TOWARD THE SYNTHESIS OF AN AROMATIC BELT

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TOWARD THE SYNTHESIS OF AN AROMATIC BELT

by

doctorandus Rudolf J. Vermeij

A thesis submitted to the
School of Graduate Studies
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requirements for the degree of
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Abstract

The work described in this thesis deals mainly with the application of the valence isomerization-dehydrogenation (VID) approach, previously developed by our group, to the synthesis of pyrenophanes with extended aromatic surfaces. As ultimate goal a fully aromatic "Vögtle" belt is proposed.

Key intermediates for the synthesis of pyrenophanes via the VID approach are syn-2,11-dithia[3.3]metacyclophanes. In Chapter 2 the results of a study of the bridge conformational behavior of these compounds is discussed. This behavior is correlated with Hammett's constant ($\sigma_m$) of the substituents in the 6- and 15-positions. The effect of the solvent is discussed and the study is completed with a DNMR study on several of the 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes.

In Chapter 3, a synthetic effort toward the synthesis of a pyrenophane with two para-phenylene units in the tether is described. In this case the VID methodology fails to give the desired pyrenophane.

A straightforward synthetic plan for the synthesis of a Vögtle belt is described in Chapter 4. The synthesis stalled due to unavoidable side reactions during ring contraction of an advanced intermediate.

The synthesis of pyrenophanes with one phenylene unit in the tether is described in Chapter 5. For two such pyrenophanes, $[2]$paracyclo$[$2$]$(2,7)$pyrenophane and $[2]$meta-cyclo$[$2$]$(2,7)$pyrenophane, a successful synthesis is reported, as well as their X-ray crystal structures. In both compounds the tether forces the pyrene unit to adopt a non-planar geometry and a spoons-like orientation of the aromatic decks is observed.
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<tr>
<td>α</td>
<td>bend angle (in cyclophanes)</td>
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<td>Å</td>
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<td>AM</td>
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<td>β</td>
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<td>Borch reagent</td>
<td>dimethoxycarbonium tetrafluoroborate</td>
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<td>b.p.</td>
<td>boiling point</td>
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<tr>
<td>mp</td>
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<td>bend angle (in pyrenophanes)</td>
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<td>triplet (in NMR)</td>
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<td>t-BuLi</td>
<td>tert-butyllithium</td>
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<td>Definition</td>
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<td>------------</td>
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<tr>
<td>$T_c$</td>
<td>coalescence temperature</td>
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<td>TCNE</td>
<td>tetracyanoethylene</td>
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<tr>
<td>Tf</td>
<td>trifluoromethylsulfonyl, CF$_3$SO$_2$-</td>
</tr>
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<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
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<td>THF</td>
<td>tetrahydrofuran</td>
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<td>TPE</td>
<td>tetraphenylenelylene</td>
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<td>triflic anhydride</td>
<td>trifluoromethanesulfonic anhydride</td>
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<tr>
<td>Ts</td>
<td>$p$-toluenesulfonyl</td>
</tr>
<tr>
<td>UV</td>
<td>ultraviolet (spectroscopy)</td>
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<td>VID</td>
<td>valence isomerization – dehydrogenation</td>
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Chapter 1

Introduction
1.1 Fullerenes and fullerene fragments

The isolation and characterization of the first fullerene (Figure 1.01) in 1985 by Kroto et al. at Rice University\(^1\) caused a surge of interest in several research areas. The now well-established cage-like structure of \(C_{60}\) had previously been predicted by other scientists to be a stable, soccer-ball-shaped molecule,\(^3\) but only after the 1985 communication by the group at Rice University could their predictions be confirmed by experimental results. The \(C_{60}\) molecule was given the name “buckminsterfullerene” in honor of Buckminster Fuller, the American architect renowned for his geodesic domes, since the shape of the molecule (a truncated icosahedron) resembles such domes.

![Figure 1.01: Structure of buckminsterfullerene 1.](image)

Buckminsterfullerene consists only of carbon atoms and can be seen as the third carbon allotrope. The other two allotropes, graphite and diamond, are available in macroscopic quantities, and the technological importance of these compounds is enormous.\(^8\) Graphite is used as a solid lubricant, in pencils and as a reinforcement material in carbon fiber...
composites.\(^8\text{-}^{12}\) Diamond is used in the jewelry industry and in drilling heads for the extraction of crude oil. This importance of graphite and diamond has been the cause for a great interest in the fullerenes from the field of material sciences. Also, all-carbon molecules are believed to be present in some stars and interstellar dust, which has caused interest from astronomers and astrophysicists\(^8,^{13}\) and the first preparation of macroscopic quantities of \(C_{60}\) was reported by a group of astronomers\(^{14}\).

In the field of synthetic organic chemistry, several groups became interested in designing synthetic approaches toward molecular carbon allotropes. One approach is based on the collapse of polyethynylated cyclic \(\pi\)-systems such as 2 (Scheme 1.01)\(^{15}\). In Fourier transform laser desorption mass spectrometric experiments on 2 the \([60]\) fullerene cation \((1^+)\) has been observed\(^{16\text{-}19}\). The precursors in this approach have not become available on a macroscopic scale yet, and isolation of fullerenes from this route has not (yet) been published. However, this approach seems promising for the synthesis of fullerenes and simple (hydrogenated) derivatives\(^20\) but is outside the scope of this thesis and will not be discussed in detail here.
Another approach is initially directed toward the synthesis of fullerene subunits with the view to the synthesis of fullerenes via elaboration of these units. This approach is based on the observation that the fullerenes can be viewed as curved aromatic surfaces. The fullerene subunits then are polycyclic hydrocarbons. One property that these polycyclic compounds must possess in order to be considered a subunit of a fullerene is an inherently curved aromatic surface (i.e., the lowest energy conformer should possess a nonplanar geometry). The smallest example of such a fullerene fragment is corannulene 3 (Figure 1.02), which maps onto the surface of most fullerenes, as illustrated with C_{60} and D_{3h}-C_{70} (4: Figure 1.02).
Corannulene 3 (or [5]circulene)\textsuperscript{21} was first synthesized in 1966 (almost two decades before the first report on buckminsterfullerene!) by Barth and Lawton in a formidable 16-step synthesis.\textsuperscript{22,23} Corannulene consists of a central 5-membered ring, annellated by five 6-membered rings. The molecule is bowl-shaped and, at room temperature, undergoes rapid bowl-to-bowl inversion (Scheme 1.02). Scott et al. estimated the energy barrier for this process to be 10 kcal mol based on a DNMR study of methylcorannulene (5, Scheme 1.02).\textsuperscript{24,25}

After the discovery of the fullerenes in 1985, an efficient synthetic strategy toward 3 became the focus of the work of several groups, as the initial synthetic route was lengthy
and low yielding. In 1992 the Scott group published a short synthesis of 3. In their approach they took advantage of the thermal isomerization of terminal bisthacetylene) 6 to give a vinylidene carbene (7) under flash vacuum pyrolysis conditions at 1000 °C. The highly reactive intermediate 7 underwent insertion of the carbene into the proximate C-H bond to form corannulene 3 in approximately 10% yield.

![Scheme 1.03: Scott's synthesis of 3](image)

For the successful formation of corannulene 3 from diethynylfluoranthene 6 the pyrolysis conditions were assumed to be crucial for both steps in the mechanism. The first step (1,2-H-shift to form vinylidene carbenes) only occurs at temperatures above 700 °C, and temperatures up to 1200 °C are frequently used for this process. In the second step (stepwise insertions of the vinylidene carbene into the C-H bond), the bowl shape of the
product is introduced. In their lowest energy conformations the intermediates 7 and 9 are less planar than 8 and 3, respectively, and the distance between the reacting centers would be too great for reaction to occur. At high temperatures, intermediates 7 and 9 will fluctuate from this planar geometry and allow the reacting centers to approach.

The pyrolytic ring closures of readily available compounds stood as the basis of several routes to corannulene 3 that were published in the years following Scott's initial report.\textsuperscript{27} Most routes employed simultaneous formation of two 6-membered rings in the final (pyrolytic) step and yields varied from 7\% to 40\%.

The first nonpyrolytic synthesis of corannulene was published in 1992 by Siegel \textit{et al.} (Scheme 1.04).\textsuperscript{27} In this synthesis they used traditional cyclophane chemistry to convert tetrabromide 10b to a dithiaocyclophane that could be ring contracted and dehydrogenated to give corannulene 3 in 7\% yield. For the ring contraction, a thermolytic step was still needed (400 °C), which is similar to a pyrolysis. This route was still quite inconvenient for large scale synthesis and did not allow for many functional groups to be introduced. In 1996 the same group reported the first truly nonpyrolytic, solution phase synthetic route to a corannulene derivative.\textsuperscript{31} In this route tetrabromide 10b was subjected to reductive coupling conditions (\ce{TiCl3/LiAlH4} or \ce{VCl3/LiAlH4}) to give 11, which was treated with DDQ to yield dimethylcorannulene 12. This synthesis is a more general one, can be employed on gram scale and tolerates more functionality in the system than the pyrolytic syntheses. Although the yield of 18\% was somewhat low, this work
demonstrated that nonpyrolytic routes might be reasonable alternatives for the synthesis of fullerene fragments (vide infra).

Over the past decade a large number of syntheses of fullerene fragments has appeared in the literature.\(^{30,32,33}\) Most syntheses employ some sort of pyrolytic ring formation as the key step. In this step, ring closures based on vinylidene carbenes have been used to form 6-membered rings, but other pyrolytic processes that involve radical or carbene intermediates have been described for the formation of 5- and 6-membered rings.
The formation of highly strained systems by ring closure of 5-membered rings, such as those in fullerene fragments, has been accomplished by Mehta et al., who employed a pyrolytic dehydrobromination of 14 to form 15. Unfortunately, the last ring closure to form the highly curved sumanene 16 did not proceed. Sumanene has been proposed as a highly curved polycyclic aromatic compound that maps onto the surface of C_{60}. Its synthesis has still not been achieved.

![Scheme 1.05: Dehydrobromination of 14 to give 15.](image)

A variation of the dehydrobromination to close 5-membered rings is based on a 1,2-H shift in aryl radicals. This hydrogen shift has been applied to the synthesis of 18 from 17. Initial homolytic cleavage of the C-Br bonds, followed by a 1,2-H shift, ring closure and loss of hydrogen radical is believed to be the reaction pathway. Pyrolysis product 18 is a 30-carbon fragment of the [60]fullerene C_{60}.
In principle, the same type of dehydrobromination pyrolysis that was used to form the 5-membered rings in 18 could be used to form 6-membered rings. Scott et al. have shown however, that, for the formation of 6-membered rings dehydrogenative pyrolysis can also be employed. This method is much more convenient, as unfunctionalized starting materials can be used, but often suffers from low yields. The dehydrogenative approach was used in the synthesis of circumtrindene 20 from commercially available 19a. This “brute force” triple dehydrogenation of 19a only yielded 0.2 - 0.6\% of the desired product. A higher yielding pyrolysis step to circumtrindene 20 was later reported using a dehydrochlorination approach of precursor 19b in 25 - 27\% yield. The overall yield of 20 from commercially available 2-chloronaphthalene (including the 5-step synthesis of 19b) was 4\%, which demonstrates the “striking superiority” of the dehydrohalogenation route. Circumtrindene is a 36-carbon fragment of C_{60} and is the largest fullerene fragment that has been synthesized to date.
Several more fullerene fragments have been synthesized using the pyrolytic approaches just described. Unfortunately, these pyrolytic approaches also are quite low yielding, and the synthesis of larger fullerene fragments becomes increasingly difficult as the volatility of starting materials decreases with increasing molecular size. Therefore the trend in this area of research seems to have been toward the development of nonpyrolytic methods for the synthesis of curved polycyclic aromatic hydrocarbons.

The first nonpyrolytic synthesis of a fullerene fragment was Siegel's 1996 synthesis of dimethylcorannulene 13 (vide supra). This was followed in 1998 by the synthesis of semibuckminsterfullerene 22 by Rabideau et al. in 20% yield from 21. In Rabideau's synthesis the same type of low-valent titanium reductive coupling was used as described by the Siegel group. Application of this coupling also led to the successful synthesis of cyclopentacorannulene 24 (20-30%) and an improved synthesis of corannulene 3 (70-75%).
More recently, palladium-catalyzed routes have become available for the construction of 5- and 6-membered rings to form curved polycyclic aromatic hydrocarbons. Scott et al. published an intramolecular arylation to yield 26 in 50 - 60\% from 25, compared to 38\% for the same conversion when it was attempted using a pyrolytic dehydrobromination.\textsuperscript{43} A similar approach led to the synthesis of 25 via palladium-catalyzed ring closure of the 5-membered rings in excellent yield (79 - 94\%).\textsuperscript{44} The functional group compatibility of these solution-phase syntheses, together with the ease of performing these conversions on a relatively large scale, demonstrates the synthetic power of these methods for future applications in the synthesis of curved polycyclic aromatic hydrocarbons.
The synthetic approaches discussed so far have all been aimed at the synthesis of fragments of the most abundant \( C_{60} \) fullerene. Not many syntheses of fragments specific to the larger fullerenes have been reported. Mehta has published a retrosynthetic analysis of the second-most abundant fullerene \( D_{2d}-C_{70} \), leading back to a fragment 29, which he called pinakene.\(^{15} \) However, to date this group has published no experimental work in this area. The key feature of pinakene that renders it specific to \( D_{3h}-C_{70} \) and other higher fullerenes is the presence of a pyrene moiety, which is not present in \( C_{60} \).

\[ \begin{align*}
\text{25} & \quad \text{Pd(PPPh}_{3}\text{)Br}_{2}, \text{DBU, DMF, } \Delta, \text{ 50 - 60\%} \\
\text{26} & \\
\text{27} & \quad \text{Pd(PCy}_{3}\text{)Cl}_{2}, \text{DBU, DMAc, } \Delta, \text{ 79 - 94\%} \\
\text{28} & \\
\end{align*} \]

Scheme 1.09: Palladium-catalyzed synthesis of 26 and 28.

\[ \begin{align*}
\text{29} & \\
\end{align*} \]

Figure 1.03: Pinakene (29).
In 1994, Plater et al. reported that pyrolysis of 30 led to formation of
cyclopenta[ca]pyrene 31 via Stone-Wales rearrangement.\textsuperscript{46} Compound 31 does not map onto the surface of \( C_{60} \), but is a fragment of the larger fullerenes. Jenneskens published a
synthesis of 31 in the same year, in which the final step was a pyrolytic
dehydrochlorination of 32 to afford 31.\textsuperscript{47} Syntheses of three isomeric
diecyclopentapyrenes 33, 34 and 35 were published by Scott in 1996.\textsuperscript{48} For the synthesis
of these compounds, pyrolytic dehydrochlorination (similar to that reported by
Jenneskens) was the key step in the simultaneous formation of the 5-membered rings.

\begin{center}
\begin{tikzpicture}
\node[rectangle, draw=black] (a) at (0,0) {\includegraphics[width=\textwidth]{pyrolysis.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 1.10:} Synthesis and structures of some \( C_{60} \) fullerene fragments.

In 1999, a computational study by Siegel and Baldridge proposed the "canastanes" 36
down to 39 (Figure 1.04) as a new curved hydrocarbon motif.\textsuperscript{49} The same paper mentioned that
"the canastane motif should provide a significant challenge to synthetic.... methods" and no experimental work in this area has been reported to date. The canastanes are fragments of the C_{70} fullerene and other higher fullerenes. These compounds also include the pyrene cores.

Figure 1.04: Structure of canastanes 36 - 39

1.2 Curvature in aromatic systems

The key synthetic feature of C_{60} and C_{70} fullerene fragments is the presence of 5-membered rings. Without these 5-membered rings, these polycyclic compounds would not exhibit the curvature that distinguishes them as fullerene fragments. The curvature of
the fullerene fragments can then be attributed to their architecture: i.e., the presence of rings other than 6-membered rings causes certain polycyclic aromatic systems to deviate from planarity. The principle of curvature originating from architecture was described by Hopf. According to his discussion, other ways to cause aromatic rings to adopt nonplanar geometry (Figure 1.05) are based on non-bonded interactions (such as in [6]helicene 40) or the tethering of non-adjacent positions of the aromatic system (e.g. [5]metacyclophe 41).

![Figure 1.05: Curvature of aromatic rings due to steric (40) and tethering (41).](image)

In 40 the two termini of the molecule would, if it were to adopt a planar geometry, have to occupy the same region of space. This steric interaction between the termini causes the molecule to adopt a helical shape. The nonplanarity that is linked inherently to this helical shape can be increased or decreased by increasing or decreasing the steric bulk on the repelling ends of the molecule. The aromatic ring in [5]metacyclophe 41 is bridged by a pentamethylene tether. This tether is too short to permit the aromatic ring to adopt a planar geometry and causes the aromatic ring to adopt a boat-like geometry. Changing the length of the tether can vary the degree of distortion from planarity in the aromatic ring.
The most successful synthetic approaches that have been used to synthesize highly curved examples of helicenes and cyclophanes are based on the formation of a curved aromatic nucleus late in the synthesis. The origin of the curvature (i.e., the steric repulsions in the helicenes and the tether in the cyclophanes) is usually already in place when the strained aromatic system is formed. The exothermicity from formation of the aromatic system (ca. 37 kcal/mol resonance energy) compensates for the introduced strain energy, permitting such reactions to be done under relatively mild conditions. This approach to introduce curvature in aromatic systems is conceptually different from the approach that has been used in the synthesis of fullerene fragments.

In the synthesis of fullerene fragments (Section 1.1) curvature is usually introduced by subjecting a starting material with a planar aromatic system to high-energy conditions. Once the system absorbs enough energy, the aromatic system will fluctuate from its planar geometry, so that the strained rings can be formed in this step. In this approach the stability of the aromatic system is not exploited, but works against formation of the desired product by its resistance to deviations from planarity.

The question then arises whether the helicene- or cyclophane-approach to introduce curvature to aromatic systems can be applied to the synthesis of fullerene fragments. Based on energetic and geometric considerations, it should be possible to incorporate the curved aromatic rings of suitably functionalized helicene or cyclophane precursors into
fullerene fragments under relatively mild conditions. Some of the fullerene fragments of the higher fullerenes (C\textsubscript{70} and larger) contain pyrene units (\textit{vide supra}) and at the outset of the work described in this thesis the Bodwell group had successfully developed methodology for the synthesis of cyclophanes containing curved pyrene units. The curvature in these systems was comparable to the bend in the pyrene units in the \textit{D}_{3h}-C\textsubscript{70} fullerene. This led to the proposal to apply this cyclophane methodology to the synthesis of fullerene fragments. This approach will be discussed in more detail in Section 1.5, after a brief overview of cyclophane chemistry in the literature (Section 1.3).

### 1.3 Cyclophanes

#### 1.3.1 Nomenclature of cyclophanes

The first occurrence of a cyclophane in the literature was in 1899, when Pellegrin reported the synthesis of what he called "di-\textit{m}-xylylene" ([2.2]metacyclophane 72). Cyclophane chemistry expanded rapidly after 1949, when Brown described the synthesis and X-ray crystal structure of [2.2]paracyclophane 42a, which he called "di-\textit{p}-xylylene".\textsuperscript{50,51} The name “cyclophane” was first introduced by Cram in 1951 when he described the synthesis of a series of para cyclophanes 42a-e (Figure 1.06).\textsuperscript{52} This name was suggested as a contraction of three terms: cyclo, phenyl and alkane. After some comments on the nomenclature issue by Schubert \textit{et al.}\textsuperscript{53} and Cram \textit{et al.}\textsuperscript{54} Vögtle
introduced a systematic nomenclature for the cyclophanes, which is now generally accepted.\textsuperscript{55,56} The only papers on nomenclature are in German, so a quite extensive description will be given in this Section. For convenience, reference to Vögtle's numbering (P-1 to P-6) and IUPAC (A-...) numbering will be given for each set of rules.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure106.png}
\caption{Structure of a paracyclophanes 42a - c.}
\end{figure}

\textbf{Rule P-1.1}\textsuperscript{57} In order to develop effectively a nomenclature system, Vögtle defined several concepts. First, "phanes" were defined as all compounds that contain at least one aromatic nucleus and at least one aliphatic bridge, which could contain any number of atoms ($n \geq 0$). For the nomenclature of the aromatic nuclei, IUPAC nomenclature is used (A-21.1 to A-22.5). A bridge is defined by the IUPAC rules (A-31.111) as "a valence compound or atom or unbranched chain of atoms that connect two parts of a molecule". The atoms that are connected directly to the bridge are bridgehead atoms and the number of atoms in the bridge is the number of "bridge members." The number of "ring members" is given by the sum of the number of bridge members ($10 + 1$ for 43 in Figure 1.07), number of bridgehead atoms (4 in 43) and the smallest number of atoms between
the bridgehead atoms of the aromatic nucleus (in 43 that is 1 for each nucleus for a total of 17 ring members).

Figure 1.07: [1,10]metacyclophe.

Rule P-1.2  The cyclophane class of compounds is first divided into two groups: the “heterophanes” and the “carbophanes” (Figure 1.08). The heterophanes are cyclophanes in which at least one of the aromatic nuclei is a heteroaromatic ring (e.g. 46 or 47) and the carbophanes only contain all-carbon aromatic nuclei (e.g. 44 or 45). The names heterophane and carbophane do not indicate the presence of heteroatoms in the bridge. Heteroatoms in the bridge are indicated with prefixes as azas-, oxas-, thia-, etc. according to IUPAC nomenclature. Based on the presence of heteroatoms in the bridge, cyclophanes can then be classified as a carba-phanes (only carbon atoms in the bridge, e.g. 44 or 46) or hetera-phanes (at least one heteroatom in the bridge, e.g. 45 or 47).
Rule P-1.3 If a phane contains carbocyclic as well as heterocyclic aromatic nuclei, the heterocycles have priority over the carbocycles.

Rule P-2.11 – P-2.14 When naming a cyclophane, the root of the name is formed by adding the ending “-o” to the name of the aromatic nucleus, followed by the suffix “phane” (P-2.11). Examples are “thiophenophane” for a thiophene-containing cyclophane and “indolophane” for a cyclophane with indole as the aromatic nucleus. If benzene is the aromatic nucleus, the root of the name is, by definition, “cyclophane” (P-2.12). If the
cyclophane structure contains two or more aromatic nuclei (single rings or fused ring-systems) that are bonded to one another, the root will be derived from the IUPAC name of the system (P-2.13). In doubtful cases the shorter or simpler name should be chosen. If the aromatic nucleus carries a charge, the ending "-o" remains and the suffix "phane" should be replaced by "phanium" (for aromatics with a positive charge) or "phanate" (for aromatics with a negative charge) (P-2.14).

**Rule P-2.21 - P-2.24** In front of the name of the aromatic nucleus, the number of aliphatic bridge members is indicated in square brackets. This number is indicated separately for each bridge, separated by a period. If two aromatic rings are bonded directly, this number is indicated as "0" (zero) (P-2.21). Heteroatoms in the bridge are indicated as usual by the prefix aza-, oxa, thia, etc. (P-2.22). When three or more bridges of equal length are present, this can be indicated by adding the number of the bridges as a subscript to the length of the bridges (P-2.23). The position of the bridges on the aromatic nuclei is indicated by a set of numbers between round brackets, separated by a comma. The numbers are based on the conventional numbering of each aromatic nucleus. For cyclophanes (carbophanes) this numbering is replaced by the prefixes ortho, meta, and para (P-2.24).
Rule P-2.25 - P-2.27 If several bridges between different aromatic nuclei are present (e.g. compound 50), the longest bridge is named first, followed by the shorter bridges (P-2.25). If more than two aromatic nuclei are present, naming (and numbering, **vide infra**) still commences with the longest bridge, followed by the next longest remaining bridge. Further naming continues in the same direction (clockwise or counterclockwise), even if this means that the shorter of the remaining bridges is named before the others (P-2.26). In the round brackets the bridgehead atom with the lowest number (in cyclophane numbering) is assigned first (P-2.27). This last, somewhat confusing rule can be illustrated with compound 50. The pyridine nucleus is assigned as ...(4,6)pyridino... and **not** as ...(4,2)pyridino... or ...(2,4)pyridino... (Figure 1.10). When a phane contains several aromatic nuclei that only differ in the positions in the bridges, the numbers in square brackets can be combined (P-2.28; e.g. [2.2][2.6][3.5]pyridinophane 51 in Figure 1.10).
Rule P-2.29 – P2.31

When one aromatic nucleus is bridged by more than one bridge, the numbers indicating each bridge length are listed separately in square brackets. The positions of the aromatic nucleus that are bridged are listed immediately after this (P-2.29; compound 52 in Figure 1.11). If several bridges link two aromatic nuclei, the number of bridge members for all bridges is listed between a single pair of brackets, separated by a period and starting with the longest bridge. The connection positions to the aromatic rings are listed (in the same order) directly after that (P-2.30; compound 53 in Figure 1.11). In cyclophanes with more than two aromatic nuclei and several (more than three) bridges, the aromatic ring containing the bridgehead atom of which the number
appeared last in the round brackets is the starting point for the next bridge system (P-2.31: compound 54 in Figure 1.12). This aromatic ring is also numbered first when the system is numbered (vide infra).

![Diagram of Cyclophanes 52 and 53](image)

**Figure 1.11:** Cyclophanes 52 and 53.

Rule P-2.31 is somewhat ambiguous when it was presented in the original papers by Vögtle. Later a different nomenclature for phanes with more than two aromatic nuclei and more than three bridges was proposed. This system describes the phane with a “layer number”, which is the number of core arene building blocks. The layer number is depicted in angular brackets [ ] and names compound 54 (Figure 1.12) as a \([k.l][1.3][m.n][4.6][1.4]\)benzenophane. Although the new system with angular brackets is inconsistent in the use of “benzenophane”, where “cyclophane” was suggested in the initial system, it is preferable when cyclophane systems become larger and more complex. Expansion of the new system to belt shaped molecules, by introducing the prefix “beta” (Figure 1.12), has been suggested as well (e.g. phane 55).
Figure 1.12: Structures and names for cyclophane 54 and phane 55

**Rule P-3.1 - P-3.3** Numbering of phanes starts at the longest bridge, closest to an aromatic nucleus and continues until a bridgehead atom is reached (P-3.1). The bridgehead atom to which the longest bridge is connected receives the lowest number of the atoms in the aromatic nucleus (P-3.1). Numbering of the aromatic nucleus continues toward the next bridgehead atom along the longest route, except when heteroatoms are present. When both routes are equal in length, the most substituted receives the lower numbers. The periphery of an aromatic nucleus is numbered in its completion before continuing on along the next bridge (P-3.3). Examples of numbering can be found in Figure 1.13 and in Figure 1.10 (compound 50).
Rule P-4.1 - P-4.2  Phanes that possess aromatic as well as aliphatic bridgehead atoms are named as the \([n]\)phane that contains the longest bridge. This phane is then numbered according to the phane nomenclature. In front of the number of bridge members (in square brackets), each bridge is indicated by the number of bridge atoms between the aliphatic bridgeheads, again separated by a period and between square brackets. The bridges are given in order of the number of bridge members, starting with the longest bridge. The position of the aliphatic bridgehead atoms is given in superscript, separated by a comma, for each bridge (P-4.1: compound \textbf{57} in Figure 1.14). In numbering, the longest bridge is numbered first, followed by the aromatic nucleus. Numbering of the bridges is then continued based on the number of bridge members (starting with the longest bridge) (P-4.2).
Rule P-5.1 – P-5.6  The last remaining issue in the nomenclature of phanes is the assignment of priorities, most of which have already been established above. Longer bridges in phanes have priority over short bridges, i.e. [3.2]meta-cyclophane and not [2.3]meta-cyclophane (P-5.1). When the bridges are of equal length, the aromatic nuclei are given in alphabetic order ("C" for cyclophane; in the cyclophane series ortho comes before meta and para) (P-5.2). If there is a heteroatom present in an aromatic nucleus, the side containing this atom will receive the lowest numbering. In the absence of heteroatoms, the longest route between bridgehead atoms in an aromatic nucleus receives lowest numbering (P-5.3). When both sides of the aromatic nucleus contain the same number of atoms, the side that carries substituents is numbered first (P-5.4). If numbering cannot be based on one of the above, the sum of the number of substituents is decisive, followed by alphabetic order (P-5.5). Once numbering has started along the longest bridge, numbering is continued in this direction (P-5.6).
In Vögtle's nomenclature system, rules P-6 describe the naming of metallocenophanes. As this area is outside the scope of this thesis it is omitted here and the reader is referred to the original literature for a discussion of the nomenclature of this type of phane.  

1.3.2 Small phanes: structure and synthesis

A naïve retросynthetic analysis of a \([n]\)cyclophane 58 might lead back to compound 59 or 60 by cleaving the bridge of the cyclophane. This approach will usually only be successful in orthocyclophanes or if the tether is sufficiently long for the atoms, between which the ring-closing bond is formed, to approach each other. For phanes with smaller tethers \([n]\)paracyclophanes \(n \leq 8\) and for \([n]\)metacyclophanes \(n \leq 7\) this ring closure process is not applicable because the reacting ends “will not meet” and, as a result, intermolecular reaction (dimerization or oligomerization) rather than intramolecular reaction (cyclophane formation) is often predominant.

\[
\begin{align*}
58 & \quad \iff \quad 59 \quad \text{or} \quad 60
\end{align*}
\]

Scheme 1.11: A retросynthetic analysis of \([n]\)cyclophanes.
The reluctance of conventional ring closure methodology to form small metacyclopahanes
and para-cyclophanes is a result of the strain that is introduced in that step. When the
bridge is smaller than 9 atoms in the para-cyclophanes, or smaller than 8 atoms in the
metacyclopahanes, the bridges become too short to span the aromatic ring in its planar
geometry. The benzene ring is then forced to adopt a boat-shaped geometry to
accommodate the short bridge.

The degree to which the benzene ring of a cyclophane is distorted is a function of the
length of the bridge and has traditionally been described with the parameters \( \alpha \) and \( \beta \n\)
(Figure 1.15). The angle \( \alpha \) describes the degree to which the aromatic ring is distorted
from planarity and \( \beta \) describes the degree to which the aromatic bridgehead carbon is
distorted from planarity. The angles can be measured from calculated or
crystallographically determined structures as follows.\(^{21,22}\). A plane \( "\mathbb{C}" \) is defined as the
mean plane formed by four aromatic carbons \( C^A, C^B, C^D \) and \( C^E \) (the atoms \( C^C \) and \( C^F \n\)
that form the “tips” or “bows” of the boat are excluded; Figure 1.15). Plane \( "\mathbb{A}" \) is then
defined by the plane of an “adjoining flap” (atoms \( C^B, C^C \) and \( C^D \) or atoms \( C^C, C^D \)
and \( C^A \) and a line \( "\mathbb{B}" \) is defined as the line that is formed by connecting the benzylic carbon
atom with a neighboring aromatic bridgehead carbon. The smallest angle that plane \( "\mathbb{A}" \)
makes with plane \( "\mathbb{C}" \) is defined as \( \alpha \). Angle \( \beta \) is then defined by the smallest angle
between plane \( "\mathbb{A}" \) and line \( "\mathbb{B}" \) (in para-cyclophanes) or by the smallest angle between
line \( "\mathbb{B}" \) and plane \( "\mathbb{C}" \) (in metacyclopahanes), whichever is smaller.
Figure 1.15: Definition of $\alpha$ and $\beta$ angles in cyclophanes.

Scheme 1.12 gives examples of two approaches to the synthesis of cyclophanes via formation of the aromatic nucleus. In the first example the precursor for cyclophane formation, compound 63, possesses a strained cyclopropane ring.\textsuperscript{13,18} The strain energy in the cyclopropane ring, combined with the energetic advantage of aromatization in the last step, has made this approach a successful one for several [5]metacyclophanes. The reactive intermediate for formation of the aromatic ring can also be generated \textit{in situ}, as illustrated by the synthesis of 69 from 66.\textsuperscript{19} In this example, carbene 68 is the highly reactive species that will lead to the desired product in the aromatization step. The disadvantage of this approach is, that in order to form the reactive intermediate, harsh
conditions are often needed. In the first approach the strain in the synthetic precursor allows for mild reaction conditions to be used in the last step. This has the advantage that a wide range of functional groups is tolerated, and labile reaction products can still be isolated.

![Diagrams](image)


A different synthetic approach to the synthesis of cyclophanes has been based on ring contraction reactions (Scheme 1.13). The systems that have been synthesized using this type of methodology are not as strained as the systems that can be formed using the approach just described. Ring contraction (Wolff rearrangement) has been used in the synthesis of [7]paracyclophane system 71 from 70.** The ring contraction is highly
exothermic due to the loss of N₂, which supplies the required energy to the system to form the strained cyclophane system. Wolff rearrangement was not successful for the synthesis of the lower homologue (6-carbon bridge)⁵⁸ which illustrates a limitation of this approach.

![Scheme 1.13: Synthesis of [7]paracyclophane derivative 71.](image)

Some more commonly used ring contraction methodologies are illustrated in Scheme 1.14. The 2,11-dithia[3,3]metacyclophane system 48 is used as an example because of its direct relation to work described later in this thesis. Photolysis of 48 in a trialkyl phosphite as the solvent leads to ring contraction and loss of the sulfur atoms to provide [2,2]metacyclophane 72 and (RO)₂P=S.⁷⁴-⁷⁵ This contraction likely occurs by a stepwise radical mechanism, in which the newly formed C-C bond is formed by the combination of two radicals. [2,2]Metacyclophane 72 can also be formed via oxidation of the thioether bridges in 48 to give disulfone 73, which can be ring contracted using thermal SO₂ extrusion.⁷⁴ Again, a stepwise process that involves radicals is presumably in operation. Ring contraction of dithiacyclophane 48 can also be achieved using Wittig⁷⁵-⁷⁷ or Stevens⁷⁵,⁷⁸-⁸⁰ rearrangement to give ring contracted products 74. Compound 74 can be reduced using Raney nickel/H₂ to give 72. Elimination of a suitably modified derivative
of 74 can lead to [2.2]metacyclophanediene 75,\(^{78,81}\) which can be hydrogenated to yield 72.\(^{78}\) Cyclophanediene 75 undergoes valence isomerization to form 10\(\beta\).10\(\epsilon\)-dihydropyrene 76,\(^{85}\) which can easily undergo dehydrogenation to give pyrene 77.\(^{75}\) This valence isomerization – dehydrogenation (VID) sequence can therefore be used for the synthesis of polycyclic aromatic hydrocarbons\(^{84}\) and is the basis for the majority of the work described in this thesis (see also Section 1.4 and Chapters 3 - 5).

Scheme 1.14: Ring contractions of 48.
Over the past decades, chemists have attempted to synthesize cyclophanes with the shortest possible bridges. For the paracyclophane system, this has led to the synthesis and isolation of [6]paracyclophane derivatives\(^{31-36}\) and synthesis and isolation of [5]paracyclophane derivatives\(^{37,39}\) but no X-ray crystal structures could be obtained due to the low stability of these phanes. Attempted syntheses of [4]paracyclophanes have suffered from decomposition of the desired products at low temperatures\(^{92,106}\) and only one successful isolation of a [4]paracyclophane has been reported\(^{97}\). The X-ray crystal structure of an unusually stable [1.1]paracyclophane 79 (Scheme 1.15) has been reported by Tsuji.\(^{98,99}\) Cyclophane 79 was generated via photoisomerization of a Dewar benzene 78. The [1.1]paracyclophane moiety in 79 readily underwent a unique transannular addition to form 80, which illustrates the effect of the strain in 79 on its reactivity. Cyclophane 79 has \(\alpha\) angles of 24.3\(^\circ\) and 25.6\(^\circ\) and \(\beta\) values of 22.9\(^\circ\) and 26.8\(^\circ\).

![Scheme 1.15: [1.1]Paracyclophane 79.]

Small metacyclophanes are much less abundant in the literature than are the paracyclophanes. Bickelhaupt \textit{et al.} have reported the synthesis and reactivity of several [5]metacyclophanes \(^{31,94,95,100,110}\) They also reported the observation of [4]metacyclophane 82 at \(-60^\circ\)C\(^{107}\) and claimed the existence of a [1.1]metacyclophane
83 as "a highly strained aromatic intermediate". X-ray crystal data for 8,11-dichloro[5]metacyclophane (81: X = CH₂, Y = Cl) showed an α angle of 22.2° and a β angle of 40.9°.

![Figure 1.16: Structures of selected metacyclophanes.](image)

1.3.3 [2.2]Phanes

A group of phanes that forms a large portion of the total number of known cyclophanes is the [2.2]phanes. The classical method for the synthesis of [2.2]paracyclophane 88 is based on a dimerization of a \( p \)-xylylene derivative 87. This (formal) [6-6] dimerization is not allowed according to the Woodward-Hoffmann rules and presumably proceeds by a stepwise mechanism. In situ generation of \( p \)-xylylene compounds can be performed on large scale via Hofmann elimination of an ammonium salt 84 or Diels-Alder reaction of a 1,2,4,5-hexatetraene (e.g. 85) and an alkyne (e.g. 86).
Scheme 1.16: Dimerization of γ-silylenes to give [2.2]paracyclophanes.

This dimerization approach has been applied in the synthesis of several interesting [2.2]phanes (Figure 1.17). [2.2]([1,4]Naphthalenophane 89 was synthesized using this approach, as were [2.2][9,10]anthracenophane 90 and [2.2][1,4]anthracenophane 91. Cyclophanes 89 and 90 were among the first reported phanes that were based on polycyclic aromatic hydrocarbons.

Figure 1.17: Structures of some [2.2]phanes.
The \( \rho \)-xylylene dimerization approach is specific for the synthesis of phanes with 1,4-positioning of the bridges and cannot be applied to the synthesis of [2.2]metacyclophanes 72. [2.2]Metacyclophanes are synthesized most conveniently via the ring contraction methodology that was discussed in Section 1.3.2. A useful alternative synthesis is the reductive (Wurtz) coupling of benzylic dibromide 92 (Scheme 1.17).\(^{124-128}\)

\[
\text{BrCH}_2\text{CHBr} \xrightarrow{\text{Na, TPE, THF}} \text{BrCH} = \text{CHBr}
\]

Scheme 1.17: Wurtz coupling to give [2.2]metacyclophane 72.

A unique method for the synthesis of \([n.2]\)phanes \((n \geq 2)\) has been developed by Nishimura.\(^{129-128}\) This methodology has not only led to the synthesis of some interesting \([n.2]\)phanes but also to the synthesis of calixarenes and crown-ethers.\(^{128}\) The key step in this approach is a [2+2]photocyclization of vinylarenes, and yields are usually reasonable if the reaction is performed in an intramolecular fashion (Scheme 1.18). Yields of the intermolecular variation are low when benzene is the aromatic nucleus of the reacting system (0 - 11\%), but increased yields are observed with polycyclic aromatic systems (naphthalene 15 - 47\%, phenanthrene 33 - 46\%).\(^{129}\)
Scheme 1.18: [2-2]Photo cyc lization to give [n,2]phanes

The sulfur extrusion ring contraction methodology that has been used for the synthesis of [2,2]metacyclophane 72 has also led to the synthesis of [2,2]pyrenophanes 100 - 105.\textsuperscript{126}
1.4 Nonplanar aromatic compounds: (2,7)pyrenophanes

Upon examination of the cyclophane literature in 1995, no systematic study of cyclophanes in which the curvature was spread over the full surface of a polycyclic aromatic system could be found. However, some interesting cyclophanes that contained nonplanar polycyclic aromatic hydrocarbons had been described (vide supra). In order to take advantage of traditional cyclophane methodology to enter the area of synthesis of fullerene fragments, a more thorough and systematic study of curved polycyclic aromatic compounds was initiated. The pyrene unit was selected as the aromatic nucleus for this project, as it maps onto the surface of some of the higher fullerenes (Figure 1.19). Based
on known cyclophane methodology (VID: Scheme 1.14), a potentially new entry into the synthesis of curved pyrenes was identified.

![Structures of compounds 106, 107, and 108](image)

**Figure 1.19:** Structures of $D_{3h}$-$C_{60}$ (106), $D_{5h}$-$C_{60}$ (107), and $D_{7h}$-$C_{60}$ (108). Double bonds have been omitted for clarity.

In Section 1.3.2, two general approaches to the synthesis of cyclophanes with curved aromatic surfaces were described. The first approach used highly reactive intermediates (generated *in situ* or as precursors) for the formation of the aromatic moiety. The second approach used ring contraction to introduce or increase nonplanarity in the aromatic nucleus. At the outset of our work in this area it was anticipated that the first approach could be applied by using the valence isomerization-dehydrogenation (VID) sequence to form a (curved) pyrene unit from a cyclophanediene precursor (Scheme 1.14). A more detailed discussion of this approach is given in Section 1.4.1.
1.4.1 Retrosynthetic analysis of \([n](2,7)\)pyrenophanes

Using curved pyrene units as the aromatic nucleus in cyclophanes, the synthetic target for the study of curved polycyclic aromatic compounds became the family of \([n](2,7)\)pyrenophanes 109 (Scheme 1.19; \(Z\) represents a bridge/tether). The first step in the retrosynthetic direction of a cyclophane (based on the outlined approach) should remove (part of) the aromatic character that is present in 109, so that in the synthetic direction the molecule is given the energetic incentive of aromatization to facilitate the final step. The retrosynthetic step can be achieved by breaking the central bond in the pyrene unit of 109 to give, \textit{via} dihydropyrene 110, a cyclophanediene 111, which still contains the tether that was present in 109. In pyrenophane 109 this tether was expected to cause the curvature of the pyrene unit, while in 111 this tether would force the metacyclophanediene unit to adopt a \(syn\) geometry.
The carbon atoms in 111 between which the central bond is formed in the synthetic direction are often referred to as the “internal” carbons and, similarly, the attached hydrogens are referred to as “internal” hydrogens. In the syn conformation of 111, the internal carbon atoms are expected to be in close proximity, which should facilitate the desired valence isomerization to give a tethered cis-dihydropyrene 110. This process is, at least in principle, reversible but 110 is expected to lose H₂ in an irreversible step. The dehydrogenation of 110 is expected to be much more facile than for the untethered trans-dihydropyrene system 76, due to the cis orientation of the hydrogen atoms in 110. Dehydrogenation of 76 had been reported to occur readily in the presence of oxygen. An X-ray crystal structure of a system very similar to 110 has been published.¹³⁹
(dioxadecamethylene tether) with methyl groups as substituents at the internal positions to prevent the irreversible dehydrogenation.

Based on the ring contraction methodology that was described in Section 1.5.2 (Scheme 1.14) a tethered cyclophanediene 111 can, retrosynthetically, lead to a tethered dithiacyclophane 112 by replacing the C-C double bonds with thioether linkages. The methodology in this area had been well developed by Boekelheide et al.\textsuperscript{78-82} and it was anticipated that the presence of the tether in 112 would not interfere with these transformations, provided certain functional groups were absent.

Scheme 1.20: Retrosynthetic analysis of a (2,7)pyrenophane 109 Part II.

The key functions of the tether in the system under consideration were the introduction of curvature to the pyrene nucleus in 109 and assurance of a syn-geometry in 111 to facilitate the V1D sequence. For the syn geometry of dithiacyclophane 112, the presence of the tether was not expected to be crucial, as Mitchell had shown the preference for the syn conformation of several untethered 2,11-dithia[3.3]metacyclophe systems.\textsuperscript{140,141} This conformational preference of a 2,11-dithia[3.3]metacyclophe for a syn-
conformation is the basis for the next retrosynthetic cuts (route "a" in Scheme 1.21), in which the tether in 112 is cleaved to give a difunctionalized dithiacyclophane 113 and an acyclic building block 114. Some initial synthetic investigations of this approach showed that synthesis of certain suitably difunctionalized dithiacyclophanes 113 was a nontrivial task and the route was eventually abandoned. As a result of these initial investigations, however, our group became interested in the conformational behavior of the 2,11-dithia[3.3]metacyclophane system. This interest has formed the basis of the work that will be presented in Chapter 2.

Scheme 1.21: Retrosynthetic analysis of a (2,7)pyrenophane 109 - Part III.
A complementary retrosynthetic approach to route "a" (Scheme 1.21) is first to cleave the thioether bridges that are present in dithiacyclophane 112. This leads to an acyclic precursor 115. Retrosynthetic analysis of 115 leads to cleavage of the tether to give two small building blocks 116 and 114. In the synthetic direction the conditions for this transformation will depend on the nature of the tether. Preference for this route in the synthesis of 112 is based on the availability of $\text{Na}_2\text{S}/\text{Al}_2\text{O}_3$ as an efficient reagent for the cyclization of 115 to give 112.

1.4.2 Synthesis of $[n](2.7)$pyrenophanes

The synthesis of several 1,n-dioxa$[n](2.7)$pyrenophanes 117 and $[n](2.7)$pyrenophanes 118 by our group has been reported in several publications.\(^{141-143}\) Due to the great similarities of the syntheses, a general discussion will be given here. For a more detailed discussion the reader is referred to the individual papers.

![Figure 1.20: Structure of pyrenophanes 117 and 118.](image)
Synthesis of 117 started with the coupling of dimethyl 5-hydroxyisophthalate 119 and \( \alpha, \omega \)-dibromoalkanes 121 to give tetraesters 123. For the synthesis of the carba-phanes 118, triflate 120 (available from triflation of 119) was coupled with diynes 122 to give 124 after catalytic hydrogenation of the products. Hydride reduction of the esters was followed by treatment of the resulting alcohols with HBr and gave tetrabromides 125 and 126. Treatment of the tetrabromides with Na\(_2\)S-Al\(_2\)O\(_3\) gave dithiacyclophanes 127 and 128.

Scheme 1.22: Synthesis of dithiacyclophanes 127 and 128.
Ring contraction of dithia cyclophanes 127 and 128 was performed to give bis(methylthio) ethers 129 and 130 (Scheme 1.23). Depending on the length of the tether, Hofmann elimination of 129 and 130 gave either cyclophanedienes 131 and 132 (131a-c and 132a-c: 6 – 8 atom tethers) or a mixture of compounds, which could be converted to pyrenophanes 117 and 118 (117d-g and 118d: 9 atoms or more in the tether). Treatment of dioxacyclophanedienes 131b and 131c and carba-cyclophanedienes 132b and 132c with DDQ led to the formation of the corresponding pyrenophanes 117b, 117c, 118b and 118c. Cyclophanedienes 131a and 132a did not form the corresponding pyrenophanes when treated with DDQ, although formation of 118a as a fleeting intermediate has been claimed. 14
1.4.3 Structure and properties of \([n](2.7)\)pyrenophanes

In the formation of pyrenophanes 117 and 118, it was observed that relatively mild reaction conditions (DDQ in refluxing benzene) often sufficed to drive the reaction, although the process was slow for the lower homologues of the series. The reactivity of the pyrenophanes increased with decreasing tether length: some of the lower homologues readily underwent apparent Diels-Alder reaction with tetracyanoethylene (TCNE), while the higher homologues were unreactive under the same conditions (Scheme 1.24). When
dioxapyrenophane 117b or 117c was reacted with t-BuLi in an attempt to perform ortho-metallation. Tether cleavage occurred. The next higher homologue 117d was unreactive under the same conditions. Attempted bromination of carba-pyrenophane 118b and treatment of 118b with a strong Lewis acid (AlCl₃) led to the formation of complex mixtures.

![Diagram](image)

**Scheme 1.24:** Diels-Alder reaction of 117b and 118b

In the ¹H NMR data of the pyrenophanes, a clear trend could be seen for the chemical shift of the protons on the aromatic nucleus. On shortening of the tether, an upfield shift of these protons occurred in both series of pyrenophanes. Some of the protons in the tethers of 117 and 118 were shifted significantly upfield, which was attributed to the positioning of these protons in the shielding cone of the aromatic nucleus.
X-Ray crystal structures of 117b-g and 118c were determined, and they revealed the extended bend over the full length of the pyrene moiety. No suitable crystals of the other carba-pyrenophanes could be obtained, partly due to their high solubility. In order to be able to compare the degree of curvature, a bend angle (θ) was defined (Figure 1.21). The angle α that is used to describe distortions from planarity in cyclophanes with monocyclic aromatic nuclei is not appropriate for the description of distortions in the pyrene unit. However, the angle β that is used for the [n]paracyclophanes is still meaningful in case of the pyrenophanes. Table 1.01 gives AM1 calculated and experimental bend angles for selected pyrenophanes.
From the 1,1-dioxa[n](2,7)pyrenophane series, it can be seen from the X-ray data that the bend angle of the pyrene unit increased with decreasing tether length. The same trend was expected for the carba-pyrenophanes, although the true value could only be obtained for 118c. AM1 calculations gave bend angles for both series that indicated the same trend.*

*In the X-ray crystal structure of 117g showed disorder in one end of the tether suggesting large error in the experimental value.
as was observed from the available X-ray data. An important result from the calculated and measured bend angles is that the calculations consistently overestimated the bend angle by 4-7°, so they seemed to be useful as a predictive tool.

The most bent pyrenophane that was stable enough to be isolated (117b; \( \theta_{X-ray} = 109.2^\circ \)) had a calculated bend angle of 113.3°, while attempts to isolate pyrenophane 118a with a calculated bend angle of 122.9° were unsuccessful. These results provided a useful tool to design future synthetic targets, as compounds with calculated bend angles larger than \( \text{ca.} 115 - 120^\circ \) were not likely to be accessible via the VID protocol. An attempt to narrow this gray area of 115 - 120° led to the attempted synthesis of 135 (\( \theta_{\text{calc}} = 117.2^\circ \)), but only a trace amount could be isolated.\(^{140}\) Synthesis of 136, as predicted correctly by the calculations (\( \theta_{\text{calc}} = 108.3^\circ \)), was more successful and from the X-ray data a bend angle of 102.9° was determined.

![Structure of pyrenophanes 135 and 136.](image)

**Figure 1.22:** Structure of pyrenophanes 135 and 136.
1.5 Outline of this thesis

In the strategy for the synthesis of fullerene fragments using our cyclophane methodology, functionalization of pyrenophanes 117b and 118b was shown to be inefficient as no selectivity for the formation of desired ring-functionalized products was observed. It was therefore decided to attempt syntheses of pyrenophanes with additional functionality in the tether. As the ultimate goal of this approach was to synthesize large fragments of fullerenes, attention was focused on the incorporation of aromatic rings in the tether. Target pyrenophanes were identified with aromatic rings incorporated in such a manner that the total aromatic component of the hypothetical pyrenophane would map onto the surface of (some of) the fullerenes. Table 1.02 gives the structure and calculated bend angles of the compounds that will be described in this thesis.
Compounds 137 and 138 can be viewed as \([n](2,7)\)pyrenophanes in which part of the aliphatic tether has been replaced by a single aromatic ring. These pyrenophanes do not directly map onto the surface of the fullerenes, but are still related to the ultimate goal. The calculated bend angles of 100.4° and 106.6° for 137 and 138, respectively, are well...
within the limits of the VID approach (pyrenophanes with $\theta_{\text{calc}} = 104.5^\circ$, $108.3^\circ$, and $113.3^\circ$ have been synthesized: vide supra). Efforts in the syntheses of these systems will be described in Chapter 5.

In compound 139, two $p$-phenylene units have been incorporated in the tether. This pyrenophane is substantially closer to a fully aromatic belt (140a) than compound 137. Pyrenophane 139 has a calculated bend angle of $114.4^\circ$ and the aromatic portion of 139 maps onto the surface of the fullerences $D_{2h}$-$C_{60}$, $D_{6h}$-$C_{84}$, and $D_{5h}$-$C_{70}$. The $\theta_{\text{calc}}$ value is slightly higher than $\theta_{\text{calc}}$ for the most curved pyrenophane that had been isolated at that point in time (117b: $\theta_{\text{calc}} = 133.3^\circ$) and thus constitutes, in principle, a useful system for further development of a calculation-based prediction method for curvature in pyrenophanes. Efforts toward the synthesis of 139 will be described in Chapter 3.

Chapter 4 of this thesis will describe a synthetic approach to the assembly of a fully aromatic belt 140b. In this compound, the tether of a $[n](2,7)$pyrenophane has been replaced by an aromatic system and, as such, the tether becomes indistinguishable from the pyrene nucleus. Values of $\theta_{\text{calc}}$ for the individual pyrene units in 140b are approximately $90.3^\circ$, which suggests these pyrene nuclei might be formed using the VID protocol.
1.6 References


(52) Cram, D. J.; Steinberg. H. J. Am. Chem. Soc. 1951, 73, 5691-5704.


(57) The rules in phane-nomenclature were numbered by Vögtle as follows: P-1 describes the phanes as a class of compounds. P-2 describes cyclophanes with only aromatic bridgehead atoms. P-3 describes numbering of the phanes. P-4 describes cyclophanes that contain aromatic as well as aliphatic bridgehead atoms. P-5 gives the priority rules for nomenclature and numbering of phanes and P-6 describes the naming of metalloccenophanes. This thesis will apply the same numbering.


(149) Bend angles of pyrene units in pyrenophanes were calculated using the Chem3D package of software (MOPAC, AM1, closed shell).
Chapter 2

NMR Investigations of the Bridge

Conformational Behavior of

6,15-Disubstituted syn-2,11-Dithia[3.3]metacyclophanes.
2.1 Introduction

When our group first became interested in \([n] \{(2,7)\text{pyrenophanes}\} 1\) as synthetic targets, two synthetic routes were investigated. The route that is currently used is described in Chapter 1 and several examples of its application can be found in Chapters 3-5. The first route received some initial attention, but is not currently used. The retrosynthetic analysis of this route is given in Scheme 2.01.

![Scheme 2.01: Alternative retrosynthetic analysis of a pyrenophane.](image)

The initial retrosynthetic cut is the central bond of the pyrene unit in 1, which can be formed in the synthetic direction using a valence isomerization-dehydrogenation (VID)
sequence.\textsuperscript{1} Cyclophanediene 2 can be derived from a dithiacyclophane 3 using standard cyclophane methodology.\textsuperscript{1,2} These retrosynthetic steps are identical with those used in the currently used synthetic approach, so for a more detailed discussion of this sequence, the reader is referred to Chapter 1. The next retrosynthetic cuts remove the tether from dithiacyclophane 3 to give 5 and a 6,15-disubstituted \textit{syn}-2,11-dithia[3.3]metaacyclophane 4.\textsuperscript{3} Introduction of a tether at this stage was anticipated to be feasible based on Mitchell's observation\textsuperscript{4} that 2,11-dithia[3.3]metaacyclophanes with H atoms as substituents on the internal (9- and 18-) positions prefer to adopt the \textit{syn} conformation. The advantage of this route is that it gives access to derivatives of 3 with different tether lengths from one common precursor 4.

Initial investigations of this synthetic route led to the synthesis of \textit{syn}-6,15-dicyano-2,11-dithia[3.3]metaacyclophane 4a\textsuperscript{1} by our group.\textsuperscript{5} This particular cyclophane shows some very unusual features in its X-ray crystal structure. Perhaps the most surprising feature is that both bridges are in the so-called \textit{pseudo-boat} conformation (sulfur "up", \textit{h,b}-4a, Figure 2.01). Neither AM1 calculations nor \textit{ab initio} calculations (3-21G(*) predict this to be the lowest energy conformer for 4a in the gas phase. AM1 calculations found the heat of formation of the \textit{pseudo-boat,pseudo-chair} (\textit{h,c}) and the \textit{pseudo-boat,pseudo-boat} (\textit{h,h}) conformer to be 0.57 kcal/mol and 1.77 kcal/mol higher than the heat of formation of the \textit{pseudo-chair,pseudo-chair} (\textit{c,c}) conformer, respectively. This difference in the gas phase can easily be outweighed by crystal packing forces.
When published X-ray crystal structures of other syn-[3,3]metacyclophanes are examined, by far the majority of structures are of parent (all-carbon) syn-[3,3]metacyclophanes and syn-2,11-dithia[3,3]metacyclophanes (some syn-2,11-diaza[3,3]metacyclophanes are known). Most structures have the bridges in the \textit{c.c} conformation. This is in agreement with the calculated gas phase structures, for which this conformation is consistently calculated to be the most stable. The only other syn-[3,3]metacyclophane derivatives reported to crystallize in the \textit{b.b} conformation are syn-1,3,10,12-tetraethia[3,3](2,6)pyridinophane \textbf{6} and syn-[3,3](2,6)pyridinophane \textbf{7} (Figure 2.02). The crystal structure of \textbf{4a} is the first (and only) one in which a syn-2,11-dithia[3,3]metacyclophane has both bridges in the \textit{pseudo-boat} conformation.

\textbf{Figure 2.02: Pseudo-boat.pseudo-boat conformations of syn-[3,3]pyridinophanes 6 and 7.}
In the case of 6, "N-S repulsions" were invoked as the cause of the unusual conformations, but no explanation was offered as to the origin of those interactions or why they would favor the \( h.h \) conformation. Upon examination of the system, it would appear as though the "N-S-repulsions" refer to an unfavorable alignment of lone pairs on the nitrogen and sulfur atoms in 6 when a bridge adopts a \textit{pseudo-chair} conformation. For 7, weak hydrogen bonding between the internal nitrogen atom and the inner hydrogens of the central methylene group in the bridges was deemed to be the primary cause for the unusual bridge conformations. The hydrogen bonding argument does not seem applicable to \textit{syn-6.15-dicyano-2.11-dithia[3.3]metacyclophane 4a}, since the heteroatom in this case is a considerably weaker donor atom (S vs. N). Furthermore this weak hydrogen bonding could presumably occur for a \textit{pseudo-chair} bridge as well as for a \textit{pseudo-boat} bridge.

The origin of the unusual bridge conformational behavior of \textit{4a} in its crystal structure was ascribed to a dipolar effect, i.e., the molecule adopts the conformation with the smallest dipole moment. The calculated (AM1) dipole moments for the \textit{c.c.} \( h.c \) and the \( h.h \) conformers of \textit{4a} are given in Figure 2.01. In the \( h.h \) conformer, the vector sum of the dipole moment of the two cyano groups directly opposes that of the four C-S bonds in the bridges. As a result, the calculated dipole moment of the \( h.h \) conformer (3.63 D) is considerably smaller than that of the \textit{c.c} conformer (7.30 D), in which the vector sums point in the same direction.
If this dipolar effect is indeed responsible for the bridge conformational behavior of 4a in the solid state it might be expected that 6.15-disubstituted syn-2.11-dithia[3.3]metacyclophanes will show a dependence of the bridge conformations on the electronic properties of the substituents in the 6- and 15- positions. Studying this effect in the solid state would not be very meaningful due to different crystal packing effects of different cyclophanes. It was therefore decided to study this effect in solution using NMR techniques, for which the conditions can be kept constant for a series of compounds.

In the following paragraphs, a short overview will be given of published studies of conformational behavior of cyclophanes. This will be followed by a detailed discussion of the bridge conformational behavior of a series of 6.15-disubstituted syn-2.11-dithia[3.3]metacyclophanes.

2.2 Overview of the literature

syn-2.11-Dithia[3.3]metacyclophane 4b was first synthesized by two independent groups in 1968. Based on observations of [2.2]metacyclophane and various internally substituted 2.11-dithia[3.3]metacyclophanes, in which the anti conformer was the sole conformer in X-ray and NMR studies, the parent 2.11-dithia[3.3]metacyclophane 4b was initially thought to exist in the anti conformation only (Scheme 2.02). The 1H NMR spectrum of 4b shows a singlet at δ 6.6 ppm for the internal aryl protons (H), which was
assumed to be an average chemical shift of all contributing conformers.\textsuperscript{12} DNMR* studies showed that the \textsuperscript{1}H NMR spectrum of \textbf{4b} did not change upon cooling to \(-90^\circ\text{C}\), indicating a low energy barrier (estimated at \(<9.3\) kcal/mol in toluene)\textsuperscript{1b} between the conformers.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textit{syn-4b}};
\node (b) at (2,0) {\textit{anti-4b}};
\path (a) edge[<->, bend left=20] (b);
\end{tikzpicture}
\end{center}

\textit{Scheme 2.02:} Proposed \textit{syn} to \textit{anti} interconversion of \textbf{4b}.\textsuperscript{12}

In a paper published in 1979,\textsuperscript{4} Mitchell and co-workers described the X-ray crystal structure of \textbf{4b} and showed not only that the \textit{syn} conformer was the sole conformer present in the solid state but that the bridge conformation of \textbf{4b} was the \textit{e.e} conformation. From a \textsuperscript{1}H NMR study Mitchell also concluded that, in solution at room temperature, \textbf{4b} exists, as in the crystalline state, only in the \textit{syn} conformation. Although no freezing of the bridges was observed in this study, wobbling of the bridges (Scheme 2.03)\textsuperscript{1b,17} was not ruled out as one of the conformational processes of \textbf{4b}. Although \textit{syn} to \textit{anti} (benzene ring) inversion was not considered a contributor to conformational processes, \textit{syn} to \textit{syn'} benzene ring inversion could not be eliminated. The \textit{syn} to \textit{syn'} inversion involves a flip of both aromatic rings so that effectively a \textit{pseudo-chair} to \textit{pseudo-boat} (or \textit{vice versa})

* DNMR: Dynamic NMR. The term VTNMR has also been used to describe the same technique.
inversion of both bridges takes place at the same time (Scheme 2.03). This syn to syn' inversion could also actually be a syn to anti to syn' process in which the anti conformer is a high energy and short-lived intermediate.

Since the appearance of Mitchell's paper, only a few bridge conformational studies of syn-2,11-dithia[3.3]metacyclophanes have appeared in the literature. Most of these describe syntheses and structures of syn-[3.3]metacyclophanes with large substituents at the internal (9- and 18-) position(s),\textsuperscript{18-20} which limits the conformational motion of the bridges and the aromatic rings. Other papers describe cyclophanes with atoms other than sulfur at the 2- and 11-positions,\textsuperscript{21,22} or cyclophanes with (hetero)aromatic units other than benzene.\textsuperscript{11,23} Since our work in this area is concerned with bridge conformational behavior of syn-2,11-dithia[3.3]metacyclophanes with substituents in the 6- and 15-
positions only, the reader is referred to an excellent review by Ernst for a comprehensive discussion of the literature since 1983 on NMR studies of other cyclophanes.

The parent [3.3]metacyclophane 8 was first synthesized in 1976. Later, several other syntheses were published, and in 1985 Semmelhack published a leading paper on the conformational behavior of this compound. Semmelhack showed that 8 is present only in the syn conformation in the solid state, with both bridges in the pseudo-chair conformation. In solution, two conformers could be observed by $^1$H-NMR (270 MHz) below 223 K. Both conformers were assigned the syn conformation based on the chemical shift of the internal protons. Based on the results of calculations, the major conformer was assigned the e.e conformation and the minor isomer was assigned the h.e conformation.

![Cyclophane 8](image)

**Figure 2.03: syn-[3.3]Metacyclophane 8.**

A conformational study of a bridged derivative of a syn-[3.3]metacyclophane was published in 1988 by Shinmyozu et al. They designed and synthesized a deuterated cyclophane 9 (Figure 2.04) with an extra bridge linking the 6- and 15 positions...
of the syn-[3.3]metacyclophane unit. The presence of the third bridge ensures that the [3.3]metacyclophane moiety can exist only in the syn conformation. The aromatic region of its $^1$H NMR spectrum is less complex than that of 7. The syn to syn' benzene ring inversion process is also eliminated due to the presence of this tether, simplifying the system for dynamic studies. Deuteration of the 2- and 11- positions of the bridges was performed to simplify the aliphatic region of the $^1$H NMR spectrum.

![Figure 2.04: Structure of 9.](image)

Conformational analysis of 9 using DNMR methods showed that (at least) three conformers of 9 are present at lower temperatures in an approximate ratio of 47 : 44 : 9 (203 K; 270 MHz $^1$H NMR in CD$_2$Cl$_2$). Based on work by Semmelhack, which suggested a stability order of e.e $>$ h.e $>$ h.b, Shinmyozu assigned the three conformers of 9 as e.e-9, h.e-9 and h.b-9, respectively (Figure 2.05). Assignment of these conformations was consistent with the observed trend of the chemical shifts of the internal protons. The proximity of two bridges to the internal proton in h.b-9 leads to greater steric deshielding of that internal proton than for the corresponding proton in the other two conformers. The strongly deshielded internal proton (two proximate bridges) in h.b-9 appears in the $^1$H NMR spectrum at $\delta$ 6.83, while the slightly less sterically deshielded internal proton (one
proximate bridge) in \textit{h.c-9} appears at $\delta$ 6.71 and the least sterically deshielded internal proton (no proximate bridges) in \textit{c.c-9} appears at $\delta$ 6.61. For the external proton the same effect can be observed. Steric deshielding of the external protons by a proximate bridge (in the \textit{c.e} conformation) causes a downfield shift of the corresponding signal ($\delta$ 6.32) relative to the chemical shift of the same proton in the \textit{h.b} conformation ($\delta$ 6.16) in which no steric deshielding occurs. In the \textit{h.e} conformer, the external protons are nonequivalent. The signal for the external proton close to the \textit{pseudo-chair} bridge (H$_e^-$: $\delta$ 6.29) was observed at approximately the same chemical shift as the signal for the external proton of the \textit{c.e} conformer ($\delta$ 6.32). The signal for the external proton in \textit{h.c-9} closest to the \textit{pseudo-boat} bridge was observed at almost the same chemical shift (H$_c$: $\delta$ 6.20) as the signal for the external proton of the \textit{h.b} conformation ($\delta$ 6.16). Activation energy barriers for the inversion of the trimethylene bridges in \textbf{9} were estimated to be 12.1-12.3 kcal mol.

\begin{center}
\includegraphics[width=\textwidth]{figures/figure2.05.png}
\end{center}

\textbf{Figure 2.05:} Bridge conformations and $^1$H NMR data of cyclophane \textbf{9} at 203 K.
The chemical shift difference between the equatorial and axial protons in the \textit{pseudo-chair} bridges was shown to be 0.48-0.49 ppm, with a coupling constant between equatorial and axial protons of 13.7-13.8 Hz. The corresponding values for the protons in the \textit{pseudo-boat} bridges are 0.67-0.71 ppm and 14.4-14.7 Hz. This information was used to assign conformations in a later paper by the same group,\(^\text{31}\) in which compound \(8\text{b-d}_4\), as well as its 6.15-dimethoxy derivative \(8\text{c-d}_4\), was studied.

![Deuterated cyclophanes](image)

\textbf{Figure 2.06:} Deuterated cyclophanes \(8\text{b-d}_4\) and \(8\text{c-d}_4\).

The results Shinmyozu obtained in his study of deuterated \textit{syn-[3.3]} metacyclophanes \(8\text{b-d}_4\) and \(8\text{c-d}_4\) were similar to that of the tethered system 9, but freezing out of only one (major) conformer was observed for each cyclophane. In all cases this major conformer was assigned the \textit{e.e} conformation. Assignment of the minor signals to a single conformer could not be made because of broadening of the signals of the benzylic protons. Shinmyozu suggested that “the presence of another dynamic process, i.e., interconversion of the minor conformers via an \textit{anti} conformer (benzene ring inversion)” was still a possibility. No evidence was presented to support this inversion or any other process at low temperature (203 K), but in the same paper it was shown that benzene ring inversion occurs at room temperature. Decomplexation of enantiomerically pure 10
yielded racemic 11, independent of which enantiomer of 10 was used (Scheme 2.04). If benzene ring inversion was prohibited, this decomplexation should have yielded a single enantiomer of 11.

Scheme 2.04: Decomplexation of cyclophanecromium tricarbonyl complex 10.

Analysis of the spectral data of Shinmyozu's "tethered" syn-[3,3]metacyclophane 9 shows that the steric shielding of an aromatic proton by a nearby dideuteriomiethylene group amounts to ca. 0.1 ppm per dideuteriomiethylene group. If this is indeed the case, then the chemical shifts of the internal and external protons in syn-2,11-dithia[3,3]metacyclophanes might be subject to a similar (additive) steric influence of, in
this case, the sulfur atoms in the bridges. Implications of this hypothesis are delineated in
the next Section.

2.3 Elaboration of a hypothesis

Low temperature $^1$H NMR studies might provide information about the bridge
conformational behavior of _syn-2,11-dithia[3.3]metacyclophanes_. At the outset of this
project, it was realized that studying a broad range of cyclophanes using DNMR would
be impractical for several reasons: (1) solubility of _syn-2,11-dithia[3.3]metacyclophanes_
is often poor at lower temperatures; and (2) Mitchell's\textsuperscript{13,12} and Sato's\textsuperscript{12,16} studies
suggested that the activation barriers for conformational processes are quite small (<9.3
kcal mol in toluene), requiring high-field spectrometers and low temperatures to observe
freezing of the processes. (We were limited to -100 °C at 300 MHz: estimated 8-9
kcal mol (33-38 kJ mol) minimum energy barrier is required to observe freezing.)

At room temperature, interconversion of the various bridge conformers will be expected
to be rapid, so the expectation is a $^1$H NMR spectrum that is a weighted average of all
conformers present.\textsuperscript{33} Unfortunately there is no easy technique by which the chemical
shifts of those different conformers at room temperature can be measured. This problem
brought us to use the method described below. 6,15-Disubstituted _syn-2,11-
dithia[3.3]metacyclophanes_ were used in this study primarily since they were of interest
to us from a synthetic point of view. A coincidental advantage of studying this class of
cyclophanes is their relatively uncomplicated $^1$H NMR spectra.$^{34}$

In our study of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes the following
assumptions have been made: (a) the only conformers that contribute to the observed $^1$H
NMR spectrum at room temperature are the c,c, the b,c and the b,b conformers (see
Figure 2.01), (b) the steric deshielding effect of a sulfur atom in a bridge is equal for each
interaction and (c) this steric deshielding effect is additive for each interaction. Validity
of these assumptions will be discussed in Section 2.4.3.1. The observed chemical shift of
the internal proton ($\delta H_{\text{obs}}$) at room temperature can then be described as follows.

![Figure 2.07: Bridge conformers of syn-2,11-dithia[3.3]metacyclophane 4.](image)
If the chemical shift of the internal proton of the e:e conformer (e:e-4) at room temperature is given by $\delta H_i^{e:e}$, and each proximate thioether bridge deshields a nearby aryl proton by an amount $x$, then the chemical shift of the internal proton of the $b:e$ ($\delta H_i^{b:e}$) and the $b:b$ conformers ($\delta H_i^{b:b}$) can be given by:

$$\delta H_i^{b:e} = \delta H_i^{e:e} + x \quad \text{(eq. 1)}$$

$$\delta H_i^{b:b} = \delta H_i^{e:e} + 2x \quad \text{(eq. 2)}$$

The conformers are present in a ratio that can be represented by their relative mole fractions ($\chi^{e:e}$, $\chi^{b:e}$, and $\chi^{b:b}$) so the observed chemical shift of the internal proton at room temperature can be given by an average that is weighted according to the mole fractions (equation 3). Substitution of equation 1 for $\delta H_i^{b:e}$ and equation 2 for $\delta H_i^{b:b}$ in equation 3 gives equation 4, which can be rewritten to give equation 5.

$$\delta H_i^{e:b} = \chi^{e:e} \delta H_i^{e:e} + \chi^{b:e} \delta H_i^{b:e} + \chi^{b:b} \delta H_i^{b:b} \quad \text{(eq. 3)}$$

$$= \chi^{e:e} \delta H_i^{e:e} + \chi^{b:e} (\delta H_i^{e:e} + x) - \chi^{b:b} (\delta H_i^{e:e} - 2x) \quad \text{(eq. 4)}$$

$$= \delta H_i^{e:e} + x (\chi^{b:e} + 2\chi^{b:b}) \quad \text{(eq. 5)}$$
For the external proton (H_e), the chemical shifts of the three conformers can be formulated similarly. Again the chemical shift of the c.e conformer is taken as a reference shift at δH_e^{c,e}. The h.e conformer should have a chemical shift that can be represented by the average of the signals of two different external protons (H_e^{b,e} and H_e^{h,e}). H_e^{b,e} is the external proton close to a *pseudo-chair* bridge and thus has a chemical shift δH_e^{b,e}, which already includes a steric deshielding factor (equation 6), and H_e^{h,e} is the proton close to a *pseudo-boat* bridge. It is not deshielded by a proximate bridge, so x is subtracted (equation 7).

\[
\delta H_e^{b,e} = \delta H_e^{c,e} \quad \text{(eq. 6)}
\]

\[
\delta H_e^{h,e} = \delta H_e^{c,e} - x \quad \text{(eq. 7)}
\]

The average chemical shift for the external protons in the h.e conformer can then be given by equation 8. Substitution of equations 6 and 7 in equation 8 gives, after rewriting of equation 9, equation 10.

\[
\delta H_e^{b,e} = \frac{1}{2} \delta H_e^{b,e} - \frac{1}{2} \delta H_e^{h,e}
\]

\[
= \frac{1}{2} (\delta H_e^{c,e} - x) - \frac{1}{2} \delta H_e^{c,e}
\]

\[
= \delta H_e^{c,e} - \frac{1}{2} \times
\]
In the $h,b$ conformer both external protons are not deshielded by a proximate bridge as for the $e,e$ conformer so their chemical shift ($\delta H_{e}^{b,h}$) is corrected by subtracting $x$ and can be given by equation 11.

$$\delta H_{e}^{b,h} = \delta H_{e}^{e,e} - x \quad \text{(eq. 11)}$$

The observed chemical shift of the external proton at room temperature can then be given by the weighted average of the chemical shifts of each conformer, in which each chemical shift is again weighted according to the mole fraction of the corresponding conformer (equation 12).

$$\delta H_{e}^{a,b} = \chi^{c,e} \delta H_{e}^{e,c} + \chi^{c,b} \delta H_{e}^{e,b} - \chi^{b,e} \delta H_{e}^{b,e} \quad \text{(eq. 12)}$$

Substitution of equation 10 for $\delta H_{e}^{e,c}$ and equation 11 for $\delta H_{e}^{b,e}$ in equation 12 gives equation 13 which can be rewritten to give equation 14.

$$\delta H_{e}^{a,b} = \chi^{c,e} \delta H_{e}^{e,c} - \chi^{b,e} (\delta H_{e}^{e,c} \cdot \frac{1}{2} x) - \chi^{b,c} (\delta H_{e}^{e,c} - x) \quad \text{(eq. 13)}$$

$$= \delta H_{e}^{c,e} - x \left( \frac{1}{2} \chi^{b,c} + \chi^{b,h} \right) \quad \text{(eq. 14)}$$

If the chemical shifts of the internal and the external protons are compared to a similarly substituted system such as the 5-substituted meta-xylene ("half cyclophane") system 12.
in which the differential steric deshielding effect of the sulfur atoms in the bridges on $H_i$ and $H_e$ is absent. The difference in chemical shift for the internal and the external protons ($\Delta \delta H_i$ and $\Delta \delta H_e$, respectively) can be defined by:

\[ \Delta \delta H_i = \delta H_i^{\text{vinylene}} - \delta H_i^{\text{cyclophane}} \]  
(eq. 15)

\[ \Delta \delta H_e = \delta H_e^{\text{vinylene}} - \delta H_e^{\text{cyclophane}} \]  
(eq. 16)

When equations 5 and 14 are substituted into equations 15 and 16, the $\Delta \delta$ values for $H_i$ and $H_e$ can be given by equation 17 and 19, which can be rewritten to give equations 18 and 20.

\[ \Delta \delta H_i = \delta H_i^{\text{vinylene}} - [\delta H_i^{c,c} - x (\chi_i^{c,c} - 2 \chi_i^{b})] \]  
(eq. 17)

\[ = (\delta H_i^{\text{vinylene}} - \delta H_i^{c,c}) - x (\chi_i^{c,c} + 2 \chi_i^{b,b}) \]  
(eq. 18)
\[ \Delta \delta H_e = \delta H_e^{xylene} - \left[ \delta H_e^{\text{iso}} - x \left( \chi^h_c + \chi^b_h \right) \right] \quad (\text{eq. 19}) \]

\[ = (\delta H_e^{xylene} - \delta H_e^{\text{iso}}) - x \left( \chi^h_c + \chi^b_h \right) \quad (\text{eq. 20}) \]

The first terms of equations 18 and 20 \((\delta H_e^{xylene} - \delta H_e^{\text{iso}})\) shows the difference in chemical shift between the xylene derivative and the \(c.c\) conformer. This part of the equation is expected to be independent of the ratio of conformers present (mole fractions) and thus independent of the nature of the substituents. It should therefore be constant for the series of compounds studied.

The second term in equation 18 \((- x \left[ \chi^h_c - 2 \chi^b_c \right] \) is opposite in sign to and double the magnitude of the second term in equation 20 \((x \left[ \chi^h_c - \chi^b_c \right] \). This part of the equation is dependent on the mole fractions of the \(h.c\) and the \(h.b\) conformers. It can be expected to vary with the electronic nature of the substituents, according to the following argument. Differing electronic influences will be expected to affect the relative magnitudes of the dipole moments of the three bridge conformers of 4 and thus, if the dipole moment or some other electronic effect is indeed important (as suggested for 4a), would lead to different mole fractions of the conformers.

If a \textit{syn}-2.11-dithia[3,3]metacyclophane has a preference for the \(h.b\) conformation in solution, this should be reflected as a large \(\Delta \delta H_e\) value and a small \(\Delta \delta H_e\) value compared to a \textit{syn}-2.11-dithia[3,3]metacyclophane that adopts mainly the \(c.c\) conformation. If the
preference of a syn-2.11-dithia[3.3]metacyclophane for one conformer over the other is indeed governed by the electronic nature of the substituents and the magnitude of the $\Delta\delta$ values is directly correlated to the distribution between the conformers (as in equations 18 and 20). It might be possible to correlate the $\Delta\delta$ values to some physical organic parameter that describes the electronic nature of substituent groups on (conformational) processes. In the following Sections, the results of correlation studies of $\Delta\delta$ values will be discussed.

2.4 Results and Discussion

In order to study the bridge conformational behavior of 6,15-disubstituted syn-2.11-dithia[3.3]cyclophanes, the synthesis of a large range of cyclophanes and their reference compounds (5-substituted meta-xylene) was required. The compounds that were synthesized are given in Figure 2.09. Samples of several of those compounds were obtained from co-workers\textsuperscript{35-40} and their syntheses will not be described. After a short discussion of the syntheses performed by the author, a discussion of the results of the correlation studies will be given.
### 2.4.1 Syntheses of *syn*-2,11-dithia[3.3]metacyclophanes and 5-substituted *meta*-xylenges

The traditional synthesis of *syn*-2,11-dithia[3.3]metacyclophanes 4 involves high dilution coupling of two building blocks: a dithiol 13 and a dibromide 14, often from a common precursor. Dithiols 13 can usually be synthesized from dibromides 14, which can be formed from *meta*-xylene derivatives 12 via free radical benzylic bromination or from isophthalates 16 via a reduction-bromination sequence. Alternatively, dibromides 14 can

---

#### Table 2.09: Legend for substituents on *syn*-2,11-dithia[3.3]metacyclophanes 4 and *meta*-xylenges 12

<table>
<thead>
<tr>
<th>Cyclophane</th>
<th>Xylene</th>
<th>R</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>12a</td>
<td>CN</td>
</tr>
<tr>
<td>4b</td>
<td>12b</td>
<td>H</td>
</tr>
<tr>
<td>4c</td>
<td>12c</td>
<td>Br</td>
</tr>
<tr>
<td>4d</td>
<td>12d</td>
<td>CO₂Et</td>
</tr>
<tr>
<td>4e</td>
<td>12e</td>
<td>CO₂H</td>
</tr>
<tr>
<td>4f</td>
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<td>NHAc</td>
</tr>
<tr>
<td>4i</td>
<td>12i</td>
<td>NO₂</td>
</tr>
<tr>
<td>4j</td>
<td>12j</td>
<td>OAc</td>
</tr>
<tr>
<td>4k</td>
<td>12k</td>
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<td>12m</td>
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<td>12n</td>
<td>SH</td>
</tr>
<tr>
<td>4o</td>
<td>12o</td>
<td>SMe</td>
</tr>
<tr>
<td>4p</td>
<td>12p</td>
<td>S(O)Me</td>
</tr>
<tr>
<td>4q</td>
<td>12q</td>
<td>S(O)₂Me</td>
</tr>
</tbody>
</table>

---

Figure 2.09: Legend for substituents on *syn*-2,11-dithia[3.3]metacyclophanes 4 and *meta*-xylenges 12
be reacted with Na₂S/Al₂O₃. This last approach often yields a mixture of dimer (desired products 4) and trimer (unwanted byproducts 15), but reduces the number of steps in the synthesis and is compatible with base-sensitive groups, which would require protection if the first approach were used.


Since meta-xylenes 12 are required as reference compounds, using these compounds as starting materials would reduce the amount of experimental work involved. Yields of twofold benzyllic brominations are often low especially in the case of electron-rich aromatic rings where ring-bromination is prevalent so this route is not always useful.
The synthesis of syn-2,11-dithia[3,3]metacyclophanes 4b, 4d, 4e and 4f (Scheme 2.05) commenced with the synthesis of the α,α'-dibromo-meta-xylene derivatives 14. For the parent system α,α'-dibromo-meta-xylene 14b is commercially available. In the case of the carboxylic acid derivatives, the meta-xylene derivative 12d was synthesized via Fischer-esterification\textsuperscript{40} from commercially available 3,5-dimethylbenzoic acid 12e in 82% yield. Benzylic bromination\textsuperscript{42} of 12d yielded dibromide 14d in 44% yield.

\[
\text{12d} \quad R = \text{CO}_2\text{Et} \quad \xrightarrow{\text{EtOH, H}_2\text{SO}_4, \Delta} \quad \xrightarrow{\text{82\%}} \quad \text{14d} \\
\text{12e} \quad R = \text{CO}_2\text{H} \quad \xrightarrow{\text{EtOH, H}_2\text{SO}_4, \Delta} \quad \xrightarrow{\text{82\%}} \quad \text{14d}
\]

\[\begin{array}{|c|c|c|c|}
\hline 
R & 14 & 13 & 4 \\
\hline
b & H & 90\% & \rightarrow 41\% \\
d & \text{CO}_2\text{Et} & 44\% & \rightarrow 37\% \\
f & \text{Me} & 40\% & \rightarrow 95\% \rightarrow 41\% \\
\hline
\end{array}\]


α,α'-Dibromo-meta-xylenes 14b and 14f were converted into their respective dithiols 13 using thiourea to form a bis(isothiouronium) salt, followed by hydrolysis of that salt under basic conditions. Coupling of dithiols 13b and 13f with an equimolar amount of the
dibromides 14b and 14f under high dilution conditions yielded \textit{syn}-2,11-dithia[3.3]metacyclophanes 4b and 4f (41\% for each). The diester 4d was synthesized via direct coupling of the dibromide 14d using Na$_2$S·Al$_2$O$_3$ (37\%). Diester 4d was saponified to give diacid 4e in 89\% yield. An X-ray crystal structure of 4e was determined and the results will be discussed in Section 2.4.2.

\textit{meta}-Xylenes 12j and 12l were synthesized from commercially available 3,5-dimethylphenol 12k (Scheme 2.06). 5-Acetoxy-\textit{meta}-xylene 12j was synthesized in 80\% yield upon treatment with Ac$_2$O HOAc. 3,5-Dimethylanisole 12l was synthesized using the reaction of 11k with iodomethane in DMSO in the presence of KOH (81\%).

Scheme 2.06: Synthesis of 12j and 12l from 12k.

\textit{2.4.2} X-Ray crystal structure of \textit{syn}-2,11-dithia[3.3]metacyclophane-6,15-dicarboxylic acid (4e)

A relatively new theme in the development of chemical sciences has been hydrogen bonding-directed organization of organic molecules to give nanostructured materials\textsuperscript{47-49}. The challenge that researchers in this area face is the design of materials that will have
"an energetic bias of sufficient magnitude that discrimination between alternate modes of assembly may be achieved (ca. 4 kcal/mol for >99.9% homogeneity)." This energy difference between competitive assemblies is on the same order of magnitude as the strength of the hydrogen bonding interactions, which makes hydrogen bonding a suitable tool for noncovalent synthesis.

In Figure 2.10 some examples of supramolecular assemblies are given. Both examples exist of building blocks that cannot form hydrogen bonds in an intramolecular fashion without adopting a high-energy conformation, which leads to dimer formation in the solid state. syn-2.11-Dithia[3.3]metacyclophane-6,15-dicarboxylic acid 4e also possesses two groups that can form relatively strong hydrogen bonds. In order for 4e to form intramolecular hydrogen bonds, the carboxylic acid groups would have to adopt highly unfavorable conformations, which led us to believe that 4e might exhibit intermolecular hydrogen bonding in its solid state.

Figure 2.10: Examples of supramolecular assemblies (17 and 18).
The three-dimensional structure of diacid 4e can schematically be represented by structure I, which can be seen as a possible building block for supramolecular structures. In the solid state 4e could form a dimer II or an infinite molecular ladder III. In order to determine which assembly 4e would form in the solid state, crystallization of 4e was attempted.

![Figure 2.11: Proposed modes of supramolecular assembly for 4e.](image)

An X-ray structural analysis of crystals of syn-2,11-dithia[3.3]metacyclophane-6,15-dicarboxylic acid 4e obtained from DMF showed formation of a symmetrical hydrogen bonded dimer II (Figure 2.12). The thioether bridges in 4e were arranged in the pseudo-chair conformation.
An interesting feature of the X-ray crystal structure of 4e is that the carboxylic acid groups in each monomer unit are aligned in such a way that it has a set of face-to-face oriented carbonyl groups and (automatically) a set of face-to-face hydroxyl groups. The position of the bridging hydrogen atoms was actually determined in the data collection. The positions of the other hydrogen atoms were calculated. The O-H bond length in the hydroxyl groups was 0.962 Å and the distance between the bridging hydrogen atoms and the carbonyl oxygen atoms was 1.551 Å, which is typical for hydrogen bonds.

The formation of a supramolecular structure of 4e in the solid state suggests that this compound might show some interesting features when co-crystallized with compounds that are capable of hydrogen bonding with 4e. The syn-conformation of 4e might cause this diacid to act as a "supramolecular clamp" to give assemblies IV and V when co-crystallized with terephthalic acid (19) or trimesic acid (20), respectively. Other
compounds containing functionalities capable of forming hydrogen bonding with 4e might also give rise to interesting structural motifs.

Initial attempts to co-crystallize 4e with terephthalic acid or trimesic acid have so far failed to give mixed crystals (by $^1$H NMR). Only DMF has been used as a solvent, so a wide range of crystallization conditions is still to be investigated. Since this project is beyond the scope of this thesis, it was not pursued further. It is a promising project however, and might well be the basis of a new direction in the application of cyclophane chemistry to the area of supramolecular assemblies.
2.4.3 NMR study of syn-2,11-dithia[3.3]meta-cyclophanes

The 300 MHz $^1$H NMR spectra of all the 6,15-disubstituted cyclophanes 4 and the 5-substituted meta-xylenes 12 were recorded at the same concentration (6 mM) and temperature (19°C) in C$_6$D$_m$, CDCl$_3$ and DMSO-$d_6$. The concentration was chosen so as to be as low as possible to still give good quality spectra while minimizing intermolecular interactions. The $^1$H NMR spectroscopic data of the series of compounds can be found in Tables A-1a-c in Appendix A.

2.4.3.1 Correlation with the Hammett constant $\sigma_m$

The experimental $\Delta \delta H$ and $\Delta \delta H_e$ values were plotted against several physical organic parameters (Hammett's $\sigma_m$ (this Section) Taft's dual parameter system (Section 2.4.3.2), Swain and Lupton's dual parameter system (Section 2.4.3.3), electronegativity values of the substituents (Appendix C) and AM1-calculated dipole moments (Appendix C). The first correlation that was studied involved the Hammett constant $\sigma_m$, for which the $\Delta \delta$ values for each solvent were plotted directly versus the literature values (Table A-2, Appendix A). The resulting graphs are given in Figures 2.14a-c. In each plot, the trend lines (calculated by linear regression) are drawn for $\Delta \delta H$ and $\Delta \delta H_e$.

* Error in $\Delta \delta$ was taken as ± 0.02 ppm.
Figure 2.14a: $\Delta \delta_H$, and $\Delta \delta_L$ versus $\sigma_m$ for spectra measured on C$_{60}$D$_{60}$ solutions.

Figure 2.14b: $\Delta \delta_H$, and $\Delta \delta_L$ versus $\sigma_m$ for solutions measured on CDCl$_3$ solutions.
When the graphs and trend lines for the different solvents are compared, several features are apparent. The trend line for \( \Delta \delta H \) has a negative slope in each solvent and the line for \( \Delta \delta H_c \) has a positive slope. Unfortunately, some data points are well off the indicated trend lines. For spectra measured in \( C_2D_2 \) solution this is the case for \( R = OAc \) (\( \sigma_m = 0.39, \Delta \delta H = 0.215, \Delta \delta H_c = 0.019 \)). For spectra measured in \( CDCl_3 \) solution, the points for \( R = OAc \) (\( \sigma_m = 0.39, \Delta \delta H = 0.124, \Delta \delta H_c = -0.013 \)) and \( R = S(O)Me \) (\( \sigma_m = 0.21, \Delta \delta H = -0.187, \Delta \delta H_c = 0.150 \)) are well off the line and for spectra measured in DMSO-\( d_6 \) solution, the anomalous points are those for \( R = NH_2 \) (\( \sigma_m = -0.09, \Delta \delta H = 0.210, \Delta \delta H_c = -0.039 \)) and \( R = S(O)Me \) (\( \sigma_m = 0.21, \Delta \delta H = -0.261 \) only). Despite the presence of some scattering, the trends are unmistakable.
The values for \( R^2 \) in Figures 2.14a-c are quite low, so that the correlations can at best be described as a trend. Scattering of data points might be the result of the choice of Hammett's \( \sigma_m \) as physical organic parameter, as it has not been designed to describe conformational processes such as those in the \( \text{syn-2,11-dithia[3,3]} \) metacyclophane system. In trying to explain the scattering of data points, the assumptions that have been made earlier should also be considered. When the hypothesis upon which this work rests was developed, it was assumed that: (a) the only conformers that contribute to the observed \(^1\text{H} \) NMR spectrum at room temperature are the \( e.e. \) the \( h.e \) and the \( h.h \) conformers, (b) the steric deshielding effect of a sulfur atom in a bridge is equal for each interaction and (c) this steric deshielding effect is additive for each interaction.

The first assumption (that only the \( e.e. \) the \( h.e \) and \( h.h \) conformers should be considered) is probably valid. It is based on reports from S"emml"eohack\(^10\) and Shinmyouzu\(^31\) who only observed these bridge conformers. In Section 2.4.5 our DNMR studies of cyclophanes 4b, 4d, 4g, 4l, 4n and 4r will be presented. These results were in agreement with S"emml"eohack and Shinmyouzu's results and supported this assumption.

The second assumption, that the steric deshielding effect of a thioether bridge is the same for every interaction, is probably only true by approximation. The amount of steric deshielding that occurs on a proton when steric crowding occurs depends on the distance between (in case of cyclophanes 4) the thioether bridge and the proton considered. The assumption that the steric deshielding of the internal proton by a \textit{pseudo-boat} bridge is
the same as the steric deshielding of the external proton by a \textit{pseudo-chair} bridge
presumes that the distance between these protons and the sulfur atoms in the bridges (or
the bond critical points of the C-S bonds) is the same. Although it would be difficult to
measure accurately the distance between the sulfur atom in a thioether bridge and a
proton in a particular conformer in solution, an estimation of these values can be made
based on AM1 level calculations. In Figure 2.15 the AM1-calculated structures and the
distances between the thioether bridges and the sterically deshielded aromatic protons are
given for the three bridge conformers of the parent system \textit{syn}-2,11-
dithia[3.3]metacyclophane 4b.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure2.15.png}
\caption{AM1 calculated structures and steric deshielding distances in \textit{c,c}-4b (left), \textit{b,c}-4b (middle)
and \textit{b,b}-4b (right).}
\end{figure}

From Figure 2.15 it can be seen that the distance between a \textit{pseudo-boat} bridge and an
external proton is calculated to be approximately 3.3 Å, but the distance between an
internal proton and a pseudo-chair bridge is calculated to be only about 2.8 Å. This difference in distance can be attributed to the non-coplanarity of the aromatic rings in each calculated structure. The smallest angle between the planes of the aromatic rings (dihedral angle: 48.5° in c.e-4b, 38.2° in b.e-4b and 38.2° b.b-4b) causes the external protons to separate, and, at the same time, to move away from the sulfur atoms in the bridge. For the internal protons the opposite is true, although the effect is not as large. From the published X-ray structure of 4b (dihedral angle 20.6°) it is obvious that the AM1-calculated dihedral angle is greatly overestimated, but any dihedral angle greater than 0° would cause a difference in distance between the internal and external protons and their corresponding bridges. This difference in distance then leads to a difference in steric deshielding, which would lead to different values for “x” in Section 2.3 for the internal and external protons. As only dihedral angles greater than 0° have ever been observed and or calculated for [3.3]metacyclopahnes (Table 2.01) it can also be expected that the steric deshielding effect for the internal proton would be more than twice as large (as previously assumed) as the effect on the external protons, which could lead to the observed ratios of slopes in Figures 2.14a-c.
<table>
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<th>Compound</th>
<th>R</th>
<th>Dihedral angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>-4a</td>
<td>CN</td>
<td>9.0°</td>
</tr>
<tr>
<td>-4b</td>
<td>H</td>
<td>20.6°</td>
</tr>
<tr>
<td>-4c</td>
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</tr>
<tr>
<td>-4d</td>
<td>CO₂H</td>
<td>9.5°</td>
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<td>-4e</td>
<td>OMe</td>
<td>15.3°</td>
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<tr>
<td>-4f</td>
<td>SO₂Me</td>
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<td>18.9°</td>
</tr>
<tr>
<td>-4h</td>
<td>CC-H</td>
<td>29.6°</td>
</tr>
</tbody>
</table>

Table 2.01: Dihedral angle in the solid state for selected syn-2,11-dithia[3.3]metaacyclophanes.

From Table 2.01 it can be seen that a great variation in dihedral angles has been observed in the solid state. No trend is obvious between the value for this angle and any molecular property such as electronic nature or steric bulk of the substituents on the syn-2,11-dithia[3.3]metaacyclophane structure. If the variation in dihedral angle also occurs in solution it can be expected that the value for "x" (Section 2.3) is not the same for all 6,15-disubstituted syn-2,11-dithia[3.3]metaacyclophanes. This might explain the significant scattering that was observed in Figures 2.14a-c.

The above discussion of the dependence of the amount of steric deshielding on the dihedral angle might also explain why certain data points in Figures 2.14a-c are well off
the trend lines. This would only hold true if the dihedral angle in these particular compounds is drastically different from the dihedral angle in the majority of the cyclophanes studied. From examination of the structures it is not clear why these particular compounds would exhibit greater dihedral angles than the greater part of the group. The compounds that correspond with the anomalous points do not have substituents that are sterically more demanding than other cyclophanes studied and also electronically these compounds are well within the range of electronic dispositions studied. Unfortunately it does not seem obvious how one would measure the dihedral angle in these systems, so it is not possible to discard the possibility that a drastically different dihedral angle in these systems would cause these particular compounds to show data points well off the expected trend lines. Another explanation for these anomalies can be found based on intramolecular interactions between the substituents and will be discussed after some comments on the remaining assumption from Section 2.3.

After considering the first two assumptions that were made in the development of our hypothesis, the third assumption (additivity of the effect of steric deshielding) should be examined. This assumption was only made for the internal protons in the $h.b$ conformer. The internal protons in the $d.e$ and $h.e$ conformers and the external protons in all three conformers are only deshielded by one proximate bridge. Only if the $h.b$ conformer were a major contributor to the conformer mixture of a particular cyclophane in solution at room temperature would the accuracy of this assumption play a role in the error in $\Delta\delta$ values. As the mole fraction of $h.b$ conformer is expected to be a function of the
electronic character of the substituent in the 6- and 15- positions (and thus $\sigma_m$). deviation from a straight line would be expected only for the compounds with strongly electron withdrawing groups in Figures 2.14a-c if this additivity were not valid. This effect is not observed.

The last effect that remains to be considered is related to the nature of the correlation that is studied. Somewhat arbitrarily, Hammett's $\sigma_m$ values were chosen for correlation studies of the $\Delta\delta$ values. By making this choice it was automatically assumed that the $\sigma_m$ value for a given substituent would be equal in the 5-substituted meta-xylene and the corresponding syn-2,11-dithia[3.3]metacyclopahne. This assumption might not hold true if in the cyclophane system significant intramolecular interactions occur between the substituents in the 6- and 15 positions, as these interactions are clearly not accounted for in the meta-xylene system. These intramolecular interactions (e.g. intramolecular hydrogen bonding of hydroxyl groups or carboxylic acid groups) might cause the substituent groups to adopt different conformations than in the meta-xylene reference compounds. Hammett's $\sigma_m$ values do not account for such interactions and changes in conformation and as a result the effective $\sigma_m$ value of these substituents might be different from the published Hammett's $\sigma_m$ value. This would lead to significant scattering of these particular data points in the plots of $\Delta\delta$ values versus $\sigma_m$. 
2.4.3.2 Correlations with Taft's dual parameter system

When considering the electronic influence of the substituents on the cyclophane system, the question arises whether this effect is a completely inductive effect, or if there might be a resonance component as well. In the literature, several systems have been described that separate the inductive and resonance components in Hammett-like systems. The two systems that will be considered are Taft's dual-parameter system and Swain and Lupton’s modification.

Figure 2.16 shows the results of plotting of \( \Delta \delta \mathrm{H} \), measured in CDC13 solutions as a function of \( \sigma \) in which \( \sigma = \sigma_1 - \alpha \sigma''_R \). Values for \( \sigma_1 \) and \( \sigma''_R \) were taken from published tables and are represented in Appendix A. Eight trend lines (best lines calculated via linear regression) have been drawn in the plot, in 0.1 increments for the value of \( \alpha \), ranging from 0.1 - 0.8. For clarity, only the data points for \( \alpha = 0.1 \) and \( \alpha = 0.8 \) are indicated on the plot, since the data points with intermediate \( \alpha \)-values will be located on a straight line, evenly distributed between these two sets of points.
In Figure 2.16 the best correlations are found for the trend lines where $\alpha = 0.4 - 0.6$. This corresponds to a ratio of inductive to resonance effects of approximately 2:1, which is not surprising, as the resonance effects of the substituent groups would be expected to have less of an impact on the ratio of conformers than the inductive effect. The inductive effect was not expected to have a great impact on the bridge conformational behavior of a syn-2,11-dithia[3.3]metacyclophane since no resonance structures could be drawn that greatly prefer one conformation over the other. When the $\Delta\delta H_1$ values in other solvents or the $\Delta\delta H_c$ values are treated in the same manner, very similar results are obtained, with optimal ratios of approximately 2:1 for inductive and resonance effects (Appendix B).
2.4.3.3 Correlation with the Swain-Lupton dual parameter system

A dual-parameter system quite similar to that of Taft is the system developed by Swain and Lupton. In this system, the Hammett \( \sigma_m \) is replaced by a new \( \sigma \), which is defined as \( \sigma = fF + rR \). The constants \( F \) and \( R \) are constants that describe the field (inductive) and resonance effect of each substituent and were obtained from published tables and are given in Appendix A. Figure 2.17 shows the result of plotting \( \Delta \delta H_i \) measured in CDCl\(_3\) solution versus \( \sigma \), where \( f \) and \( r \) are varied from a ratio \( f = 0.70 / r = 0.30 \) in 0.02 increments for \( f \) and \( -0.02 \) for \( r \) to a final ratio of \( f = 0.90 / r = 0.10 \). In total, 11 lines are indicated on the plot and again only the data points at the extremes for \( \sigma \) are indicated since the other data points lie in between.

![Figure 2.17: \( \Delta \delta H_i \) measured on CDCl\(_3\) solution versus \( \sigma = fF + rR \).](image-url)
The results from Figure 2.17 (Swain and Lupton system) are quite similar to those from Figure 2.16 (Taft’s system). Again it can be observed, that the inductive (field) effects are more important in determining the bridge conformational behavior of syn-2.11-dithia[3.3]metacyclophanes than resonance effects. In the case of the Swain and Lupton variation a ratio of approximately 0.86 / 0.14 seems to be optimal, giving a ratio of approximately 5:1 of inductive compared to resonance influence. The discrepancy in ratios (2:1 compared to 5:1) between the two dual-parameter systems is not surprising, since the systems define their constants differently. For Taft’s system, $^{13}$C NMR data are used to determine the values for $\sigma_i$ and $\sigma^0$ and Swain and Lupton used experimental data from various reactions to try to separate resonance and field effects. The importance of the two dual-parameter systems in the case of the bridge conformational behavior of syn-2.11-dithia[3.3]metacyclophanes is that they both suggest the inductive effect is more important than the resonance effect.

Other parameters with which the $\Delta\delta$ values might show a correlation were investigated, but no correlations were found when the relation between $\Delta\delta$ values and AM1-calculated dipole moments or group electronegativities was studied. A summary of these results can be found in Appendix C.
2.4.3.4 Solvent Effects

In the plots of $\Delta \delta$ values versus the Hammett constants (Figure 2.14a-c) the slope for $\Delta \delta H_i$ shows some variation with the nature of the solvent (-0.62 in C$_6$D$_6$, -0.61 in CDCl$_3$ and -0.44 in DMSO-d$_6$) and seems to become less negative with increasing polarity of the solvent. For the slope of $\Delta \delta H_e$ no significant difference is observed (0.21 in C$_6$D$_6$, 0.20 in CDCl$_3$ and 0.23 in DMSO-d$_6$). The trend in slopes for $\Delta \delta H_i$ can be explained by invoking the principle that a polar solvent will accommodate a molecule with a large dipole moment better than will a nonpolar solvent.$^{32}$ This would cause the substituents to have a less pronounced effect in polar solvents, leading to smaller slopes in the plots of $\Delta \delta$ versus the Hammett constant. This suggests there might be a correlation between the slopes in the different solvents and some constant describing the polarity of the solvent. When the values of the slopes of $\Delta \delta H_i$ and $\Delta \delta H_e$ are plotted against the solvent dielectric constant ($\varepsilon$) the plot in Figure 2.18 arises.
From the plot in Figure 2.18 it can be seen, that at least for the internal protons, a strong correlation exists between the slope of $\Delta \delta H_i$ versus $\sigma_m$ and the solvent polarity. For the external protons, this trend seems to be absent. In both cases, care must be taken when interpreting the data, since only three different solvents were used to determine the solvent effect on the $\Delta \delta$ values and two of these have similar values for their dielectric constants. When the slopes from Figures 2.14a-c are plotted versus Reichardt’s empirical measure of solvent polarity ($E_{11}(30)$), the correlation is worse (Figure 2.19). Measurements of these values in more solvents would be necessary to obtain more reliable data, but the small amount of data available so far gives an indication of a correlation between the solvent polarity and the magnitude of the effect of the
substituents of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes on the bridge conformational behavior.

![Figure 2.19: Slope of $\Delta \delta \text{H}_1$ and $\Delta \delta \text{H}_2$ versus Reichardt's $E_\tau(30)$.](image)

The preceding discussion of the conformational behavior of syn-2,11-dithia[3.3]metacyclophanes as a function of the Hammett constant of the substituents in the 6- and 15-positions of the cyclophanes described some noteworthy correlations. Not only does it seem that the electronic properties of the substituents have an influence on the conformational preferences of the sulfur-containing bridges, there also seems to be a solvent effect on the conformational behavior of syn-2,11-dithia[3.3]metacyclophanes. Unfortunately, no technique is currently available to determine the actual ratios of the different bridge conformers of syn-2,11-dithia[3.3]metacyclophane at room temperature.
If such a technique would be available it would be interesting to compare its results with the results that were presented in this Chapter.

More study is required into the behavior of specific cyclophanes (4a, 4j, 4l and 4r) to determine why the data points corresponding to these compounds are well off the trend lines in Figure 2.14a-c. Maybe the situation in these particular cyclophanes is not as the hypothesis contends and the hypothesis might have to be re-examined with this in mind. Additional data for the library of compounds in other solvents are also required, in order to establish with confidence a correlation between solvent polarity and the magnitude of the influence of the substituent groups on the bridge conformational behavior of syn-2,11-dithia[3.3]metacyclophanes.

2.4.5 DNMR studies of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes

In order to study further the conformational behavior of syn-2,11-dithia[3.3]metacyclophanes, some DNMR studies were performed. It was hoped that an explanation could be found using this technique for the scattering of data points that occurred in the plots of \( \Delta \delta H \) values versus \( \sigma_m \) (Figures 2.14a-c). For the DNMR studies, compounds 4b (R = H), 4d (R = CO₂Et), 4g (R = Me), 4i (R = OAc), 4n (R = OMe) and 4r (R = S(O)Me) were chosen, since the electronic character of the substituent groups ranges from electron-withdrawing (4d \( \sigma_m = 0.35 \), 4i \( \sigma_m = 0.39 \)) to electron-donating (4g
\[
\sigma_m = -0.06.
\]
All DNMR experiments were performed in CD\(_2\)Cl\(_2\) at 500 MHz between 183 and 273 K.

The results from the DNMR studies of each 6,15-disubstituted \(\text{syn-2,11-dithia[3,3]metacyclophane}\) are quite similar. Therefore, the typical results of 4d will be discussed here first, followed by short discussions of the results from the other cyclophanes.

### 2.4.5.1 \(\text{syn-6,15-Bis(ethoxycarbonyl)-2,11-dithia[3,3]metacyclophane (4d)}\)

At 273 K the spectrum of 4d shows two singlets in the aromatic region (7.31 ppm (H\(_1\)) and 7.49 ppm (H\(_{15}\))). Broadening of each signal occurs as the temperature is lowered and at 223 K each signal has resolved into two broad singlets. Integrations suggest that these signals arise from two conformers that are present in a 3:2 ratio. The major conformer shows a signal at 7.43 ppm for the internal and 7.40 ppm for the external proton (183 K). The corresponding signals of the minor conformer appear at 7.17 ppm and 7.53 ppm (183 K) (Figure 2.20). The same conformer ratio is obtained from the integration of the signals for the benzylic protons in the bridges. The singlet for these protons at room temperature resolves at 203 K to give an AB system for the minor conformer, which is overlapped with a broad singlet for the major conformer (Figure 2.20).

* For this and subsequent DNMR studies the data are consistent with two conformers. There is no evidence for more conformers, although their presence cannot be ruled out.
2.4.5.2 syn-6,15-Diacetox-2,11-dithia[3.3]metacyclophane (4j)

The results from the DNMR study of syn-6,15-diacetox-2,11-dithia[3.3]metacyclophane 4j are quite similar to those of syn-6,15-bis(ethoxycarbonyl)-2,11-dithia[3.3]metacyclophane 4d. At 273 K, the aromatic region showed two singlets (6.68 ppm and 6.85 ppm; integration ratio 2 : 1) and the benzylic protons appeared as a singlet at 3.80 ppm. Upon cooling, all signals broadened and, at lower temperatures, two sets of signals could be observed. The aromatic region showed the presence of two conformers at temperatures below 223 K in a ratio of 2.3 : 1 (Figure 2.21). At the same temperature the signal for the benzylic protons had resolved into an AB system, which was overlapped by a broad singlet (Figure 2.21).

![DNMR spectra of 4j](image)

The major conformer gives rise to the signals at 6.82 ppm ($H_i$) and 6.61 ppm ($H_e$) and the AB system for the benzylic signals. Based on the upfield shift of the signal for the internal proton, the major conformer could be assigned the $c,c$ conformation (analogous to the results for 4d). The minor conformer showed signals at 7.13 ppm ($H_i$), 6.51 ppm...
signal (no *pseudo-chair*-like signal is observed). However, calculations on *syn*-2,11-dithia[3.3]metacyclophanes that suggest that the *h.h* conformer is the highest energy conformer\(^5\) so it would be expected that it would be observed in lower concentrations than the *pseudo-boat*, *pseudo-chair* conformer. The absence of any evidence for the presence of the *h.e* conformer renders this explanation unlikely.

Another explanation is that the signals that are observed for the major conformer are actually the result of a fast interconversion between two conformers, even at 183 K. This would not only explain the broad singlet that appears as the only signal for the benzylic protons, but would also explain why only two signals are observed in the low temperature NMR spectrum. The two interconverting conformers are probably not the *h.e* and *h.h* conformers based on the expectation that the energy barrier (and thus the coalescence temperature) for the interconversion process between these two conformers is similar to that for interconversion between the *e.e* and *h.e* conformers, which would have led to resolution of the signal for the bridge protons at approximately the same temperature (differences in \(\Delta V\) and \(J\) values will lead to only a small difference in \(T_c\)).\(^3\) The observation of a broad singlet for the benzylic protons at low temperature can be explained by fast *syn* to *syn*\(^\prime\) interconversion of a *h.e* conformer (Scheme 2.07). This interconversion process would exchange the environment of the axial and equatorial protons in the bridges and thus lead to a broad singlet for these protons. The observation of a singlet for the external proton is also consistent with this process. Shinmyozu obtained similar results in his DNMR studies of \(\text{d}_4\)-8b and \(\text{d}_4\)-8c.\(^3\) A notable result in our
study is the ratio of 2 : 3 between the e.e and h.e conformers in favor of the h.e conformer, which was calculated to be 0.3 kcal/mol (1.4 kJ/mol; AM1 level calculations)\textsuperscript{10} higher in energy than the (minor) e.e conformer. This ratio of e.e and h.e conformers is consistent with dipole minimization as discussed for syn-6,15-dicyano-2,11-dithia[3.3]metacyclophane 4a (Section 2.1).

Scheme 2.07: Some interconversion processes of different conformers of 4d at 183 K.

For the e.e to h.e interconversion, the activation energy can be estimated to be 10.2±0.3 kcal mol\(^{-1}\) (42.7±1.1 kJ mol\(^{-1}\); based on \(T_e = 213±5\) K; \(\Delta v = 55.2±0.2\) Hz and \(J = 15.0±0.2\) Hz).\textsuperscript{15} 5 If the signals for the major conformer can indeed be attributed to a fast syn to syn\textsuperscript{−} equilibrium, the energy difference between the e.e and the h.e conformers can be estimated at 0.15 kcal mol\(^{-1}\) (0.62 kJ mol\(^{-1}\)) since the syn-h.e and the syn\textsuperscript{−}-h.e are degenerate structures.
2.4.5.2 syn-6,15-Diacetoxy-2,11-dithia[3.3]metacyclophane (4j)

The results from the DNMR study of syn-6,15-diacetoxy-2,11-dithia[3.3]metacyclophane 4j are quite similar to those of syn-6,15-bis(ethoxycarbonyl)-2,11-dithia[3.3]metacyclophane 4d. At 273 K, the aromatic region showed two singlets (6.68 ppm and 6.85 ppm; integration ratio 2 : 1) and the benzylic protons appeared as a singlet at 3.80 ppm. Upon cooling, all signals broadened and, at lower temperatures, two sets of signals could be observed. The aromatic region showed the presence of two conformers at temperatures below 223 K in a ratio of 2.3 : 1 (Figure 2.21). At the same temperature the signal for the benzylic protons had resolved into an AB system, which was overlapped by a broad singlet (Figure 2.21).

![Figure 2.21: DNMR spectra of 4j.](image)

The major conformer gives rise to the signals at 6.82 ppm (H_i) and 6.61 ppm (H_e) and the AB system for the benzylic signals. Based on the upfield shift of the signal for the internal proton, the major conformer could be assigned the c,c conformation (analogous to the results for 4d). The minor conformer showed signals at 7.13 ppm (H_i), 6.51 ppm
(Hc) and 3.79 ppm (broad singlet for the benzylic protons) and, as for 4d, is probably the result of a fast syn to syn' equilibrium for the b,c conformer. The ratio of the signals of approximately 2.3:1 in favor of the c,c conformer indicates a greater preference of 4j for the c,c conformer than for 4d, which is consistent with the dipole minimization effect discussed earlier. The energy barrier for the bridge-wobbling process between the c,c and the b,c conformers can be estimated to be $10.8 \pm 0.2$ kcal/mol ($45.2 \pm 1.0$ kJ/mol; $T_c = 223 \pm 5$ K; $\Delta v = 49.7 \pm 0.2$ Hz; $^2J = 21.9 \pm 0.2$ Hz) and that the b,c conformer is approximately 0.3 kcal/mol (1.3 kJ/mol) higher in energy than the c,c conformer.

2.4.5.3 syn-6,15-Dimethyl-2,11-dithia[3.3]metacyclophane (4f)

The DNMR study of syn-6,15-dimethyl-2,11-dithia[3.3]metacyclophane 4f was limited by the properties of the solvent, CD$_2$Cl$_2$. At the lowest temperature that can be used with this solvent (183 K), the spectrum shows clear signs of resolution into different conformers, but the resolution is not sufficient to draw conclusions (Figure 2.22).
2.4.5.4 *syn*-6,15-Bis(sulfoxymethyl)-2,11-dithia[3.3]metacyclopahne (4p)

The DNMR study of *syn*-6,15-bis(sulfoxymethyl)-2,11-dithia[3.3]metacyclopahne 4p was complicated by the presence of two diastereomers of the cyclophane as a result of the asymmetry at the sulfur atoms in the substituents. As a result, the $^1$H NMR spectrum of 4p at 273 K showed a set of signals for each diastereomer (Figure 2.23). At lower temperatures, this led to complicated and overlapping signals in the aromatic region of at least two conformers (each probably with two diastereomers), of which analysis proved too difficult to assign unambiguously the signals to any conformer. The signals for the benzylic protons were not resolved.

![Figure 2.23: DNMR spectra of 4p.](image-url)
2.4.5.5 *syn*-6,15-Dimethoxy-2,11-dithia[3.3]metacyclophane (4l)

In its DNMR study, *syn*-6,15-dimethoxy-2,11-dithia[3.3]metacyclophane 4l showed results similar to 4d and 4j. At 183 K, the spectrum showed the presence of at least two conformers, although some overlapping of signals occurred (Figure 2.24). The signal of the benzylic protons, which is a singlet at 3.67 ppm at 273 K, had not resolved into an AB system at 183 K, although considerable broadening was observed. The aromatic region changed from two singlets at 273 K to a set of broad peaks at 183 K. Resolution of the signals at 183 K was not sufficient to draw conclusions.

![Figure 2.24: DNMR spectra of 4l.](image)
2.4.5.6 syn-2,11-Dithia[3.3]metacyclophane (4b)

DNMR study of the parent system syn-2,11-dithia[3.3]metacyclophane 4b showed similar features to the systems described in the preceding Sections. Since the substituents in the 6- and 15-positions are now hydrogen, the aromatic region (at 273 K) is more complex than cyclophanes with other substituents in these positions. At 273 K, the benzylic protons appeared as a singlet (3.80 ppm). As the temperature was lowered, all signals broadened and resolution of the aromatic region into two conformers occurred below 213 K (Figure 2.23). The signal for the benzylic protons resolved into an AB system, overlapped with a broad singlet in a ratio 1:6:1 at that temperature (Figure 2.25). Assignment of the signals in the aromatic region was complicated by the splitting of some of the signals. Based on the results from the previous Sections and the electronic nature of the substituents on the 6- and 15 positions (H), the AB system (of the major conformer) was expected to result from the e,e conformer.

The minor conformer (based on the integration of the signals in the benzylic region) gave rise to a singlet at 7.08 ppm (H) and a broad singlet at 3.77 ppm for the benzylic protons, which suggests a fast equilibrium between at least two conformers. Based on the observations on the previously discussed cyclophane systems, this equilibrium is probably a fast syn to syn'-equilibrium of the h,e conformer. The AB system in the benzylic region can be assigned to the e,e conformer and it can then be estimated that the energy barrier for the bridge wobbling process between the e,e and the h,e conformers is
approximately $10.2 \pm 0.3$ kcal/mol ($42.7 \pm 1.0$ kJ/mol; $T_c = 213 \pm 5$ K; $\Delta v = 57.2 \pm 0.2$ Hz; $^2J = 14.3 \pm 0.2$ Hz). The energy difference between the $c,c$ and the $b,c$ conformers can be estimated to be $0.2$ kcal/mol ($0.7$ kJ/mol).

In order to study further the conformational behavior of $4b$ at lower temperatures, a $^{13}$C NMR spectrum was collected of the conformer mixture at $183$ K (Figure 2.26). Two sets of signals in a ratio of approximately $3:2$ were observed, which corresponds to the $1.6:1$ ratio that was observed in the $^1$H NMR spectrum at the same temperature. The major conformer could be assigned the $^{13}$C resonances at $\delta 137.5, 131.6, 128.3, 126.1$ (overlap with minor conformer) and $38.7$ ppm and the signals at $\delta 136.7, 130.6, 127.5, 126.1$ (overlap with major conformer) and $36.2$ ppm can be attributed to the minor conformer (Figure 2.26). The major conformer was assigned the $c,c$ conformer based on the results from the $^1$H NMR spectrum and the signals of the minor conformer can be attributed to the $b,c$ conformer in rapid syn to syn' equilibrium.
2.4.5.7 Conclusions and future work on DNMR studies

In this Section the results of our DNMR studies of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes 4 have been presented. To our knowledge this is the first DNMR study of these compounds that has shown resolution of the $^1$H and $^{13}$C NMR spectra at lower temperatures.

The results of the DNMR studies of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes (Sections 2.4.5.1-2.4.5.6) show strong similarities. For cyclophanes 4b ($R = H$), 4d ($R = CO_2 Et$) and 4j ($R = OAc$), freezing of the $c,c$ to $b,c$ interconversion was observed. The activation energy for the bridge-wobbling process was estimated to be 10-11 kcal/mol, which is in good agreement with Shinmyozu's estimate of 11.6 kcal/mol for the all-carbon [3.3]metacyclophanes.$^{30,31}$ The $b,c$ conformers in the frozen mixtures still underwent fast syn to syn' interconversion similar to Shinmyozu's results.$^{31}$ The presence of $b,b$ conformers was not observed directly in any case, but could
not be ruled out. In order to observe this conformer, it might be necessary to introduce an extra tether in the cyclophane system (e.g. compound 21, Figure 2.27), which was the strategy that led to observation of a $b,b$ conformer by Shinmyoza.  

![Figure 2.27: Tethered cyclophane 21.](image)

A further observation was the preference of syn-6,15-histethoxy carbonyl)-2,11-dithia[3.3]metacyclophane 4d (with electron withdrawing groups) to prefer the $b,c$ conformation (e.g.: $b,c = 2 : 3$), whereas the parent system (syn-2,11-dithia[3.3]metacyclophane 4b) and the more electron rich syn-6,15-diacetoxy-2,11-dithia[3.3]metacyclophane 4j prefer the $e,e$ conformation (e.g.: $b,c = 1.6 : 1$ and $2.3 : 1$, respectively). This is again consistent with the hypothesis that the electronic nature of the substituents is an important factor in determining the bridge conformational behavior of syn-2,11-dithia[3.3]metacyclophanes. It would be interesting to expand the DNMR studies to cyclophane systems with stronger electron withdrawing properties (e.g. syn-6,15-dicyano- and syn-6,15-dinitro-2,11-dithia[3.3]metacyclophane 4a and 4i), since a considerable preference of these systems for the $b,c$ conformer is expected and perhaps
even the \( h, h \) conformer can be observed. However, low solubility of these systems (in \( \text{CD}_2\text{Cl}_2 \)) has so far prevented us from studying these compounds using DNMR.

2.5 Experimental

**General.** All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40-63 \( \mu \text{m} \), 230-400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed at the Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta. Mass spectral (MS) data were recorded on a V. G. Micromass 7070HS instrument. \(^1\)H NMR (300.1 MHz) and \(^13\)C NMR (75.47 MHz) were obtained on a General Electric GE 300-NB spectrometer: \(^1\)H shifts are relative to internal tetramethylsilane; \(^13\)C shifts are relative to the solvent resonance (\( \text{CDCl}_3; \delta = 77.0 \)). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under nitrogen unless otherwise noted. Solvents were dried and distilled according to standard procedures.

**Ethyl 3,5-dimethylbenzoate (12d)**

To a well-stirred solution of 3,5-dimethylbenzoic acid 12e (17.66 g, 118 mmol) in EtOH (abs.) (400 mL) was added concentrated sulfuric acid (15 mL), and the solution was
refluxed for 24 h. The reaction mixture was cooled, concentrated \textit{in vacuo} to approximately 30\% of the original volume and poured into H$_2$O (150 mL) and EtOAc (150 mL). The aqueous layer was extracted with EtOAc (150 mL). The organic extracts were combined, washed with saturated aqueous NaHCO$_3$ solution (2 x 100 mL), H$_2$O (100 mL) and saturated aqueous NaCl solution (75 mL), dried (MgSO$_4$) and concentrated \textit{in vacuo} to yield a yellow oil. Purification by vacuum distillation (93 – 95 °C / 4-6 mmHg) yielded 12d (17.16 g, 96.3 mmol, 82\%) as a colorless oil: IR (Nujol, cm$^{-1}$): 1723 (s), 1609 (m), 1307 (s), 1216 (s), 1115 (m), 1035 (m), 866 (w), 767 (m); $^1$H NMR (CDCl$_3$) $\delta$ 7.67 (s, 2H), 7.17 (s, 1H), 4.56 (q, 2H, $J = 6.8$ Hz), 2.36 (s, 6H), 1.39 (t, 3H, $J = 6.8$ Hz); $^{13}$C NMR (CDCl$_3$) $\delta$ 166.9, 137.9, 134.4, 130.3, 127.2, 60.8, 21.1, 14.3; EI-MS (70 eV) $m/z$ (\%) 178 (26, M$^+$), 150 (21), 133 (100), 105 (49).

5-Acetoxy-meta-xylene (12j)

To a solution of 3,5-dimethylphenol 12k (6.54 g, 53.5 mmol) in acetic anhydride was added concentrated sulfuric acid (10 drops), and the reaction mixture was stirred under an atmosphere of nitrogen for 6 h. The mixture was poured into ice water (600 mL) and EtOAc (150 mL) was added. The aqueous layer was re-extracted with EtOAc (150 mL). The organic extracts were combined, washed successively with saturated aqueous NaHCO$_3$ solution (3 x 150 mL), water (100 mL) and saturated aqueous NaCl solution (150 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was
distilled in vacuo to yield 5-acetoxy-meta-xylene 12j (7.07 g, 43.1 mmol, 80%) as a colorless oil (b.p. 86 - 86.5°C 4-6 mm Hg): IR (Nujol, cm⁻¹) 1766 s, 1618 m, 1591 (w), 1296 (w), 1208 (s), 1138 (m), 1032 (m), 948 (w), 899 (w), 869 (w), 835 (w); ¹H NMR (CDCl₃) δ 6.86 (s, 1H), 6.69 (s, 2H), 2.31 (s, 6H), 2.27 (s, 3H); ¹³C NMR (CDCl₃) δ 169.7, 150.5, 139.2, 127.6, 119.1, 21.2, 21.1; EI-MS (70 eV) m/z (%): 164 (10, M⁺), 122 (100), 107 (28).

3.5-Dimethylanisole (12l)

Powdered KOH (10.81 g, 85% purity, 164 mmol) was slurried in DMSO (50 mL) and the mixture was stirred at room temperature for 5 min under an atmosphere of nitrogen. 3,5-Dimethylphenol 12k (5.00 g, 40.9 mmol) was added, followed by iodomethane (5.1 mL, 82 mmol). After 30 min the reaction mixture was poured out into cold water (100 mL) and extracted with dichloromethane (2 x 75 mL). The combined organic extracts were washed with water (5 x 100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO₄) and concentrated in vacuo. The residual yellow oil was distilled in vacuo to yield 3,5-dimethylanisole 12l (4.50 g, 33 mmol, 81%) as a colorless oil (b.p. 60.5 - 61 °C /20-25 mm Hg; lit.⁹⁹ 193 °C); ¹H NMR (CDCl₃) δ 6.61 (s, 1H), 6.54 (s, 2H), 3.78 (s, 3H), 2.30 (s, 6H); ¹³C NMR (CDCl₃) δ 159.6, 139.1, 122.4, 111.6, 55.0, 21.4; EI-MS (70 eV) m/z (%): 136 (100, M⁺), 121 (21).
Ethyl 3,5-bis(bromomethyl)benzoate (14d)

N-Bromosuccinimide (22.97 g, 129.1 mmol) was added in two equal portions to a warm solution of ethyl 3,5-dimethylbenzoate 12d (10.00 g, 56.11 mmol) in CH₂Cl₂ (175 mL). After each addition, a spatula-tip of benzoyl peroxide was added and the mixture was stirred at reflux while it was irradiated with a 100 W lamp for 2 h. The mixture was cooled to room temperature and washed with H₂O (100 ml), saturated aqueous NaHCO₃ solution (2 x 100 mL), H₂O (100 mL) and saturated aqueous NaCl solution (75 mL). The organic layer was dried (MgSO₄), concentrated in vacuo and crystallized twice from heptane to give 14d (8.34 g, 24.8 mmol, 44%) as a colorless solid: mp: 88.0 - 89.0 °C; IR (Nujol, cm⁻¹): 1699 (m), 1313 (m), 1228 (w); ¹H NMR (CDCl₃) δ 8.00 (s, 2H), 7.62 (s, 1H), 4.51 (s, 4H), 4.40 (q, 2H, J = 6.7 Hz), 1.41 (t, 3H, J = 6.7 Hz); ¹³C NMR (CDCl₃) δ 165.4, 138.9, 133.8, 131.7, 130.0, 61.4, 21.3, 14.3; MS (El, 70 eV) m/z (%): 535 (5, M⁺), 291 (16), 255 (100), 211 (32), 177 (18), 148 (22), 152 (27); Anal. Calc’d for C₁₁H₁₂Br₂O₂: C, 39.32; H, 7.86. Found: C, 79.89; H, 8.18.

3,5-Bis(bromomethyl)methylbenzene (14f)

N-Bromosuccinimide (75.21 g, 422.6 mmol) was added in three equal portions to a warm solution of mesitylene 12f (25.02 g, 208.2 mmol) in CH₂Cl₂ (450 mL). After each addition, a spatula-tip of benzoyl peroxide was added and the mixture was stirred at reflux while it was irradiated with a 100 W lamp for 2 h. The mixture was cooled to room
temperature and washed with saturated aqueous NaHCO₃ solution (2 x 200 mL), H₂O (150 mL) and saturated aqueous NaCl solution (150 mL). The organic layer was dried (MgSO₄), concentrated in vacuo and crystallized from heptane to give an off-white solid that was purified by column chromatography (SiO₂; 10% CHCl₃ / hexanes) to yield 14f (6.53 g, 25.5 mmol, 11%) as a colorless solid. From the heptane mother liquor, additional 14f (17.0 g, 61 mmol, 29%) could be isolated by extensive column chromatography. For 14f: mp 63.5 - 65 °C (lit. 67 - 67 °C); ¹H NMR (CDCl₃) δ 7.23 (s, 1H), 7.16 (s, 2H), 4.46 (s, 4H), 2.36 (s, 5H); ¹³C NMR (CDCl₃) δ 139.3, 138.2, 129.9, 126.7, 33.0, 21.2; EIMS (70 eV) m/z (p%): 278 (M⁺, 9), 197 (100), 118 (79).

1,3-Bis(mercaptopymethyl)benzene (13b)

To a solution of α,α'-dibromo-meta-xylene 14b (5.00 g, 18.9 mmol) in EtOH (abs.) (100 mL) was added thiourea (2.96 g, 38.9 mmol) and the mixture was refluxed under an atmosphere of nitrogen for 16 h and concentrated in vacuo to give a white solid. The solid was suspended in a degassed solution of KOH (6.25 g, 85% purity, 94.7 mmol) in H₂O (110 mL) and EtOH (420 mL) and the mixture was stirred under reflux overnight. After cooling to room temperature, 9 M H₂SO₄ was added until the mixture became slightly acidic. The mixture was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic layers were washed with H₂O (100 mL) and saturated aqueous NaCl solution (75
mL). dried (MgSO₄) and concentrated in vacuo to yield 13b (2.89 g, 17.0 mmol, 90%) as a light yellow oil that was used without further purification in the next step.

### 3.5-Bis(mercaptomethyl)methylbenzene (13f)

A solution of thiourea (1.25 g, 16.4 mmol) and α,α'-dibromomesitylene 14f (2.22 g, 7.99 mmol) in degassed EtOH (100 mL) was stirred for 3 h at reflux under an atmosphere of nitrogen. A degassed solution of KOH (2.64 g, 85% purity, 40.0 mmol) in H₂O (25 mL) was added and the reaction mixture was stirred for an additional 3 h under reflux. The mixture was cooled in an ice bath, acidified using 9 M H₂SO₄ and poured into a mixture of CH₂Cl₂ (50 mL) and H₂O (50 mL). The aqueous layer was extracted with CH₂Cl₂ (50 mL), and the combined organic extracts were washed with H₂O (50 mL) and saturated aqueous NaCl solution (50 mL), dried (MgSO₄) and concentrated in vacuo to yield 13f (1.40 g, 7.60 mmol, 95%) as a light yellow-brown oil that was used without further purification in the next step.

### syn-2,11-Dithia[3.3]metacyclopahne (4b)

A degassed solution of dithiol 13b (1.44 g, 8.45 mmol) and α,α'-dibromo-meta-xylene 14b (2.23 g, 8.45 mmol) in benzene (250 mL) was added by dropping funnel over 2.5 h to a mechanically stirred, degassed solution of KOH (2.79 g, 85% purity, 42.3 mmol) in H₂O (75 mL) and EtOH (250 mL) under an atmosphere of nitrogen. After 15 h the
reaction mixture was concentrated \textit{in vacuo} to a volume of ca. 100 mL and then CH$_2$Cl$_2$ (100 mL) and H$_2$O (100 mL) were added. The aqueous layer was extracted with CH$_2$Cl$_2$ (100 mL) and the combined organic extracts were washed with H$_2$O (100 mL) and saturated aqueous NaCl solution (75 mL), dried (MgSO$_4$) and concentrated \textit{in vacuo}. The residue was purified using column chromatography (SiO$_2$: 50% CH$_2$Cl$_2$ : hexanes) to yield 4b (0.95 g, 3.5 mmol, 41\%o) as a colorless solid; mp: 118 - 119.5 °C (hexanes) (lit:\textsuperscript{1} 119 - 121 °C); \textsuperscript{1}H NMR (CD$_2$Cl$_2$) $\delta$ 6.99 (t. 2H, $J = 7.4$ Hz), 6.94 (d. 4H, $J = 7.0$ Hz), 6.92 (s. 2H), 3.80 (s. 8H); \textsuperscript{13}C NMR (CD$_2$Cl$_2$) $\delta$ 137.7, 132.1, 128.7, 127.3, 38.3; El-MS (70 eV) $m/z$ (\%): 272 (68, M$^+$), 167 (17), 137 (47), 105 (100).

\textit{syn}-6,15-Bis(ethoxycarbonyl)-2,11-dithia[3,3]metacyclophane (4d)

To a vigorously stirred solution of 12d (3.40 g, 10.1 mmol) in CH$_2$Cl$_2$ (600 mL) and EtOH (abs.) (60 mL), Na$_2$S$_2$Al$_2$O$_3$ (9.02 g, 2.69 mmol g, 24.3 mmol) was added in 3 portions over 1 h. The reaction mixture was stirred for an additional hour, filtered through a plug of Celite, concentrated \textit{in vacuo} and purified by column chromatography (SiO$_2$: CH$_2$Cl$_2$) followed by crystallization from EtOH to yield 4d (0.78 g, 1.9 mmol, 37\%o) as colorless crystals and trimer 15d (0.35 g, 0.62 mmol, 19\%o) as colorless crystals.

Dimer 4d: mp 104.5-106 °C; IR (Nujol. cm$^{-1}$): 1734 (s), 1285 (m), 1272 (m), 1122 (w), 1072 (w); \textsuperscript{1}H NMR (CDCl$_3$) $\delta$ 7.51 (s. 4H), 7.24 (s. 2H), 4.31 (q. 4H, $J = 7.6$ Hz), 3.83 (s. 4H), 1.38 (t. 6H, $J = 7.6$ Hz); \textsuperscript{13}C NMR (CDCl$_3$) $\delta$ 165.7, 137.3, 135.1, 130.5, 128.2, 60.7, 37.4, 14.1; MS (El, 70 eV) $m/z$ (\%): 416 (48, M$^+$), 370 (30), 342 (5), 327 (6), 309
(11), 295 (7), 270 (7), 239 (8), 209 (29), 69 (100); Anal. Calc'd for C_{12}H_{24}O_{4}S_{2}: C. 63.43; H. 5.81. Found: C. 63.26; H. 5.69.

Trimer 15d: mp 150-151.5 °C; IR (Nujol, cm⁻¹) 1720 (m), 1304 (w). 1281 (w); ¹H NMR (CDCl₃) δ 7.97 (s. 6H), 7.33 (s. 3H), 4.40 (q. 6H, J = 7.0 Hz), 3.61 (s. 12 H), 1.42 (t, 9H, J = 7.0 Hz); ¹³C NMR (CDCl₃) δ 166.1, 138.5, 133.8, 131.6, 129.1, 36.2, 34.9, 14.3; MS (El. 70 eV) m/z (%): 624 (9, M⁺), 578 (42), 532 (37), 468 (22), 447 (19), 415 (36), 401 (35), 371 (60); Anal. Calc'd for C_{15}H_{18}O₅₅: C. 63.43; H. 5.81. Found: C. 63.36; H. 5.44.

**syn-2,11-Dithia[3.3]metacyclophane-6.15-dicarboxylic acid (4e)**

Cyclophane 4d (0.43 g, 1.0 mmol) was dissolved in a degassed solution of KOH (0.29 g, 85% purity, 4.4 mmol) in H₂O (20 ml) and EtOH (20 ml), and the reaction mixture was stirred for 16 h at reflux temperature under an atmosphere of nitrogen. The mixture was allowed to cool to room temperature before it was poured into H₂O (20 ml). The mixture was extracted with diethyl ether (2 x 25 ml). The aqueous layer was acidified with 1% HCl and cooled in an ice bath. Suction filtration followed by drying in vacuo yielded 4e (0.33 g, 0.92 mmol, 89%) as a colorless solid, of which a small portion was recrystallized from DMF to give transparent crystals: mp: > 280 °C; IR (Nujol, cm⁻¹): 1699 (m). 1317 (m), 1258 (w), 1238 (w); ¹H NMR (DMSO-d₆) δ 12.6 (bs. 2H), 7.41 (s. 2H), 7.37 (s. 4H), 3.91 (s. 8H); ¹³C NMR (DMSO-d₆) δ 196.8, 137.9, 135.4, 130.6, 127.8, 36.8; El-MS (70 eV) m/z (%): 36 (83, M⁺), 342 (24), 314 (12), 211 (22), 181 (48), 149 (100).
**syn-6,15-Dimethyl-2,11-dithia[3.3]metacyclopahne (4f)**

A degassed solution of dithiol 12f (3.50 g, 19.0 mmol) and dibromide 13f (5.28 g, 19.0 mmol) in benzene (625 mL) was added via a dropping funnel over 2.5 h to a mechanically stirred, degassed solution of KOH (6.27 g, 85% purity, 95 mmol) in H$_2$O (190 mL) and EtOH (975 mL) under an atmosphere of nitrogen. The reaction mixture was stirred for an additional 10 h and the reaction mixture was concentrated *in vacuo* to a volume of ca. 100 mL. and CH$_2$Cl$_2$ (250 mL) and H$_2$O (250 mL) were added. The aqueous layer was extracted with CH$_2$Cl$_2$ (100 mL) and the combined extracts were washed with H$_2$O (2500 mL) and brine (150 mL), dried (MgSO$_4$) and concentrated *in vacuo*. The residue was purified using column chromatography (SiO$_2$: 25%, CH$_2$Cl$_2$/hexanes) crude 4f that was crystallized from heptanes to give 6,15-dimethyl-2,11-dithia[3.3]metacyclopahne 4f (2.34 g, 7.79 mmol, 41%) as colorless needles: mp: 103 - 104 °C (lit.$^8$ 104-105.5 °C); $^1$H NMR (CDCl$_3$, 500 MHz) δ 6.73 (s, 4H), 6.62 (s, 2H), 3.71 (s, 4H), 2.18 (s, 6H); $^{13}$C NMR (CDCl$_3$) δ 157.9, 136.9, 129.0, 127.8, 37.7, 21.0; El-MS (70 eV) $^a$ (m/z): 300 (58, M$^+$), 181 (14), 151 (40), 120 (100).
2.6 References


(3) In this chapter a large number of 6,15-disubstituted syn-2.11-dithia[3.3]metacyclophanes 4a-q will be described. For a complete list of compounds the reader is referred to Figure 2.09.


(8) See also Section 2.4.2.

(9) The c-c conformer has been calculated as the lowest energy conformer for the parent system syn-[3.3]metacyclophane (EFF) and for the syn-2.11-dithia[3.3]metacyclophane system (AM1 and 3-21Gt*).


(33) Observed signals for each proton are the weighted averages of the chemical shift values for that proton in each of the conformers. The weighting of each of the chemical shift values depends on the mole fractions of the conformers.
The $^1$H-NMR-spectra of 6,15-disubstituted syn-2,11-dithia[3.3]metacyclopahnes at room temperature (300 MHz) show a singlet for the benzylic protons, and two signals for the aromatic region, as well as signals derived from the substituents in the 6- and 15-positions. The signals in the aromatic region often appear as singlets, due to the small value for the meta-coupling between the internal and the external protons.


For compounds 4j and 4k: Mannion, M. R. Unpublished results.

For compounds 4m, 4n, 4o, 4p, 4q, 12m, 12o, 12p, and 12q: Li. J. Unpublished results.

Compounds 12a, 12b, 12c, 12e, 12f, 12g, 12i, 12k, and 12n were purchased from the Aldrich Chemical Company.

For compounds 4g, 4h, and 4i: Pottie, I. R. Unpublished results.


(53) Bodwell, G. J. Unpublished results.

(54) This work.


(60) Calculations were performed using version 5.0a37 of the Chem3D Pro package of software (MOPAC, AM1, closed shell).


(63) \[ \Delta G^\circ = RT_c (22.96 - \ln T_c - \ln \Delta V^\circ) \]

\[ \Delta V^\circ = (\Delta V^2 + 6\bar{F})^{1/2} \]


Chapter 3

Attempted Synthesis of

[4](1,4)Benzeno[0](2,7)pyreno[4](1,4)benzenophane
3.1 Introduction

It was anticipated that the synthesis of pyrenophane 1 (Figure 3.01) would represent a significant step forward in our approach to synthesize a Vögtle belt.\textsuperscript{1,2} Pyrenophane 1 contains a pyrene unit that could be synthesized using the valence isomerization-dehydrogenation (VID) protocol from biphenylophane diene 2.\textsuperscript{3} Two \textit{para}-phenylene moieties in the tether of 1 constitute the very beginnings of a fully aromatic tether and were chosen in this synthetic target so that the aromatic portion of 1 maps onto the surface of Vögtle belt 4. The tetramethylene tether in 1 constitutes the remnants of a third \textit{para}-phenylene ring which is present in a more advanced synthetic target 3 (Figure 3.01). The calculated bend angle\textsuperscript{1,4} of 114.4° for the pyrene unit in 1 is only slightly larger than that of the "record holder" (1.7-dioxa[7]2.7)pyrenophane: $\theta_{\text{calc}} = 113.9^\circ$, $\theta_{\text{conv}} = 109.2^\circ$) so it seemed to be a reasonable target.

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{structures.png}
\caption{Structures of pyrenophanes 1 and 3, biphenylophane diene 2 and Vögtle belt 4.}
\end{figure}
Biphenylophane diene 2, the direct precursor of 3, seems to be a viable synthetic target, since other groups have synthesized similar, more strained structures (*vide infra*). In Section 3.1.1 a more detailed discussion of the literature in this area is given. Section 3.1.2 will describe the retrosynthetic analysis of biphenylophane diene 2.

### 3.1.1 Biphenylophanes in the literature

Several groups have published syntheses of biphenylophanes and these compounds have received interest from different areas in (organic) chemistry. A small (2,3'-bridged) biphenylophane 5 has been described by Bickelhaupt *et al.* in conjunction with ongoing research in the area of small strained meta-cyclophanes, and another small (2,2'-bridged) biphenylophane 6 has been described by Vögtle *et al.* as a part of their work in the synthesis of chiral compounds devoid of stereogenic centers. Although both compounds showed some unique properties, in this Section discussion of the literature will remain limited to larger biphenylophanes containing at least two biphenyl units, which more closely resemble biphenylophane diene 2.

![Figure 3.02: Biphenylophanes 5 and 6.](image-url)
A number of large biphenylophanes containing more than two biphenyl units has been synthesized by Vögtle et al. (Scheme 3.01).\textsuperscript{8} Cyclophane 9 was reported in 1996 and was synthesized from compounds 7 and 8 via high-dilution coupling. This tube-shaped molecule was characterized by X-ray crystallography, and the molecular structure showed no signs of appreciable strain (i.e., contracted or elongated bond lengths, distorted bond angles, etc.) in the molecule.

![Scheme 3.01: Vögtle's synthesis of biphenylophane 9.](image)

In the same year Vögtle reported a series of "concave hydrocarbons",\textsuperscript{9} some of which are "part of the framework of fullerene C_{60}".\textsuperscript{9} Two of the cyclophanes reported were biphenylophane 10 (with three biphenyl subunits) and biphenylophane 11 (with four biphenyl subunits). Both compounds were synthesized via sulfur dioxide extrusion from
the bridges. They were tested for ion selective extraction of cations, but were not found to be efficient ligands for any of the metal salts tested.

![Figure 3.03: Structure of concave cyclophanes 10 and 11.](image)

Some smaller biphenylophanes have been reported by Lyoda (naphthalene bridged biphenylophane 12) and Staab ([2.2][4,4]biphenylophane 14). Both groups were interested in the π-π interactions that occur when the biphenyl units are held in a face-to-face orientation. An X-ray crystal structure of 12 revealed that the aromatic rings were almost planar and ring strain was evident from large β angles. No molecular structure of biphenylophane 14 was reported, but the relatively high yield in the sulfur dioxide extrusion step from 13 (47%o) and the relative stability of 14 suggested that biphenylophane 2 was a viable synthetic target.
In 1978 Vögtle reported the synthesis of several biphenyllophanes with 3 bridges. In the synthetic approach to these systems, thermal sulfur dioxide extrusion as well as Stevens rearrangements were used to ring contract sulfur-containing bridges to give the 2-carbon bridges in 16 and 17. Biphenyllophanes 16 and 17 are structurally quite similar to biphenyllophane diene 2, but their syntheses do not allow for straightforward modification that would permit the introduction of the tetramethylene tether that is required for synthesis of 2. The success of the three-fold Stevens rearrangement and Hoffmann elimination to form 17 from 15 suggests that formation of biphenyllophane diene 2 using this methodology is viable.

Figure 3.04: Vögtle’s biphenyllophanes 15 – 17.
The last biphenyllophanes that should be mentioned here are biphenyllophanes 20 (Scheme 3.03) and 26 (Scheme 3.04). Biphenyllophanes 19 have been reported by Nishimura, who synthesized these compounds via intramolecular [2+2] photocyclization of 18 to give 19. Dissolving-metal reduction of 19 then afforded 20.\textsuperscript{13,14} At the outset of this project, compounds 19 were the only known biphenyllophanes containing both a 2-membered bridge and a longer bridge. However, intramolecular [2+2] photocyclization of a derivative of 19 with a tetramethylene tether failed to give the desired product, thus rendering this type of approach less likely to be successful for the synthesis of 2.

\begin{center}
\textbf{Scheme 3.03: Nishimura’s synthesis of biphenyllophanes 20}
\end{center}

Biphenyllophanes 25 and 26 were reported in 1995 by Tani \textit{et al.} (Scheme 3.04).\textsuperscript{15} A mixture of the two biphenyllophanes was obtained from photolytic ring contraction of a mixture of the corresponding tetraselencyclophanes 23 and 24, which was obtained from high dilution coupling of 21 and 22. Biphenyllophanes 25 and 26 were characterized by
spectroscopic techniques and X-ray crystallography. A similar synthesis with the sulfur analogues was reported to yield only the "crossed" product 29 (Scheme 3.05).\textsuperscript{16}

\begin{center}
\begin{tikzpicture}
\node (21) at (0,0) {\includegraphics[width=0.5\textwidth]{21.png}};
\node (NaBH4) at (2,0) {\text{NaBH}_4};
\node (23) at (4,0) {\includegraphics[width=0.5\textwidth]{23.png}};
\node (22) at (2,-2) {\includegraphics[width=0.5\textwidth]{22.png}};
\node (24) at (4,-2) {\includegraphics[width=0.5\textwidth]{24.png}};
\node (25) at (0,-4) {\includegraphics[width=0.5\textwidth]{25.png}};
\node (26) at (2,-4) {\includegraphics[width=0.5\textwidth]{26.png}};
\end{tikzpicture}
\end{center}


The X-ray crystal structure of 25 revealed a dihedral angle between the aromatic rings in each biphenyl unit of approximately 25° and a short intramolecular distance of only 2.77 Å as the shortest distance between the internal carbons of the faced biphenyl rings, comparable to the corresponding distance in [2.2]paracyclophane.\textsuperscript{17-18} Synthetic target 2 is expected to be less strained than biphenylophane 25, since, in 2, two of the
dimethylene bridges of 25 are replaced by a single tetramethylene tether, which by virtue of its greater length, should release much of the strain that is present in 25.

\[
\begin{array}{c}
\text{Br} \quad \text{Br} \\
\text{Br} \quad \text{Br}
\end{array} + 
\begin{array}{c}
\text{HS} \quad \text{SH} \\
\text{HS} \quad \text{SH}
\end{array} \xrightarrow{\text{Base}} 
\begin{array}{c}
\text{S} \quad \text{S} \\
\text{S} \quad \text{S}
\end{array}
\]

Scheme 3.05: Synthesis of biphenylophane 29.

3.1.2 Retrosynthetic analysis of pyrenophane 1

The first stages of the retrosynthetic analysis of 1 (Scheme 3.06) are analogous to that of the \([n](2.7)\) pyrenophanes discussed in Chapter 1. In the first retrosynthetic step, the key bond in the pyrene unit of 1 was cut using a valence isomerization-dehydrogenation (VID) sequence.\(^{19}\) For pyrenophanes with longer tethers (9 atoms or more; \(\theta_{\text{calcd}} \leq \text{cut} 80^\circ\)) this sequence has been observed to be spontaneous, but for more strained cyclophanes (less than 9 atoms: \(\theta_{\text{calcd}} 87.0 - 113.3^\circ\)) reflux in benzene in the presence of DDQ has been necessary to accomplish this key conversion.\(^3\) Cyclophanediene 2 could come from dithiacyclophe 30.\(^{19,20}\) Tethered dithiacyclophe 30 with tethers other than
that in 30 have been synthesized previously by our group using the Na\textsubscript{2}S/Al\textsubscript{2}O\textsubscript{3} reagent\textsuperscript{21} and it was anticipated that this reagent would also be successful in this case, thus leading back to tetrafunctionalized intermediate 31.

Scheme 3.06: Retrosynthetic analysis of pyrenophane I.

For intermediate 31, various retrosynthetic schemes were considered. Initially an approach based on Wittig-type chemistry was developed (Scheme 3.07). In this approach, tetrafunctionalized compound 31 could be derived from a diene 32, which could be a mixture of E/Z isomers, since hydrogenation of the double bonds would give rise to only
a single compound 31. The biphenyl units in 32 could be formed in a Suzuki-Miyaura coupling\textsuperscript{22-27} of a diaryldiene 35 and an arylboronic acid derivative 33. The latter could be formed by a sequence of functional group interconversions from isophthalic acid 34 and the diene 35 could be derived (using Wittig and / or Horner-Wadsworth-Emmons reactions) from commercially available 4-hydroxybenzaldehyde 36.

![Scheme 3.07: Retrosynthetic analysis of 31 based on Wittig-type chemistry.](image-url)
In a second retrosynthetic approach (Scheme 3.08), the biphenyl units in 25 were also envisioned as being formed via a Suzuki-Miyaura coupling to give, in the retrosynthetic direction, an arylboronic acid 33 and a 1,4-diarylbutane 37. Compound 37 could be formed from a suitably functionalized para-disubstituted aromatic ring 38 and 1,4-dibromobutane 39.

![Scheme 3.08: Retrosynthetic analysis of 31 to give 38 and 39](image)

Both synthetic approaches to compound 31 were investigated. Since it was anticipated that the conversion of 31 to pyrenophane 1 might not be high yielding, a fast, reliable and high yielding route to compound 31 was required. In the following Sections, the attempts aimed at the synthesis of 1 are described.
3.2 Results and discussion

3.2.1 Initial approach to the synthesis of 31

Synthetic efforts aimed at the total synthesis of pyrenophane 1 commenced with 4-hydroxybenzaldehyde 36, which was converted to its triflate 40 upon treatment with trifluoromethanesulfonic acid anhydride and pyridine in CH₂Cl₂ (78%). At a later stage in the synthesis, a triflate was required at this position of the aromatic ring for the Suzuki-Miyaura coupling. It was hoped that its introduction at this early stage would also serve to protect the phenolic hydroxyl group. A more common protecting group could have been used if the triflate group proved to be ineffective, but this would require two extra steps in the synthesis. Triflate 40 was then reacted in a Horner-Wadsworth-Emmons reaction with the anion of triethylphosphonoacetate to give α,β-unsaturated ethyl ester 41 (81%). Reduction of ethyl ester 41 was attempted using LiBH₄ in methanol,³⁸ but this gave a mixture of 1,2- and 1,4-reduced products. Reduction of 41 using DIBAL-H in dichloromethane at lower temperatures cleanly yielded the allylic alcohol 42 (92%).
Conversion of the alcohol 42 to its allylic bromide 43 was attempted using PPh₂Br₂ (51%)[30] and PPh₂CBr₂ (43%)[30,31] but the best yield was obtained using PBr₃ (63%). The bromide 43 was then reacted with triphenylphosphine in refluxing toluene to give the desired phosphonium salt 44 in 97% yield. The phosphonium salt 44 was converted to its ylide using n-butyllithium and reacted with aldehyde 40 to give only 47% of butadiene 45 (83 : 17 E,E : E,Z by ¹H NMR), which is set up for the anticipated Suzuki-Miyaura coupling. The disappointing yield in this last step prompted the investigation of an alternative approach, in which the complementary version of the Wittig reaction was used (Scheme 3.10).
Oxidation of allylic alcohol 42 with the Dess-Martin periodinane\textsuperscript{12} yielded the desired aldehyde 46 in 75\% yield. In a parallel process, aldehyde 40 was reduced to a benzylic alcohol 47 using DIBAL-H in dichloromethane (77\%). Treatment of this alcohol with PBr\textsubscript{3} yielded benzylic bromide 48 (68\%), which could readily be converted to its triphenylphosphonium salt 49 in quantitative yield. Deprotonation of the triphenylphosphonium salt 49 with n-butyllithium, followed by treatment with aldehyde 46 yielded diene 45, this time in 61\% yield (85 : 15 E,E : E,Z by \textsuperscript{1}H NMR). A noteworthy feature of both approaches to 45 is that the triflate group proved to be a satisfactory protecting group.

In order to accomplish the anticipated Suzuki-Miyaura coupling, another building block, 55, had to be synthesized (Scheme 3.11). Synthesis of 55 commenced from commercially
available isophthalic acid 34, which was brominated at the 5-position in 93% to give 5-
bromo isophthalic acid 51.\textsuperscript{33} Fischer esterification\textsuperscript{34} of diacid 51 yielded methyl ester 52 in 87% yield. Reduction of the diester 52 with LiAlH\textsubscript{4} (89%), followed by methylation of the resulting diol 53 gave the trisubstituted aromatic compound 54 (83%). Boronic acid 55 was formed via lithium-halogen exchange on the aromatic bromide 55, followed by reaction with trimethyl borate to yield a boronic ester, which was not isolated, but was hydrolyzed immediately under mild acidic conditions. Yields of 55 were usually in the range of 80-87% from 54 and due to the short shelf life of 55 (less than two days at -18 °C) it was used directly in the next step. It is important that the halogen-lithium exchange be done at -50 °C. Reaction at higher temperatures gave a mixture of products (probably 
\textit{ortho}-metallation occurred) and, at lower temperatures, no lithiation occurred.
Scheme 3.11: Synthesis of boronic acid 55 from isophthalic acid 34.

In the next step (Scheme 3.12), boronic acid 55 and ditrillate 45 were coupled to give the desired product 56 in 60% yield using a modified Suzuki-Miyaura coupling with ethyleneglycol dimethyl ether as the solvent. The low isolated yield of this reaction was presumably due to the low solubility of compound 56. Compound 56 could be hydrogenated in dilute solutions in benzene using Pearlman’s catalyst (Pd(OH)₂) together with a drop of glacial acetic acid to give compound 57 (99%), which was much more soluble than 56. Unfortunately the low solubility of 56 limited the applicability of this synthetic route greatly.
Due to the poor prospects for the preparation of sufficient quantities of the required synthetic intermediates using the approaches described above, attention was turned to other synthetic routes, which are discussed in the following Section.

3.2.2 Alternative approaches to the synthesis of 57

The first alternative approach that was investigated was the coupling of anisole 58a or bromobenzene 58b via a two-fold Friedel-Crafts acylation with succinoyl chloride 59 (Scheme 3.13). Attempts to accomplish this conversion failed when using 1,2-
dichloroethane as the solvent or when the reaction was attempted without solvent in the presence of aluminum chloride. The only product that was often isolated after aqueous workup of the reaction mixture was carboxylic acid 61, which was identical with the reaction product of the Friedel-Crafts acylation of 58a or 58b with succinic anhydride 60.

![Scheme 3.13: Friedel-Crafts acylations of anisole 58a and bromobenzene 58b](image)

Carboxylic acids 61 were treated with thionyl chloride in order to generate the acid chlorides 62. The thionyl chloride was removed from the reaction mixture by distillation and a solution of anisole or bromobenzene in 1,2-dichloroethane was added. This initially led to a reaction mixture from which only starting materials could be isolated after aqueous workup. When the reaction mixture was heated to temperatures higher than 30 °C a strongly exothermic reaction took place, after which the reaction mixture solidified to a highly water-sensitive black solid. No product of this reaction was isolated.
Another approach to the synthesis of tetrafunctionalized compound 57 was based on a publication by Mori,15 who described the copper(I)-promoted oxidative homocoupling reaction of substituted trimethylsilylacetylenes to give symmetrically disubstituted butadiynes. This homocoupling reaction must be done in highly polar solvents (DMSO or DMF) under aerobic conditions. Oxygen from the air serves as the oxidant. This homocoupling-based approach is given in Scheme 3.14.

![Scheme 3.14: Synthesis of 57 via Cu(I) promoted homocoupling of a trimethylsilylacetylene.](image)

The starting material for this approach was either 4-bromoanisole 63a or 4-iodoanisole 63b. Sonogashira-Hagihara coupling of these anisole derivatives with
trimethylsilylacetylene gave ((4-methoxyphenyl)ethynyl)trimethylsilane 64 (85% from 63a: 86% from 63b). When 64 was subjected to the oxidative homocoupling conditions with cuprous chloride in DMF, a yellow solid formed in the reaction mixture, and, after several hours of reaction, a 72% yield of butadiyne 65 was isolated. Unfortunately, this compound was not very soluble in organic solvents, which prevented large amounts of material to be carried through this route. Hydrogenation of slurries of 65 in benzene in the presence of Pearlman's catalyst and a catalytic amount of acetic acid yielded almost quantitative amounts of 1,4-disubstituted butane 66. Conversion of this compound to the desired tetramethoxy compound 57 was accomplished in 3 steps from 66 by removal of the methyl protecting groups (76% when using HBr·HOAc 42 97% with BBr3). conversion of the resulting bis(phenol) 67 to the ditriflate 68 (81%) and Suzuki-Miyaura coupling with boronic acid 55 to give key intermediate 57 (55%).

Although this synthesis of 50 is shorter and higher yielding than the Wittig-based approaches (Section 3.2.1), the oxidative homocoupling reaction still posed problems due to the low solubility of 65. This prevented synthesis of large amounts of material through this sequence. While this route was being investigated, another route was designed in which 1,4-diarylbutane derivative 66 might be formed in a single step from a Grignard reagent derived from 4-bromoanisole 63a and 1,4-dibromobutane 39 (Scheme 3.15).
Scheme 3.15: Synthesis of 66 using the coupling of Grignard reagent 69 with 1,4-dibromobutane 39.

Initial attempts to accomplish this conversion failed and often the only isolable product was 4,4'-dimethoxybiphenyl 70. This product was likely formed as soon as 4-bromoanisole 63a was treated with magnesium, even before Grignard reagent 69 could be reacted with 1,4-dibromobutane 39. It was soon found that formation of this side product could be minimized when activated magnesium turnings\(^{43}\) were used, instead of commercially-available magnesium. Activation with iodine prior to use, followed by thermal activation (5 minutes at 150 °C) proved to be sufficient, and no more than approximately 15% 4,4'-dimethoxybiphenyl was formed when this type of magnesium was used. When organomagnesium compound 69 was reacted with 1,4-dibromobutane 39, it was found that in order to obtain the desired reaction product, 69 had to be added
slowly at 0 °C to a well-stirred solution of 1,4-dibromobutane 39 and dilithium tetrachlorocuprate. This catalyst can be formed in situ by dissolving lithium chloride and cuprous chloride in dry THF. When the addition was performed slowly, yields of 70-73% of 66 were obtained. The reaction was scaled up to yield several grams of product. When the temperature was not controlled carefully or the addition was performed too fast, the reaction products were similar to those obtained when the reaction was performed without catalyst (probably due to elimination of HBr from 1,4-dibromobutane 39 or reaction intermediates).

3.2.3 Attempted synthesis of pyrenophane 1

Using the methodology described in Sections 3.2.1 and 3.2.2, multigram quantities of 57 were available and attention was focused on the next task: synthesis of a cyclophanediene 2, the direct synthetic precursor of pyrenophane 1. Scheme 3.16 shows the synthetic approach aimed at accomplishing these conversions.

Scheme 3.16: Synthesis of cyclophanediene 2.
Tetramethoxy compound 57 was converted to the corresponding tetrabromide 71 using BBr₃ in dichloromethane in 56% yield. For this reaction it was important that it was not left longer than required, since the product decomposed slowly under the reaction conditions at room temperature. Treatment of tetrabromide 64 with Na₂S/Al₂O₃ gave 30. However, dithiaecyclophane 30 could not be purified using column chromatography, due to decomposition of the cyclophane under these conditions. Recrystallization of crude samples of 30 did not lead to greater purities of the samples. Fortunately, fast filtration of the concentrated reaction mixture through a short plug of silica using CH₃Cl₂ as the eluent yielded dithiaecyclophane 30 of sufficiently high purity to be used in the next steps (72% crude yield).

Crude 30 was then subjected to the standard sequence of reactions to form cyclophanediene 2. During this 4-step process, characterization of the intermediates was not attempted (analogous to other syntheses by our group), since all intermediates are present as mixtures of isomers and some intermediates are poorly soluble tetrafluoroborurate salts. In the first step, 30 was treated with Borch reagent ([(CH₃O)₂CHBF₄] and the resulting bist(methylsulfonium) salt was subjected to Stevens rearrangement conditions (KO-t-Bu, THF) to yield a mixture of thioethers. Treatment of this mixture with Borch reagent, followed by Hoffman elimination using KO-t-Bu gave cyclophanediene 2 in 40% yield (4 steps) from tetrabromide 71. Unfortunately, no crystals of 2 that were suitable for X-ray analysis could be obtained.
Cyclophane diene 2 showed accidental chemical shift degeneracy of some of its aromatic protons in the $^1$H NMR spectra when CDCl$_3$ was used as the solvent. The 300 MHz spectrum of 2 in C$_6$D$_6$ showed a single peak for its internal protons at $\delta$ 6.80 and a single peak at $\delta$ 6.78 for the protons meta to the internal protons. The para-phenylene ring of 2 showed an AA'BB' system centered at $\delta$ 7.00 and $\delta$ 6.67 in benzene. These data are in good agreement with other tethered cyclophanediene that have been synthesized by our group.$^{48,49}$

![Diagram of compounds 1 and 2 with reaction scheme]

Scheme 3.17: Attempted synthesis of pyrenophane 1.

Cyclophanediene 2 is only one step away from the target compound pyrenophane 1 by the VID protocol.$^3$ When solutions of cyclophanediene 2 in benzene or toluene were treated with DDQ at reflux temperatures, not even trace amounts of the desired pyrenophane 1 were isolated and slow decomposition of the starting material to intractable materials was observed. Unfortunately, it has not been possible to determine whether this decomposition process was a result of initial formation of the dihydropyrene or the pyrenophane 1, followed by decomposition or if cyclophanediene 2 decomposed...
via other routes. The desired transformation was also attempted photochemically (irradiation with a mercury lamp (254 nm) in the presence of air as the oxidant)\textsuperscript{50} and pyrolytically (flame sublimation\textsuperscript{48} or continuous flow flash vacuum pyrolysis).\textsuperscript{51} No products could be isolated from the irradiation experiments (starting material was consumed) and the pyrolytic methods led to almost quantitative recovery of starting material. The mass spectrum of cyclophanediene 2 showed the molecular ion of 2 to be the most abundant species ($m = 410$). No trace of the molecular ion of 1 was observed ($m = 408$).

In order to explain the reluctance of cyclophanediene 2 to give pyrenophane 1, semi-empirical (AM1) calculations were performed on both systems.\textsuperscript{52} The first factor that might contribute is the expected high bend angle of the pyrene unit in pyrenophane 1 ($\theta_{\text{calc}} = 114.4^\circ$). This angle for the pyrene unit is slightly higher than that calculated for the most bent pyrenophane that has yet been isolated by our group (O-(CH\textsubscript{2})\textsubscript{2}-O tether: $\theta_{\text{calc}} = 113.3^\circ$, $\theta_{\text{X-ray}} = 109.2^\circ$).\textsuperscript{53} It is possible that the actual bend angle is too large for 1 to be formed using the VID protocol.

The \textit{para}\textendash phenylene units in the calculated structure of 1 showed $\alpha$ angles of \textit{ca.} 10\textdegree and $\beta$ angles of 16.7\textdegree at the positions that are linked to the pyrene moiety. In the calculated structure of cyclophanediene 2 these angles were considerably smaller ($\alpha < 5^\circ$, $\beta = 6.1^\circ$). This suggested that in going from 2 to 1, the strain in these \textit{para}\textendash phenylene units increased considerably. In the computation-based prediction that pyrenophanes with $\theta_{\text{calc}}$
smaller than \( \text{ca. } 115^\circ - 120^\circ \) might be synthesized using the VID approach (Section 1.5). The formation of other strained aromatic nuclei was not taken into account. The actual borderline value for \( \theta_{\text{calc}} \) in systems like 1 might very well be lower than for the \([n](2,7)\)pyrenophanes. Synthesis of systems with lower \( \theta_{\text{calc}} \) values will have to be undertaken to investigate the limitations of the VID approach towards the synthesis of this class of pyrenophanes.

Another factor that might limit the reactivity of 2 towards the VID reactions is the dihedral angle around the biaryl bonds, i.e., twist in the biphenyl systems. This twist was calculated to be approximately \( 18^\circ \) and the closest distance between the hydrogen atoms ortho to this bond was calculated to be \( 1.9 - 2.1 \) Å. By comparison, AM1 calculations on a single biphenyl unit gave \( 41^\circ \) for the dihedral angle and \( 2.3 \) Å for the distance between the ortho hydrogens. In the VID process, the aromatic portion of the molecule moves towards the adoption of a belt-like structure. In such a situation the two para-phenylene units become increasingly boat-shaped. In order to adopt most effectively this geometric requirement, both biphenyl units in 2 must adopt unfavorable coplanar conformations (0° dihedral angles). If the VID sequence were to proceed with each biphenyl unit in its preferred twisted arrangement, then the para-phenylene groups of 1 would be required to form with in-plane distortions. This entails bond length distortions, which are much more demanding energetically than the bend angle distortions associated with the adoption of boat conformations.
The reluctance of cyclophanediene 2 to form pyrenophane 1 might very well be a combination of the effects described above. In order to overcome the first problem (too much bend in the pyrene unit) a cyclophane diene with a longer tether could be synthesized, which might undergo the VID reactions more easily to give a pyrenophane. Pyrenophanes 72, 73 and 74 (Figure 3.05) appear to be reasonable synthetic targets. They have slightly longer tethers than pyrenophane 1 and, as a result, their calculated bend angles are smaller (θ_{calcd} 108.9°, 110.1° and 111.1° respectively). With the smaller calculated bend angles for 72 - 74 than for 1, these synthetic targets might provide the necessary data to develop meaningful cut-off values in computational methods to predict the limitations of the VID protocol for synthesis of (2,7)pyrenophanes with two para-phenylene units in the tether.

Figure 3.05: Structures for future synthetic targets 72 - 74.
The other way to facilitate the desired VID reactions would be to try and reduce the dihedral angle in the biaryl units of the cyclophanedienes. This can be done by placing ethano bridges on the biaryl units. Cyclophanedienes 75 and 77 (Scheme 3.18) then present themselves as promising candidates for this modification. The additional ethano bridges that are present in 75 and 77 should dehydrogenate under the conditions used for the VID reactions. Through this dehydrogenation the biaryl units in 2 are effectively replaced by phenanthrene (75) and pyrene (77) units, which reduces the dihedral angles (the corresponding dihedral angles in phenanthrene and pyrene are calculated to be 0°).52 Not only do the new ethano bridges serve to reduce the dihedral angle of the biaryl moieties, but they also manifest themselves in the Vögtle belts 4. As a further point of interest, the transoid orientation of the phenanthrene units in 75 and 76 introduces an element of chirality to the system. A similar system with a cisoid orientation of the phenanthrene units can also be proposed, but this is achiral.
3.2.4 Retrosynthetic analysis of 76 and 78

From Scheme 3.18 it can be seen that synthesis of 76 and 78 requires first that cyclophane dienes 75 and 77 be synthesized. Scheme 3.19 shows a retrosynthetic analysis of phenanthrenophane diene 75.
Analogous to the retrosynthetic approach for pyrenophane 1, a retrosynthesis for phenanthrenophane 75 could lead back to a tetramethoxy compound 80 via a dithiacyclophane 79. Cutting of the bonds connecting the ethanobridges to the biaryl system in compound 80 (path a) gives 81, which could be envisioned as the Suzuki-
Miyaura coupling product of ditriflate 82 and boronic acid 55. The ring closure from 81 to 80 might be achieved photochemically\textsuperscript{54-56} or using a palladium-catalyzed cyclization reaction.\textsuperscript{57} In the latter case, it might be possible to convert ditriflate 82 and 55 in a one-pot process to compound 80. Cutting of the central biaryl bonds in 80 in a complementary retrosynthetic approach (path b) could lead back to compound 83. Compound 83 can come from Wittig-type olefination of a dialdehyde 84 with a phosphorous ylide derived from bromide 85. The substituent “X” on compounds 83 and 84 could be used as a directing group for the installation of the formyl groups in 84. In the cyclization step to form 80, this substituent will be eliminated as “HX”.

Dithiacyclophane 79, phenanthrenophanediene 75 and pyrenophane 76 all possess an element of planar chirality. Unfortunately, this means that in the ring-closing step in which the dithiacyclophane 79 is formed (and the element of chirality is introduced) two diastereomers could be produced: an achiral dithiacyclophane 86 and the \( \text{C}_2 \) symmetric dithiacyclophane 79. This may cause problems with purification and characterization, but 86 could conceivably also be brought through to a partial belt.

![Figure 3.06: Structures of dithiacyclophanes 79 (\( \text{C}_2 \) symmetry) and 86 (achiral).]
Nishimura et al. have synthesized compounds akin to distyryl compound 82, but they used anisole derivatives, which placed methoxy groups where triflate groups are required. Due to the sensitivity to acid of the styrene units in the product, functional group interconversions to give the desired ditriflate 82 are likely to be problematic so another approach was investigated.

Attempts to synthesize distyrylbutanes like 82 have so far been unsuccessful (Scheme 3.20). When an ortho-vinylation reaction described by Yamaguchi was used to attempt divinylation of bis(phenol) 67 (corresponding to the synthesis of 76 and 78 with \( n = 1 \)) several small fractions of what was thought to be a mixture of vinylated compounds (at least 3) was obtained from column chromatography of the reaction mixture. In Scheme 3.20 several possible structures are shown, although no direct evidence for any of these products has been obtained. Most chromatographic fractions obtained from this
reaction proved to be very unstable and polymerized readily even under refrigeration at -18 °C, forming transparent, gel-like material. The low yield of isolated material, together with the instability of the products made this approach unattractive, so an alternative synthesis of 80 was investigated (Scheme 3.21).

Scheme 3.21: Attempted syntheses of 84 and 85.

For this approach, two coupling partners for a Wittig-type olefination had to be synthesized: a derivative of dialdehyde 84 (where X is a leaving group) and a benzylic bromide 85. Initial attention went to the synthesis of a suitable derivative of 84, where introduction of X as a triflate group was anticipated (compound 92). Formation of precursor 91 from bis(phenol) 67 was accomplished in approximately 60% yield using the Duff reaction.\(^{51,52}\) (Purification of dialdehyde 91 proved difficult due to low solubility and instability.) Unfortunately, reaction of 91 with triflic anhydride was sluggish and the
only material that was recovered from the reaction mixture was a small amount of
starting material.

Synthesis of benzylic bromide 85 was attempted using several conditions for
bromomethylation of electron-rich aromatic rings, but in no case was the desired
compound isolated. The only product isolated was often \( \alpha,\alpha' \)-dibromo-meta-xylene,
resulting from nucleophilic displacement of the methoxy groups on starting material 93.
Due to the failure of this route as well as the previous route, this project was set aside in
favor of more promising targets. For completeness, a short discussion of a proposed
synthesis of cyclophanediene 77 will be given here. This project has not been pursued by
the author.
A retrosynthetic analysis of cyclophanediene 77 (Scheme 3.22) proceeds, along the same route as the one for phenanthrenophane 75 to a tetramethoxy compound 95, which could be derived from an organomagnesium compound 97 and 1,4-dibromoalkane 96. Compound 97 could possibly be derived from a dithiacyclophane 98 using established procedures. First a [2.2]metacyclophane could be formed, whose central bond is closed using iron filings and bromine to give a tetrahydropyrene. Dithiacyclophane 98 could be formed from a coupling between diester 99 and tribromide 100.
Pyrenophane 78, if its synthesis were successful, would contain a curved aromatic surface with 36 sp²-hybridized carbon atoms that would map onto the surfaces of \( D_{5h} C_{70} \), \( D_{5d} C_{80} \) and \( D_{nh} C_{84} \). Curved aromatic surfaces of this size have not yet been synthesized using cyclophane methodology and accomplishment of this synthesis would constitute a landmark in the field of cyclophane chemistry. Preliminary work in this area by another researcher in this group has led to the synthesis of a small amount of dithiacyclophane 98. Obviously, large quantities of this compound will be required in order to accomplish its transformation into 77 and 78, but the groundwork has been laid for a serious assault on a very challenging target.

3.3 Experimental

General. All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40-63 µm, 230-400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed at the Micro-Analytical Service Laboratory, Department of Chemistry, University of Alberta. Mass spectroscopic (MS) data were obtained on a V. G. Micromass 7070HS instrument. \(^1\)H NMR (300.1 MHz) and \(^{13}\)C NMR (75.47 MHz) were obtained on a General Electric GE 300-NB spectrometer: \(^1\)H shifts are relative to internal tetramethylsilane; \(^{13}\)C shifts are relative to the solvent resonance (CDCl₃: \( \delta = 77.0 \)). All experiments with moisture- or air-sensitive compounds were
performed in anhydrous solvents under nitrogen unless otherwise stated. Solvents were
dried and distilled according to standard procedures.

4-(Trifluoromethylsulfonyloxy)benzaldehyde (40). To a stirred 0 °C solution of 4-
hydroxybenzaldehyde 36 (25.00 g, 204.7 mmol) and pyridine (17.8 mL, 17.4 g, 220
mmol) in dichloromethane (500 mL) was added triflic anhydride (28.6 mL, 47.9 g, 170
mmol) by syringe through a septum over 15 min. The reaction was allowed to warm to
room temperature before it was quenched with 2.5% a aqueous HCl solution (100 mL).
The aqueous layer was extracted with dichloromethane (2 x 100 mL). The combined
organic layers were washed with saturated aqueous Na₂CO₃ solution (2 x 100 mL), water
(100 mL) and brine (75 mL), dried (MgSO₄) and concentrated in vacuo. The residue was
purified by column chromatography (SiO₂; CH₂Cl₂) to yield triflate 40 (33.63 g, 132.4
mmol, 78%) as a colorless oil; IR (cm⁻¹): 2725 (w), 1716 (s), 1597 (s), 1434 (s), 1217 (s),
1142 (s), 1015 (m), 884 (s), 732 (m); ¹H NMR (CDCl₃) δ 10.08 (s, 1H), 8.04 (d, 2H, J =
8.5 Hz), 7.50 (d, 2H, J = 8.3 Hz); ¹³C NMR (CDCl₃) δ 190.2, 153.2, 135.9, 131.7, 122.1,
118.6 (q, J = 332 Hz); EI-MS (70 eV) m/z (%): 254 (61, M⁺), 189 (100), 161 (14).

Ethyl (E)-3-(4-(trifluoromethylsulfonyloxy)phenyl)propenoate. To a stirred 0 °C
suspension of NaH (1.71 g, 60% in mineral oil, 42.6 mmol) in dry THF (200 mL) was
added triethylphosphonoacetate (7.81 mL, 8.82 g, 39.4 mmol). After stirring for 10 min, a
solution of 40 (8.33 g, 32.8 mmol) in dry THF (25 mL) was added, and the mixture was stirred at 0 °C for 1 h, then under reflux for 20 h. The mixture was cooled to room temperature. 2% aqueous HCl solution (50 mL) was added and the mixture was concentrated to ca. 1/3 of the original volume under reduced pressure. Dichloromethane (100 mL) was added and the aqueous layer was extracted with dichloromethane (100 mL). The combined extracts were washed with water (100 mL), dried (MgSO₄) and concentrated in vacuo to yield a brown oil that was purified by column chromatography (SiO₂: CH₂Cl₂) to yield 41 (8.58 g, 26.5 mmol, 81%) as a light-yellow oil: IR (cm⁻¹) 1724 (m), 1644 (m), 1503 (m), 1532 (s), 1215 (s), 1143 (s): ¹H NMR (CDCl₃) δ 7.67 (d, 1H, J = 16.5 Hz), 7.61 (d, 2H, J = 8.5 Hz), 7.32 (d, 2H, J = 8.6 Hz), 6.45 (d, 2H, J = 16.1 Hz), 4.29 (q, 2H, J = 7.1 Hz), 1.36 (t, 3H, J = 7.5 Hz); ¹³C NMR (CDCl₃) δ 166.4, 150.2, 142.1, 134.8, 129.7, 121.9, 120.1, 118.6 (q, J = 319), 60.8, 14.3; EI-MS (70eV) m/z (%): 324 (56, M⁺), 296 (14), 279 (88), 191 (69), 163 (100), 146 (47); HRMS Calc’d for C₁₃H₁₁F₂O₃S: 324.0278, found 324.02625.

(E)-3-(4-(Trifluoromethylsulfonyleoxy)phenyl)-2-propen-1-ol (42). To a solution of ethyl ester 41 (1.00 g, 3.08 mmol) in dry CH₂Cl₂ (30 mL) at −35°C under an atmosphere of nitrogen was added diisobutylaluminium hydride (1 M solution in hexanes). The reaction mixture was stirred for 1.5 h while it was allowed to warm slowly. Aqueous HCl solution (3 M, 20 mL) was added, and the aqueous layer was extracted with dichloromethane (30 mL). The organic layers were combined, washed with brine (30
mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (SiO₂: CH₂Cl₂) to yield alcohol 42 (0.80 g, 2.8 mmol, 92%) as a yellow oil: ¹H NMR (CDCl₃) δ 7.42 (d, 2H, J = 9.5 Hz), 7.21 (d, 2H, J = 9.5 Hz), 6.61 (d, 1H, J = 15.6 Hz), 6.37 (dt, 1H, J = 15.4 Hz, 6.0 Hz), 4.33 (d, 2H, J = 5.9 Hz), 2.25 (br s, 1H); ¹³C NMR (CDCl₃) 148.7, 137.1, 130.8, 128.7, 128.0, 121.5, 118.7, 63.3; EI-MS (70 eV) m/z (%): 282 (65), 240 (10), 226 (6), 175 (9), 149 (35), 55 (100).

(E)-1-Bromo-3-(4-trifluoromethylsulfonyloxy)phenyl)-2-propene (43). A solution of PBr₃ (0.32 g, 1.2 mmol) in dichloromethane (10 mL) was added slowly to a solution of alcohol 42 (0.66 g, 2.3 mmol) in dichloromethane (25 mL). After 30 min the reaction was quenched with water (10 mL). The organic layer was washed with water (4 x 15 mL) and brine (15 mL), dried (MgSO₄) and concentrated in vacuo. The residue was purified by column chromatography (SiO₂: CH₂Cl₂) to yield bromide 43 (0.51 g, 1.5 mmol, 63%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.46 (d, 2H, J = 9.0 Hz), 7.25 (s, 2H, J = 9.0 Hz), 6.64 (d, 1H, J = 15.5 Hz), 6.42 (dt, 1H, J = 15.5 Hz, 7.7 Hz), 4.15 (d, 2H, J = 7.7 Hz); ¹³C NMR (CDCl₃) δ 149.1, 136.2, 132.3, 128.3, 127.4, 121.6, 118.7 (q, J = 320.0 Hz), 32.4; EI-MS (70 eV) m/z (%): 346 (1, M⁺), 344 (1), 265 (70), 131 (100), 115 (68).

(E)-[3-(4-Trifluoromethylsulfonyloxy)allyl]triphenylphosphonium bromide (44). A solution of bromide 43 (1.47 g, 4.26 mmol) and triphenylphosphine (1.23 g, 4.69 mmol) in toluene (15 mL) was stirred at reflux under an atmosphere of nitrogen for 1.5 h. The resulting mixture was concentrated to approximately 5 mL under reduced pressure. The
product was isolated by suction filtration, washed with petroleum ether (bp. 30-60 °C) and dried in vacuo to give phosphonium salt 44 (2.50 g, 4.12 mmol, 97%) as a white solid that was used without purification.

(\(E,E\))- And (\(E,Z\))-1,4-Bis(4-(trifluoromethylsulfonyloxy)phenyl)-1,3-butadiene (45). To a -78 °C suspension of phosphonium salt 44 (1.29 g, 2.12 mmol) in dry THF (30 mL) was added n-BuLi (1.08 M in hexanes, 1.8 mL, 1.9 mmol). The reaction mixture was slowly warmed to room temperature, and a solution of aldehyde 40 (0.59 g, 2.3 mmol) in dry THF (5 mL) was added. The mixture was stirred at room temperature for 1 hour, and water was added (10 mL) followed by dichloromethane (100 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL). The organic extracts were combined and washed with brine (50 mL). After drying (MgSO\(_4\)), the organic layer was concentrated in vacuo and the residue was purified by column chromatography (SiO\(_2\); 50% CH\(_2\)Cl\(_2\) petroleu ether (bp. 30-60 °C)) to yield diene 45 (0.50 g, 1.0 mmol, 47%) as a light yellow solid; mp 111.0 - 113.0 °C; IR (Nujol, cm\(^{-1}\)): 1497 (w), 1422 (m), 1210 (s), 1138 (s), 994 (w), 891 (m), 859 (w); \(^1\)H NMR (Only signals for \(E,E\)-isomer are listed; CDCl\(_3\)) \(\delta\) 7.51 (m, 4H), 7.26 (m, 4H), 6.94 (m, 2H), 6.70 (m, 4H); \(^13\)C NMR (Only signals for \(E,E\)-isomer are listed; CDCl\(_3\)) \(\delta\) 148.1, 137.4, 131.8, 130.4, 128.0, 121.7, 120.8, 118.4 (q, \(J = 318\) Hz); EI-MS (70 eV) \(m/z\) (\%): 502 (59), 369 (100), 236 (66); HRMS Calc'd for C\(_{18}\)H\(_{12}\)F\(_5\)O\(_8\)S\(_2\): 501.9978, found 501.9894.
(E)-3-(4-Trifluoromethylphenyl)propenal (46). To a solution of alcohol 42 (1.10 g, 3.90 mmol) in dichloromethane (20 mL) under an atmosphere of nitrogen was added over 10 min a suspension of the Dess-Martin periodinane (2.35 g, 5.39 mmol). After stirring for 30 min the reaction mixture was washed with 1.3 M aqueous KOH solution (3 x 20 mL), water (30 mL) and brine (25 mL). After the organic layer was dried (MgSO4) it was concentrated in vacuo, and the residue was passed through a plug of SiO2 to give aldehyde 46 (0.82 g, 2.9 mmol, 74%) as a light yellow oil. 1H NMR (CDCl3) δ 9.85 (d, 1H, J = 6.7 Hz), 7.78 (d, 2H, J = 8.4 Hz), 7.59 (d, 1H, J = 15.1 Hz), 7.47 (d, 2H, J = 8.4 Hz), 6.83 (dd, 1H, J = 15.3 Hz, 6.9 Hz); 13C NMR (CDCl3) δ 193.1, 150.9, 149.7, 134.3, 130.2, 130.1, 122.2, 118.7 (tq, 320.6 Hz); EI-MS (70 eV) m/z (rel %): 324 (5, M+), 280 (19), 147 (76), 91 (100).

4-(Hydroxymethyl)-1-(trifluoromethylsulfonyloxy)benzene (47). To a −30°C solution of aldehyde 40 (1.00 g, 3.93 mmol) in dichloromethane (15 mL) under an atmosphere of nitrogen was added diisobutylaluminium hydride (1 M solution in hexanes, 5.9 mL, 5.9 mmol) over 5 min. The reaction mixture was allowed to warm to room temperature and was quenched with 3 M aqueous HCl solution (15 mL). The aqueous layer was extracted with dichloromethane (2 x 10 mL), and the combined organic extracts were washed with brine, dried (MgSO4) and concentrated in vacuo. The residue was purified by column chromatography (SiO2; CH2Cl2) to yield 47 (0.78 g, 0.30 mmol, 77%) as a colorless oil, that was used directly in the next step. 1H NMR (CDCl3) δ 7.44 (d, 2H, J = 8.9 Hz), 7.26 (d, 2H, J = 8.9 Hz), 4.71 (s, 2H), 2.16 (br s, 1H); 13C NMR (CDCl3) δ 148.7, 141.3,
128.4, 121.3, 118.7 (q, J = 320 Hz). 64.0: EI-MS (70 eV) m/z (%): 256 (51, M⁺), 227 (5), 191 (5), 175 (4), 123 (28), 107 (29), 67 (100).

4-(Bromomethyl)-1-(trifluoromethylsulfonyloxy)benzene (48). To a solution of alcohol 47 (9.46 g, 36.9 mmol) in dichloromethane (100 mL) was added a solution of PBr₃ (2.5 mL, 7.2 g, 26 mmol) in dichloromethane (15 mL) over 3 min. After 45 min the reaction mixture was quenched with water (25 mL). The organic layer was washed with water (3 x 25 mL), dried (MgSO₄) and concentrated in vacuo and purified by column chromatography (SiO₂: 25% CH₂Cl₂ / petroleum ether (bp. 30-60°C)) to give 48 (7.62 g, 23.9 mmol, 65%) as a colorless oil: ¹H NMR (CDCl₃) δ 7.49 (d, 2H, J = 8.4 Hz), 7.26 (d, 2H, J = 8.5 Hz), 4.48 (s, 2H); ¹³C NMR (CDCl₃) δ 149.1, 138.3, 130.9, 121.7, 118.7 (q, J = 324 Hz), 31.4; EI-MS (70 eV) m/z (%): M⁺ not observed, 239 (100), 175 (53).

(E,E)- And (E,Z)-1,4-di(4-(trifluoromethylsulfonyloxy)phenyl)-1,3-butadiene (45).

To a solution of benzylic bromide 48 (2.20 g, 6.89 mmol) in toluene (10 mL) was added triphenylphosphine (1.81 g, 6.90 mmol) and the reaction mixture was stirred under an atmosphere of nitrogen at reflux for 1.5 h. The reaction mixture was concentrated in vacuo to give phosphonium salt 49 (4.00 g, 6.88 mmol, 100%) that was used without purification in the next step.

Phosphonium salt 49 (4.00 g, 6.88 mmol) was suspended in dry THF (50 mL) and cooled to −78°C. At that temperature was added n-BuLi (1.08 M solution in hexanes, 6.1 mL, 6.1 mmol). The reaction mixture was warmed up to room temperature over 30 min and a
solution of aldehyde 46 (1.95 g, 6.96 mmol) in dry THF (25 mL) was added. The reaction mixture was stirred for 65 h, concentrated and 0.1 M aqueous HCl solution (50 mL) and dichloromethane (100 mL) were added. The aqueous layer was extracted with dichloromethane (50 mL) and the organic extracts were combined, washed (100 mL water and 75 mL brine), dried (MgSO₄) and concentrated in vacuo. The residue was purified using column chromatography (SiO₂: CH₂Cl₂) to give diene 45 (2.08 g, 4.14 mmol, 68% E,E- and E,Z-mixture) as a colorless solid.

**5-Bromoisophthalic acid (51).** To a 2 L, 3-necked round-bottomed flask, equipped with a mechanical stirrer and a reflux condenser with calcium chloride drying tube, containing isophthalic acid (36.51 g, 210 mmol), silver sulfate (40.01 g, 128 mmol) and bromine (15 mL) was added concentrated sulfuric acid (500 mL). The mixture was stirred at reflux for 48 h. The mixture was allowed to cool to room temperature, and it was carefully poured onto 750 mL of crushed ice. The precipitate was filtered by suction filtration, washed with water, dissolved in saturated aqueous NaHCO₃ solution and suction filtered into 6 M aqueous sulfuric acid, after which the crude product was isolated by suction filtration. Recrystallization from acetone water yielded 51 (41.25 g, 77%) as colorless needles: mp: > 280 °C (lit. 282 - 283 °C); IR (Nujol. cm⁻¹) 3540 (m), 1715 (s), 1296 (m), 1255 (w), 1213 (s), 1164 (w); ^1H NMR (acetone-d₆) δ 8.64 (t, 1H, J = 2.4 Hz), 8.38 (d, 2H, J = 2.3 Hz); ^13C NMR (acetone-d₆) δ 123.1, 130.3, 134.1, 137.2, 165.6; EI-MS (70 eV) m/z (%): 244 (100, M⁺), 227 (66), 199 (19), 143 (19), 75 (39).
**Dimethyl 5-bromoisophthalate (52).** To a solution of 5-bromoisophthalic acid 51 (41.13 g, 168 mmol) in methanol (500 mL) in a 1 L round-bottomed flask, equipped with a dropping funnel and a reflux condenser with drying tube was added concentrated H$_2$SO$_4$ (20 mL) via the dropping funnel. The resulting solution was refluxed overnight. After cooling to room temperature, the reaction mixture was concentrated under reduced pressure, dissolved in ethyl acetate (500 mL) and washed with water (350 mL), saturated aqueous NaHCO$_3$ solution (2 x 300 mL), water (250 mL) and brine (200 mL), dried (MgSO$_4$) and concentrated under reduced pressure to yield 52 (39.85 g, 87%) as colorless crystals; mp: 86 - 86.5 °C (lit:**b** 88 - 89 °C); IR (Nujol, cm$^{-1}$): 1726 (s), 1575 (m), 1260 (s), 1003 (m), 938 (w), 753 (m), 733 (m); $^1$H NMR (CDCl$_3$) δ 8.60 (t, 1H, J = 1.5 Hz), 8.34 (d, 2H, J = 1.5 Hz), 3.96 (s, 6H); $^{13}$C NMR (CDCl$_3$) δ 164.9, 136.6, 132.2, 129.2, 122.5, 52.7; EI-MS (70 eV) $m/z$ (rel. int.): 272 (36, M$^+$), 241 (100), 213 (22), 198 (37).

**1-Bromo-3,5-bis(hydroxymethyl)benzene (53).** To a vigorously stirred, 0 °C suspension of LiAlH$_4$ (4.17 g, 110 mmol) in dry diethyl ether (100 mL) in a 1 L 3-necked round-bottomed flask, equipped with a reflux condenser under nitrogen and a dropping funnel, was added a solution of dimethyl 5-bromoisophthalate 52 (15.02 g, 55 mmol) in dry diethyl ether (500 mL), over ca. 30 min. The reaction mixture was allowed to warm to room temperature and after 16 h, the mixture was cooled in an ice-water bath and ethyl acetate (100 mL) was carefully added via the dropping funnel, followed by dropwise addition of water (50 mL). The mixture was poured into 3 M aqueous HCl solution (100 mL) and the
aqueous layer was extracted with diethyl ether (3 x 100 mL). The combined organic layers were washed with aqueous HCl solution (3 M, 100 mL), water (2 x 100 mL) and brine (100 mL) and dried (MgSO₄). Concentration under reduced pressure yielded a white solid, which could be recrystallized from methanol to give 53 (10.55 g, 88\%o) as colorless needles: mp: 79 - 80.5 °C (methanol) (lit.: 90 - 91 °C); IR (Nujol, cm⁻¹): 3220 (s), 1576 (m), 1238 (m), 1061 (m), 1012 (m), 863 (m), 807 (m), 706 (m): ¹H NMR (acetone-d₆) δ 7.42 (s, 2H), 7.31 (s, 1H), 4.62 (s, 4H), 3.86 (s, 2H); ¹³C NMR (acetone-d₆) δ 146.2, 128.6, 124.2, 122.6, 64.0; EI-MS (70 eV) m/z (°a): 216 (43, M⁺), 199 (8), 185 (21), 169 (12), 158 (37), 107 (59), 91 (100), 79 (96), 77 (87); Anal. Calc'd for C₈H₈BrO₂: C, 44.27; H, 4.18. Found: C, 44.68; H, 4.16.

1-Bromo-3,5-bis(methoxymethyl)benzene (54). To a round-bottomed flask containing powdered KOH (9.71 g, 173 mmol) in DMSO (80 mL) was added 1-bromo-3,5-bis(hydroxymethyl)benzene 53 (5.00 g, 23.0 mmol), followed by iodomethane (12.28 g, 86.5 mmol). The reaction mixture was stirred for 1 h at room temperature and poured into water (100 mL). Dichloromethane was added and the aqueous layer was extracted with another portion of dichloromethane (100 mL). The combined organic layers were washed with water (5 x 100 mL), brine (75 mL), dried (MgSO₄) and concentrated under reduced pressure. Vacuum distillation (145 - 149 °C, 5 - 7 mmHg) yielded 54 (4.38 g, 78\%o) as a colorless oil: ¹H NMR (CDCl₃) δ 7.40 (s, 2H), 7.21 (s, 1H), 4.40 (s, 4H), 3.38 (s, 6H); ¹³C
NMR (CDCl₃) δ 140.8, 129.8, 125.3, 122.7, 73.9, 58.5. EI-MS (70 eV) m/z (%): 244 (11, M⁺), 199 (27), 165 (44), 104 (51), 45 (100).

3.5-Bis(methoxymethyl)phenylboronic acid (55). To a -50 °C solution of 1-bromo-3.5-bis(methoxymethyl)benzene 54 (8.64 g, 35 mmol) in dry THF (50 mL) was added n-BuLi (1.6 M solution, 24.23 mL, 39 mmol) over 10 min, and the reaction mixture was stirred for 15 min. At -50 °C, trimethylborate (12.0 mL, 106 mmol) was added over 10 minutes and the reaction mixture was stirred overnight, slowly warming up to room temperature. The reaction mixture was quenched with 5% aqueous HCl solution until pH 6 and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane, washed with brine, dried over MgSO₄ and concentrated in vacuo, yielding crude 55 as a foamy white solid (7.13 g, 33.9 mmol 96%), which was used without purification in the next step.

(E,E)-1,4-Bis-4-(3,5-bis(methoxymethyl)phenyl)phenyl-1,3-butadiene (56). Ditriflate 45 (2.06 g, 4.10 mmol) was added to a solution of Pd(PPh₃)₄ (0.28 g, 0.25 mmol) in degassed ethylene glycol dimethyl ether (50 mL) in a 3-necked round-bottomed flask with reflux condenser under an atmosphere of nitrogen. After 5 min, a solution of boronic acid 55 (2.58 g, 12.3 mmol) in a minimum of degassed ethanol was added, followed by a solution of Na₂CO₃ (1.74 g, 16.4 mmol) in H₂O (9 mL) and the resulting mixture was refluxed for 18 h. After cooling the reaction mixture to room temperature, it was concentrated in vacuo.
CHCl₃ (250 mL) was added and the mixture was washed with saturated aqueous NH₄Cl solution (2 x 50 mL), water (50 mL) and brine (50 mL). The organic layer was dried (MgSO₄), concentrated in vacuo and the residue was purified using column chromatography to yield 56 as a light yellow solid (0.13 g, 0.24 mmol, 6% E,E- and E,Z mixture): mp. 188.0 – 191.5 °C (CHCl₃); ¹H NMR (Only signals for E,E-isomer are listed): CDCl₃ δ 7.61 (m, 4H), 7.53 (s, 4H), 7.52 (m, 4H), 7.30 (s, 2H), 7.03 (m, 2H), 6.74 (m, 2H), 4.54 (s, 8H), 3.44 (s, 12H); ¹³C NMR (Only signals for E,E-isomer are listed): CDCl₃ δ 141.0, 139.9, 139.0, 136.5, 132.4, 129.4, 127.4, 126.8, 125.9, 125.5, 74.6, 58.3; EI-MS (70 eV) m/z (%): 534 (100, M⁺), 520 (9), 457 (5), 355 (4), 255 (17); HRMS Calc’d for C₁₈H₂₁O₄: 534.2768, found 534.2764.

1,4-Bis(4-(3,5-bis(methoxymethyl)phenyl)phenyl)butane (57). To a solution of diene 56 (0.11 g, 0.21 mmol) in degassed C₆H₆ (200 mL) was added a spatula-tip Pearlman’s catalyst, followed by 3 drops of glacial acetic acid. The mixture was stirred vigorously under an atmosphere of hydrogen (1.1 bars) for 1 h and nitrogen was bubbled through the mixture to displace the hydrogen gas. Filtration over a plug of MgSO₄ followed by in vacuo concentration of the reaction mixture yielded 57 (0.11 g, 0.20 mmol, 99%) as a colorless solid: mp: 71.0 – 72.0 °C (ethyl acetate : hexanes); ¹H NMR (CDCl₃) δ 7.50 (s, 4H), 7.40 (A₂B₂ system, 8H), 4.52 (s, 8H), 3.43 (s, 12H), 2.70 (br m, 4H), 1.73 (br m, 4H); ¹³C NMR (CDCl₃) δ 141.8, 141.4, 138.8, 138.3, 128.8, 127.0, 125.6, 74.6, 58.2, 35.4, 31.0; EI-MS (70 eV) m/z (%): 538 (1, M⁺), 506 (24), 491 (19), 474 (25), 459 (13).
[(4-Methoxyphenyl)ethynyl]trimethylsilane (64). To a suspension of
bistriphenylphosphine)palladium(II) chloride (0.27 g, 0.4 mmol) and Cul (0.27 g, 1.4
mmol) in dry benzene (50 mL) in a 100 mL, 3-necked round-bottomed flask with
condenser under nitrogen was added 4-iodoanisole (1.80 g, 7.7 mmol), followed by DBU
(1.76 g, 11.5 mmol) and trimethylsilyl ethyne (1.13 g, 98.22 mmol). The mixture was
stirred at room temperature for 14 h. and the reaction mixture was poured in petroleum
ether (bp. 30-60 °C, 50 mL), filtered and concentrated in vacuo. To the residue was added
petroleum ether (bp. 30-60 °C, 75 mL) and the solution was washed with 3 M aqueous
HCl solution (3 x 50 mL), water (2 x 30 mL) and brine, dried over MgSO4 and
concentrated under reduced pressure. After column chromatography (20%, ethyl
acetate petroleum ether (bp. 30-60 °C), vacuum distillation yielded 64 (1.16 g, 74%o) as a
colourless oil. bp 110 - 112 °C 7 mmHg; 1H-NMR (CDCl3) δ 7.70 (d, 2H, J = 9.0 Hz).
6.53 (d, 2H, J = 9.1 Hz), 3.81 (s, 3H), 0.25 (s, 9H); 13C-NMR δ 133.4, 113.8, 105.2, 92.4,
55.2, 0.1; EI-MS (70 eV) m/z (%): 204 (27, M+), 189 (100), 174 (8), 146 (13); Anal.
Calc'd for C22H10OSi: C, 70.53; H, 7.89. Found: C, 70.34; H, 8.12.

1,4-Bis(4-methoxyphenyl)butadiyne (65). To a solution of 64 (1.62 g, 7.9 mmol) in
DMF (40 mL) was added copper(1) chloride (0.86 g, 8.7 mmol) and the flask was equipped
with a condenser. The mixture was stirred vigorously overnight at 60 °C and allowed to cool to room temperature. Approximately 5 g of citric acid was added, followed by water (10 mL) and the mixture was stirred for an additional 1 h at room temperature, after which diethyl ether (30 mL) was added. The aqueous layer was extracted with diethyl ether (20 mL) and the combined organic layers were washed with 5% aqueous citric acid solution (25 mL), water (25 mL) and brine (25 mL), dried over MgSO₄ and concentrated under reduced pressure to yield 65 as a yellow solid (1.93 g, 93% crude), which could be recrystallized from ethanol/water mixtures to give 65 (1.79 g, 86%) as slightly yellow needles. mp: 137.5 - 139.0 °C; IR (Nujol, cm⁻¹): 2137 (w), 1598 (m), 1504 (m), 1294 (m), 1255 (s), 1167 (m), 1027 (m), 841 (m); ¹H NMR (CDCl₃) δ 7.48 (d, 4H, J = 8.7 Hz), 6.88 (d, 4H, J = 8.8 Hz), 3.84 (s, 6H); ¹³C NMR δ 160.2, 154.0, 114.1, 116.9, 81.2, 72.9, 55.3; El-MS (70 eV) m/z (%): 262 (100, M⁺), 247 (58), 219 (14), 176 (18); Anal. Calc'd for C₁₅H₂₃O₃: C, 82.42; H, 5.38. Found: C, 82.00; H, 5.16.

1,4-Bis(4-methoxyphenyl)butane (66). To a solution of 1,4-bis(4-methoxyphenyl)butadiyne 66 (2.03 g, 7.7 mmol) in benzene (50 mL), was added 20% Pd(OH)₂ C (Pearlman's catalyst, approximately 0.3 g), followed by glacial acetic acid (2 drops). The mixture was degassed and placed under an atmosphere of hydrogen (1.1 bar). Once hydrogen consumption ceased, the reaction mixture was filtered and the filtrate was concentrated in vacuo to yield 1,4-di(4-methoxyphenyl)butane 66 (2.09 g, 100%) as a white solid. mp 75-76.5 °C (ethyl acetate/hexanes); ¹H NMR (CDCl₃) δ 7.08 (d, 4H, J =
8.6 Hz), 6.82 (d, 4H, $J = 8.8$ Hz), 3.79 (s, 6H), 2.57 (br m, 4H), 1.62 (br m, 4H); $^{13}$C NMR δ 157.6, 134.7, 129.2, 113.6, 55.2, 34.8, 31.3; EI-MS (70 eV) $m/z$ (%): 270 (11, M$^+$), 121 (100).

1,4-Bis(4-methoxyphenyl)butane (66). Iodine (0.70 g, 2.8 mmol) was added to a 100 mL 3-necked round-bottomed flask containing magnesium turnings (1.58 g, 65.0 mmol) in dry benzene (30 mL) and dry diethyl ether (2.0 mL) equipped with a distillation head under an atmosphere of nitrogen. The mixture was stirred vigorously for 15 min and most of the color disappeared. The solvent was distilled off under an atmosphere of nitrogen. The residue was stirred at 150 °C for 5 min and was allowed to cool to room temperature. Dry THF (10 mL) was added, the mixture was cooled to 0 °C, and a solution of 4-bromoanisole 63a (7.45 g, 39.8 mmol) in dry THF (40 mL) was added over 1 h and the cooling-bath was removed. The suspension was added dropwise over 30 minutes to a 0 °C solution of 1,4-dibromobutane 39 (2.15 g, 9.96 mmol), LiCl (0.04 g, 1 mmol) and CuCl$_2$·2H$_2$O (0.08 g, 0.5 mmol) in dry THF (40 mL) under an atmosphere of nitrogen. The mixture was stirred for 16 h at room temperature, quenched with H$_2$O (10 mL) and concentrated in vacuo to a volume of ca. 25 mL. The residue was slurried in diethyl ether (75 mL) and filtered, washing the residue with diethyl ether (50 mL). The filtrate was washed with water (75 mL) and brine (50 mL), dried (MgSO$_4$) and concentrated in vacuo. The residue was purified by column chromatography (SiO$_2$: 5% diethyl ether/hexanes) to yield 66 (1.89 g, 6.97 mmol, 70%o) as a colorless solid.
1,4-Bis(4-hydroxyphenyl)butane (67). To a ~ -30 °C (dry ice/acetone bath) solution of 1,4-di(4-methoxyphenyl)butane 66 (1.46 g, 5.4 mmol) in dichloromethane (30 mL) in a 50 mL 3-necked flask under nitrogen, was added borontribromide (1.53 mL, 16 mmol) dropwise over 10 min. The mixture was allowed to warm to room temperature, and, after stirring for 3 h at room temperature, ethanol (5 mL) was added, followed by water (15 mL). The aqueous layer was extracted with dichloromethane (30 mL). The combined organic layers were extracted with 3 M aqueous KOH solution (2 x 30 mL) and the combined alkaline layers were acidified using 6 M aqueous HCl solution. The mixture was then extracted with diethyl ether (2 x 50 mL). The combined organic layers were washed with water (25 mL) and brine (25 mL), dried over MgSO₄ and concentrated under reduced pressure. Column chromatography of the residue (SiO₂; 60% ethyl acetate hexanes) yielded 67 as a white solid (1.23 g, 94%), mp 152-153.5 °C (ethyl acetate); IR (Nujol, cm⁻¹): 3405 (s), 1511 (s), 1236 (m), 815 (m); ¹H NMR (acetone-d₆) δ 7.01 (td, 4H, J = 8.4 Hz), 6.74 (td, 4H, J = 8.4 Hz), 3.83 (s, 2H), 2.54 (br m, 4H), 1.59 (br m, 4H); ¹³C NMR (acetone-d₆) δ 152.4, 130.4, 126.4, 112.16, 31.83, 28.5; EI-MS (70 eV) m/z (%): 242 (12, M⁺), 186 (16), 107 (100).

1,4-Bis(4-(trifluoromethanesulfonyloxy)phenyl)butane (68). To a solution of 1,4-bis(4-hydroxyphenyl)butane 67 (1.27 g, 5.24 mmol) and pyridine (0.93 mL, 11.5 mmol) in dichloromethane (30 mL) at 0 °C, was added triflic anhydride (1.94 mL, 11.5 mmol) dropwise over 10 min under nitrogen. After addition was complete the reaction mixture
was stirred for 2 h at room temperature and 5\(^{\circ}\) aqueous HCl solution (10 mL) was added. The organic layer was washed with 5\(^{\circ}\) aqueous HCl, water and brine, dried over MgSO\(_4\), and concentrated in vacuo. Column chromatography (25\(^{\circ}\) ethyl acetate/hexanes) of the residue yielded 68 (2.38 g, 4.70 mmol, 90\(^{\circ}\)) as a white solid. mp: 84.0 – 86.0 °C (ethyl acetate : hexanes); IR (Nujol, cm\(^{-1}\)): 1504 (m), 1248 (w), 1213 (m), 1174 (w), 1143 (m), 892 (m), 717 (w); \(^1\)H NMR (CDCl\(_3\) \(\delta\) 7.21 (AA'BB', 8H), 2.67 (br m, 8H), 1.67 (br m, 8H); \(^{13}\)C NMR \(\delta\) 147.7, 142.8, 130.0, 121.1, 118.7 (q, \(J = 320 \text{ Hz}\)), 35.0, 30.7; El-MS (70eV) \(m/z\) (\(^{\circ}\)): 506 (26, M\(^+\)), 373 (15), 279 (19), 239 (100), 175 (82). Anal. Calc'd for C\(_{18}\)H\(_{16}\)F\(_8\)O\(_8\)S\(_2\): C, 42.69; H, 3.18. Found: C, 42.65; H, 2.93.

1,4-Bis(4-(3,5-bis(methoxymethyl)phenyl)phenyl)butane (57). To a suspension of tetrakis(triphenylphosphine) palladium(0) (0.15 g, 0.13 mmol) in dry anhydrous dimethoxyethane (35 mL) in a 50 mL 3-necked round bottom flask equipped with magnetic stirrer and reflux condenser under nitrogen, was added 68 (2.22 g, 4.41 mmol), followed after 10 min by DBU (2.6 mL, 18 mmol) and a solution of 3,5-bis(methoxymethyl)phenylboronic acid 55 (3.64 g, 17.3 mmol) in 5 mL anhydrous ethanol. The mixture was refluxed for 20 h, and allowed to cool to room temperature. The reaction mixture was filtered and the filtrate was concentrated in vacuo, dichloromethane (20 mL) was added and the organic solution was washed with 3 M aqueous HCl solution (2 x 25 mL), water (25 mL) and brine, dried over MgSO\(_4\) and concentrated under reduced pressure.
The residue was subjected to column chromatography (SiO₂: 75% CH₂Cl₂/hexanes) to yield 57 (1.29 g, 55%) as a white solid.

1,4-Bis-4-(3,5-bis(bromomethyl)phenyl)phenyl)butane (71). To a −30 °C solution of 57 (1.36 g, 2.5 mmol) in dichloromethane (20 mL) under nitrogen, was added dropwise borontribromide (1.9 mL, 20 mmol). The reaction mixture was allowed to warm slowly to ca. −10 °C. When no more starting material could be detected by TLC, ethanol (5 mL) was added followed by water (10 mL). The organic layer was washed with water and brine, dried (MgSO₄) and concentrated under reduced pressure. Column chromatography (50% dichloromethane/hexanes) yielded 71 (0.97 g, 52%) as a white solid; mp: 143 – 145 °C (dec.); ¹H NMR (CDCl₃) δ 7.54 (s, 4H), 7.50 (d, 4H, J = 8.1 Hz), 7.38 (s, 2H), 7.27 (dd, 4H, J = 7.9 Hz), 4.53 (s, 8H), 2.71 (br s, 4H), 1.73 (br s, 4H); ¹³C NMR (CDCl₃) δ 142.5, 142.4, 138.9, 137.3, 129.0, 128.1, 127.8, 127.0, 125.4, 32.9, 31.0; HR-MS (70 eV) m/z (%): M⁺ not observed. 573 (3), 493 (3), 413 (2), 353 (9), 287 (18), 193 (32), 80 (100); Anal. Calc'd for C₇₃H₄₄Br₄: C, 52.35; H, 4.12. Found: C, 52.48; H, 4.05.

18,33-Dithia[4.3.3][4'.3.5]biphenylophane (30). To a vigorously stirred solution of 71 (1.11 g, 1.5 mmol) in dichloromethane (540 mL) and absolute ethanol (60 mL) in a 1 L Erlenmeyer flask was added Na₂S·Al₂O₃ (1.36 g, 2.44 mmol/g) over 15 minutes. When all of the starting material was consumed (TLC), the reaction mixture was filtered and
concentrated under reduced pressure. Filtering through a short plug of silica (60% ethyl acetate/hexanes) yielded 30 (0.54 g, 75% crude) as an off-white solid that was immediately used in the next step: $^1$H NMR (CDCl$_3$) δ 7.17 (s, 2H), 7.03 (s, 4H), 7.02 (d, 4H, $J = 8.0$ Hz), 6.75 (d, 4H, $J = 8.1$ Hz), 3.89 (narrow AB system, 8H), 2.41 (br m, 4H), 1.75 (br m, 4H); $^{13}$C NMR (CDCl$_3$) δ 140.7, 140.3, 137.4, 136.9, 130.1, 128.8, 125.8 (2C), 38.4, 35.5, 28.7;

[4.2.2](4',3.5)Biphenylophane-17,31-diene (2). To a solution of dithiabiphenylophane 30 (0.50 g, 1.0 mmol) in dichloromethane (50 mL) under nitrogen, was added Borch reagent (0.42 mL, 4.2 mmol). After stirring for 5 h, the solvent was removed under reduced pressure. 80% aqueous methanol was added (5 mL) and the precipitate was collected by suction filtration as a beige-white solid (0.59 g, 83% crude) that was used without purification. The solid was suspended in dry THF (75 mL). Potassium tert-butoxide (0.29 g, 2.6 mmol) was added, and the mixture was stirred under nitrogen for 5 h. The reaction was quenched with saturated aqueous NH$_4$Cl solution (10 mL), and the mixture was concentrated under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated aqueous NH$_4$Cl, water and brine, dried (MgSO$_4$) and concentrated under reduced pressure, which yielded a yellow foamy solid, which was used immediately in the next step.
The yellow solid was dissolved in dry dichloromethane (75 mL). Borch reagent (0.26 mL, 2.6 mmol) was added and the mixture was stirred for 1.5 h. The solvent was removed under reduced pressure. A solution of 5\%a methanol in ethyl acetate was added and the mixture was concentrated in vacuo, to give a brown oil, which was immediately used in the next step.

To a suspension of the brown oil in 1:1 tert-butanol and dry THF (50 mL) was added potassium tert-butoxide (0.75 g, 6.7 mmol), and the mixture was stirred overnight under nitrogen. The reaction was quenched with saturated aqueous \( \text{NH}_4\text{Cl} \), and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane and washed with saturated aqueous \( \text{NH}_4\text{Cl} \), water and brine, dried over MgSO\(_4\) and concentrated in vacuo. Column chromatography (50\%a dichloromethane hexanes) yielded 2 (0.25 g, 48\%a from crude 30, 40\%a from tetrabromide 71) as a colorless solid: mp: $\sim$ 270 $^\circ$C (dec.); \(^1\)H NMR (CDCl\(_3\)) \( \delta \) 7.35 (s, 4H), 7.08 (d, 4H, \( J = 8.3 \) Hz), 6.78 (d, 4H, \( J \) unresolved), 6.77 (s, 6H), 2.41 (br, m, 4H), 1.70 (br, m, 4H); \(^1\)H NMR (CD\(_2\)Cl\(_2\)) \( \delta \) 7.14 (s, 4H), 7.00 (d, 4H, \( J = 8.4 \) Hz), 6.80 (s, 2H), 6.78 (s, 4H), 6.67 (d, 4H, \( J = 8.4 \) Hz); \(^{13}\)C NMR (CDCl\(_3\)) \( \delta \) 141.2, 139.0, 137.6, 136.4, 128.4, 125.2, 125.1, 120.3, 34.9, 29.5; \(^{13}\)C NMR (CD\(_2\)Cl\(_2\)) 139.9, 138.1, 136.8, 136.7, 136.5, 135.5, 127.4, 124.2 (2C), 33.9, 28.5; MS (El, 70 eV) m/z (%): 410 (100, M\(^{+}\)), 381 (7), 363 (2), 291 (41); HRMS Calc'd for C\(_{25}\)H\(_{20}\): 410.2033, found 410.2027.
Attempts to synthesize [4](1,4)benzeno[0](2,7)pyreno[0](1,4)benzeno<3>phane (1).
Cyclophane diene 2 was dissolved in dry and degassed solvent (benzene or toluene) and DDQ (1-3 equivalents) was added. The flask was equipped with a reflux condenser and the mixture was refluxed under nitrogen while reaction progress was monitored by TLC. The mixture was concentrated (after 6 h for benzene, 4 h for toluene) under reduced pressure, and the residue was filtered through a plug of silica using 50% dichloromethane/hexanes to give cyclophane diene 2 as the only identifiable component.

Attempted ortho-vinylation of 67. In a 250 mL 3-necked round-bottom flask under an atmosphere of nitrogen chlorobenzene (75 mL) was cooled to −50 °C using a dry ice acetone bath and SnCl₂ was added (7.7 mL, 66 mmol) followed by Bu₃N (15.7 mL, 65.9 mmol) and ethyne was bubbled through the reaction mixture for 30 min at this temperature. Bis(phenol) 60 (2.00 g, 8.25 mmol) was added, the ethyne flow was stopped and the mixture was heated at 60 °C for 1.5 hours. Methanol was added and the mixture was kept at 60 °C for 30 min and cooled to room temperature. The mixture was poured into diethyl ether (150 mL) and saturated aqueous KHSO₄ solution (100 mL) and filtered through Celite. The aqueous layer was re-extracted with diethyl ether (2 x 75 mL) and the organic extracts were washed (75 ml brine), dried (MgSO₄) and the diethyl ether was removed under reduced pressure. Acetic anhydride (20 mL) and pyridine (20 mL) were added to the concentrate and the mixture was stirred overnight under an atmosphere of nitrogen. The reaction mixture was poured into saturated KHSO₄ solution (100 mL) and EtOAc (100 mL)
was added. The aqueous layer was extracted with EtOAc (100 mL), the organic extracts were combined, washed with saturated NaHCO₃ solution (2 x 100 mL), brine (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was subjected to column chromatography (10-35% EtOAc/hexanes) and several fractions were collected. All fractions were yellow oils and were mixtures of several compounds and formed insoluble gel-like substances within hours of isolation.

1,4-Bis(3-formyl-4-hydroxyphenyl)butane (91). To a suspension of 67 (2.11 g, 9.12 mmol) in trifluoroacetic acid (70 mL), hexamethylenetetramine (2.56 g, 18.2 mmol) was added and the mixture was refluxed for 90 min. After cooling to room temperature, the mixture was poured into 3 M aqueous HCl solution (300 mL) and stirred overnight. Dichloromethane (150 mL) was added, and the aqueous layer was re-extracted with dichloromethane (150 mL). The combined organic extracts were washed with 3 M aqueous HCl solution (2 x 150 mL) and extracted with 3 M aqueous KOH solution (3 x 100 mL). After separation the basic aqueous layers were acidified with 6 M aqueous HCl solution and extracted with EtOAc (3 x 250 mL). The combined EtOAc extracts were washed with saturated aqueous NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure to yield crude 91 as a sparingly soluble waxy yellow substance (1.72 g, 5.50 mmol, 60%): ¹H NMR (CDCl₃) δ 10.87 (s, 2H), 9.87 (s, 2H), 7.34 (d, 2H, J = 7.9 Hz), 7.33 (s, 2H), 6.93 (d, 2H, J = 7.9 Hz), 2.64 (br m, 4H), 1.66 (br m, 4H); ¹³C NMR (CDCl₃) δ 196.5, 159.8, 137.3, 133.7, 132.8, 120.3, 117.5, 34.5, 30.8.
3.4 References


(2) The name Vögtle belt has been proposed by us for a (so far hypothetical) fully aromatic belt like 4. For a more detailed discussion refer to Section 4.1 and references therein.


(4) In Section 1.4 a more detailed discussion of AM1 calculations on [n](2.7)pyrenophanes can be found.

(5) Bend angles of pyrene units in pyrenophanes were calculated using the Chem3D package of software (MOPAC, AM1, closed shell).


(48) Houghton, T. J. Ph.D. Dissertation, Memorial University of Newfoundland. **1999**.

(49) Mannion, M. R. Ph.D. Dissertation, Memorial University of Newfoundland. **1999**.


(52) Calculations were performed using version 5.0a37 of the Chem3D Pro package of software (MOPAC, AM1, closed shell).


Chapter 4

Attempted Synthesis of a Vögtle Belt
4.1 Introduction

Our group has proposed the name “Vögtle Belts”\textsuperscript{1,2} for fully aromatic belts like 1 since Vögtle\textsuperscript{3,4} was the first to propose this class of molecules as synthetic targets. Aromatic belts such as 1 map directly onto the equators of the $D_{5h}$-C\textsubscript{70} and $D_{6h}$-C\textsubscript{84} fullerenes. Upon the recognition of a repeating pyrene unit in 1 it was anticipated that the pyrene-forming VID methodology might be applied to its synthesis.

When investigations toward the synthesis of model compounds for the Vögtle belts failed (Chapter 3) it came to mind that, rather than attempting to synthesize partial aromatic belts, at least one attempt should be made to synthesize a fully aromatic belt. The relatively low calculated bend angle ($\theta_{\text{calc}} = 90.3^\circ$) for each of the pyrene units in 1 ($n = 1$) suggested that the VID protocol might be applicable for its synthesis. As the “tether” in 1 consists entirely of pyrene units (indistinguishable from the cyclophane pyrene

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{structures.png}
\caption{Structures of a “Vögtle belts” 1 and $D_{6h}$-C\textsubscript{84} 2.}
\end{figure}
nucleus) the dihedral angles around the biaryl bonds are expected to be small, which makes this synthetic target a logical step forward from the synthetic targets that were proposed in Section 3.2.4.

4.1.1 Molecular belts in the literature

Since the initial proposal of molecular structures like 1, not much progress toward the synthesis of 1 or related compounds has been reported. Some reports on attempted syntheses of similar structural motifs describe projects aimed toward the \([n]\)cyclacenes 3. Several approaches have been followed and have led to the synthesis of advanced intermediates (e.g. 4-6, Figure 4.02). \(^{4-11}\)

![Figure 4.02: Structure of \([n]\)cyclacene 3 and possible precursors 4, 5 and 6.](image)
Another structural motif that falls under the category of belt-like molecules is the cyclic oligo-para-phenylene motif. Several approaches have been reported in this area and have led to the synthesis of macrocycles 7 – 9 (Figure 4.03).

![Figure 4.03: Belt-shaped molecules 7, 8, and 9.](image)

Vögtle et al.\textsuperscript{16,17,18} have described syntheses of several tube-shaped molecules. Their approach is based on high-dilution coupling of two (or more) partners to form macrocyclic structures that should, in principle, after ring contraction, lead to possible precursors for 1. In 1991 the synthesis of cyclophane 10 was described,\textsuperscript{19} although no
unequivocal proof for this structure was provided. DNMR study of 10 showed the presence of (at least) two conformers at room temperature, which was ascribed to the slow (syn to syn' -like) equilibrium between conformers 10a and 10b with an activation barrier of 15-17 kcal/mol (65-70 kJ/mol). A notable feature of cyclophane 10 is that it contains both nitrogen and sulfur atoms in the bridges. For the conformers of 10 it was not determined which bridge contained which heteroatom.

![Diagram](image)

\[ X, Y = S, N \]

**Scheme 4.01:** Structure and conformational interconversion of cyclophane 10

Later, the Vögtle group published the synthesis and molecular structures of some smaller tube-shaped molecules (1117 and 1217) and a larger cyclophane 1318 (Figure 4.04). So far, only cyclophanes with tosylamine-containing bridges have been reported, together with some pyridine-based tube-shaped cyclophanes.19 Synthesis of the tube-shaped cyclophanes with sulfur atoms as the only heteroatoms in the bridges and benzene rings as the only aromatic units has not been successful due to the reported instability of some of the intermediates.18,20 Compound 13 is a precursor to a Vögtle belt 1 (n = 0). Ring contraction of the sulfur-containing bridges seems feasible, since it has been used
successfully in many cases, but ring-contraction of the nitrogen-containing bridges appears to be a nontrivial task.

![Diagram of molecules 11, 12, and 13 with labeled N-Tos](image)

Figure 4.04: Tube-shaped cyclophanes 11–13.

### 4.1.2 Retrosynthetic analysis of a Vögtle belt

In the first part of the retrosynthesis of Vögtle belt 1, two pyrene units in the belt are broken down to dithiacyclophane moieties to give a tetrathiacyclophane 14. Compound 14 contains tetrahydropyrene units rather than pyrene units, since the former are expected to impart greater solubility to 14 and its precursors. Dehydrogenation of the tetrahydropyrene units was expected to be accomplished in the last step of the synthesis, during which DDQ is used to accomplish the conversion of the cyclophane diene systems to the pyrene units.
Tetrathiacyclophane 14 could be formed from a coupling reaction of a tetrathiol (15b: X = SH) with a tetrabromide (15a: X = Br) under high dilution conditions. The tetrathiol (15b: X = SH) can be formed from the precursor tetrabromide (Scheme 4.03).
Compound 15a contains two tetrahydropyrene units. This type of structural feature can usually be formed in high yield from [2.2]meta[1]cyclophanes using iron filings and bromine in the dark or using pyridinium perbromide. These conditions are sufficiently mild to not dehydrogenate the product.

Meta[1]cyclophanes containing four dimethylene bridges like 16 are known for \( R = H \) and have previously been synthesized by building up the two cyclophane units separately. For our purposes, this synthetic route would be too long and low yielding, since appreciable quantities of building block 16 are needed. A shorter approach to the synthesis of 16 would be to form the two meta[1]cyclophane units at the same time. This can be done using the Stevens rearrangement for ring contraction followed by reductive removal of the sulfur-containing groups or \( \text{via} \) pyrolysis of the sulfones or photolysis of the sulfide linkages. In all cases, retrosynthetic analysis of meta[1]cyclophane 16 leads back to tetrathiabenzene-3-oxide 17.

Tetrathiabenzene-3-oxide 17 could be formed in a single step from the tetrathiol 19 (derived from tetrabromodurene) and a dibromide 18 in a high-dilution coupling. Couplings of this type have been described by Vögtle et al., who have described the synthesis of compounds similar to 17 using coupling of 18 and 19. For the synthesis of 17 it was decided to apply Vögtle's approach, but with some minor modifications.
4.2.1 Synthesis of tetrathiabenzeno<3>phanes

Vögtle's synthesis\textsuperscript{16,20} started with dichloride 20b, which was oxidized using KMnO\textsubscript{4} under basic conditions to yield diacid 21 in 71\%, presumably \textit{via} the diol 20c that is formed \textit{in situ}. We chose to use dibromide 20d as starting material, as it was readily available from other research projects. It was synthesized in 56\% yield by the double bromomethylation of \textit{meta}-xylene.\textsuperscript{26} However, the oxidation of 20d under conditions that were reported for 20a was found to be problematic, since yields varied (20-45\%).\textsuperscript{27} In order to increase the reactivity of dibromide 20d, it was decided to synthesize diacetate 20e (99\% from 20d), which could form diol 20c by saponification of the ester moieties. This saponification was expected to be more effective than the nucleophilic substitution that is required to convert dibromide 20d to diol 20c. Oxidation of diacetate 20e under basic conditions yielded the desired diacid 21 in 80\% yield. Although the overall yield of this process is not higher than Vögtle's process,\textsuperscript{20} the results were reproducible.
Diacid 21 was esterified to provide diester 22 in 76\% yield via the bistacid chloride. When Fischer esterification conditions were used in this step (reflux in EtOH with catalytic H2SO4), the diester was formed in only 57\%. Double free radical benzylic bromination of 22 yielded 23 in 40\% yield. The yields for these steps (21 -> 22 -> 23) were comparable to those reported by Vögtle.

Building block 23 is one of the partners required for the coupling reaction to form the required tetrathiacyclophanes. The other building block is tetrabromodurene 26, which is commercially available. It can also be synthesized by the fourfold free radical benzylic bromination of durene 27\textsuperscript{28} or by a reduction-bromination sequence from pyromellitic acid derivatives, e.g. 24 (Scheme 4.05). It was decided to apply the second synthetic approach.
Scheme 4.05: Synthesis of tetrabromodurene 26.

In the first step, pyromellitic anhydride 24 was converted to tetramethyl pyromellitate in 86% using Fischer esterification conditions. The tetramethyl ester 25 was reduced using LiAlH₄ and workup of the reaction mixture without isolating the intermediate 1,2,4,5-tetrakis(hydroxymethyl)benzene with concentrated hydrogen bromide in acetic acid yielded the desired tetrabromodurene 26 (66%).
Tetrabromodurene 26 was converted into tetrathiol 19 by converting it into tetrakist(isothiouronium) salt, followed by hydrolysis to give 19 (90%). Coupling of this tetrathiol with 23 under high dilution conditions in the presence of a base yielded a mixture of both possible isomers, 28a and 28b, which could be separated using column...
chromatography to give 13% of the desired cyclophane 28a and 19% of the unwanted orthometacyclophe 28b. (Differentiation between the isomers could be made based on 1H NMR data.)20 This outcome is similar to that described by Vögtle et al. (28a : 28b = 18% : 27%).20 The same group described the conversion of tetraesters 28a and 28b to tetraacetates 29a and 29b and tetraalcohols 30a and 30b. However, other functional group interconversions (PBr3 or SOBr2) were reported to be unsuccessful, due to acid sensitivity of cyclophanes 28 - 30. This suggested that the required functional group interconversions on the ester functionalities would be better left until a later stage in the synthesis and ring contraction of cyclophane 28a should be performed first. For future synthetic applications, this might obviate the need to separate 28a and 28b, since ring contraction of dithia[3,3]orthometacyclophe 28b should lead to mainly other (decomposition) products.31

4.2.2 Attempted ring contraction of tetrathiabenzeno<3>phane 28a

4.2.2.1 General

Several known routes are available for the ring contraction of dithia[3,3]metacyclophe to give [2.2]metacyclophe.31,32 A route that is used often is the “pyrolysis route,” in which the sulfur atoms in the bridges are first oxidized to sulfones, SO2 is then extruded with concomitant ring contraction using flash vacuum pyrolysis techniques.32 This methodology has some major drawbacks when applied to our system. The oxidation step
should produce intermediates that contain one or more sulfoxide or sulfone functionalities before forming tetrakis(sulfone) 31. As sulfoxides and sulfones are usually not very soluble, the reaction might not proceed to completion due to precipitation of some of the reaction intermediates. The second (pyrolytic) step often suffers from low yields, especially when two or three bridges are contracted. In case of 31, four sulfone groups are to be extruded. The last drawback is the anticipated low volatility of 31, which might make flash vacuum pyrolysis an inappropriate technique for synthesis of appreciable amounts of 32.

Scheme 4.07: The proposed routes to form 32 from 28a.

The conversion of tetrathiabenzeno<3>phane 28a to benzeno<3>phane 32 could also be achieved using the photolysis of sulfide linkages to give C-C bonds.\textsuperscript{13-17} In this procedure
triethylphosphite acts as a thiophilic reagent (formation of \((\text{EtO})_3\text{P} = \text{S}\)) as well as the solvent.

Other routes that can be followed is to ring contract the dithiacyclophane 28a using a Stevens\(^{31,38}\) or Wittig\(^{31,39,40}\) rearrangement. Both routes lead to the same product, but are complementary in mechanism. For the Stevens rearrangement, the sulfur atoms in the bridges are methylated, after which a base (e.g. KO-\(t\)-Bu) can induce the rearrangement to yield 33. When a thiacyclocphane is treated directly with a strong base (e.g. BuLi), Wittig rearrangement can occur. The rearranged product is then methylated to give the same product as the Stevens rearrangement (33). Both approaches are expected to yield a mixture of isomeric thioethers (33), which can be carried through without separation. Reductive cleavage of the thioether groups of such mixtures with Raney nickel has proved to be effective in related systems\(^{41}\) and should not reduce the ester functionalities that are present in 33 and 32.\(^{42}\)

**Scheme 4.08:** Proposed conversion of 28a to 32 using Stevens or Wittig rearrangements.
The problem with the Wittig rearrangement of 28a could be the choice of a suitable base. Alkyllithium species, which are normally used, are not appropriate, since the starting material has four ester functional groups that are susceptible to reaction with strong nucleophiles such as alkyllithium reagents. Less nucleophilic bases like LDA or LHMDS might be required. Another potential problem in this approach might be intramolecular reaction of the intermediate thiolate ions with proximate ester groups (Scheme 4.09: 34 -> 35). Deprotonation of a thioether bridge in 28a is expected to occur preferentially at the benzylic position ortho to an ester group, which leads to the precursor for this intramolecular cyclization. Obviously this side reaction could also occur in an intermolecular manner, which would lead to oligomerization.
Raney nickel desulfurization of the reaction products should yield 32. In 28a, however, four reductions are taking place as opposed to only one or two, which will probably be reflected in the yield. If one of the rearrangements did not go to completion (i.e., one or more of the bridges in the cyclophane system still contains the original thioether), this thioether will be cleaved the Raney nickel reduction, yielding methylbenzene moieties.
A further complication arises when 32 is actually formed. Layered cyclophanes, such as 32, have been described to exist in (at least) two distinct conformations, namely the "up,up" and the "up,down" conformers (Scheme 4.10). Formation of this mixture will complicate separation and characterization of 32. However, in the anticipated synthesis both conformers should, ultimately, lead to the formation of a single compound 37.

![Scheme 4.10: Structures of "up-up"-32, "up-down"-32 and compound 37](image)

Based on the preceding discussion, it was expected that the projected ring contraction would not be accomplished easily. Most projected complications seem to arise from solubility problems, so one alternative to the Stevens and Wittig methodology described above was also considered as an option. In 1975 Boekelheide described the benzyne-Stevens rearrangement as a useful alternative for the ring-contraction of dithia[3.3]cyclophanes. This reaction was performed on several known
[3,3]cyclophane systems and it was concluded that this methodology was superior in the case of cyclophanes containing ortho- and para-substituted rings. For metacyclophanes, this methodology gave slightly lower yields than the traditional conditions for the Stevens rearrangement (29% with benzyne-Stevens vs. 33% using Stevens rearrangement and 33% using Wittig rearrangement for formation of pyrene from 2,11-dithia[3,3]metacyclophane 38).31

No mechanistic study has been reported to date for the benzyne-Stevens rearrangement. A likely mechanism would be a similar order of events as for the regular Stevens rearrangement45 and a schematic representation is given in Scheme 4.11 for the 2,11-
dithia[3,3]metacyclopahne system 38. A key feature of the benzyne-Stevens rearrangement is that for each individual bridge contraction from a neutral starting material, neutral products are formed, even though the reaction might proceed via a series of zwitterionic species (i.e. 39 or 40). In this manner, the formation of multiply charged reaction intermediates and/or products is avoided. Therefore the anticipated solubility problems for the Stevens and Wittig rearrangements probably do not apply to this procedure. After the bridges in a dithiacyclophan e have undergone ring contractions, the thiophenyl substituents can also be desulfurized using Raney nickel to give the desired cyclophane products.

4.2.2.2 Results and discussion

Irradiation of a well-stirred saturated solution of cyclophane 28a in trimethylphosphite did not lead to formation of 32. Instead, starting material was consumed to give a complex mixture of compounds, from which no single product was isolated. When cyclophane 28a was subjected to methylation using Borch reagent in dichloromethane or chloroform at room temperature or reflux, a yellow or sometimes black oil would form. After treatment of this oil with base to initiate the Stevens rearrangement, it could be seen from the $^1$H NMR spectrum that a complex mixture of products was produced as expected. No conclusions regarding nature of the mixture could be drawn from the spectroscopic data. Unfortunately, attempted reduction of the mixture with Raney nickel did not yield even trace amounts of 32, but rather another complex mixture of products.
from which no single compound could be isolated. The problematic step in this reaction sequence is presumably the methylation. The low solubility of the di- and trimethylated intermediates in this reaction might cause them to precipitate from solution and not react further to give the desired tetramethylated intermediates.

Wittig rearrangement of cyclophane 28a was attempted by treatment with LDA in THF, followed by treatment with iodomethane. This gave (by $^1$H NMR) a complex mixture of products comparable to that formed in the Stevens rearrangement. Again attempted desulfurization with Raney Nickel did not lead to the formation of any of the desired products.

After the disappointing results that were obtained using the photolytic extrusion of sulfur from the bridges and the Stevens and Wittig rearrangements, attention was focused on the benzyne-Stevens rearrangement. When cyclophane 28a was subjected to the conditions for the benzyne-Stevens rearrangement as described by Boekelheide using 5 equivalents of benzyne (from anthranilic acid and excess isoamyl nitrite), a mixture of compounds was formed. Desulfurization of this mixture again led to the formation of a complex mixture of compounds. In this case, column chromatographic separation of this mixture led to the isolation of a single compound. However, its $^1$H NMR spectrum did not correspond to either conformer of structure 32. In the mass spectrum, this new compound 43 showed a peak at $m/z$ 704. From the results from $^1$H NMR, $^{13}$C NMR and the mass spectroscopic data, structure 43 was proposed (Figure 4.05). This structure was later
confirmed by X-ray crystallography, although the quality of the data set was low.\textsuperscript{46} When 5 – 15 equivalents of benzylene were used, the yield of 43 was 15-18\%.

\begin{center}
\includegraphics[width=0.8\textwidth]{structure.png}
\end{center}

**Figure 4.05:** Structure of compound 43

Structure 43 seems to be the result of a Diels-Alder reaction between the central aromatic ring in the desired product up.down-32 (or precursor thereof) and benzylene (Scheme 4.12). In going from 28a to 32, the strain in the system (specifically in the central aromatic ring) increases with each consecutive ring contraction. At a certain stage during the ring contractions the energy loss due to loss of aromaticity that occurs during the Diels-Alder reaction, will be offset by the energy that is gained upon relief of the strain that occurs in the Diels-Alder reaction. \textsuperscript{[4-2]} Cycloaddition reactions of benzylene with aromatic rings has been described quite extensively\textsuperscript{17-52} and an example of an intramolecular benzylene cycloaddition in the [3.3]paracyclopheane system has been reported.\textsuperscript{53} Apparent Diels-Alder reaction of some [5]metacyclopheanes with other dienophiles has also been reported.\textsuperscript{54} The proposed Diels-Alder reaction to form 43, can only occur if the reacting cyclophane adopts the “up.down” conformation. In this
conformation the central aromatic ring is expected to possess a boat-like geometry\textsuperscript{24} and the Diels-Alder reaction can occur at the internal carbon atoms of this cyclophane.

![Reaction scheme](image)

Scheme 4.12: Formation of compound 43 from 28a.

4.3 Conclusions and future work

In this Chapter a novel approach to the synthesis of a “Vögtle belt” has been proposed. Unfortunately, the inability to cause 28a to undergo the desired ring contraction has so far greatly limited the application of this approach to the synthesis of advanced
intermediates. A novel structure 43 was found to be the only isolable product from benzylne-Stevens rearrangement of 28a after desulfurization of the reaction mixture. The approach has not led to the synthesis of an aromatic belt so far, so the viability if the VID approach for the synthesis of Vögtle belts has not been determined.

In order to attempt further application of this approach to the synthesis of a fully aromatic belt, compounds of the general structure 15 (Scheme 4.03) are required. As the approach described in this Chapter has failed, an alternative approach would be to form a fourfold bromomethylated cyclophane 46 from cyclophane 45 via free radical bromination with NBS (Scheme 4.15). This type of selective bromination of [2.2]meta-cyclophanes has been described in the literature.\(^5\) However, synthesis of cyclophane 45 might suffer from the same complications that have been described in this Chapter. Its synthesis might have to be performed in a more classical (and low-yielding) stepwise approach,\(^4\) but as stated earlier multigram quantities are required for serious attempts to the synthesis of aromatic belts. Future work in this area should therefore be directed toward the development of better methodology to synthesize [2.2]meta-cyclophanes. All of the currently used methodology was discovered in the 60's and 70's and it is not easily applied to the multigram scale synthesis of cyclophanes such as 32 and 46. The use of more modern reactions for the synthesis of [2.2]meta-cyclophanes might therefore be a fruitful area of future research.
4.4 Experimental

General. All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40-63 μm, 230-400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed at the MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta. Mass spectroscopic (MS) data were obtained on a V. G. Micromass 7070HS instrument. \(^1\)H NMR (300 MHz) and \(^{13}\)C NMR (75.47 MHz) were obtained on a General Electric GE 300-NB spectrometer; \(^1\)H shifts are relative to internal tetramethylsilane; \(^{13}\)C shifts are relative to the solvent resonance (CDCl\(_3\); \(\delta = 77.0\)). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under nitrogen unless otherwise stated. Solvents were dried and distilled according to standard procedures.
1,3-Bis(bromomethyl)-4,6-dimethylbenzene (20d). meta-Xylene 20a (12.21 mL, 0.100 mol), paraformaldehyde (6.15 g, 0.200 mol), glacial acetic acid (50 mL) and concentrated hydrogen bromide in acetic acid (30%, 40 mL) were stirred at approximately 85 °C for 8 h. The reaction mixture was cooled and poured into water (150 mL). The resulting yellow precipitate was collected by suction filtration and crystallized from heptane to give 20d (16.4 g, 56.2 mmol, 56%) as colorless needles; mp 104-106 °C; $^1$H NMR (CDCl₃) δ 7.27 (s, 1H), 7.03 (s, 1H), 4.49 (s, 4H), 2.38 (s, 6H); $^{13}$C NMR (CDCl₃) δ 138.3, 134.0, 133.6, 131.7, 32.0, 18.7; El-MS m/z (%): 290 (8, M⁺•Br•Br), 211 (100), 132 (80), 115 (15), 91 (17); Anal. Calc. For C₁₀H₁₂Br₂: C 41.13, H 4.14; found C 41.03, H 3.91.

1,3-Bis(acetoxyethyl)-4,6-dimethylbenzene (20e). To a solution of dibromide 20d (5.00 g, 17.1 mmol) in acetonitrile (150 mL) was added sodium acetate (11.65 g, 85.6 mmol), and the mixture was stirred at reflux temperature for 24 h. The mixture was concentrated in vacuo, and ethyl acetate and water were added until all material dissolved. The aqueous layer was extracted with ethyl acetate (2 x 100 mL). The combined organic layers were washed with water (100 mL), saturated NaHCO₃ solution (100 mL), water (100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure to yield 20e (4.24 g, 17.0 mmol, 99%) as a light yellow oil that was used without further purification; $^1$H NMR (CDCl₃) δ 7.28 (s, 1H), 7.05 (s, 1H), 5.09 (s, 4H), 2.32 (s, 6H), 2.09 (s, 6H); $^{13}$C NMR (CDCl₃) δ 171.0, 137.6, 132.7, 131.6, 130.9, 64.5, 21.1, 18.6; El-MS m/z (%): M⁺ not observed, 190 (33), 130 (48), 119 (24), 115 (16), 91 (28), 43 (100).
**4,6-Dimethylisophthalic acid (21).** To a solution of potassium hydroxide (85% purity, 4.33 g, 65.6 mmol) in water (200 mL) was added diacetate 20e (4.10 g, 16.4 mmol). The flask was equipped with a reflux condenser and the mixture was stirred vigorously for 6 h at reflux temperature. The heat source was removed, the mixture was stirred for 10 min and potassium permanganate (6.86 g, 43.1 mmol) was slowly added (fast addition led to a strong exotherm!). The mixture was stirred at room temperature for 18 h and filtered using suction filtration to produce a clear colorless filtrate that was acidified to pH ~1 with concentrated hydrochloric acid. The precipitate was collected by suction filtration and recrystallized from ethanol to yield 21 (2.56 g, 13.1 mmol, 80% yield) as a colorless solid: mp 295 - 297 °C (lit. 320 °C); \(^1\)H NMR (DMSO-d<sub>6</sub>) δ 8.39 (s, 1H), 7.25 (s, 1H), 2.56 (s, 6H); \(^13\)C NMR (DMSO-d<sub>6</sub>) δ 167.9, 143.4, 135.1, 133.0, 127.7, 21.3; EI-MS m/z (%): 194 (94, M⁺), 176 (100), 148 (27), 103 (12), 91 (13).

**Diethyl 4,6-dimethylisophthalate (22).** Thionyl chloride (40.0 mL, 462 mmol) was added dropwise to diacid 15 (17.04 g, 87.8 mmol) in a 100 mL, 3-necked round-bottomed flask equipped with condenser and calcium chloride drying tube. Three drops of N,N-dimethylformamide were added, and the mixture was stirred at reflux temperature for 4 h. Excess thionyl chloride was removed using distillation and absolute ethanol (25 mL, 426 mmol) was added carefully while the mixture was cooled in an ice-water bath. After the addition was complete, the mixture was stirred at reflux temperature for 20 min, cooled to room temperature and concentrated under reduced pressure to give a yellow-brown solid that was crystallized from methanol to yield 22 (16.7 g, 66.7 mmol, 76% yield) as colorless
Diethyl 4,6-bis(bromomethyl)isophtalate (23). To a solution of diester 22 (3.50 g, 14.0 mmol) and NBS (3.50 g, 19.7 mmol) in dichloromethane (50 mL) was added a spatula tip benzyol peroxide. The mixture was stirred at reflux temperature for 3 h while it was irradiated with a 100 W halogen lamp. Another portion of NBS (2.28 g, 12.8 mmol) was added followed by a spatula tip of benzyol peroxide, and the mixture was stirred with irradiation at reflux temperature for 2.5 h and then cooled to room temperature. The reaction mixture was washed with water (200 mL), saturated aqueous sodium carbonate solution (2 x 100 mL), water (100 mL) and saturated aqueous sodium chloride solution (100 mL), dried (MgSO₄) and concentrated in vacuo to give an orange solid that was crystallized from cyclohexane to yield 23 (2.29 g, 7.88 mmol, 40% yield) as colorless crystals: mp 78-80 °C (lit.° 78-81°C); IR (Nujol, cm⁻¹): 1719 (s), 1366 (m), 1296 (s), 1236 (m), 1137 (w), 1101 (m), 1044 (w); ¹H NMR (CDCl₃) δ 8.52 (s, 1H), 7.55 (s, 1H), 4.92 (s, 4H), 4.43 (q, 4H, J = 7.2 Hz), 1.43 (t, 6H, J = 7.2 Hz); ¹³C NMR (CDCl₃) δ 165.6, 143.3, 135.0, 134.5, 129.6, 62.0, 30.2, 14.4; EI-MS m/z (q): 408 (12, M⁺, Br²⁺, Br), 363 (27), 299 (100), 192 (45), 148 (36), 134 (18), 102 (28), 91 (36).
Tetramethyl 1,2,4,5-benzenetetracarboxylate (25). To a well-stirred suspension of pyromellitic anhydride 24 (20.06 g, 91.97 mmol) in methanol (700 mL) in a 1000 mL 3-necked round-bottomed flask equipped with a reflux condenser with CaCl₂ drying tube was carefully added H₂SO₄ (concentrated, 20 mL) and the reaction mixture was stirred at reflux temperature for 18 h. The reaction mixture was cooled in an ice bath. Suction filtration and washing with small amounts of cold methanol yielded 25 (24.52 g, 79.03 mmol, 86%) as colorless crystals; mp: 138 – 139 °C; IR (Nujol, cm⁻¹): 1732 (s), 1303 (s), 1103 (s), 953 (m), 918 (m), 796 (m), 742 (m); ¹H NMR (CDCl₃) δ 8.09 (s, 2H), 3.96 (s, 12H); ¹³C NMR (CDCl₃) δ 166.3, 134.1, 129.5, 53.0; EI-MS (70 eV) m/z (²⁹) 310 (3, M⁺), 279 (100).

1,2,4,5-Tetrais(bromomethyl)benzene (26). To a well-stirred slurry of LiAlH₄ (3.94 g, 104 mmol) in dry THF (200 mL), was added dropwise a solution of 25 (7.04 g, 22.7 mmol) in dry THF (150 mL). The reaction mixture was stirred at reflux temperature for 5.5 h and cooled in an ice-bath. Carefully, EtOAc (100 mL) was added and the mixture was concentrated under reduced pressure to give a gray solid. To the solid was added dropwise 48% aqueous HBr (200 mL) (caution: vigorous exotherm), followed by concentrated H₂SO₄ (100 mL; caution: exotherm). The reaction mixture was stirred at reflux temperature for 1.5 h, cooled in an ice bath, poured into ice water (500 mL) and extracted with CH₂Cl₂ (3 x 100 mL). The combined organic extracts were washed with water (2 x 100 mL), saturated aqueous NaHCO₃ solution (2 x 150 mL), water (150 mL) and saturated aqueous NaCl solution (100 mL). After drying (MgSO₄) the organic layers
were concentrated in vacuo and the residue was crystallized from toluene to yield 26 (6.74 g, 15.0 mmol, 66%) as slightly brown crystals that were pure enough for further synthetic purposes; mp 150 – 151.5 °C; 1H NMR (CDCl₃) δ 7.38 (s, 2H), 4.61 (s, 8H); 13C NMR (CDCl₃) δ 137.6, 133.6, 28.7; El-MS (70 eV) m/z (%) 450 (3, M⁺ (⁷⁹Br)₂(⁸¹Br)₂), 369 (100), 290 (24), 209 (47).

1,2,4,5-Tetrakis(thiomethyl)benzene (19). Thiourea (6.24 g, 82.0 mmol) was added to a well-stirred suspension of tetrabromide 26 (9.00 g, 20.0 mmol) in absolute ethanol (250 mL) in a 500 mL round bottom flask. The mixture was stirred at reflux temperature for 6 h and concentrated under reduced pressure. To the residue was added a solution of potassium hydroxide (85 % purity; 13.21 g, 200.1 mmol) in degassed water (150 mL), and the mixture was heated at reflux temperature under an atmosphere of nitrogen for 16 h. After cooling to room temperature, the mixture was acidified using 9 M aqueous sulfuric acid and extracted with dichloromethane (3 x 75 mL). The organic layers were combined and washed with water (100 mL) and saturated aqueous sodium chloride solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure to yield 19 (4.73 g, 18.0 mmol, 90%) as a yellow-brown solid that was used without purification in the next step.
5,7,23,25-Tetrakis(ethoxycarbonyl)-2,11,20,29-tetraphia[3.3](1,3)(1,3)[3.3](4.6)(1,3)-benzo<3>phane (28a) and 5,7,23,25-Tetrakis(ethoxycarbonyl)-2,11,20,29-tetraphia[3.3](1,3)(1,2)[3.3](4,5)(1,3)-benzo<3>phane (28b). Tetrathiol 19 (0.90 g, 3.4 mmol) and dibromide 13 (2.80 g, 6.86 mmol) were washed into a 3000 mL 3-necked round bottom flask using 2000 mL 1:1 degassed absolute ethanol and degassed benzene. The solution was stirred vigorously using a mechanical stirrer and potassium carbonate (1.90 g, 13.7 mmol) was added. The mixture was stirred for 2.5 d and concentrated in vacuo onto silica gel (3.1 g). Column chromatography of the residue (SiO₂: 2.5 % EtOAc CHCl₃) first yielded 28b (0.61 g, 0.81 mmol, 19% o, colorless solid) followed by 28a (0.34 g, 0.45 mmol, 13% o, colorless solid).

28a: mp: 215 - 217.5 °C (lit.²⁰ 209-211 °C); IR (Nujol, cm⁻¹) 1723 (s), 1709 (s), 1244 (s); ¹H NMR (CDCl₃) δ 7.79 (s, 2H), 6.96 (s, 2H), 6.57 (s, 2H), 4.29 (q, 8H, J = 7.6 Hz), 4.05 (br s, 8H), 3.85 (br s, 8H), 1.36 (t, 12H, J = 7.4 Hz); ¹³C NMR (CDCl₃) δ 166.6, 142.3, 135.7, 135.5, 133.3, 133.2, 128.1, 61.2, 37.5, 36.1, 14.2; EI-MS m/z (η%): M⁺ not observed. 750 (1), 713 (4), 505 (22), 473 (28), 191 (100).

28b mp: 248 - 251 °C (dec.) (lit.²⁰ 250-252 °C); IR (Nujol, cm⁻¹) 1707 (s), 1287 (m); ¹H NMR (CDCl₃) δ 8.53 (s, 2H), 8.07 (s, 2H), 6.40 (s, 2H), 4.42 (q, 8H, J = 7.0 Hz), 4.10 (br s, 8H), 3.34 (s, 8H), 1.43 (t, 12H, J = 7.9 Hz); ¹³C NMR (CDCl₃) δ 165.7, 142.5, 136.6, 135.3, 134.6, 130.3, 127.9, 61.4, 33.4, 28.8, 14.3; EI-MS m/z (η%): M⁺ not observed. 713 (3), 704 (1), 506 (3), 473 (100).
**Attempted ring contraction of 28a: photolytic method.** Cyclophane 28a (0.35 g, 0.46 mmol) was dissolved as well as possible in freshly distilled trimethylphosphite (15 mL) and filtered to remove undissolved material. The solution was placed in a quartz tube in a photolysis apparatus (Rayonet Photochemical Reactor) and was stirred while being irradiated (254 nm, 112 W) for 22 h. The mixture was concentrated *in vacuo* and subjected to column chromatography. A small amount of starting material was recovered (< 0.02 g) together with several fractions of unidentified materials.

**Attempted ring contraction of 28a: Wittig rearrangement.** Cyclophane 28a (0.50 g, 0.66 mol) was dissolved in dry tetrahydrofuran (50 mL) under an atmosphere of nitrogen and cooled in an ice water bath. A solution of LDA (1.5 M in cyclohexane, 2.2 mL, 3.3 mmol) was added over 10 minutes. The reaction mixture was allowed to warm up to room temperature and stirred for 2 h. A drop of water was added, followed directly by iodomethane (0.25 mL, 4.0 mmol) and the reaction mixture was concentrated *in vacuo*. Dichloromethane (50 mL) was added and the mixture was washed with water (25 mL) and saturated sodium chloride solution (25 mL), dried (MgSO4) and concentrated under reduced pressure to give a yellow-brown oil. Absolute ethanol (25 mL) was added and the mixture was heated to reflux temperature. Freshly prepared Raney Nickel (3 spatula tips) was added and the mixture was stirred at reflux temperature for 20 min. Two more portions of Raney Nickel (3 spatula tips each) were added and after each addition the mixture was stirred at reflux temperature for 20 min. The mixture was cooled to room temperature and the solid was removed using suction filtration and washed with ethyl
acetate (2 x 5 mL). The filtrate was concentrated under reduced pressure and the residue was subjected to column chromatography to yield several fractions of unidentified composition.

**Attempted ring contraction of 28a: Stevens rearrangement.** To a solution of cyclophane 28a (0.50 g, 0.66 mmol) in dichloromethane (50 mL) was added Borch reagent (1.08 g, 6.7 mmol) and the reaction mixture was stirred for 14 h under an atmosphere of nitrogen. The mixture was concentrated *in vacuo* and ethyl acetate (10 mL) and methanol (2 mL) were added and again the mixture was concentrated *in vacuo*. To the residue was added dry tetrahydrofuran (50 mL), followed by potassium tert-butoxide (0.38 g, 3.4 mmol) and the mixture was stirred at room temperature for 16 h under an atmosphere of nitrogen. Saturated aqueous ammonium chloride solution (1 mL) was added and the mixture was concentrated under reduced pressure. Saturated aqueous ammonium chloride solution (25 mL) and dichloromethane (50 mL) were added and the aqueous layer was extracted with dichloromethane (50 mL). The organic layers were combined and washed with water (50 mL) and saturated aqueous sodium chloride solution (50 mL). After drying (MgSO₄) and concentration under reduced pressure the residue was passed through a plug of silica using dichloromethane and the eluent was concentrated under reduced pressure. To the residue was added absolute ethanol (25 mL) and the mixture was heated to reflux temperature. Raney nickel (3 spatula tips) was added and after each addition the reaction mixture was stirred at reflux temperature for 20 min. The reaction mixture was cooled to room temperature and the solid was removed
using suction filtration and washed using ethyl acetate. The mother liquor was concentrated under reduced pressure to yield an inseparable mixture of unidentified compounds. (No indication was found for formation of the desired product 32.)

Several variations to this procedure were attempted, varying solvent (dichloromethane or chloroform for the first step, ethanol or ethyl acetate for the desulfurization), temperature (room temperature to reflux), amount of reagent used (10 or 20 equivalents Borch reagent, 5, 7 or 10 equivalents potassium tert-butoxide, 3, 7 or 10 additions of Raney Nickel) and reaction times (1-24 hours). Results were comparable for each variation and no indication of formation of 32 was observed.

**Attempted ring contraction of 28a: benzene-Stevens rearrangement.** A solution of anthranilic acid (0.30 g, 2.2 mmol) in 1,2-dichloroethane (50 mL) was added dropwise over 1 h to a refluxing solution of cyclophane 28a (0.33 g, 0.44 mmol) and isoamyl nitrite (1.1 mL, 7.9 mmol) in 1,2-dichloroethane (35 mL). The reaction mixture was stirred at reflux temperature for an additional 30 min, concentrated under reduced pressure, filtered over a plug of silica using 5% ethyl acetate chloroform and concentrated again under reduced pressure. The residue was dissolved in a refluxing mixture of ethanol (70 mL) and ethyl acetate (10 mL) and Raney Nickel (2 spatula tips) was added and the mixture was heated at reflux temperature for 5 min. The mixture was cooled to room temperature, filtered using suction filtration (the residue was washed with ethyl acetate) and the residue was concentrated under reduced pressure. Hexanes was added to the residue and a colorless precipitate formed that was isolated using suction filtration and dried to yield 43
(- 0.05 g, 0.071 mmol, ~15 %): mp > 280 °C: IR (Nujol, cm⁻¹) 1712 (s), 1558 (s, 2H), 1530 (m, 4H), 1465 (w), 1456, 1360, 1341, 1261, 1227, 1209, 1120, 1101, 1055, 1032, 838, 835, 764, 703, 657, 543, 407 (s, 2H), 279 (s, 2H), 279 (s, 2H), 279 (s, 2H). HRMS Calcd for (C₁₄H₁₄O₈)⁺: 703.3268. Found: 703.3271.

4.5 References

(1) The name Vögtle belt has been proposed by us for a (so far hypothetical) fully aromatic belt like 4. For a more detailed discussion refer to Section 4.1 and references therein.


(25) For a more detailed discussion on the use of angular brackets <> in cyclophane nomenclature see Section 1.3.1 and references therein.


The quality of the structural data is not optimal since an incomplete dataset was collected due to time constraints. Inclusion of solvent molecules and the presence of 2 conformers of 43 caused complications in the calculation of the structure as well.


(49) Friedman, L.; Lindlow, F. J. Am. Chem. Soc. 1968, 90, 2329-2333.


Chapter 5

Synthesis of

[2]Paracyclo[2](2,7)pyrenophane

and

[2]Metacyclo[2](2,7)pyrenophane
5.1 Introduction

After the failed attempt to synthesize a fully aromatic belt 1 (Chapter 4) and the failed model study of a (2,7)pyrenophane 2 with two para-phenylene rings in the tether (Chapter 3) it was decided to focus attention to the synthesis of a simpler model compound, 3. This (2,7)pyrenophane contains one para-phenylene ring in the tether, which is connected to the pyrene unit via dimethylene bridges. Part of the tether consists of a para-phenylene ring and 3 is a model compound for 4, which maps onto the surface of aromatic belt 1 (n = 0).

![Figure 5.01: Synthetic targets 1 - 4.](image-url)
AM1 level calculations show a bend angle ($\theta_{\text{calc}}$) of the pyrene unit in 3 of 100.4°. This suggests that (2,7)pyrenophane 3 should synthetically be accessible using the valence isomerization-dehydrogenation (VID) protocol. Using the same calculations for a constitutional isomer of 3, with a meta-phenylene unit in the tether (Figure 5.02: compound 5) the bend angle was calculated to be 106.6°. As this is still a smaller angle than for some of the most strained (2,7)pyrenophanes that have been synthesized by our group, cyclophane 5 was also identified as a synthetic target. Due to the meta positioning of the tethers in 5 this compound does not map onto the surface of fullerenes or aromatic belts. Nonetheless it was considered an interesting target in the context of our ongoing research in the areas of novel cyclophanes and nonplanar aromatic compounds. The ortho-phenylene isomer 6 has a $\theta_{\text{calc}}$ of 130.4°, which is well beyond the estimated cut-off value (115° - 120°) for the VID approach, so its synthesis was not considered worth pursuing.

![5 and 6](image)

**Figure 5.02:** Structure of pyrenophanes 5 and 6.

Cyclophanes containing a para-phenylene, meta-phenylene or pyrene unit that is bridged with two tethers of equal length with another aromatic unit have been described quite
extensively in the literature. Figure 5.03 contains some examples of cyclophanes with dimethylene tethers.\(^5\)

![Figure 5.03: Some cyclophanes containing 2 aromatic units.](image)

The [2,2]cyclophanes that have been described in the literature most extensively are probably [2,2]para-cyclophane \(7\)^7-8, [2,2]meta-cyclophane \(8\)^9\(^{10}\) and [2,2]meta-para-cyclophane \(9\)^11. [2,2][2,7]Pyrenophane \(10\)^12-14 is also a relevant example when cyclophanes 3 and 5 are considered. To our knowledge, no examples of mixed cyclophanes with two dimethylene tethers bridging a (2,7)pyrene unit with another aromatic unit have been described. Pyrenophanes 3 and 5 would then constitute the first examples of this class of compounds.

The syntheses of cyclophanes \(7 - 10\) involve formation of the dimethylene bridges in the last (or a very late) step either via [6+6] dimerization of para-xylylene (for 7 only)^15, Wurtz coupling (for 7 and 8)^16-19 or SO\(_2\) extrusion from a dithia[3,3]cyclophane.\(^12\)-14,20,21

None of these cyclophanes has been synthesized by forming one of the aromatic units in
the last step, which is the approach our group has applied to the synthesis of several pyrenophanes by forming the pyrene unit in these systems via the VID sequence.\textsuperscript{34}

5.1.1 Retrosynthetic analysis

Since the retrosynthetic analyses of [2]paracyclo[2](2,7)pyrenophane 3 and [2]metaacyclo[2](2,7)pyrenophane 5 differ only in the substitution pattern of one of the starting materials, these analyses are presented together (Scheme 5.01).

\begin{center}
\textbf{Scheme 5.01: Retrosynthetic analysis of pyrenophanes 3 and 5.}
\end{center}
Using the VID protocol that has proven successful for many (2.7)pyrenophanes, compounds 3 and 5 could retrosynthetically be derived from cyclophanediene 11.\textsuperscript{3,4} Cyclophane dienes then lead back to syn-dithiacyclophanes 12 via ring contraction methods.\textsuperscript{22} Syn-Dithiacyclophanes like 12 have previously been synthesized successfully using our Na\textsubscript{2}S/Al\textsubscript{2}O\textsubscript{3} reagent,\textsuperscript{23} thus leading back to a tetrafunctionalized precursor 13. In this compound, the dimethylene tethers that ultimately become the bridges in the target compound are already present, making this approach a conceptually novel one. The dimethylene tethers in 13 could be derived from alkyne units, i.e., 14. An advantage of this retrosynthetic step is that unsymmetrically substituted alkynes like 14 are readily synthesized using Sonogashira chemistry,\textsuperscript{24-27} thus leading back to compounds 15 and 16.

5.2 Results and discussion

For the synthesis of [2]paracyclo[2][2.7]pyrenophane 3, two complementary routes starting from 1,4-diodobenzene 17 and triflate 21\textsuperscript{28} were initially investigated. One of these routes was ultimately applied to the successful synthesis of 5. Therefore the synthesis of 3 will be discussed first, followed by the synthesis of 5.
5.2.1 Synthesis of [2]paracyclo[2](2,7)pyrenophane 3

Sonogashira coupling of 1,4-diiodobenzene 17 with two equivalents of trimethylsilylacetylene 18 gave diyne 19 (95%), which was protodesilylated to yield 1,4-diethynylbenzene 20 (77%). Due to the volatility of 20, it was purified using sublimation at atmospheric pressure. When performed carefully on a small scale, this sublimation was successful. However, in one case where purification was attempted with approximately 4 g of material, an explosive decomposition took place. Compound 20 was subjected to Sonogashira conditions using two equivalents of triflate 21 to form tetraester 22 in 57% yield. The low solubility of diyne 22 complicated its purification. This might be the reason for the relatively low recovery of product in this step.

Scheme 5.02: Synthesis of 22 from 1,4-diiodobenzene 17.
Due to the explosive character of 1,4-diethynylbenzene 20, an alternative route to 22 was investigated in which the order of the Sonogashira couplings was reversed (Scheme 5.03). Starting from triflate 21, Sonogashira coupling with trimethylsilylacetylene yielded compound 23 in 71% yield. Protodesilylation gave terminal alkyne 24 (91%), which was coupled with 1,4-diodobenzene 17 under Sonogashira conditions to yield diyne 22 in 91% yield (based on 1,4-diodobenzene). Again, the low solubility of 22 complicated purification of the material, but the crude mixture from this particular Sonogashira coupling was of higher purity than in the initial route, which made the second approach the preferred method to produce large quantities of 22.

Scheme 5.03: Alternative synthesis of diyne 22.

With a convenient synthesis of 22 in hand, attention was focused on the functional group interconversions of 22 that were necessary to form the appropriate dithiacyclophane (Scheme 5.04). Catalytic hydrogenation of the alkyne units in 22 gave tetraester 25.
which contained the dimethylene tethers that would ultimately become the bridges of pyrenophane 3. The hydrogenation of 22 was somewhat problematic due to its low solubility. Small-scale hydrogenations could be performed using saturated (dilute) solutions of 22 in THF or benzene, but when larger amounts of 25 were required this method became impractical due to the large volumes of solvent required. For the catalytic hydrogenation of larger quantities of 22, slow addition of a slurry of 22 in THF to a suspension of catalyst in THF under an atmosphere of hydrogen proved to be the most convenient method (both methods gave 25 in approximately 95% yield). Tetraester 25 was reacted with excess LiAlH4 in THF followed by HBr·HOAc to provide tetrabromide 26 (85%). This method has previously been used by our group for the synthesis of similar tetrabromides. When tetrabromide 26 was subjected to standard conditions (Na2S·Al2O3) to form dithiacyclophane 27, less than a 3% yield of 27 was obtained in low purity (~25% of an unidentified impurity by 1H NMR). However, when the reaction was performed at reflux temperature, dithiacyclophane 27 was formed in 28% yield. Changing the solvent mixture from CH2Cl2·EtOH to CHCl3·EtOH in order to increase the reflux temperature did not increase the yield.
Bridge contraction of dithiacyclophane 27 was accomplished by methylation of the sulfur atoms in 27 using Borch reagent, followed by treatment of the resulting bis(methylsulfonyl) salt with potassium tert-butoxide to induce Stevens rearrangement. This yielded 28 as a mixture of isomers (70% crude from 27). Methylation of the sulfur atoms in 28 (Borch reagent) followed by Hofmann elimination gave a mixture (ca. 1:1 by $^1$H NMR) of cyclophanediene 29 and the desired [2]paracyclo[2](2,7)pyrenophane 3. The mixture could be converted cleanly to pyrenophane 3 by treatment of the mixture with DDQ in benzene to yield 3 in 14% overall yield from dithiacyclophane 27. Crystals of 3 were obtained from heptane, and its molecular structure was determined using X-ray crystallography. This will be discussed together with its $^1$H NMR spectrum in Section 5.2.3.
The spontaneous formation of 3 in the Hofmann elimination step was somewhat surprising, since the formation of pyrenophanes with comparable calculated bend angles (Section 1.4) usually requires treatment of the corresponding cyclophanediene with DDQ in hot benzene. The reactivity of 29 can be explained by the presence of the rigid para-phenylene unit in the tether, which forces open the syn-[2.2]metacyclophanediene unit relative to those present in the precursors to the [n](2,7)pyrenophanes. The resulting increase in the inter-ring angle, moves the internal C atoms closer to one another and presumably lowers the activation energy to the formation of a bond between them.

Scheme 5.05: Synthesis of [2]paracyclo[2](2.7)pyrenophane 3.
The overall yield of the synthesis of 3 from triflate 21 is a disappointingly low 2% (longest linear sequence: 3% from 17). The low yield of this synthesis can be traced back to two particular synthetic transformations: the cyclization to furnish dithiacyclophane 27 and the methylation-Hofmann elimination sequence to form the mixture of 29 and 3. The cyclization step has been somewhat optimized, but needs closer examination. As many examples of dithiacyclophanes with different tether lengths are known to form with Na₂S/Al₂O₃ under standard conditions, it can be assumed that the presence of the para-phenylene unit in the tether somehow causes the low yield in this key step. Perhaps the rigidity of this unit prevents easy initial cyclization of tetrabromide 26 to form an intermediate like 30 (Scheme 5.06). Another effect could be that the second step in this transformation (ring closure of 30 to give 27) has an unexpectedly high energy barrier due to the rigidity of the para-phenylene unit, which forces the two aromatic systems in 30 away from each other.

Scheme 5.06: Formation of dithiacyclophane 27 via intermediate 30.
The second stumbling block in the synthesis was the methylation-Hofmann elimination sequence. This problem has also been observed in the synthesis of other (but not all) pyrenophanes that have been prepared in this group, and it is not clear what causes the yields in this transformation to be so erratic. Other groups\textsuperscript{22,30,31} have observed that in similar eliminations, by-products are found that are derived from Stevens rearrangement of the methylated intermediates. In our case, this Stevens rearrangement of bis(methylsulfonium) salt 31 would form intermediate 33, which could undergo Hofmann elimination to form 33 or a second Stevens rearrangement to form 34. Compound 34 could also be formed by sequential Hofmann elimination and Stevens rearrangement of 30 via intermediate 32. No particular effort was made in order to detect by-products 34 or 35, as attention was focused on the isolation of the desired product only.
Despite the low overall yield, it was highly gratifying to obtain the targeted pyrenophane 3. A very important feature of the synthesis is the novel way in which the dimethylene bridges were installed. This clearly establishes the viability of the approach, which has great potential for the synthesis of related compounds.
5.2.2 Synthesis of [2]metacyclo[2](2,7)pyrenophane

The synthesis of 3 began with Sonogashira coupling of 1,3-diiodobenzene 36 with alkyne 24, which proceeded in 76% yield to give diyne 37. Fortunately, diyne 37 is more soluble than its constitutional isomer 22, so it could easily be purified using column chromatography. Catalytic hydrogenation of the product proceeded smoothly to yield tetraester 38 in quantitative yield.

Reduction of 38 with excess LiAlH₄ in THF, followed by treatment of the reaction mixture with HBr HOAc yielded tetrabromide 39 in 54% yield. When tetrabromide 39 was subjected to standard cyclization conditions using Na₂S/Al₂O₃, dithiacyclophane 40 formed smoothly in 68%. This result is in line with the results that our group has.
observed for cyclization of other tetrabromides and suggests that the geometric requirements of the \textit{para}-phenylene unit in 26 are probably the cause for the low yield in the cyclization of 26 to give 27.

\[ \text{Scheme 5.09: Synthesis of dithiacycophane 40.} \]

Methylation of the sulfur atoms in the bridges of dithiacycophane 40 with Borch reagent followed by treatment of the resulting bis(methylsulfonium) salt with potassium tert-butoxide yielded 41 as a mixture of isomers in 88\% crude yield from 40. After treatment of the isomer mixture 41 with Borch reagent to methylate the sulfur atoms, the bis(methylsulfonium) salt was treated with potassium tert-butoxide (Hofmann elimination) to form cyclophanediene 42 in 61\% yield from dithiacycophane 40. Although this yield is not very high, it is considerably better than the yield that was obtained for the system with the \textit{para}\-phenylene unit in the tether. Another notable result in this particular project is that, in the formation of cyclophanediene 42, not even trace
amounts of pyrenophane 5 were observed in the $^1$H NMR spectrum. Treatment of a
solution of cyclophanadiene 42 in benzene led to clean formation of the desired
[2]metacyclo[2][2.7]pyrenophane 5 (97%), even at room temperature. The $^1$H NMR
spectrum of pyrenophane 5 will be discussed in Section 5.2.3. In that Section the results
of the X-ray crystal structure of 5 will also be discussed.


A notable feature of the synthesis of 5 is that it was accomplished in a single run.
Without any optimization, the overall yield was 17% from 1,3-diiodobenzene 36. This
bodes well for the use of the use of this approach for the synthesis of related systems
(Section 5.3).
5.2.3 Molecular structure of pyrenophanes 3 and 5

5.2.3.1 X-ray crystallography

Fortunately it proved to be possible to obtain crystals of pyrenophanes 3 (from heptane) and 5 (from toluene) that were suitable for X-ray crystallographic analysis. In Appendices F and G full crystallographic details are given. For the discussion of the structures in this Section, the crystallographic numbering of the carbon atoms will be used, which is different from the systematic numbering.

For pyrenophane 3 a bend angle $\theta_{\text{bend}}$ of 89.7$^\circ$ was determined and the curvature is spread out quite evenly over the pyrene surface. The bend angle is an anomalously 10.7$^\circ$ less than the AM1 calculated value ($\theta_{\text{calcd}} = 100.4^\circ$). In the $[n](2,7)$pyrenophanes this difference is usually only 4 – 7$^\circ$. The $\beta$ angles were measured to be 16.1$^\circ$ (for C(26)) and 16.3$^\circ$ (for C(17)), which is more than the usually observed values for $\beta$ in the solid state ($< 9.0^\circ$) or those in the AM1 calculated structure (11.0$^\circ$).
The isolated benzene ring in 3 has very small α values (α < 1°) and, thus, is essentially planar. Considerable β angles were observed (β_{C(25)} = 4.0° and β_{C(17)} = 4.6°), indicating a distortion of the para-xylylene unit. The direction of this distortion from planarity, although subtle, is in the direction of the concave face of the pyrene unit. So far, this is the first and only example of such a “spoons-like” arrangement of the areas in one molecule. Usually the aromatic units are bowed away from one another (e.g. in compounds 7 and 10 in Figure 5.03). The dimethylene bridges are close to being fully eclipsed, with a torsion angle about the central C-C axis of 1(1)° and 7(7)°, which causes the pyrene and benzene decks to be almost perfectly aligned.
The most striking feature of the bridges in the molecular structure of 3 is the unusually large bond angles at the carbon atoms benzylic to the benzene ring (123.7(5)° and 124.8(6)°). Another unusual feature is the unusually short bond lengths of the central bonds of the dimethylene bridges (1.468(9) Å and 1.439(8) Å). The thermal ellipsoids at C(25) and (especially) C(18) are large and the exact values for these bond angles and bond lengths should not be viewed with a high degree of confidence. There is little doubt however, that the bond angles are indeed quite large and the bond lengths unusually short. The AM1 level calculations do not predict these large bond angles or short bond lengths. Normal tetrahedral angles at C(25) and C(18) would push the benzene deck well into the concave face of the pyrene deck and cause the benzene ring to adopt a nonplanar conformation. Repulsions between the π clouds of the opposing arene decks presumably disfavor the adoption of this arrangement. The short bond lengths in the dimethylene tethers can be explained by the rigid nature of the para-phenylene unit in the tether. If the lengths of these bonds would be in the range of normal C-C bonds, the distance between C(18) and C(25) would decrease. The result of this would be a curved or compressed para-phenylene unit.

In the X-ray crystal structure of 5 two slightly different molecules (5a and 5b; Figure 5.05) are present in the unit cell. The bend angles are $\theta_{X\text{-ray}} = 97.1^\circ$ for 5a and $\theta_{X\text{-ray}} = 96.9^\circ$ for 5b. only 7.4° (average) less than the AM1 calculated value ($\theta_{\text{calc}} = 104.4^\circ$). This is in line with previously observed values.\cite{3,4,28,32,33} The β angles (5a $\beta_{C17} = 17.7^\circ$
and $\beta_{C1201} = 16.5^\circ$; 5b $\beta_{C1431} = 17.3^\circ$ and $\beta_{C152} = 16.8^\circ$) are even larger than in 3 and the $[n](2,7)$pyrenophanes.

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Figure 5.05: ORTEP representation of 5 in the crystal.\textsuperscript{15}

The isolated aromatic ring in 5 is similar to that in 3, essentially planar ($\alpha < 2.5^\circ$, $\beta_{5aC118} = 3.9^\circ$, $\beta_{5aC125} = 3.3^\circ$, $\beta_{5bC44} = 7.0^\circ$ and $\beta_{5bC151} = 3.6^\circ$) and bowed towards the concave face of the pyrenophane deck. The bridges in 5 are in a staggered conformation, with a torsional angle around the dimethylene bond of $51^\circ$, and the aromatic decks are not perfectly aligned, but rather slightly offset from one another.
5.2.3.2 NMR spectroscopy

In the 500 MHz $^1$H NMR spectrum of 3, the signal for the protons on the isolated aromatic ring ($\delta$ 5.54) were observed ca. 1.5 ppm upfield from the corresponding signal of para-xylene ($\delta$ 7.07). This indicated that the isolated aromatic ring in 3 is located in the shielding cone of the pyrene unit, which was also apparent from the X-ray crystal structure. Due to the difference in size between the pyrene deck and the isolated benzene rings, only the shielding effect of the pyrene rings on the protons of the isolated aromatic rings could be observed: the protons on the pyrene unit appeared to experience little magnetic anisotropy from the benzene ring. The signals of protons on the pyrene system of 3 appeared at $\delta$ 7.67 and 7.40, which was comparable to those of [8](2,7)pyrenophane ($\delta$ 7.84 and 7.59; $\theta$$_{X-ray}$ = 80.8°) and 1,8-dioxa[8](2,7)pyrenophane ($\delta$ 7.84 and 7.44; $\theta$$_{X-ray}$ = 87.8°). This observation fitted well with the previously observed trend that increased curvature of the pyrene unit caused an upfield shift of the signals of the protons on that pyrene unit (Table 5.02).

Pyrenophane 5 showed more signals in its 500 MHz $^1$H NMR spectrum than initially might be expected. The pyrene deck showed four signals instead of the usual two, and four signals could be observed for the protons on the dimethylene bridges. This chemical inequivalence could be attributed to “freezing” of the conformational flip of the isolated benzene ring on the NMR time scale to give two degenerate conformers (Scheme 5.11).
The internal proton in 5 was located in the shielding cone of the pyrene unit and its signal appeared at δ 4.18. This is almost identical with that of anti[2.2]metacyclophane 8. A smaller shielding effect was observed for the remaining protons on the isolated aromatic ring, which were observed as a triplet at δ 6.56 and a doublet at δ 6.31. A shielding effect was also observed for one of the protons on the dimethylene bridges (ddd at δ 1.21; vide infra). The appearance of four signals for the protons on the pyrene system in 5 was the result of the restricted flip of the isolated benzene ring. This caused the isolated benzene ring to shield the protons one side of the pyrene unit (H₆ and H₉) more than the others (Figure 5.07). Using several NMR experiments, the signals in the ¹H NMR spectrum of 5 could be assigned as indicated in Figure 5.06 and 5.07.
Figure 5.06: The 500 MHz $^1$H NMR spectrum of 5.

Figure 5.07: Assignment of the signals in the $^1$H NMR spectrum of 5.
Based on the chemical shift of the internal proton on the isolated benzene ring (\(H^3\)) and the multiplicity of the signals of the other protons on that ring (\(H^b\) and \(H^f\)), these signals could be assigned directly. One of the bridge protons was observed as a ddd around \(\delta 1.21\), which indicated it was shielded by one of the aromatic units. When a three-dimensional structure of 5 was examined, only \(H^d\) was situated in the shielding cone of the pyrene unit, and the ddd that appeared at unusually high field (\(\delta 1.21\)) could tentatively be assigned to this proton. This assignment was later confirmed by a 2.6\% enhancement of the signal for \(H^3\) when the signal for \(H^d\) was irradiated in a NOESY experiment (1.7\% for the reverse experiment). Using HMQC correlation data, it could then be deduced that \(H^d\) (ddd at \(\delta 2.31\)) was bonded to the same carbon atom as \(H^f\), since both \(H^d\) and \(H^f\) showed a cross peak with the signal at \(\delta 38.0\) in the \(^{13}\)C NMR spectrum.

When the signal for \(H^b\) was irradiated in an NOESY experiment an enhancement was observed for three signals (\(\delta 7.15\), \(\delta 2.69\) and \(\delta 2.31\)). The signal for \(H^e\) (\(\delta 2.31\)) showed an enhancement of 1.5\%, confirming the assignment for that proton. The ddd at \(\delta 2.69\) was enhanced by 2.0\%, indicating that this signal might be assigned to \(H^f\). The enhancement of 1.2\% of the singlet at \(\delta 7.15\) made it possible to assign this signal one of the protons on the "front" side of the pyrene unit (most likely \(H^h\); Figure 5.07). Based on the small coupling of the signal at \(\delta 7.15\) with the signal at \(\delta 7.47\), these signals must belong to \(H^h\) and \(H^l\). In conjunction with the previous NOESY data, \(H^b\) could thus be assigned to the signal at \(\delta 7.15\). That the chemical shift value for \(H^b\) is at higher field than
that for H' can be explained by the situation of H\(^b\) in the shielding cone of the \textit{meta}-phenylene group.

The last NMR experiment necessary for complete assignment of the signals of 5 was NOESY irradiation of the signal for H' at \(\delta\) 7.47. Irradiation experiment of this signal showed an enhancement of 1.9\% of the ddd around \(\delta\) 3.09, which could then be assigned to H\(^f\). This also confirms the assignment of H'. Irradiation of the signal for H' also showed an enhancement of the singlet at \(\delta\) 7.68 by 1.2\%, which allowed for assignment of this signal to H\(^b\) and, by elimination, the signal at \(\delta\) 7.32 could be assigned to H'. This assignment was in line with the shielding of H' by the shielding cone of the isolated benzene ring compared to H\(^b\).

The slow flipping motion of the isolated aromatic ring in 5 led us to further study this effect by a DNMR study. In the flipping process the environments of H\(^d\) and H\(^f\), H' and H\(^f\), H' and H\(^b\), and H' and H\(^b\) are exchanged. At temperatures above the coalescence temperature for this process, each set of protons (i.e. H\(^d\) and H\(^f\), etc.) is expected to show one signal at approximately the average chemical shift of the contributing values. The signals for H\(^d\), H\(^b\) and H\(^f\) are not expected to undergo coalescence, as their environments in the two conformers are the same.

For the DNMR experiment, a solution of [2]meta-cyclo[2](2,7)pyrenophane in DMSO-\(d_6\) was warmed up slowly from room temperature to 120 °C, while a 500 MHz \(^1\)H NMR
spectrum was collected every 10 °C (Figure 5.08). At temperatures above approximately 70 °C, considerable broadening of the signals in the \textsuperscript{1}H NMR spectra was observed, but no coalescence of signals occurred when the temperature limit of the spectrometer had been reached (120 °C). The broadening of the signals indicated, however, that conformational interconversion of the two conformers of 5 was occurring at increasing rates. As expected, the signals for the protons on the meta-phenylene ring did not show any significant broadening.

From the shapes of the signals it was estimated that the coalescence temperature for this process probably lies in the range 130-160 °C, but unfortunately the equipment available does not allow for acquisition at these temperatures. Using equations 1 and 2\textsuperscript{37,38} and the \textsuperscript{1}H NMR data of \textsuperscript{1}H\textsuperscript{d} and \textsuperscript{1}H\textsuperscript{e} (\(\Delta\text{H}_{\text{H},\text{H}} = 560\) Hz, \(J = 13.5\) Hz), an activation barrier for the interconversion process of approximately 19 kcal/mol (80 kJ/mol) was calculated.
\[ \Delta G^\circ = RT(22.96 + \ln T - \ln \Delta v) \]

\[ \Delta v = \left( \Delta H_{\text{exp}} - 6 \nu^2 \right)^{1/2} \]

Equation 1

Equation 2

From the same equations it can be determined that if the same experiment were to be performed on a 60 MHz instrument, these estimated values would correspond to a coalescence temperature of 100-130°C, which is within the limits of such an instrument. Unfortunately this capability was not available to our group.

5.3 Conclusions and future work

In Section 5.2 the successful syntheses of [2]para-cyclo[2](2,7)pyrenophane 3 and [2]meta-cyclo[2](2,7)pyrenophane 5 were described. The overall yield for the synthesis of 3 was quite low at only 3%. The low yield is due primarily to two low-yielding steps in the synthesis. For the synthesis of 5 the overall yield was a satisfying 17%, which can probably be increased by optimizing the reaction conditions for some steps. The successful syntheses of 3 and 5 demonstrate the use of a novel approach to the formation of ethano-bridged cyclophanes, and further establishes the VPD protocol as a powerful method for the formation of nonplanar pyrene containing systems.

The molecular structures of 3 and 5 were determined by X-ray crystallography. Both cyclophanes exhibit an unprecedented “spoons-like” arrangement with the isolated
aromatic ring in each cyclophane bowed toward the pyrene deck. The bend angles of the pyrene units in 3 and 5 are 89.7° and 97.0°, respectively, and unusually large β angles were observed for both compounds.

The 500 MHz ¹H NMR spectrum of pyrenophane 3 displayed no unusual features. Due to the shielding effect of the pyrene ring, the signal of the protons on the para-xylyl ring appear at a chemical shift of δ 5.54. With cyclophane 5 this shielding effect causes the "internal" proton of the meta-xylyl ring to appear at δ 4.18. The most striking feature of the ¹H NMR spectrum of 5 is probably the observation of restricted interconversion between two degenerate conformers. The energy barrier for this interconversion was estimated to be approximately 19 kcal mol⁻¹ (80 kJ mol⁻¹) by extrapolation of the DNMR results.

The unusual bond angles and bond lengths in the bridges of 3 indicated that these bridges might be less strained if the carbon atoms in these bridges are sp²-hybridized (pyrenophanediene 43: Figure 5.09). The AM1-calculated bend angle of this pyrenophane is 102.6°, only 2.2° more than the calculated value for 3. The shorter-than-usual bond lengths and bond angles in the X-ray crystal structure of 3 suggest that the formation of pyrenophanediene 43 should be feasible.
Another project would be the synthesis of diketones 44 and 46 (Scheme 5.12). The keto/enol ratios in 44 and 46 should display the relative stability of the double C-C bond (enol) versus the single C-C bond (ketone). It is anticipated that, even though the aromatic units are orthogonal to the keto and enol π-systems, the enol form might be preferred. Based on the large bond angle that was observed in the X-ray crystal structure of 3 it can be expected that the 44 will enolize more readily than 46.

Scheme 5.12: Keto-enol equilibria of 44 and 46.
Other synthetic targets that can be derived from [2]paracyclo[2][2.7]pyrenophane 3 are given in Figure 5.10. Cyclophane 48 has Dewar benzene units in the positions where pyrenophane 3 had dimethylene bridges and is a direct precursor of aromatic belt 4 (Figure 5.01). Synthesis of 48 is expected to be quite challenging, however.

Pyrenophane 49 is an example of a cyclophane with planar chirality. If in 49 the substituent R is a chiral substituent, with the same absolute configuration in (S)-49 and (R)-49, two diastereomers are created. Since these compounds should be distinguishable by $^1$H NMR spectroscopy, these compounds would provide an elegant opportunity to study the rotation of the para-phenylene unit in the cyclophane. (This "skipping rope"-type rotation would interconvert the two diastereomers). A notable feature of pyrenophane 3 is that substitution at any of the carbon atoms renders a chiral cyclophane. Substitution on the bridges leaves a stereogenic center and substitution on any of the aromatic carbons gives a cyclophane of planar chirality.

![Figure 5.10: Future synthetic targets based on the [2]paracyclo[2][2.7]pyrenophane system.](image-url)
Based on the successful synthesis of [2]metacyclo[2](2,7)pyrenophane 5 some similar future synthetic targets can be proposed (Figure 5.11). The pyrenophanediene 50 can be proposed, similar to 43 and has an AM1 calculated bend angle of 115.1°, which is 8.5° more than the value calculated for 5. This suggests that introduction of the double bonds in the metacyclophane 50 structure has a much greater effect than in the paraacyclophane structure 43. This is supported by the X-ray crystal structures of 3 and 5, since introduction of double bonds in the dimethylene tethers would drastically change their conformation in 5, but not as much in 3, which already shows short bond lengths and large bond and torsion angles. Similar to the substitution of pyrenophane 3, substitution on cyclophane 5 can render a cyclophane of planar chirality like 5-51.

Using similar methodology as for the synthesis of 3 and 5, it should be possible to synthesize pyrenophanes 52 and 54 (Scheme 5.13). If sufficient amounts of these materials can be made available, it might be possible to build up larger structures like 53 and 55. For 53 other isomers can be drawn, but they have been omitted for clarity. Compound 55 should still undergo a “skipping-rope” motion of the pyrene units around
the central aromatic ring, which would make it an interesting topic for dynamic studies. Both compounds can be seen as fullerene isosteres, although they are calculated (AM1) to contain pyrene units at greater intramolecular distance (8.2 - 11.7 Å) than D[56]-C[70] (6.82 Å).\textsuperscript{32}

![Diagram](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>Distance (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53a X = S</td>
<td>11.7 Å</td>
</tr>
<tr>
<td>53b X = bond</td>
<td>11.4 Å</td>
</tr>
<tr>
<td>55</td>
<td>8.2 Å</td>
</tr>
</tbody>
</table>

Scheme 5.13: Future synthetic targets 52 - 55

5.4 Experimental

**General.** All chemicals were reagent grade and were used as received. Chromatographic separations were performed on Merck silica gel 60 (particle size 40-63 μm. 230-400 mesh). Melting points were determined on a Fisher-Johns apparatus and are uncorrected. Elemental analyses were performed at the MicroAnalytical Service Laboratory, Department of Chemistry, University of Alberta. Mass spectroscopic (MS) data were
obtained on a V. G. Micromass 7070 HS instrument. $^1$H NMR (500 MHz) and $^{13}$C NMR (126 MHz) were obtained on a Bruker spectrometer. $^1$H shifts are relative to internal tetramethylsilane; $^{13}$C shifts are relative to the solvent resonance (CDCl$_3$: $\delta = 77.0$). All experiments with moisture- or air-sensitive compounds were performed in anhydrous solvents under nitrogen unless otherwise stated. Solvents were dried and distilled according to standard procedures.

1.4-Bis(trimethylsilylethynyl)benzene (19).$^{40}$

To a solution of 1,4-diiodobenzene 17 (10.25 g, 31.07 mmol) in degassed benzene (225 ml) under a nitrogen atmosphere, were added (Ph$_3$P)$_2$PdCl$_2$ (1.05 g, 1.50 mmol) and Cul (1.00 g, 5.25 mmol), followed after 5 min by trimethylsilylacetylene 18 (7.65 g, 77.9 mmol) and DBU (14.19 g, 93.21 mmol). The reaction mixture was stirred at room temperature for 2 h, washed with saturated aqueous NH$_4$Cl solution (100 ml), water (2 x 100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was purified by column chromatography (hexanes, silica) to give 19 (7.99 g, 29.5 mmol, 95%$^{a}$) as colorless crystals: mp 118 – 119 °C (hexanes) (lit.$^{40}$ 122 °C); IR (nujol, cm$^{-1}$) 2155 (s), 1492 (m), 1246 (s); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.40 (s, 4H), 0.25 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 131.7, 123.1, 104.6, 96.3, -0.1; EI-MS (70 eV) $m/z$ (%): 270 (27, M$^+$), 255 (100).
1,4-Diethynylbenzene (20). [11]

K₂CO₃ (3.54 g, 25.61 mmol) and 1,4-bis(trimethylsilyl)ethynylbenzene 19 (2.77 g, 13.3 mmol) were added to methanol (50 mL) and the reaction mixture was stirred for 1 h. The mixture was poured into ice water (100 mL) and filtered under suction. The residue was sublimed at atmospheric pressure (ca. 95 °C oil bath; CAUTION: in one instance this procedure led to explosive decomposition of the material !) to give 20 (0.99 g, 77%) as colorless plates: mp: 94 - 95 °C (sublimes slowly above 76 °C) (lit. 10 95 - 96 °C). [11] ^1H NMR (300 MHz, CDCl₃) δ 7.45 (s, 4H), 3.18 (s, 2H); [13] ^13C NMR (75 MHz, CDCl₃) δ 132.0, 122.5, 82.9, 79.2.

1,4-Bis(3,5-bis(methoxycarbonyl)phenylethynyl)benzene (22).

To a solution of triflate 21 (3.22 g, 9.41 mmol) in degassed benzene (80 mL) under a nitrogen atmosphere, were added (Ph₃P)₂PdCl₂ (0.08 g, 0.1 mmol) and Cul (0.08 g, 0.4 mmol), followed after 5 min by 1,4-diethynylbenzene 20 (0.54 g, 4.3 mmol) and DBU (1.95 g, 12.8 mmol). The reaction mixture was refluxed for 18 h, concentrated under reduced pressure, and the residue was dissolved in CHCl₃ (250 mL), and saturated aqueous NH₄Cl solution (100 mL). The aqueous layer was extracted with CHCl₃ (100 mL) and the combined organic layers were washed with water (2 x 100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO₄) and concentrated under reduced pressure. The residue was purified by column chromatography (chloroform.
silica) to give 22 (1.25 g, 57%) as an off-white solid: mp: decomposes $> 290^\circ$C
(chloroform): IR (nujol, cm$^{-1}$): 1732 (s), 1247 (m); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.66 (s. 2H), 8.39 (s. 4H), 7.56 (s. 4H), 3.99 (s. 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 165.6,
136.5, 131.7, 131.1, 130.1, 124.1, 122.9, 90.7, 89.4, 52.5; EI-MS (70 eV) $m$ z ($^\%$): 510
(100, M$^+$), 479 (10), 224 (10); HRMS Calc'd for C$_{31}$H$_{25}$O$_4$: 510.1313, found 510.1334

Alternative route (preferred):
To a solution of 1,4-diiodobenzene (6.03 g, 18.28 mmol) in 400 mL degassed benzene
under a nitrogen atmosphere, was added (Ph$_3$P)$_2$PdCl$_2$ (0.64 g, 0.91 mmol) and Cul (0.35
g, 1.8 mmol), followed after 5 min by dimethyl 5-ethynylisophtalate 24 (9.98 g, 45.7
mmol) and DBU (8.35 g, 54.8 mmol). The reaction mixture was stirred for 2.5 h.
concentrated under reduced pressure and the residue was dissolved in CHCl$_3$ (1000 mL)
and saturated aqueous NH$_4$Cl solution (500 mL). The aqueous layer was extracted with
CHCl$_3$ (500 mL) and the combined organic layers were washed with water (2 x 500 mL)
and saturated aqueous NaCl solution (500 mL), dried (MgSO$_4$) and concentrated under
reduced pressure. The residue was purified by column chromatography (chloroform,
silica) to give 22 (8.51 g, 16.7 mmol, 91%) as an off-white solid.
Dimethyl 5-(trimethylsilylethynyl)benzene-1,3-dicarboxylate (23).

To a solution of (Ph₃P)₂PdCl₂ (2.57 g, 3.66 mmol) and CuI (1.39 g, 7.30 mmol) in degassed benzene (400 mL), was added trflate 21 (25.07 g, 73.25 mmol), followed, after 10 min, by a solution of trimethylsilylacetylene 18 (10.07 g, 102.5 mmol) in degassed benzene (200 mL) and DBU (16.70 g, 109.7 mmol). The mixture was stirred under a nitrogen atmosphere for 2 h, concentrated under reduced pressure and dissolved in chloroform (250 mL) and saturated NH₄Cl solution (200 mL). The aqueous layer was extracted with chloroform (150 mL). The organic extracts were combined and washed successively with water (200 mL) and saturated aqueous NaCl solution (200 mL), dried (MgSO₄), concentrated in vacuo, and purified by column chromatography (SiO₂, 10% ethyl acetate hexanes) to yield 23 (14.92 g, 51.38 mmol, 70%) as a colorless solid; mp: 100 - 101.5 °C; IR (nujol, cm⁻¹): 2159 (w), 1734 (s), 1593 (w), 1332 (m), 1242 (s); ¹H NMR (500 MHz, CDCl₃) δ 8.61 (s, 1H), 8.30 (s, 2H), 3.96 (s, 6H), 0.27 (s, 9H); ¹³C NMR (126 MHz, CDCl₃) δ 165.5, 136.8, 130.8, 130.3, 124.2, 102.7, 96.7, 52.5, -0.22; EI-MS (70 eV) m/z (%): 290 (10, M⁺), 275 (100), 259 (9), 201 (10).
Dimethyl 5-ethynylbenzene-1,3-dicarboxylate (24).

Dimethyl 5-(trimethylsilylthynyl)benzene-1,3-dicarboxylate 23 (14.92 g, 51.38 mmol) and K$_2$CO$_3$ (9.23, 66.8 mmol) were weighed into a 1 L round-bottom flask and 650 mL methanol was added. The mixture was stirred under a nitrogen atmosphere for 1.5 h and poured into 1 L water. Dimethyl 5-ethynylisophthalate 24 (10.19 g, 46.70 mmol, 91%) was isolated by suction filtration, washed with water (2 x 100 mL) and dried in vacuo as a colorless powder; mp: 127 - 128 °C; $^1$H NMR (500 MHz, CDCl$_3$) δ 8.53 (s, 2H), 8.07 (s, 4H), 7.11 (s, 4H), 3.95 (s, 12H), 3.04-2.97 (m, 4H), 2.96-2.89 (s, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ 166.4, 142.9, 138.9, 133.9, 130.6, 128.6 (2C), 52.3, 37.6, 37.2; EI-MS (70 eV) m/z (99): 218 (50, M$^+$), 187 (100), 159 (28), 144 (22).

1,4-Bis(2-(3,5-bis(methoxycarbonyl)phenyl)ethyl)benzene (25).

To a solution of diyne 22 (0.64 g, 1.3 mmol) in degassed benzene (300 mL) was added Pd(OH)$_2$ (Pearlman's catalyst, 0.40 g), and the suspension was stirred vigorously under an atmosphere of hydrogen for 2 h. The flask was subjected to reduced pressure and let down to nitrogen several times before being filtered through a plug of Celite. Removal of solvent under reduced pressure afforded tetrabase 25 (0.62 g, 95%) as a colorless solid; mp: 146 - 147.5 °C (chloroform + hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 8.56 (s, 2H), 8.10 (s, 4H), 7.14 (s, 4H), 3.98 (s, 8H), 3.04 (m, 4H), 2.96 (m, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$) δ
166.4, 142.7, 138.8, 133.9, 130.6, 128.5 (2C), 52.3, 37.6, 37.2; El-MS (70 eV) \( m/z \) (\%): 518 (6, M\(^+\)), 486 (55), 426 (5), 311 (33), 281 (100), 207 (79), 104 (45).

1,4-Bis(2-(3,5-bis(bromomethyl)phenyl)ethyl)benzene (26).

A solution of tetraester 25 (2.16 g, 4.17 mmol) in THF (100 mL) was added dropwise to a well-stirred suspension of LiAlH\(_4\) (1.90 g, 50.1 mmol) in THF at 0 °C under nitrogen. The mixture was stirred at reflux for 16 h, cooled in an ice-bath and quenched with ethyl acetate (10 mL). The mixture was concentrated under reduced pressure, suspended in glacial acetic acid (100 mL), 30\% HBr HOAc (10 mL, 50 mmol) was added and the mixture was refluxed for 30 min. After cooling to room temperature, the mixture was poured into water (200 mL) and extracted with CH\(_2\)Cl\(_2\) (2 x 200 mL). The combined organic layers were washed with water (2 x 150 mL), saturated aqueous NaHCO\(_3\) solution (2 x 150 mL), water (100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO\(_4\)) and concentrated under reduced pressure. The residue was purified by column chromatography (50\% CHCl\(_3\); hexanes, silica) to afford tetrabromide 26 (2.33 g, 85\%) as a white solid; mp 142.5-143.5 °C (hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \( \delta \) 7.26 (overlapped with solvent, s, 2H), 7.13 (s, 4H), 7.09 (s, 4H), 4.45 (s, 8H), 2.89 (s, 8H); \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \( \delta \) 143.1, 138.9, 138.3, 129.3, 128.5, 127.2; El-MS (70 eV) \( m/z \) (\%): 658 (5, M\(^+\) (\(^{81}\)Br)\(_2\)(\(^{79}\)Br)\(_2\)), 497 (17), 417 (27), 381 (100); HRMS Calc'd for C\(_{39}\)H\(_{22}\)(\(^{79}\)Br)\(_4\): 653.8765, found 653.8772.
Belta-2,11-dithia[3.3](1,3)(1,3)[2](5)(1)[2](4)(5)benzeno<3>phane (27).

To a well-stirred refluxing solution of tetrabromide 26 (2.48 g, 3.77 mmol) in degassed 10% ethanol (abs) CH₂Cl₂ (825 mL) was added Na₂S·Al₂O₃ (7.83 g, 19.4 mmol) in three roughly equal portions over 1 h. After stirring for 1.5 h at reflux temperature, the reaction mixture was cooled to room temperature, suction filtered through a plug of Celite and concentrated under reduced pressure. Column chromatography (25% CHCl₃/hexanes) afforded dithiacyclophane 27 (0.43 g, 28%) as a colorless, foamy solid: mp > 280 °C; ¹H NMR (500 MHz, CDCl₃) δ 6.96 (br s, 2H), 6.87 (s, 4H), 6.52 (s, 4H), 3.71 (narrow AB system, 8H), 2.99 (t, J = 7.0 Hz, 4H), 2.86 (t, J = 6.9 Hz, 4H); ¹³C NMR (126 MHz, CDCl₃) δ 140.4, 137.2, 137.0, 129.1, 128.7, 128.0, 40.5, 34.9, 32.8; El-MS (70 eV) m/z (%): 402 (100, M⁺), 369 (27), 338 (36); HRMS Calc'd for C₂₅H₂₀S₂: 402.1475, found 402.1493.

Belta[2.2](1,3)(1,3)[2](5)(1)[2](4)(5)benzeno<3>phane-1,9-diene (29) and [2]paracyclo[2](2,7)pyrenophane (3).

To a stirred solution of dithiacyclophane 27 (0.60 g, 1.5 mmol) in degassed CH₂Cl₂ (120 mL) under an atmosphere of nitrogen, was added (MeO)₂CHBF₄ (1.21 g, 7.47 mmol) and after 3 h the mixture was concentrated under reduced pressure. Ethyl acetate (50 mL) was added to the residue, the mixture was stirred for 5 min and suction filtered to give a beige solid that was washed with ethyl acetate (2 x 3 mL) and dried in vacuo to yield a
bis(sulfonium tetrafluoroborate) salt. This was slurried in degassed THF (120 mL) under nitrogen and t-BuOK (0.50 g, 4.5 mmol) was added. The reaction mixture was stirred overnight. Saturated aqueous NH$_4$Cl solution (50 mL) was added and the mixture was concentrated under reduced pressure. The residue was taken up in degassed CH$_2$Cl$_2$ (100 mL) and washed with saturated aqueous NH$_4$Cl solution (50 mL), water (50 mL) and brine (50 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was passed through a plug of silica (CHCl$_3$) and concentration of the eluents afforded a mixture of bis(methylthio)cyclophane isomers (0.45 g, 70% from 27) as a foamy, light yellow solid. The solid was dissolved in degassed CH$_2$Cl$_2$ (100 mL) under an atmosphere of nitrogen and slowly (MeO)$_2$CHBF$_4$ (0.85 g, 5.3 mmol) was added, and after 3 h the mixture was concentrated under reduced pressure. Ethyl acetate (15 mL) and methanol (5 mL) were added, the mixture was stirred for 5 min and concentrated under reduced pressure to give a brown oil. This oil was slurried in degassed 1:1 t-BuOH/THF (100 mL) under nitrogen and to this mixture t-BuOK (0.35 g, 3.4 mmol) was added. After stirring for 16 h, saturated aqueous NH$_4$Cl solution (20 mL) was added and the mixture was concentrated under reduced pressure. The residue was taken up in degassed CH$_2$Cl$_2$ (100 mL) and saturated aqueous NH$_4$Cl solution (75 mL) and the aqueous layer was extracted with degassed CH$_2$Cl$_2$ (50 mL). The combined organic layers were washed with water (100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO$_4$) and concentrated under reduced pressure. The residue was concentrated under reduced pressure to afford a mixture of cyclophanediene 29 and [2]para[cyclo[2]2.7]pyrenophane 3 (0.08 g, 16% from 27) as a colorless solid. The mixture was dissolved in degassed
benzene (25 mL) under nitrogen. DDQ was added (0.04 g, 0.2 mmol) and after 10 min the mixture was concentrated under reduced pressure and purified by preparative TLC (silica, 60% CHCl₃/hexanes) to yield [2]paracyclo[2](2.7)pyrenophane 3 (0.07 g, 14% from 27) as a colorless solid, that was crystallized from heptane; mp 216 – 219 °C; ¹H NMR (500 MHz, CDCl₃) δ 7.67 (s, 4H), 7.40 (s, 4H), 5.54 (s, 4H), 2.99 (t, J = 7.3 Hz, 4H), 2.32 (t, J = 7.2 Hz, 4H); ¹³C NMR (126 MHz, CDCl₃) 135.7, 134.2, 131.3, 129.3, 128.6, 128.0, 126.1, 36.5, 33.8; EI-MS (70 eV) m/z (%) 332 (11, M⁺), 228 (100).

1,3-Bis(3,5-bis(methoxycarbonyl)phenylethynyl)benzene (37)

To a solution of (Ph₃P)₂PdCl₂ (0.39 g, 0.56 mmol) and CuI (0.39 g, 2.0 mmol) in degassed benzene (250 mL) under nitrogen, was added 1,3-diodobenzene 36 (3.66 g, 11.1 mmol), followed after 5 min by a solution of 24 (5.33 g, 24.4 mmol) in degassed benzene (150 mL) and DBU (4.23 g, 27.8 mmol). The reaction mixture was stirred at room temperature under an atmosphere of nitrogen for 3 h, concentrated under reduced pressure and dissolved in CHCl₃ (200 mL) and saturated aqueous NH₄Cl solution (100 mL). The aqueous layer was extracted with CHCl₃ (150 mL) and the combined organic layers were washed with saturated aqueous NH₄Cl (100 mL), water (100 mL), brine (100 mL), dried (MgSO₄) and concentrated in vacuo. The residue was subjected to column chromatography (SiO₂, 2% EtOAc : CHCl₃) to yield 37 (4.31 g, 8.44 mmol, 76%o) as a beige solid that was crystallized from EtOH:CHCl₃: mp: 176 – 177.5 °C (ethanol/chloroform); IR (nujol, cm⁻¹): 2216 (w), 1734 (s), 1290 (w), 1249 (m), 1008 (w), 751 (w);
$^1$H NMR (500.1 MHz; CDCl$_3$): $\delta$ 8.65 (s, 2H), 8.38 (s, 4H), 7.76 (s, 1H), 7.56 (d, $J$ = 7.9 Hz, 2H), 7.04 (t, $J$ = 7.7 Hz, 1H), 3.98 (s, 12H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 165.6, 136.5, 134.9, 131.9, 131.0, 130.3, 128.7, 124.1, 123.0, 90.2, 88.1, 52.6; EI-MS (70 eV) m/z (%): 510 (100, M$^-$), 479 (25), 224 (25); HRMS Calc'd for C$_{30}$H$_{22}$O$_8$: 510.1313, found 510.1295.

1,3-Bis(2-(3,5-bis(methoxycarbonyl)phenyl)ethyl)benzene (38)

To a solution of 37 (4.31 g, 8.44 mmol) in degassed benzene (700 ml), was added 20% Pd C (0.35 g) and acetic acid (0.1 ml), and the suspension was stirred under a H$_2$-atmosphere for 16 h. The reaction mixture was degassed by bubbling nitrogen through the mixture for 20 min, filtered through a plug of MgSO$_4$ and concentrated in vacuo to yield 38 (4.37 g, 8.44 mmol, 100%) as a colorless oil, that solidified upon standing; mp: 150 - 151.5 °C (benzene); $^1$H NMR (500.1 MHz; CDCl$_3$): $\delta$ 8.53 (s, 2H), 8.05 (s, 4H), 7.22 (t, $J$ = 7.4 Hz, 1H), 7.04 (d, $J$ = 7.6 Hz, 2H), 6.98 (s, 1H), 3.94 (s, 9H), 2.99 (m, 4H), 2.92 (m, 4H); $^{13}$C NMR (126 MHz; CDCl$_3$): $\delta$ 166.4, 142.6, 141.1, 133.9, 130.6, 128.7, 128.6, 128.5, 126.3, 52.3, 37.6; EI-MS (70 eV) m/z (%): 518 (6, M$^-$), 486 (83), 311 (22), 281 (100), 207 (50), 177 (10), 104 (17).
1,3-Bis(2-(3,5-bis(bromomethyl)phenyl)ethyl)benzene (39)

A solution of 38 (4.33 g, 8.35 mmol) in dry THF (150 mL) was added over 45 min to a well-stirred, 0 °C suspension of LiAlH₄ (3.80 g, 10.0 mmol) in dry THF (200 mL) under a nitrogen atmosphere. The mixture was stirred at room temperature for 22 h, cooled in an ice-bath, quenched with ethyl acetate (20 mL) and concentrated in vacuo. HBr in acetic acid (30% 125 mL) was carefully added to the residue, and the mixture was heated to reflux, cooled and poured into ice water (300 mL). CH₂Cl₂ (100 mL) was added, and the aqueous layer was extracted with CH₂Cl₂ (2 x 100 mL). The combined organic extracts were washed with saturated aqueous NaHCO₃ solution (3 x 100 mL), water (100 mL) and saturated aqueous NaCl solution (100 mL), dried (MgSO₄) and concentrated under vacuum. The residue was purified by column chromatography to yield 39 (2.95 g, 4.48 mmol, 54%) as a white solid; mp: 109 - 111.5 °C (CHCl₃:hexanes); ¹H NMR (500.1 MHz; CDCl₃): δ 7.27 (s, 2H), 7.22 (t, J = 7.5 Hz, 1H), 7.14 (s, 4H), 7.02 (d, J = 7.5 Hz, 2H), 6.94 (s, 1H), 4.45 (s, 8H), 2.89 (s, 8H); ¹³C NMR (126 MHz; CDCl₃): δ 143.1, 141.3, 138.4, 129.3, 128.7, 128.5, 127.2, 126.2, 37.6, 37.5, 33.0; EI-MS (70 eV) m/z (%): 658 (5, M⁺ (⁸¹Br)₂(⁷⁹Br)₂), 577 (3), 497 (59), 417 (87), 381 (100), 335 (29), 219 (43).

Belta-2,11-dithia[3.3](1,3)(1,3)[2](5)(1)[2](3)(5)benzenophane (40)

To a vigorously stirred solution of 39 (2.35 g, 3.57 mmol) in ethanol (abs: 200 mL) and CH₂Cl₂ (1800 mL) was added Na₂S / Al₂O₃ (12.01 g, 4.0 mmol; 3.0 mmol/g) in three
approximately equal portions over 30 min. The reaction mixture was stirred for 1.5 h.
filtered over a plug of celite and concentrated in vacuo. The residue was subjected to
column chromatography (50% SiO₂, CHCl₃ / hexanes) to yield 40 (0.98 g, 2.4 mmol.
68%) as a colorless crystalline solid: mp: > 218 °C (dec.) (CHCl₃/hexanes): ¹H NMR
(500.1 MHz: CDCl₃): δ 7.25 (t, J = 7.6 Hz, 1H), 7.10 (s, 2H), 7.06 (d, J = 7.8 Hz 2H).
6.56 (s, 4H), 6.31 (s, 1H), 3.74 (m, 8H), 2.96 (m, 4H), 2.80 (m, 4H); ¹³C NMR (125
MHz: CDCl₃): δ 140.5, 140.3, 136.9, 129.3, 129.0, 128.0, 127.0, 125.9, 39.3, 35.1, 34.2;
EI-MS (70 eV) m/z (%): 402 (100, M⁺), 369 (23), 338 (25), 217 (14), 119 (29); HRMS
Calc'd for C₇₇H₆₅S₂: 402.1475, found 402.1479.

Betta[2.2][1.3](1.3)[2](5)(1)[2](3)(5)benzeno<3>phane-1,9-diene (42)

To a well-stirred solution of 40 (0.98 g, 2.4 mmol) in CH₂Cl₂ (200 mL) was added Borch
teatant (1.18 g, 7.3 mmol). After 10 h the reaction mixture was concentrated in vacuo.
quenched with ethyl acetate (5 mL) and suction filtered, to yield (after drying in vacuo) a
white solid (1.41 g) that was suspended in THF (200 mL). KO-t-Bu (1.37 g, 12.2 mmol)
was added and the mixture was stirred vigorously. After 3.5 h, saturated aqueous NH₄Cl
solution (5 mL) was added, and the mixture was concentrated in vacuo. The residue was
dissolved in CH₂Cl₂ (75 mL) and H₂O (25 mL), and the aqueous layer was extracted with
CH₂Cl₂ (30 mL). The organic extracts were combined and washed with H₂O (50 mL) and
saturated aqueous NaCl solution (50 mL), dried over MgSO₄ and concentrated in vacuo.
The residue was passed through a plug of silica gel using CHCl₃ to yield the isomeric mixture 41 (0.92 g, 2.1 mmol, 88% crude from 40) as a light yellow solid.

The solid was dissolved in CH₂Cl₂ (200 mL) and Borch reagent (1.04 g, 6.4 mmol) was added dropwise over 5 min, while the mixture was stirred vigorously. After 2 h the mixture was concentrated in vacuo, quenched with ethyl acetate (5 mL) and methanol (1 mL) and concentrated again. The residue was slurried into THF (200 mL) and HO-t-Bu (2 mL) and KO-t-Bu (1.20 g, 10.7 mmol) were added. The mixture was stirred vigorously for 3.5 h and the reaction was quenched with saturated aqueous NH₄Cl solution (5 mL). The reaction mixture was concentrated and CH₂Cl₂ (50 mL) and H₂O (25 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (40 mL), the organic extracts were combined and washed with H₂O (25 mL) and saturated aqueous NaCl solution (20 mL). dried (MgSO₄), concentrated and subjected to column chromatography (SiO₂, 25%) CHCl₃/hexanes) to yield 42 (0.50 g, 1.4 mmol, 61% from 40) as a colorless crystalline solid: mp 204–205 °C (chloroform/hexanes); ¹H NMR (500.1 MHz; CDCl₃): δ 7.67 (s, 2H), 7.16 (t, J = 7.5 Hz, 1H), 7.11 (s, 4H), 6.96 (d, J = 7.5 Hz, 2H), 6.27 (s, 4H), 5.95 (s, 1H), 2.81 (m, 4H), 2.71 (m, 4H); ¹³C NMR (126 MHz; CDCl₃): δ 140.3, 137.1, 135.6, 135.5, 132.6, 131.4, 128.0, 125.6, 125.5, 36.3, 35.5; El-MS (70 eV) m/z (%): 334 (36, M⁺), 229 (100), 215 (67); HRMS Calc’d for C₂₉H₄₅: 334.1720, found 334.1726.

To a solution of 42 (0.26 g, 0.78 mmol) in degassed benzene (20 mL) was added a solution of DDQ (0.19 g, 0.86 mmol) in degassed benzene (5 mL) over 10 min. The reaction mixture was stirred for an additional 5 min, concentrated in vacuo and the residue was filtered over a plug of silica using CHCl₃ to yield 5 (0.25 g, 0.75 mmol, 97% yield) as a crystalline slightly yellow solid, that could be recrystallized from heptanes; mp: 184–186 °C (chloroform); ¹H NMR (500.1 MHz; CDCl₃): δ 7.68 (s, 2H), 7.47 (s, 2H), 7.32 (s, 2H), 7.15 (s, 2H), 6.56 (t, J = 7.5 Hz, 1H), 6.31 (d, J = 7.5 Hz, 2H), 4.18 (s, 1H), 3.09 (ddd, J = 13.0 Hz, J = 1.9 Hz, J = 5.8 Hz, 2H), 2.69 (ddd, J = 13.0 Hz, J = 5.3 Hz, 2H), 13.3 Hz, 2H), 2.31 (ddd, J unresolved, 2H), 1.21 (ddd, J = 13.3 Hz, J = 5.8 Hz, J = 13.9 Hz, 2H); ¹³C NMR (126 MHz; CDCl₃): δ 137.4, 134.0, 133.0, 131.1, 130.3, 129.8, 129.4, 127.9, 126.2, 126.0, 125.1, 125.1, 38.0, 55.3; EI-MS (70 eV) m/z (%): 332 (100, M⁺), 317 (10), 228 (97), 213 (8), 202 (7), 166 (17). HRMS Calc’d for C₂₆H₂₆: 332.1564, found 332.1562.

5.5 References

(1) Calculations were performed using version 5.0a37 of the Chem3D Pro package of software (MOPAC, AM1, closed shell).

(2) In Section 1.4 a more detailed discussion of AM1 calculations on [n](2.7)pyrenophanes can be found.


(34) The crystallographic numbering shown differs from the systematic numbering. The crystallographic data for 3 can be found in Appendix F.

(35) The crystallographic numbering shown differs from the systematic numbering. The crystallographic data for 5 can be found in Appendix G.


Appendix A
Table A-1a: NMR Data for 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes and 5-substituted meta-xylenes in C6D6.

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Table A-1b: NMR Data for 6,15-disubstituted syn-2,11-dithia[3.3]metacyclopheanes and 5-substituted meta-xylenes in CDCl$_3$.

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<td>0.09</td>
</tr>
<tr>
<td>(b)</td>
<td>6.86</td>
<td>6.95</td>
<td>6.98</td>
<td>7.01</td>
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<tr>
<td>(c)</td>
<td>6.97</td>
<td>7.07</td>
<td>6.91</td>
<td>7.14</td>
<td>-0.06</td>
<td>0.07</td>
</tr>
<tr>
<td>(d)</td>
<td>7.24</td>
<td>7.51</td>
<td>7.19</td>
<td>7.30</td>
<td>-0.05</td>
<td>0.15</td>
</tr>
<tr>
<td>(e)</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>(f)</td>
<td>6.63</td>
<td>6.74</td>
<td>6.84</td>
<td>6.84</td>
<td>0.21</td>
<td>0.10</td>
</tr>
<tr>
<td>(g)</td>
<td>6.19</td>
<td>6.37</td>
<td>6.43</td>
<td>6.35</td>
<td>0.24</td>
<td>-0.02</td>
</tr>
<tr>
<td>(h)</td>
<td>6.68</td>
<td>7.15</td>
<td>6.67</td>
<td>7.19</td>
<td>-0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>(i) ****</td>
<td>7.71</td>
<td>7.50</td>
<td>7.33</td>
<td>7.86</td>
<td>-0.38</td>
<td>0.36</td>
</tr>
<tr>
<td>(j)</td>
<td>6.75</td>
<td>6.72</td>
<td>6.88</td>
<td>6.71</td>
<td>0.13</td>
<td>-0.01</td>
</tr>
<tr>
<td>(k)</td>
<td>6.51</td>
<td>6.44</td>
<td>6.60</td>
<td>6.47</td>
<td>0.09</td>
<td>0.03</td>
</tr>
<tr>
<td>(l)</td>
<td>6.51</td>
<td>6.49</td>
<td>6.61</td>
<td>6.54</td>
<td>0.10</td>
<td>0.05</td>
</tr>
<tr>
<td>(m)</td>
<td>6.93</td>
<td>6.99</td>
<td>7.03</td>
<td>7.03</td>
<td>0.10</td>
<td>0.04</td>
</tr>
<tr>
<td>(n)</td>
<td>6.79</td>
<td>6.86</td>
<td>6.76</td>
<td>6.89</td>
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<td>0.05</td>
</tr>
<tr>
<td>(o)</td>
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<td>6.79</td>
<td>6.78</td>
<td>6.90</td>
<td>-0.02</td>
<td>0.11</td>
</tr>
<tr>
<td>(p) ***</td>
<td>7.33/7.31</td>
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<td>7.13</td>
<td>7.27</td>
<td>-0.19</td>
<td>0.15</td>
</tr>
<tr>
<td>(q)</td>
<td>7.67</td>
<td>7.50</td>
<td>7.30</td>
<td>7.58</td>
<td>-0.37</td>
<td>0.08</td>
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Table A-1c: NMR Data for 6,15-disubstituted syn-2,11-dithia[3.3]metacyclophanes and 5-substituted meta-xylenes in DMSO-$d_6$.

<table>
<thead>
<tr>
<th>Compound</th>
<th>$\delta_{H_i}^{cyclophane}$</th>
<th>$\delta_{H_c}^{cyclophane}$</th>
<th>$\delta_{H_i}^{xylene}$</th>
<th>$\delta_{H_c}^{xylene}$</th>
<th>$\Delta\delta_{H_i}$</th>
<th>$\Delta\delta_{H_c}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>(a) *****</td>
<td>****</td>
<td>****</td>
<td>7.47</td>
<td>7.38</td>
<td>0.08</td>
<td>0.13</td>
</tr>
<tr>
<td>(b)</td>
<td>7.08</td>
<td>6.84</td>
<td>7.00</td>
<td>6.97</td>
<td>-0.08</td>
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<tr>
<td>(c)</td>
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<td>7.01</td>
<td>7.20</td>
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<td>0.19</td>
</tr>
<tr>
<td>(d)</td>
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<td>7.29</td>
<td>7.58</td>
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<td>0.22</td>
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<tr>
<td>(e)</td>
<td>7.41</td>
<td>7.37</td>
<td>7.25</td>
<td>7.56</td>
<td>-0.16</td>
<td>0.19</td>
</tr>
<tr>
<td>(f)</td>
<td>6.79</td>
<td>6.64</td>
<td>6.78</td>
<td>6.78</td>
<td>-0.01</td>
<td>0.14</td>
</tr>
<tr>
<td>(g)</td>
<td>5.93</td>
<td>6.21</td>
<td>6.14</td>
<td>6.17</td>
<td>0.21</td>
<td>-0.04</td>
</tr>
<tr>
<td>(h)</td>
<td>6.68</td>
<td>7.15</td>
<td>6.67</td>
<td>7.19</td>
<td>-0.01</td>
<td>0.04</td>
</tr>
<tr>
<td>(i) *****</td>
<td>****</td>
<td>****</td>
<td>7.51</td>
<td>7.88</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(j)</td>
<td>7.00</td>
<td>6.61</td>
<td>6.90</td>
<td>6.74</td>
<td>-0.10</td>
<td>0.15</td>
</tr>
<tr>
<td>(k)</td>
<td>*****</td>
<td>*****</td>
<td>6.41</td>
<td>6.37</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(l)</td>
<td>6.68</td>
<td>6.41</td>
<td>6.57</td>
<td>6.55</td>
<td>-0.11</td>
<td>0.14</td>
</tr>
<tr>
<td>(m)</td>
<td>7.18</td>
<td>6.81</td>
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<td>7.00</td>
<td>-0.09</td>
<td>0.19</td>
</tr>
<tr>
<td>(n)</td>
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<td>6.75</td>
<td>6.90</td>
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<td>0.10</td>
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<tr>
<td>(o)</td>
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<td>6.77</td>
<td>6.87</td>
<td>-0.20</td>
<td>0.16</td>
</tr>
<tr>
<td>(p) ***</td>
<td>7.43</td>
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<td>7.17</td>
<td>7.28</td>
<td>-0.26</td>
<td>0.19</td>
</tr>
<tr>
<td>(q)</td>
<td>7.66</td>
<td>7.35</td>
<td>7.39</td>
<td>7.56</td>
<td>-0.27</td>
<td>0.21</td>
</tr>
</tbody>
</table>

* Compound not soluble enough to collect a $^1$H NMR spectrum.
** Overlap of the signals with the signals of an unidentified impurity does not allow for unambiguous assignment.
*** Mixture of diastereomers. Average values are given for $\delta_{H_i}^{cyclophane}$ and $\delta_{H_c}^{cyclophane}$.
**** Impurity present.
***** Not enough material available to obtain spectrum of reasonable quality.
Table A-2: Values for Hammett’s $\sigma_m$ [Isaacs 1987 533 /id] and for the dual parameter systems of Taft ($\sigma_1$ and $\sigma_R^0$) [Isaacs 1987 533 /id] and Swain and Lupton ($\mathcal{F}$ and $\mathcal{K}$) [Carroll 1998 772 /id].

<table>
<thead>
<tr>
<th>Compound</th>
<th>Hammett</th>
<th>Taft</th>
<th>Swain / Lupton</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>$\sigma_m$</td>
<td>$\sigma_1$</td>
<td>$\sigma_R^0$</td>
</tr>
<tr>
<td>(a)</td>
<td>0.62</td>
<td>0.52</td>
<td>0.14</td>
</tr>
<tr>
<td>(b)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>(c)</td>
<td>0.37</td>
<td>0.45</td>
<td>-0.16</td>
</tr>
<tr>
<td>(d)</td>
<td>0.35</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>(e)</td>
<td>0.35</td>
<td>0.31</td>
<td>0.15</td>
</tr>
<tr>
<td>(f)</td>
<td>-0.06</td>
<td>-0.05</td>
<td>-0.10</td>
</tr>
<tr>
<td>(g)</td>
<td>-0.09</td>
<td>0.1</td>
<td>-0.48</td>
</tr>
<tr>
<td>(h)</td>
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<td>-0.22</td>
</tr>
<tr>
<td>(i)</td>
<td>0.71</td>
<td>0.64</td>
<td>0.19</td>
</tr>
<tr>
<td>(j)</td>
<td>0.39</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>(k)</td>
<td>0.13</td>
<td>0.27</td>
<td>-0.44</td>
</tr>
<tr>
<td>(l)</td>
<td>0.10</td>
<td>0.26</td>
<td>-0.41</td>
</tr>
<tr>
<td>(m)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>(n)</td>
<td>*</td>
<td>*</td>
<td>*</td>
</tr>
<tr>
<td>(o)</td>
<td>0.14</td>
<td>0.19</td>
<td>-0.17</td>
</tr>
<tr>
<td>(p)</td>
<td>0.21</td>
<td>0.25</td>
<td>0.00</td>
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<tr>
<td>(q)</td>
<td>0.64</td>
<td>0.64</td>
<td>0.12</td>
</tr>
</tbody>
</table>

* No literature value available.
Figure B-1a: $\Delta \delta H_e$ measured in CDCl$_3$ solutions versus $\sigma = \sigma_1 + \alpha \sigma^0_R$ (Taft's system for $\alpha = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ and $4.0$).

Figure B-1b: $\Delta \delta H_i$ measured in C$_6$D$_6$ solutions versus $\sigma = \sigma_1 + \alpha \sigma^0_R$ (Taft's system for $\alpha = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ and $4.0$).
Figure B-1c: $\Delta \delta H_c$ measured in C$_6$D$_6$ solutions versus $\sigma = \sigma_l + \alpha \sigma_R$ (Taft's system for $\alpha = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ and $4.0$).

Figure B-1d: $\Delta \delta H_t$ measured in DMSO-d$_6$ solutions versus $\sigma = \sigma_l + \alpha \sigma_R$ (Taft's system for $\alpha = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ and $4.0$).
Figure B-1c: $\Delta \delta H_c$ measured in DMSO-$d_6$ solutions versus $\sigma = \sigma_I + \alpha \sigma_R$ (Taft's system for $\alpha = 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5$ and $4.0$).

Figure B-2a: $\Delta \delta H_c$ measured in CDCl$_3$ solutions versus $\sigma = fF + r\mathcal{R}$ (Swain and Lupton's system for $f/r = 0.90/0.10, 0.85/0.15, 0.80/0.20, 0.75/0.25, 0.70/0.30, 0.65/0.35$ and $0.60/0.40$).
Figure B-2b: \( \Delta \delta H_t \) measured in C\(_6\)D\(_6\) solutions versus \( \sigma = f \mathcal{F} + r \mathcal{R} \) (Swain and Lupton's system for \( f/r = 0.90/0.10, 0.85/0.15, 0.80/0.20, 0.75/0.25, 0.70/0.30, 0.65/0.35 \) and \( 0.60/0.40 \)).

Figure B-2c: \( \Delta \delta H_c \) measured in C\(_6\)D\(_6\) solutions versus \( \sigma = f \mathcal{F} + r \mathcal{R} \) (Swain and Lupton's system for \( f/r = 0.90/0.10, 0.85/0.15, 0.80/0.20, 0.75/0.25, 0.70/0.30, 0.65/0.35, 0.60/0.40, 0.55/0.45 \) and \( 0.50/0.50 \)).
Figure B-2d: $\Delta \delta H_i$ measured in DMSO-\textsubscript{d6} solutions versus $\sigma = fF + rR$ (Swain and Lupton's system for $f/r = 0.90/0.10, 0.85/0.15, 0.80/0.20, 0.75/0.25, 0.70/0.30, 0.65/0.35$ and $0.60/0.40$).

Figure B-2e: $\Delta \delta H_i$ measured in DMSO-\textsubscript{d6} solutions versus $\sigma = fF + rR$ (Swain and Lupton's system for $f/r = 0.70/0.30, 0.65/0.35, 0.60/0.30, 0.55/0.45, 0.50/0.50, 0.45/0.55, 0.40/0.60, 0.35/0.65$ and $0.30/0.70$).
Appendix C
Table C-1: Published group electronegativity moments for substituents of 6.15-disubstituted syn-2.11-dithia[3.3]metacyclophanes and AM1 calculated dipole moments for 6.15-disubstituted syn-2.11-dithia[3.3]metacyclophanes.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Published group electronegativity value</th>
<th>Calculated group dipole moment *</th>
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<tr>
<td></td>
<td></td>
<td>c,c-4 (cyclolophane)</td>
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<tr>
<td>(a)</td>
<td>3.208</td>
<td>7.294</td>
</tr>
<tr>
<td>(b)</td>
<td>2.176</td>
<td>1.471</td>
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<tr>
<td>(c)</td>
<td>**</td>
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<td>(d)</td>
<td>2.832</td>
<td>3.73</td>
</tr>
<tr>
<td>(e)</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>(f)</td>
<td>2.472</td>
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<td>2.992</td>
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</tr>
<tr>
<td>(h)</td>
<td>**</td>
<td>***</td>
</tr>
<tr>
<td>(i)</td>
<td>3.421</td>
<td>***</td>
</tr>
<tr>
<td>(j)</td>
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</tr>
<tr>
<td>(k)</td>
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<td>2.242</td>
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</tr>
<tr>
<td>(m)</td>
<td>**</td>
<td>0.369</td>
</tr>
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<td>2.583</td>
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<tr>
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<tr>
<td>(p)</td>
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<td>4.342</td>
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<tr>
<td>(q)</td>
<td>2.998</td>
<td>9.452</td>
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</table>

* Dipole moments were calculated with the same conformation of the substituent for the c,c and b,b conformer. Conformations were chosen in such a way that they aligned with the central axis of the molecule.

** No literature value available.

*** Calculations failed to coalesce to a reasonable conformation.
Figure C-1a: $\Delta \delta H_i$ and $\Delta \delta H_e$ measured in C$_6$D$_6$ solutions versus published group electronegativity moments for substituents R.

Figure C-1b: $\Delta \delta H_i$ and $\Delta \delta H_e$ measured in CDCl$_3$ solutions versus published group electronegativity moments for substituents R.
Figure C-1c: $\Delta \delta H_1$ and $\Delta \delta H_c$ measured in DMSO-$d_6$ solutions versus published group electronegativity moments for substituents R.
Figure C-2a: $\Delta \delta H_i$ and $\Delta \delta H_e$ measured in C$_6$D$_6$ solutions versus difference in calculated dipole moments between the $c,c$ and $b,b$-conformers.

Figure C-2b: $\Delta \delta H_i$ and $\Delta \delta H_e$ measured in CDCl$_3$ solutions versus difference in calculated dipole moments between the $c,c$ and $b,b$-conformers.
Figure C-2c: $\Delta \delta H_i$ and $\Delta \delta H_c$ measured in DMSO-$d_6$ solutions versus difference in calculated dipole moments between the $c,c$ and $b,b$-conformers.
X-ray Structure Report

For
Dr. G. J. Bodwell

Prepared by
David O. Miller

December 3, 1999

Introduction

Collection, solution and refinement all proceeded normally. Hydrogens were introduced in calculated or difference map positions with isotropic thermal parameters set twenty percent greater than those of their bonding partners at the time of their inclusion. The carboxylic acid protons were found in the difference map.

Please acknowledge Dr. Bob McDonald, University of Alberta for data collection.
**Experimental**

**Data Collection**

A colourless prism crystal of $\text{C}_{18}\text{H}_{16}\text{O}_{4}\text{S}_{2}$ having approximate dimensions of 0.20 x 0.05 x 0.02 mm was mounted on a glass fiber. All measurements were made on a Bruker P4/CCD system with graphite monochromated Mo-Kα radiation and a rotating anode generator.

Cell constants corresponded to a primitive monoclinic cell with dimensions:

\[
\begin{align*}
a &= 6.8646(4) \text{ Å} \\
b &= 14.891(1) \text{ Å} \\
c &= 15.923(1) \text{ Å} \\
V &= 1627.7(2) \text{ Å}^3
\end{align*}
\]

For $Z = 4$ and F.W. = 360.44, the calculated density is 1.47 g/cm$^3$. The systematic absences of:

- $h0l$: $h+l \pm 2n$
- $0k0$: $k \pm 2n$

uniquely determine the space group to be:

$P2_1/n$ (#14)

The data were collected at a temperature of $-80 \pm 1^\circ\text{C}$. The full hemisphere of data was collected with 30s.. 0.3 deg. frames to a maximum 2θ value of 52.8°.
Data Reduction

Of the 8164 reflections which were collected, 3486 were unique ($R_{int} = 0.048$). The linear absorption coefficient, $\mu$, for Mo-Kα radiation is 3.5 cm$^{-1}$. The Siemens area detector absorption routine (SADABS) was used to correct the data with maximum and minimum effective transmissions of 0.971679 and 0.559440 respectively. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods$^1$ and expanded using Fourier techniques$^2$. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement$^3$ on $F$ was based on 2232 observed reflections ($I > 2.00\sigma(I)$) and 217 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \frac{\sum |F_o| - |F_c|}{\sum |F_o|} = 0.048$$

$$R_w = \frac{\sqrt{\sum w (|F_o| - |F_c|)^2}}{\sum w F_o^2} = 0.043$$

The standard deviation of an observation of unit weight$^4$ was 1.34. The weighting scheme was based on counting statistics Plots of $\sum w (|F_o| - |F_c|)^2$ versus $|F_o|$, reflection order in data collection, $\sin \theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.34 and -0.33 e$^-$/Å$^3$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber$^5$. Anomalous dispersion effects were included in $F_{calc}^6$; the values for $\Delta f$ and $\Delta f'$ were those of Creagh and McAuley$^7$. The values for the mass attenuation coefficients are those of Creagh and Hubbell$^8$. All calculations were performed using the teXsan$^9$ crystallographic software package of Molecular Structure Corporation.
References


(3) Least Squares function minimized:

\[ \Sigma w(|F_{o}|-|F_{c}|)^2 \]

(4) Standard deviation of an observation of unit weight:

\[ \left[ \Sigma w(|F_{o}|-|F_{c}|)^2/(N_{o}-N_{v}) \right]^{1/2} \]

where:  
\[ N_{o} = \text{number of observations} \]  
\[ N_{v} = \text{number of variables} \]


EXPERIMENTAL DETAILS

A. Crystal Data

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<th>Value</th>
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</thead>
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</tr>
<tr>
<td></td>
<td>b = 14.891(1) Å</td>
</tr>
<tr>
<td></td>
<td>c = 15.923(1) Å</td>
</tr>
<tr>
<td></td>
<td>$\beta$ = 90.263(1) $^\circ$</td>
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<tr>
<td></td>
<td>V = 1627.7(2) Å$^3$</td>
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<td>$\mu$(MoK$\alpha$)</td>
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### B. Intensity Measurements

<table>
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<tr>
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<td>Temperature</td>
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<td>Scan Rate</td>
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<td>SADABS correction</td>
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<td>(trans. factors: 0.971679 –</td>
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C. Structure Solution and Refinement

<table>
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<tr>
<th>Structure Solution</th>
<th>Direct Methods (SHELX97)</th>
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<tr>
<td>Refinement</td>
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<td>Function Minimized</td>
<td>$\sum w (</td>
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<td>Least Squares Weights</td>
<td>$1/\sigma^2(F_o) = 4F_o^2/\sigma^2(F_o^2)$</td>
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<td>Anomalous Dispersion</td>
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<td>Minimum peak in Final Diff. Map</td>
<td>-0.33 e^-/Å³</td>
</tr>
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Appendix E
X-ray Structure Report

For
Dr. G. J. Bodwell

Prepared by
David O. Miller

April 6, 2001

Introduction

Collection, solution and refinement all proceeded normally. Hydrogen atoms were introduced in calculated or difference map positions with isotropic thermal parameters set twenty percent greater than those of their bonding partners at the time of their inclusion. They were not refined.

The refinement values on this structure are not adequate for publication. There is also a shortage of data due to the presence of two molecules in the asymmetric unit. For this reason most of the atoms are not refined anisotropically.
Experimental

Data Collection

A colourless prism crystal of $C_{44}H_{49}SO_{75}$ having approximate dimensions of 0.40 x 0.40 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Mo-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 21 carefully centered reflections in the range $23.50 < 2\theta < 35.04^\circ$ corresponded to a primitive triclinic cell with dimensions:

- $a = 16.021(2)$ Å
- $b = 19.314(3)$ Å
- $c = 14.232(3)$ Å
- $\alpha = 100.47(2)^\circ$
- $\beta = 112.29(1)^\circ$
- $\gamma = 89.61(1)^\circ$
- $V = 3997(1)$ Å³

For $Z = 4$ and $FW = 734.37$, the calculated density is 1.22 g/cm³. Based on a statistical analysis of intensity distribution and the successful solution and refinement of the structure, the space group was determined to be $P-1$ (#2).

The data were collected at a temperature of 26 ± 1°C using the θ-2θ scan technique to a maximum 2θ value of 45°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.38° with a take-off angle of 6°. Scans of $(1.73 + 0.35 \tan \theta)^\circ$ were made at a speed of 4°/min (in θ). The weak reflections ($I < 10.0\sigma(I)$) were rescanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm; the crystal to detector distance was 400 mm, and the detector aperture was 6.0 x 3.0 mm (horizontal x vertical).
Data Reduction

Of the 10958 reflections which were collected, 10508 were unique ($R_{int} = 0.046$). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, $\mu$, for Mo-K\textsubscript{$\alpha$} radiation is 0.9 cm$^{-1}$. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.98 to 1.00. The data were corrected for Lorentz and polarization effects.

Structure Solution and Refinement

The structure was solved by direct methods\textsuperscript{1} and expanded using Fourier techniques\textsuperscript{2}. Some non-hydrogen atoms were refined anisotropically, while the rest were refined isotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement\textsuperscript{3} on F was based on 4835 observed reflections ($I > 2 \sigma(I)$) and 573 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of:

$$R = \sum |Fo| - |Fc| / \sum |Fo| = 0.168$$

$$R_w = [\sum w (|Fo| - |Fc|)^2 / \sum w Fo^2]^{1/2} = 0.163$$

The standard deviation of an observation of unit weight\textsuperscript{4} was 7.62. The weighting scheme was based on counting statistics and included a factor ($p = 0.010$) to downweight the intense reflections. Plots of $\sum w (|Fo| - |Fc|)^2$ versus $|Fo|$, reflection order in data collection, sin $\theta/\lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 1.02 and -0.55 e$^{-}/$Å$^{3}$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber\textsuperscript{5}. Anomalous dispersion effects were included in Fcale\textsuperscript{5}; the values for $\chi'$ and $\chi''$ were those of Creagh and McAuley\textsuperscript{7}. The values for the mass attenuation coefficients are those of Creagh and Hubbell\textsuperscript{8}. All calculations were performed using the teXsan\textsuperscript{9} crystallographic software package of Molecular Structure Corporation.
References


(3) Least Squares function minimized:

$$
\sum w(|F_o|-|F_c|)^2 \text{ where}
$$

$$
w = 1/[\sigma^2(F_o)] = [\sigma^2_c(F_o) + \rho^2 F_o^2/4]^{-1}
$$

$$
\sigma_c(F_o) = \text{e.s.d. based on counting statistics}
$$

$$
\rho = \text{p-factor}
$$

(4) Standard deviation of an observation of unit weight:

$$
[\sum w(|F_o|-|F_c|)^2/(N_o-N_v)]^{1/2}
$$

where

$$
N_o = \text{number of observations}
$$

$$
N_v = \text{number of variables}
$$


EXPERIMENTAL DETAILS

A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
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<td>Empirical Formula</td>
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<td>Formula Weight</td>
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<td>Crystal Color, Habit</td>
<td>colourless, prism</td>
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<td>Crystal Dimensions</td>
<td>0.40 X 0.40 X 0.40 mm</td>
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<tr>
<td>Crystal System</td>
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<tr>
<td>Lattice Type</td>
<td>Primitive</td>
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<tr>
<td>No. of Reflections Used for Unit</td>
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<td>Cell Determination (2θ range)</td>
<td></td>
</tr>
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<td>Omega Scan Peak Width</td>
<td>0.38°</td>
</tr>
<tr>
<td>at Half-height</td>
<td></td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a = 16.021(2) Å</td>
</tr>
<tr>
<td></td>
<td>b = 19.314(3) Å</td>
</tr>
<tr>
<td></td>
<td>c = 14.232(3) Å</td>
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<td></td>
<td>α = 100.47(2) °</td>
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<td></td>
<td>β = 112.29(1) °</td>
</tr>
<tr>
<td></td>
<td>γ = 89.61(1) °</td>
</tr>
<tr>
<td></td>
<td>V = 3997(1) Å³</td>
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<tr>
<td>Space Group</td>
<td>P-1 (#2)</td>
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<tr>
<td>Z value</td>
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<tr>
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<td>F000</td>
<td>156600</td>
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<td>μ(MoKα)</td>
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B. Intensity Measurements

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<td>Rigaku AFC6S</td>
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<tr>
<td>Radiation</td>
<td>MoKα (λ = 0.71069 Å)</td>
</tr>
<tr>
<td></td>
<td>graphite monochromated</td>
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</tr>
<tr>
<td>Detector Aperture</td>
<td>6.0 mm horizontal</td>
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<td></td>
<td>3.0 mm vertical</td>
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<tr>
<td>Crystal to Detector Distance</td>
<td>400 mm</td>
</tr>
<tr>
<td>Voltage, Current</td>
<td>50kV, 27.5mA</td>
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<tr>
<td>Temperature</td>
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<tr>
<td>Scan Type</td>
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<td>Scan Rate</td>
<td>4 °/min (in θ) (up to 5 scans)</td>
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<tr>
<td>Scan Width</td>
<td>(1.73 + 0.35 tan θ°)</td>
</tr>
<tr>
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<td>No of Reflections Measured</td>
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<tr>
<td></td>
<td>Unique 10508 (Rint = 0.046)</td>
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<td>Corrections</td>
<td>Lorentz-polarization</td>
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<tr>
<td></td>
<td>Absorption</td>
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<td></td>
<td>(trans factors: 0.9805 - 1.0000)</td>
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### C. Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Structure Solution</th>
<th>Direct Methods (SHELX97)</th>
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<tr>
<td>Refinement</td>
<td>Full-matrix least-squares on F</td>
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<tr>
<td>Function Minimized</td>
<td>$\Sigma w (</td>
</tr>
<tr>
<td>Least Squares Weights</td>
<td>$1/\sigma^2(F_o) = 4F_o^2/\sigma^2(F_o^2)$</td>
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<tr>
<td>p-factor</td>
<td>0.0100</td>
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<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
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<td>No. Observations (I&gt;2 000σ(I))</td>
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<td>Max Shift/Error in Final Cycle</td>
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<td>Maximum peak in Final Diff. Map</td>
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<tr>
<td>Minimum peak in Final Diff. Map</td>
<td>-0.55 e⁻³ Å⁻³</td>
</tr>
</tbody>
</table>
Collection, solution and refinement all proceeded normally. Hydrogen atoms were introduced in calculated positions with isotropic thermal parameters set twenty percent greater than those of their bonding partners at the time of their inclusion. They were optimized by positional refinement but were fixed for the final round of least squares. This structure was refined on F-squared to maximize the data to parameter ratio.
Experimental

Data Collection

A colourless prism crystal of C_{26}H_{20} having approximate dimensions of 0.30 x 0.15 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu-Kα radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 25 carefully centered reflections in the range 46.01 < 2θ < 59.65° corresponded to a primitive orthorhombic cell with dimensions

- a = 12.451(2) Å
- b = 15.773(3) Å
- c = 9.203(2) Å
- V = 1807.4(5) Å³

For Z = 4 and F W = 332 44, the calculated density is 1.22 g/cm³. The systematic absences of

h00  h ± 2n
0k0  k ± 2n
00l  l ± 2n

uniquely determine the space group to be

P2₁2₁2₁ (#19)

The data were collected at a temperature of 26 ± 1°C using the ω-2θ scan technique to a maximum 2θ value of 120°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.27° with a take-off angle of 6.0°. Scans of (0.84 + 0.14 tan θ)° were made at a speed of 4°/min (in ω). The weak reflections (I < 10 0σ(I)) were rescanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2:1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was 4.5 x 3.0 mm (horizontal x vertical).
Data Reduction

A total of 1577 reflections were collected. The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, μ, for Cu-Kα radiation is 5.2 cm⁻¹. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.93 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 1.79589e-005).

Structure Solution and Refinement

The structure was solved by direct methods¹ and expanded using Fourier techniques². The non-hydrogen atoms were refined anisotropically. The final cycle of full-matrix least-squares refinement³ on F² was based on 1556 observed reflections and 284 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of

\[ R1 = \frac{\sum |F_o|-|F_c|}{\sum |F_o|} = 0.059 \]
\[ wR2 = \left( \frac{\sum w(F_o^2 - F_c^2)^2}{\sum w(F_o^2)^2} \right)^{1/2} = 0.085 \]

The standard deviation of an observation of unit weight⁴ was 1.84. The weighting scheme was based on counting statistics and included a factor (p = 0.010) to downweight the intense reflections. Plots of Σ w (|F_o| - |F_c|)² versus |F_o|, reflection order in data collection, sin θ/λ, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.18 and -0.21 e⁻/Å³, respectively.

Neutral atom scattering factors were taken from Cromer and Waber⁵. Anomalous dispersion effects were included in Fcalc⁶, the values for δf and λf were those of Creagh and McAuley⁷. The values for the mass attenuation coefficients are those of Creagh and Hubbell⁸. All calculations were performed using the teXsan⁹ crystallographic software package of Molecular Structure Corporation.
References


(3) Least Squares function minimized:
\[ \sum w(F_o^2 - F_c^2)^2 \]
where
\[ w = \frac{1}{n^2(F_o)} = \frac{n^2 c(F_o) + p^2 F_F^2/4}{1} \]
\[ s(F_o) = \text{based on counting statistics} \]
\[ p = \text{p-factor} \]

(4) Standard deviation of an observation of unit weight:
\[ \left[ \sum w(F_o^2 - F_c^2)^2 / (N_o - N_v) \right]^{1/2} \]
where
\[ N_o = \text{number of observations} \]
\[ N_v = \text{number of variables} \]


### EXPERIMENTAL DETAILS

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<td>Cell Determination (2θ range)</td>
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<td>Omega Scan Peak Width</td>
<td>a = 12.45(2) Å</td>
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<tr>
<td>at Half-height</td>
<td>b = 15.773(3) Å</td>
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<tr>
<td>Lattice Parameters</td>
<td>c = 9.203(2) Å</td>
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<tr>
<td>V = 1807.4(5) Å³</td>
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B. Intensity Measurements

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<td>Rigaku AFC6S</td>
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<td>CuKα (λ = 1.54178 Å)</td>
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<td>Detector Aperture</td>
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<tr>
<td>Crystal to Detector Distance</td>
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<tr>
<td>Voltage, Current</td>
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<tr>
<td>Temperature</td>
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<td>Scan Type</td>
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<td>Scan Rate</td>
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<tr>
<td>Scan Width</td>
<td>0.84 + 0.14 tan θ°</td>
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<td>2θmax</td>
<td>120.0°</td>
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<tr>
<td>No. of Reflections Measured</td>
<td>Total: 1577</td>
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<td>Corrections</td>
<td>Lorentz-polarization Absorption</td>
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<td></td>
<td>(trans factors 0.9261 - 1.0000)</td>
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<td></td>
<td>Secondary Extinction</td>
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<td>(coefficient 1.79589e-005)</td>
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C. Structure Solution and Refinement

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<tr>
<th>Structure Solution</th>
<th>Direct Methods (SIR92)</th>
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<tr>
<td><strong>Refinement</strong></td>
<td><strong>Full-matrix least-squares on F^2</strong></td>
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<td><strong>Function Minimized</strong></td>
<td>[ \sum \text{w}(\text{Fo}^2 - \text{Fc}^2)^2 ]</td>
</tr>
<tr>
<td><strong>Least Squares Weights</strong></td>
<td>[ \frac{1}{\sigma^2(\text{Fo})} = 4\text{Fo}^2/\sigma^2(\text{Fo}^2) ]</td>
</tr>
<tr>
<td><strong>p-factor</strong></td>
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<tr>
<td><strong>Anomalous Dispersion</strong></td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td><strong>No. Observations (I&gt;0 00\sigma(I))</strong></td>
<td>1556</td>
</tr>
<tr>
<td><strong>No Variables</strong></td>
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<td><strong>Reflection/Parameter Ratio</strong></td>
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<td><strong>Residuals R1, wR2</strong></td>
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<td><strong>Goodness of Fit Indicator</strong></td>
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<td><strong>Max Shift/Error in Final Cycle</strong></td>
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<td><strong>Maximum peak in Final Diff. Map</strong></td>
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<td><strong>Minimum peak in Final Diff. Map</strong></td>
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Appendix G
X-ray Structure Report

For
Dr G J Bodwell

Prepared by
David O Miller

March 13, 2001

Introduction

Collection, solution and refinement all proceeded normally. Hydrogen atoms were introduced with thermal parameters set twenty percent greater than those of their bonding partners at the time of their inclusion. They were optimized by positional refinement but were fixed for the final round of refinement due to the shortage of data. Refinement was carried out on F-squared to maximize the data/variable ratio.
Data Collection

A colourless prism crystal of C\textsubscript{26}H\textsubscript{20} having approximate dimensions of 0.30 x 0.30 x 0.40 mm was mounted on a glass fiber. All measurements were made on a Rigaku AFC6S diffractometer with graphite monochromated Cu-K\textsubscript{a} radiation.

Cell constants and an orientation matrix for data collection, obtained from a least-squares refinement using the setting angles of 24 carefully centered reflections in the range 58.55 < 2\(\theta\) < 59.77° corresponded to a primitive monoclinic cell with dimensions:

\[
\begin{align*}
    a &= 9.282(2) \text{ Å} \\
    b &= 14.383(3) \text{ Å} \\
    c &= 13.412(2) \text{ Å} \\
    \beta &= 92.11(1)° \\
    V &= 1789.4(6) \text{ Å}^3
\end{align*}
\]

For \(Z = 4\) and \(FW = 332.44\), the calculated density is 1.23 g/cm\(^3\). Based on the systematic absences of:

0k0: \(k \pm 2n\)

packing considerations, a statistical analysis of intensity distribution, and the successful solution and refinement of the structure, the space group was determined to be

\[P2_1(\#4)\]

The data were collected at a temperature of 26 ± 1°C using the \(\omega-2\theta\) scan technique to a maximum 2\(\theta\) value of 120°. Omega scans of several intense reflections, made prior to data collection, had an average width at half-height of 0.26° with a take-off angle of 6.0°. Scans of (1.73 + 0.14 tan \(\theta\))° were made at a speed of 4.0°/min (in \(\omega\)). The weak reflections \((l < 10.0\sigma(l))\) were rescanned (maximum of 5 scans) and the counts were accumulated to ensure good counting statistics. Stationary background counts were recorded on each side of the reflection. The ratio of peak counting time to background counting time was 2.1. The diameter of the incident beam collimator was 1.0 mm, the crystal to detector distance was 400 mm, and the detector aperture was 4.5 x 3.0 mm (horizontal x vertical).
**Data Reduction**

Of the 2985 reflections which were collected, 2794 were unique ($R_{int} = 0.014$). The intensities of three representative reflections were measured after every 150 reflections. No decay correction was applied.

The linear absorption coefficient, $\mu$, for Cu-Kα radiation is 5.3 cm$^{-1}$. An empirical absorption correction based on azimuthal scans of several reflections was applied which resulted in transmission factors ranging from 0.95 to 1.00. The data were corrected for Lorentz and polarization effects. A correction for secondary extinction was applied (coefficient = 3.81012e-005).

**Structure Solution and Refinement**

The structure was solved by direct methods$^1$ and expanded using Fourier techniques$^2$. The non-hydrogen atoms were refined anisotropically. Hydrogen atoms were included but not refined. The final cycle of full-matrix least-squares refinement$^3$ on $F^2$ was based on 2786 observed reflections and 469 variable parameters and converged (largest parameter shift was 0.00 times its esd) with unweighted and weighted agreement factors of

$$R1 = \frac{\sum |F_o| - |F_c|}{\sum |F_o|} = 0.036$$

$$wR2 = \frac{\sum w(Fo^2 - Fc^2)^2}{\sum w(Fo^2)^2}^{1/2} = 0.059$$

The standard deviation of an observation of unit weight$^4$ was 2.03. The weighting scheme was based on counting statistics and included a factor ($p = 0.008$) to downweight the intense reflections. Plots of $\sum w(Fo^2 - Fc^2)$ versus $F_o$, reflection order in data collection, $\sin \theta / \lambda$, and various classes of indices showed no unusual trends. The maximum and minimum peaks on the final difference Fourier map corresponded to 0.10 and -0.11 e$^\text{+}\text{A}^{-3}$, respectively.

Neutral atom scattering factors were taken from Cromer and Waber$^5$. Anomalous dispersion effects were included in $Fcalc^6$, the values for $\Delta p$ and $\Delta f$ were those of Creagh and McAuley$^7$. The values for the mass attenuation coefficients are those of Creagh and Hubbell$^8$. All calculations were performed using the teXsan$^9$ crystallographic software package of Molecular Structure Corporation.
References


(3) Least Squares function minimized:

$$
\sum w(F_o^2 - F_c^2)^2 \text{ where}
$$

$$
w = 1/\sigma^2(Fo) = [\sigma^2_c(Fo) + p^2/Fo^2/4]^{-1}
$$

$$
\sigma_c(Fo) = \text{e s.d. based on counting statistics}
$$

$$
p = \text{p-factor}
$$

(4) Standard deviation of an observation of unit weight:

$$
[\sum w(F_o^2 - F_c^2)^2/\{N_0 - N_v\}]^{1/2}
$$

where $N_0 = \text{number of observations}$

$N_v = \text{number of variables}$


EXPERIMENTAL DETAILS

A. Crystal Data

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>( \text{C}<em>{26}\text{H}</em>{20} )</td>
</tr>
<tr>
<td>Formula Weight</td>
<td>332.44</td>
</tr>
<tr>
<td>Crystal Color, Habit</td>
<td>Colourless, prism</td>
</tr>
<tr>
<td>Crystal Dimensions</td>
<td>( 0.30 \times 0.30 \times 0.40 , \text{mm} )</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Lattice Type</td>
<td>Primitive</td>
</tr>
<tr>
<td>No. of Reflections Used for Unit Cell Determination (2(\theta) range)</td>
<td>24 (58.5 - 59.8°)</td>
</tr>
<tr>
<td>Omega Scan Peak Width at Half-height</td>
<td>0.26°</td>
</tr>
<tr>
<td>Lattice Parameters</td>
<td>( a = 9.282(2) , \text{Å} )</td>
</tr>
<tr>
<td></td>
<td>( b = 14.383(3) , \text{Å} )</td>
</tr>
<tr>
<td></td>
<td>( c = 13.412(2) , \text{Å} )</td>
</tr>
<tr>
<td></td>
<td>( \beta = 92.11(1)^\circ )</td>
</tr>
<tr>
<td></td>
<td>( V = 17894(6) , \text{Å}^3 )</td>
</tr>
<tr>
<td>Space Group</td>
<td>( P2_1(#4) )</td>
</tr>
<tr>
<td>Z value</td>
<td>4</td>
</tr>
<tr>
<td>( D_{\text{calc}} )</td>
<td>1.234 g/cm(^3)</td>
</tr>
<tr>
<td>( F_{\text{000}} )</td>
<td>704.00</td>
</tr>
<tr>
<td>( \mu(\text{CuK}\alpha) )</td>
<td>5.26 cm(^{-1})</td>
</tr>
</tbody>
</table>
### B. Intensity Measurements

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diffractometer</td>
<td>Rigaku AFC6S</td>
</tr>
<tr>
<td>Radiation</td>
<td>CuKα (λ = 1.54178 Å)</td>
</tr>
<tr>
<td>graphite monochromated</td>
<td></td>
</tr>
<tr>
<td>Take-off Angle</td>
<td>6.0°</td>
</tr>
<tr>
<td>Detector Aperture</td>
<td>4.5 mm horizontal</td>
</tr>
<tr>
<td></td>
<td>3.0 mm vertical</td>
</tr>
<tr>
<td>Crystal to Detector Distance</td>
<td>400 mm</td>
</tr>
<tr>
<td>Voltage, Current</td>
<td>50kV, 27.5mA</td>
</tr>
<tr>
<td>Temperature</td>
<td>26.0°C</td>
</tr>
<tr>
<td>Scan Type</td>
<td>ω-2θ</td>
</tr>
<tr>
<td>Scan Rate</td>
<td>4.0°/min (in ω) (up to 5 scans)</td>
</tr>
<tr>
<td>Scan Width</td>
<td>(1.73 + 0.14 tan θ)°</td>
</tr>
<tr>
<td>2θ/ω max</td>
<td>120°</td>
</tr>
<tr>
<td>No of Reflections Measured</td>
<td>Total: 2985</td>
</tr>
<tr>
<td></td>
<td>Unique: 2794 (R int = 0.014)</td>
</tr>
<tr>
<td>Corrections</td>
<td>Lorentz-polarization</td>
</tr>
<tr>
<td></td>
<td>Absorption</td>
</tr>
<tr>
<td></td>
<td>(trans. factors: 0.9544 - 1.0000)</td>
</tr>
<tr>
<td></td>
<td>Secondary Extinction</td>
</tr>
<tr>
<td></td>
<td>(coefficient: 3.81012e-005)</td>
</tr>
</tbody>
</table>
C. Structure Solution and Refinement

<table>
<thead>
<tr>
<th>Structure Solution</th>
<th>Direct Methods (SIR92)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Refinement</td>
<td>Full-matrix least-squares on $F^2$</td>
</tr>
<tr>
<td>Function Minimized</td>
<td>$\sum w(F_o^2 - F_c^2)^2$</td>
</tr>
<tr>
<td>Least Squares Weights</td>
<td>$1/\sigma^2(F_o) = 4F_o^2/\sigma^2(F_c^2)$</td>
</tr>
<tr>
<td>p-factor</td>
<td>0.0080</td>
</tr>
<tr>
<td>Anomalous Dispersion</td>
<td>All non-hydrogen atoms</td>
</tr>
<tr>
<td>No. Observations ($I&gt;10.00\sigma(I)$)</td>
<td>2786</td>
</tr>
<tr>
<td>No. Variables</td>
<td>469</td>
</tr>
<tr>
<td>Reflection/Parameter Ratio</td>
<td>5.94</td>
</tr>
<tr>
<td>Residuals. R1: wR2</td>
<td>0.036, 0.059</td>
</tr>
<tr>
<td>Goodness of Fit Indicator</td>
<td>2.03</td>
</tr>
<tr>
<td>Max Shift/Error in Final Cycle</td>
<td>0.00</td>
</tr>
<tr>
<td>Maximum peak in Final Diff Map</td>
<td>0.10 e$^{-}$/Å$^3$</td>
</tr>
<tr>
<td>Minimum peak in Final Diff Map</td>
<td>-0.11 e$^{-}$/Å$^3$</td>
</tr>
</tbody>
</table>