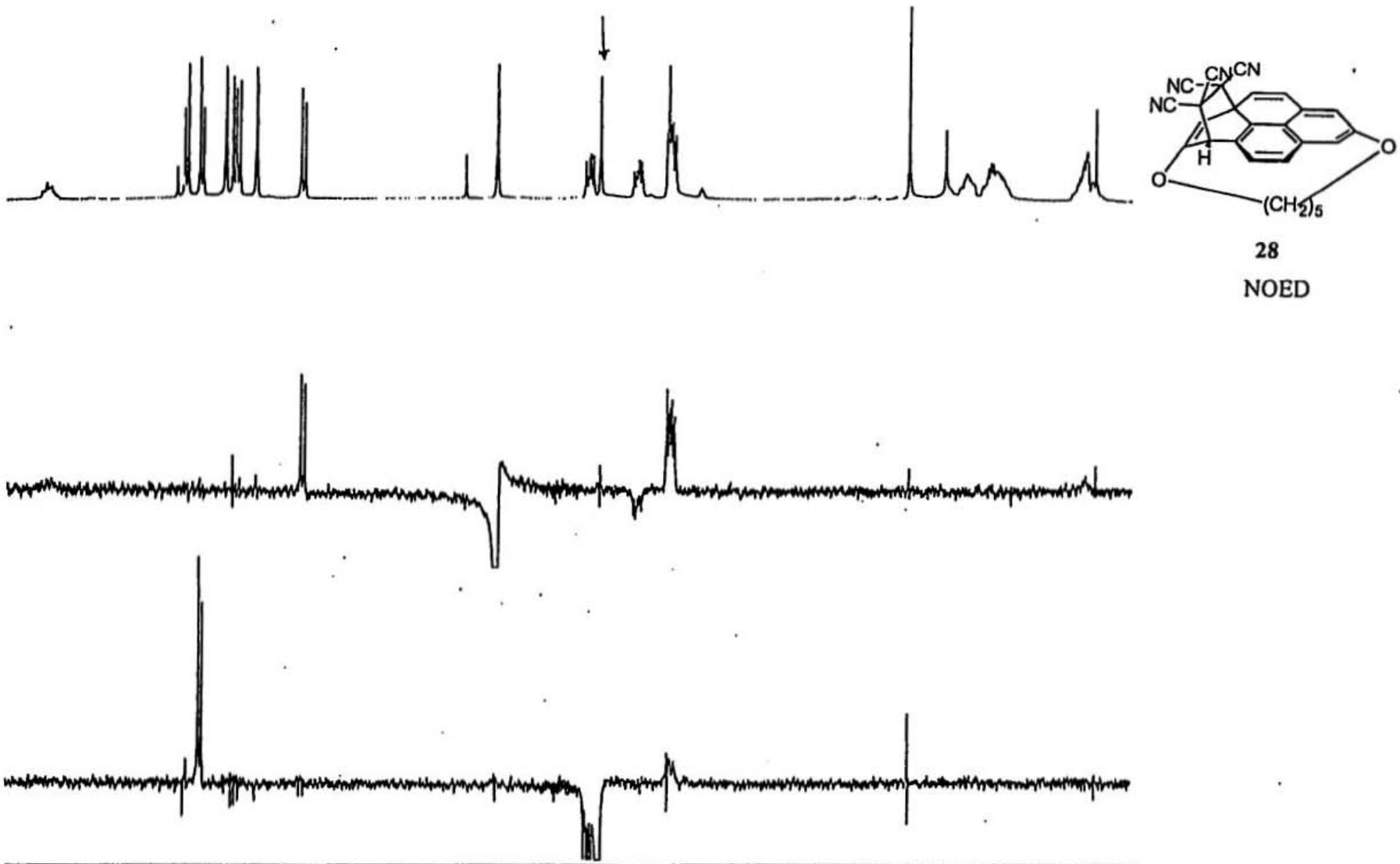
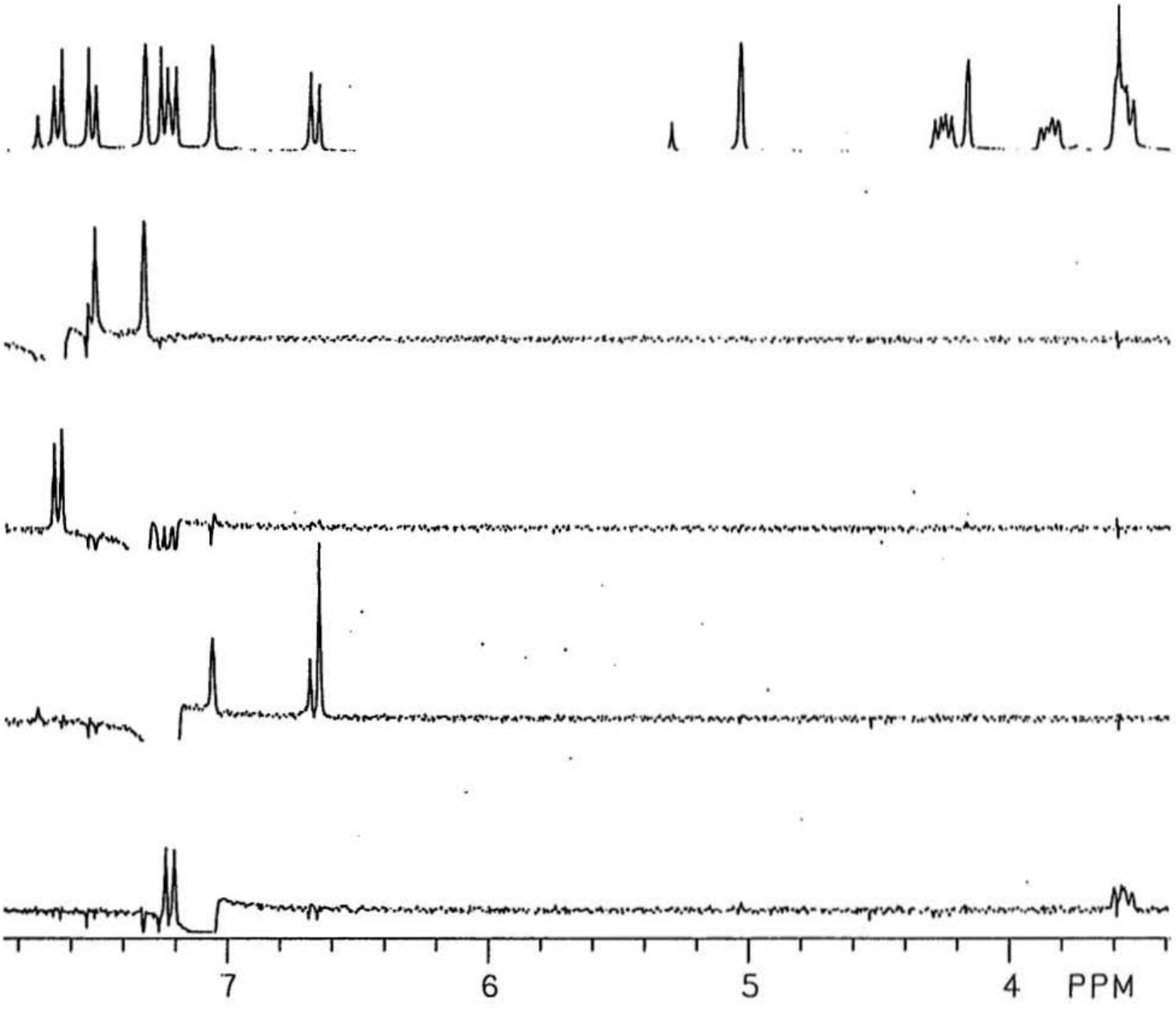
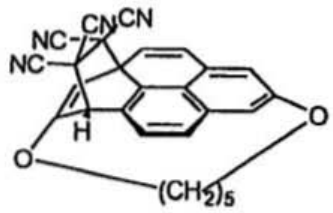


28

NOED





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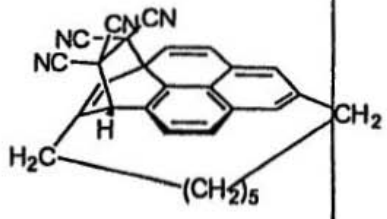

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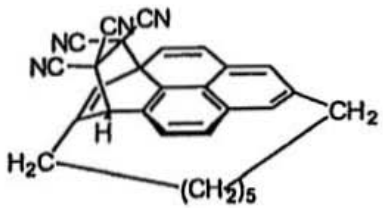

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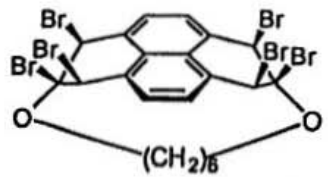

41

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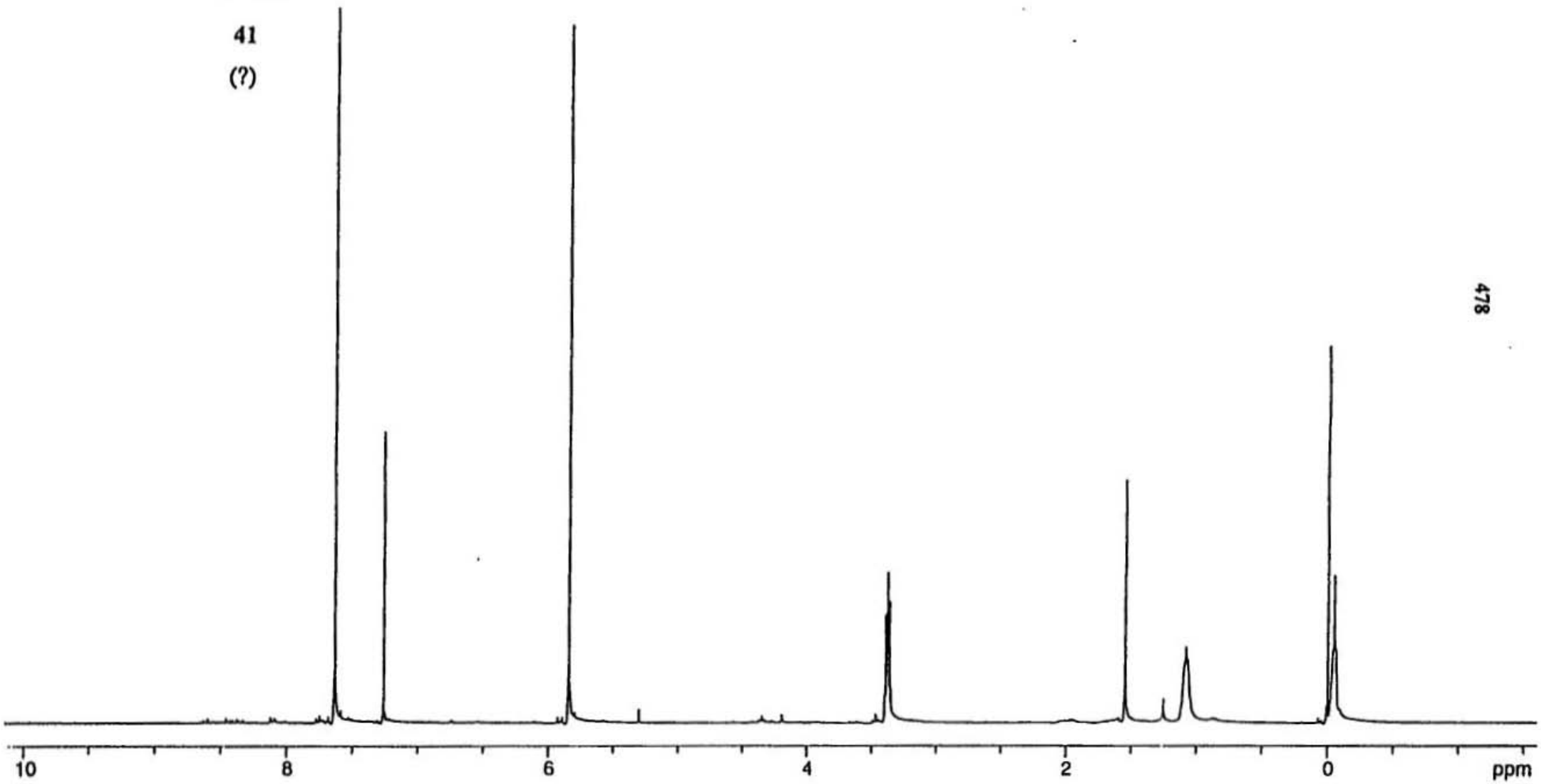
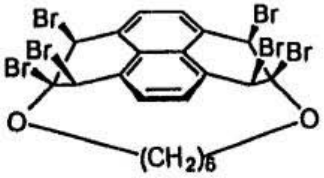
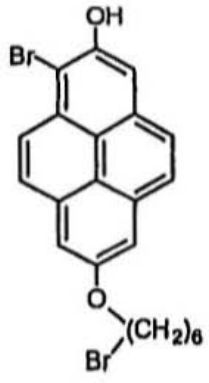


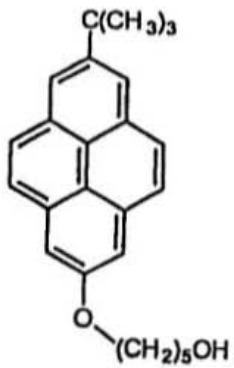


41

(?)



43



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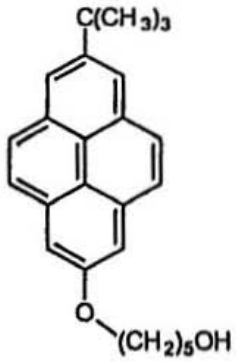
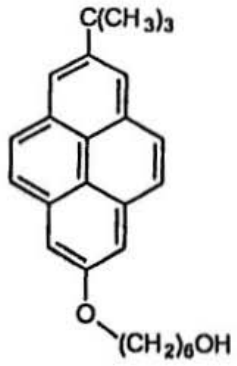
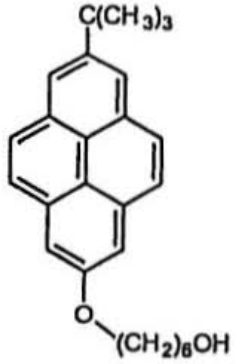


55a

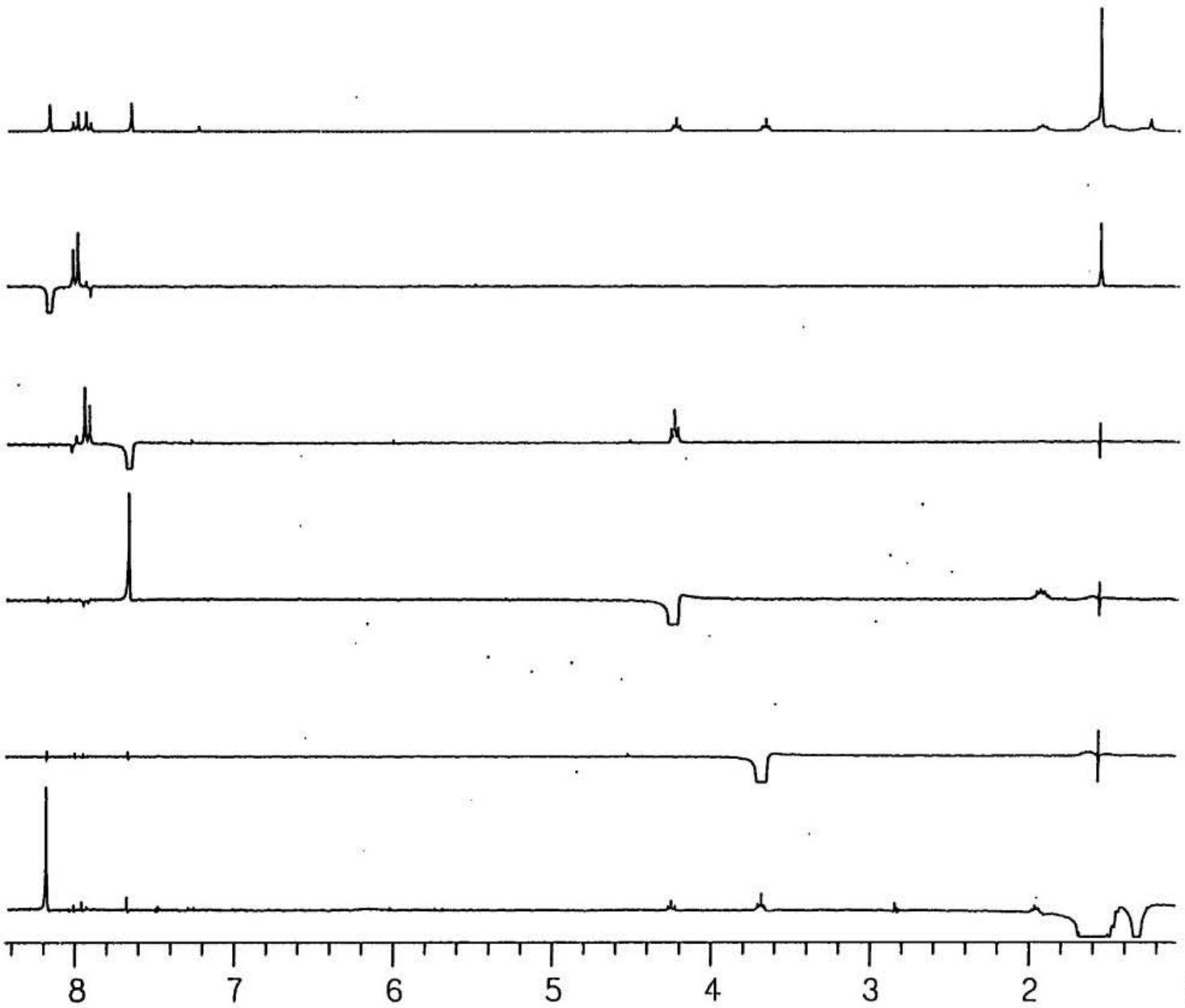
200 150 100 50 ppm

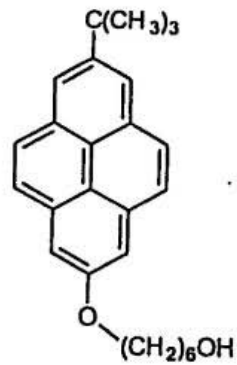


55b



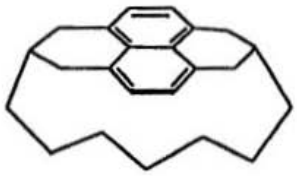
55b





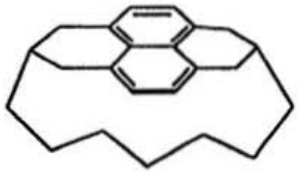
55b

NOED



59

(Impure)



59

(Impure)

200 150 100 50 0 ppm