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REVIEW

Cyclophanes Containing Large Polycyclic Aromatic Hydrocarbons§

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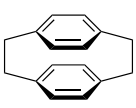
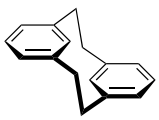
Cyclophanes have been firmly entrenched as a distinct class of compounds for well over half a century. The two main factors that have kept this field of chemistry going so strongly for such a long time are tremendous structural diversity and the interesting behaviour that is often observed. Although a very large number cyclophanes has been reported, only a very small proportion of them contain polycyclic aromatic systems that can be thought of as "large", *i.e*. with ≥4 rings. This Review puts the spotlight on such cyclophanes, illuminating both the chemistry that was used to synthesize them and what was learned from studying them. Context for the main body is provided by the careful consideration of the anatomy of a cyclophane and the classification of general synthetic approaches. The subsequent sections cover eleven different PAHs and are organized primarily according to increasing size of the aromatic system, starting with pyrene (C_{16}, the only large polycyclic aromatic system to have been incorporated into numerous cyclophanes) and ending with hexabenzo[*bc,ef,hi,kl,no,qr*]coronene (C_{42}).

1. Introduction

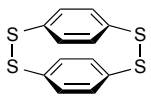
Cyclophane chemistry came into existence with a resounding bang in the middle of the 20th century with Brown and Farthing's isolation of [2.2]paracyclophane (**1**)[1] from the pyrolysate of *p*-xylene and Cram's subsequent rational synthesis.[2] Although Pellegrin's likely synthesis of *anti*-[2.2]metacyclophane (**2**) in 1899[3] and Parekh and Guha's synthesis of 1,2,9,10-tetrathia[2.2]paracyclophane (**3**) in 1934[4] (and also 1,8-dithia[1.1]paracyclophane(!)) long predate these seminal papers, the concept of bridged aromatic compounds (cyclophanes) and all of its trappings only took hold within the chemical community decades later. Once in place, it flourished and cyclophane chemistry developed rapidly into a vibrant and multifaceted field of study.[5]



1
Brown and Farthing, 1949
Cram 1951



2
Pellegrin, 1899



3
Parekh and Guha, 1934

[2.2]Paracyclophane (**1**), which is still widely regarded as the quintessential cyclophane, immediately caught the eye of researchers in diverse areas of chemistry. As such, interest in cyclophanes was triggered for a variety of reasons. These included symmetry, unusual structural features (especially nonplanar aromatic systems), synthetic challenge, through-space interactions between aromatic systems, conformational behaviour, the physical and chemical consequences of strain, and chirality. Over the ensuing decades, the reach of cyclophane chemistry extended into such diverse fields as host-guest chemistry, supramolecular chemistry, asymmetric synthesis, natural products, organometallic chemistry, polymer chemistry, functional pi systems and materials science. In accord with such broad interest, a very large and diverse array of cyclophanes has been reported.[5]

The tremendous breadth and unlimited scope of cyclophane chemistry has its root in the open-ended nature of what consititutes a cyclophane.[6] From the perspective of an aromatic system, it can become part of a cyclophane when two of its peripheral skeletal atoms are connected by a chain of atoms called a bridge. In the case of benzene, there are six peripheral skeletal atoms and three unique ways in which pairs of them can be bridged (bridging motifs), namely (1,2), (1,3) and (1,4) (Figure 1). The (1,2) bridging motif is equivalent to ring fusion and "orthocyclophanes" are consequently excluded from most discussions of cyclophane chemistry. This is not to say that there is no room for orthocyclophanes under the cyclophane umbrella. Indeed, there are circumstances where a cyclophane treatment is entirely appropriate[7] and there is consequently a significant body of literature on this subject.[8] It is, however, dwarfed by that pertaining to the (1,3) and (1,4) bridging motifs, *i.e*. metacyclophanes and paracyclophanes. In addition to the basic bridging motifs considered above, there are several higher bridging motifs that involve anywhere from three to all six of benzene's peripheral positions. Indeed, multibridged cyclophanes are well-known.[9]

The full structural scope of cyclophanes comes into focus when one considers that the number (≥1) and nature (benzenoid, heteroaromatic, homoaromatic, antiaromatic, polycyclic and even nonaromatic(!)[10]) of the aromatic system(s) can be varied

along with the bridging motifs of each individual aromatic system. On top of this, there can be as many bridges as allowed by the aromatic system(s) and each one of them can have variable length (≥0 contiguous atoms) and constitution (C and/or heteroatom of any hybridization).

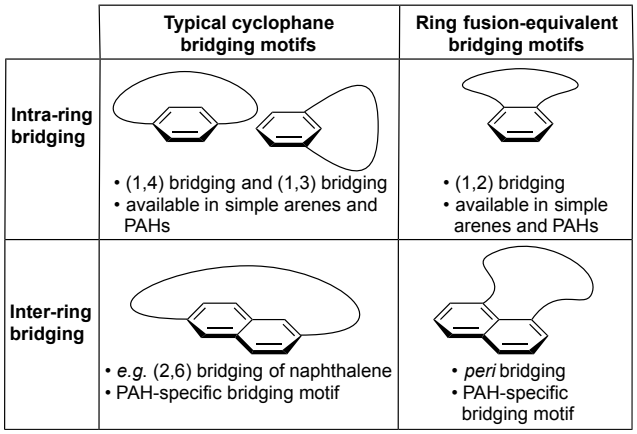


Fig 1 Basic bridging motifs for aromatic compounds.

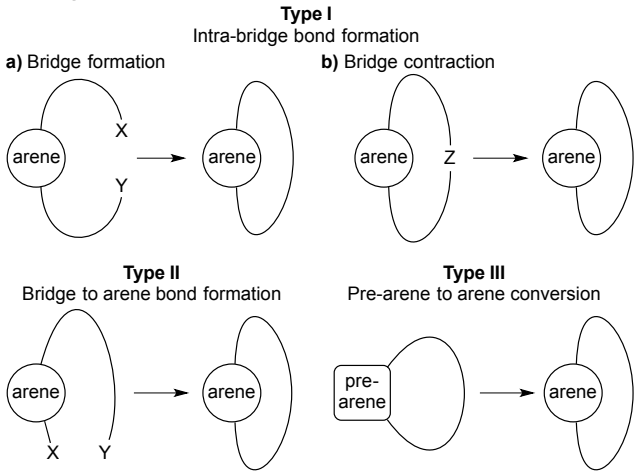
Even with benzene as the only available aromatic system, a very large number of cyclophanes can be envisaged. In fact, benzene-based cyclophanes are by far the most numerous of known cyclophanes. In moving to the next largest benzenoid aromatic system, naphthalene, the situation becomes more complex and the possibilities for cyclophane formation increase considerably. Of the ten peripheral carbon atoms in naphthalene, the two quaternary atoms can be excluded from consideration as connection points for the bridges because the aromatic system would be destroyed if they were to function as bridgeheads. In addition to the basic bridging motifs present in benzene (intra-ring bridging), new motifs that connect positions in different rings (inter-ring bridging), *e.g.* (2,6), become available. By the same token, new ring-fusion-equivalent motifs, *e.g.* (1,8), also emerge (Figure 1). The exclusion of all *ortho* motifs as well as all *peri* motifs leaves seven basic bridging motifs for naphthalene: (1,3), (1,4), (1,5), (1,6), (1,7), (2,6) and (2,7), all of which have been realized.[11] Numerous bridging motifs for multibridged naphthalenophanes are also available.

As the aromatic system becomes progressively larger through the fusion of additional benzene rings, the number of bridging motifs and ring-fusion-equivalent motifs (where bridgeheads are connected by a peripheral pathway consisting solely of quaternary carbon atoms) increases dramatically. In stark contrast to this trend, the increase in size is accompanied by an even more dramatic drop in the number of known examples. Indeed, relatively few cyclophanes that contain aromatic systems with four or more rings are known. Considering that aromatic systems become increasingly interesting as they become larger, it would seem that the relatively small set of cyclophanes containing large polycyclic aromatic hydrocarbons (≥4 more rings for the purpose of this review) merits a closer look. Thus, the objective of this review is to provide information about how such systems are synthesized, how they behave and what has been learned from them. With the prime focus being on benzenoid PAHs, polynuclear heteroaromatic systems and partially hydrogenated PAHs have been excluded.

2. General Synthetic Considerations

The diversity in cyclophane structure is far greater than that of the synthetic methodology that has been employed in their synthesis. From a strategic perspective, most cyclophane syntheses can be categorized neatly according to the event that results in cyclophane formation (with the complete aromatic system under consideration) (Scheme 1). Type I strategies involve the formation of a bond between two atoms in a bridge, either during bridge (and cyclophane) formation (Type I-a) or during contraction of an existing bridge (Type I-b). This is easily the most common strategy for cyclophane synthesis. Since the cyclization step (cyclophane-forming step) in a Type I-a reaction is intramolecular, moderate to high dilution conditions are normally beneficial, if not a necessity. This strategy is not generally very successful in the synthesis of even moderately strained cyclophanes, although some reactions (*e.g.* Wurtz coupling) fare better than others (*e.g.* ring-closing metathesis).

Type I-a reactions require one or more appropriately substituted aromatic compounds (most often disubstituted) as starting materials. Benzylic bromides and thiols feature prominently in this regard (S_N2 reactions). The synthesis of cyclophane precursors is not normally an issue when small aromatic systems are involved, but can be quite problematic for larger PAHs. Direct difunctionalization of large PAHs, if at all successful, provides access to only a very limited number of substitution patterns and can proceed with low regioselectivity for the ones that it does deliver. For example, the bromination of pyrene affords roughly equal amounts of 1,6- and 1,8-dibromopyrene. The separation of these two purchasable (but expensive) isomers from one another and small amounts of the 1,3 isomer is achievable, but laborious. Obviously, substitution patterns that are inaccessible through functionalization of a PAH must be accessed using multistep synthesis. In this regard, some substitution patterns can pose far stiffer synthetic challenges than others.[12] With low solubility (and even lability on occasion – *e.g.* benzylic bromides of certain PAHs) added to the equation, it becomes clear why there are so few cyclophanes with large PAHs.



Scheme 1 Strategies for the synthesis of cyclophanes.

Type I-b reactions involve the conversion of an existing cyclophane into another. In most cases, a larger cyclophane (such as a thiacyclophane obtained from thiol-bromide coupling) is subjected to a ring contraction reaction to form a

smaller and usually more strained cyclophane.[13] In the process, a new bond is formed between two previously unbonded atoms in the bridge. For many of the most frequently used ring contraction reactions (Stevens rearrangement, Wittig rearrangement, sulphone pyrolysis, photolysis in the presence of a phosphite), a bridge-opened reactive intermediate (*cf*. Type 1-a reactions) is passed through. As such, this approach works best when the target cyclophane has two or more bridges. Bridge contraction is a tried and tested strategy for synthesizing moderately strained cyclophanes,[14] but it is usually ineffective when called upon to access highly strained systems.[15]

Type II strategies involve the formation of a bond between an aromatic unit and a bridge. Reactions in this category are also intramolecular and suffer from the same drawbacks as Type I-a strategies. They are much less common than Type I strategies and have typically been applied to the synthesis of relatively unstrained cyclophanes.[16] Transition metal-catalysed cross-coupling reactions feature prominently in this category.

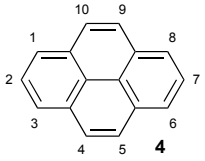
Type III strategies involve the generation of the aromatic system of a cyclophane from a bridged pre-arene in the cyclophane-forming reaction. In many cases, the conversion of the pre-arene to the corresponding arene is accompanied by a substantial amount of aromatic stabilization energy (ASE), which can serve as a weighty counterbalance to developing strain. As such, this approach is the best-suited one for the synthesis of more highly strained cyclophanes.[17] In this regard, the pre-arene often has a shape that more easily accommodates the bridge than the aromatic system it is destined to become and is thus relatively unstrained.

For the cyclophanes discussed in the following sections, only the key aspects of their syntheses will be presented at most. Full details of the synthetic pathways can be found in the cited publications.

3. Cyclophanes Containing PAHs with Four or More Rings

3.1 Pyrenophanes.

Pyrene (**4**) is the smallest *peri*-condensed benzenoid polycyclic aromatic hydrocarbon. It is especially interesting and useful because of its photophysical and photochemical properties.[18] Owing to the sensitivity of its fluorescence to its environment, it has long been used as a fluorescent probe in a broad range of applications. Indeed, it has been described as being endowed with "the status of gold standard as a molecular probe of microenvironments".[19] More recently, the importance of pyrene as a key structural unit in designed π systems has been steeply ascendant.[20,21] Since it is also the only large PAH to have been incorporated into a cyclophane on more than just a sporadic basis, a full cyclophane analysis is warranted. The reader is referred to the ESI for detailed analyses of the other PAHs dealt with in this review.

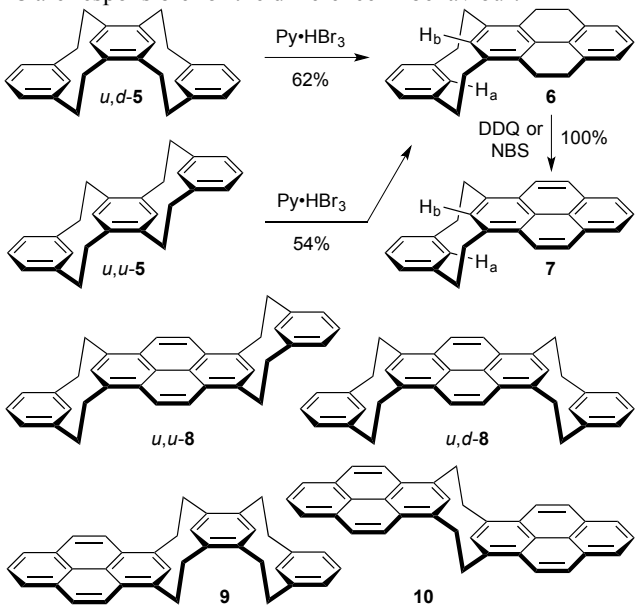


- 4 rings
- 16 total carbon atoms
- 10 non-quaternary atoms on the periphery
- 12 basic bridging motifs are available
- 7 basic bridging motifs are known

Pyrene has ten non-quaternary carbon atoms on its periphery and there are twelve basic bridging motifs for cyclophane formation, *i.e.* (1,3), (1,4), (1,5), (1,6), (1,7), (1,8), (1,9), (2,4), (2,5), (2,7), (4,9) and (4,10). To date, only the (1,3), (1,6), (1,7), (1,8), (2,4), (2,7) and (4,9) motifs have been realized. A handful of multibridged pyrenophanes have also been reported (Section 3.1.8). Despite the incomplete complement of basic bridging motifs, the known pyrenophanes have proved to be interesting and instructive, not only from a synthetic and structural perspective, but also because they have provided insight into a variety of fundamental phenomena and concepts.

3.1.1 (1,3)Pyrenophanes.

The very first pyrenophanes to be reported were the (1,3)pyrenophanes **7** and **8**,[22] the latter of which was synthesized in both its "*up,up*" (*u,u*) and "*up,down*" (*u,d*) conformations (Scheme 2). The syntheses highlight a common tactic for the construction of pyrene derivatives, *i.e*. the conversion of a [2.2]metacyclophane into a comparatively soluble 4,5,9,10-tetrahydropyrenophane[23] followed by dehydrogenation. For example, treatment of either conformer (*u,u* or *u,d*) of the layered [2.2]metacyclophane **5** with pyridinium perbromide afforded tetrahydropyrenophane **6**, which was then aromatized using DDQ (or NBS) to give **7**. Quadruple-layered [2.2]metacyclophanes served as precursors to *u,u*-**8** and *u,d*-**8**. Similar chemistry was used to prepare the related (1,3)pyrenophanes *u,d*-**9** and **10**.[24] The first lesson learned from these systems was that pyrene exerts a much stronger magnetic anisotropic effect than benzene. In going from **6** to **7**, the chemical shift of the "internal" proton of the benzene deck (H_a) was observed to move upfield substantially ($\Delta\delta$ = –0.82 ppm) whereas the corresponding proton on the polycyclic deck (H_b) moved to lower field by a similar amount ($\Delta\delta$ = 0.88 ppm). Also worthy of note is that the two isomers of **8** do not interconvert thermally up to 60 °C, whereas the two isomers of **5** interconvert readily. Presumably, *peri* interactions in **8** are responsible for the difference in behaviour.

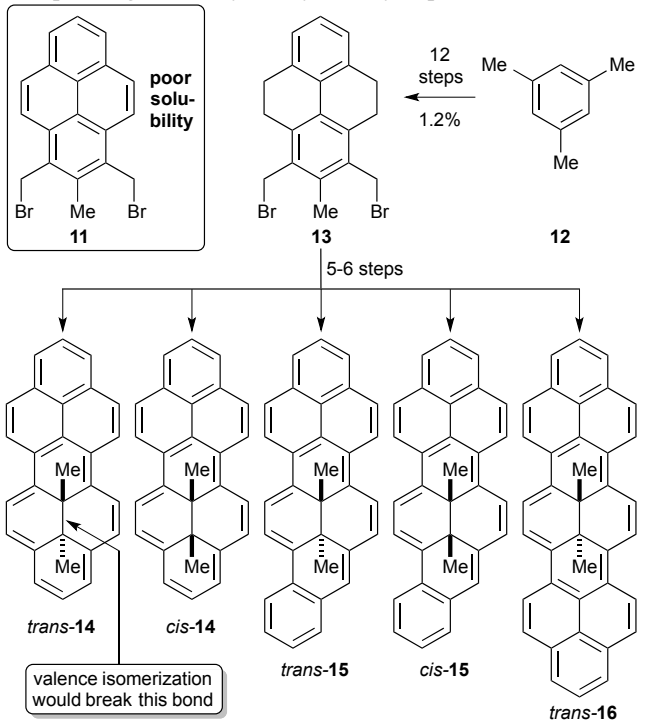


Scheme 2 (1,3)Pyrenophanes obtained from multilayered metacyclophanes.

The absorption spectra of the (1,3)pyrenophanes **7**-**10** are similar to that of pyrene, although the bands are a little broader and somewhat red-shifted (20–30 nm).[25,26] Since very similar changes also occur upon simple substitution at the 1 and 3

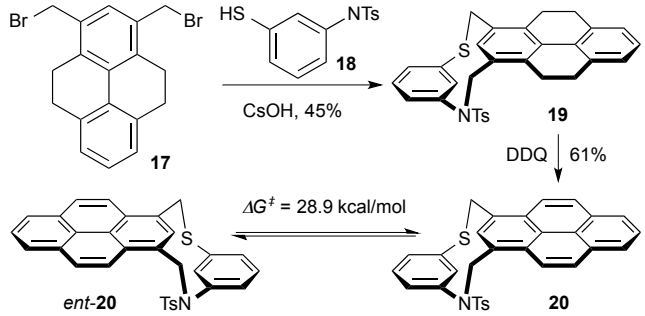
positions, it was concluded that there is little interaction between the two π systems. More interesting is the effect of solvent polarity on the fluorescence spectrum of *anti*-[2.2](1,3)pyrenophane **10**. In nonpolar solvents such as methylcyclohexane, its fluorescence spectrum consists of a band at about 410 nm originating from its locally excited state (monomer emission). However, in polar solvents such as acetonitrile, a broad featureless band centered at 475 nm was observed. This band was assigned to an intramolecular excimer state ("solvent-induced polarization state") that necessitates a conformational flip from *anti* to *syn*. This is remarkable, considering that the *syn* conformer of [2.2]metacyclophane has been calculated at the B3LYP/6-31+G(d,p) level of theory to be 10.3 kcal/mol higher in energy than the *anti* conformer.[27]

The highly diatropic benzannulated dimethyldihydropyrenes **15-17** are valence isomers of the corresponding internally substituted (1,3)pyrenophanedienes (not shown).[28,29] These systems are worth mentioning because their synthesis highlights the challenges associated with constructing PAH-based cyclophanes (Scheme 3). The originally intended (1,3)pyrenophane precursor **11** was not sufficiently soluble to be used in further synthetic work, so the analogous tetrahydropyrene **13** was synthesized. Although this compound was sufficiently soluble to be elaborated further, it required a 12-step synthesis from mesitylene (**12**). Five to six subsequent steps were then needed to reach the target systems **14-16**, which did not show any evidence of valence isomerization to the corresponding internally methylated cyclophanedienes.



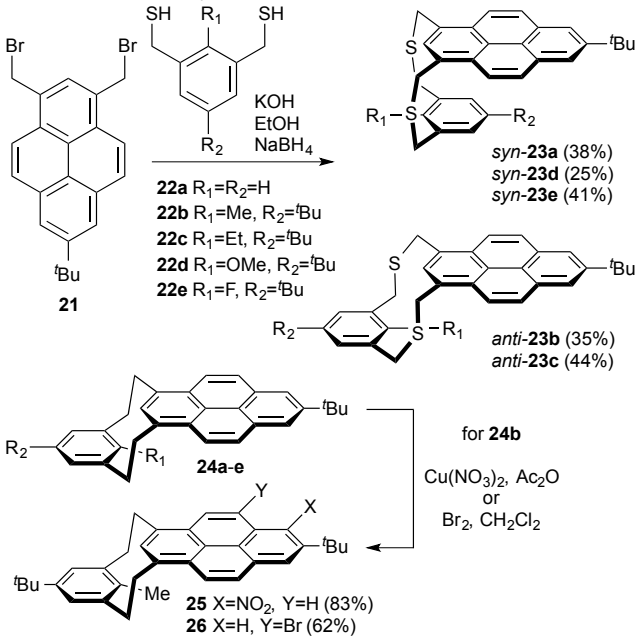
Scheme 3 Valence isomers of some internally substituted (1,3)pyrenophanes

The synthesis of the helically chiral (1,3)pyrenophane **24** also involved the intermediacy of tetrahydropyrenes (Scheme 4).[30] Dibromide **21**, which came from a [2.2]metacyclophane precursor, was reacted with 3-thio-*N*-tosylaniline **22** in the presence of CsOH to afford tetrahydropyrenophane **23**. Dehydrogenation with DDQ then delivered **24**. A partial separation of the enantiomers was achieved using chiral HPLC and this allowed the kinetics of racemization to be studied. The barrier to racemization (*anti–anti'* ring inversion) was determined to be 28.9 kcal/mol.



Scheme 4 Synthesis of helically chiral (1,3)pyrenophane **20**

The most recently reported (1,3)pyrenophanes are the only ones to have been synthesized without recourse to tetrahydropyrene intermediates.[31] The key to success in this work was the introduction of a *t*-butyl group at the non-business end of the pyrene system. Although this tactic improved the solubility, it came at the expense of synthetic expedience. A common pyrenophane precursor, 1,3-bis(bromomethyl)-7-*t*-butylpyrene **26** was accessed via a six-step sequence (23%) from pyrene (**4**). The final step of this sequence (not shown) was a tricky free radical benzylic bromination that only proceeded well with the correct combination of solvent (benzene) and initiator (V-65). Dibromide **26** was reacted with a series of dithiols to afford dithiapyrenophanes **28a-e**, each of which was obtained as a single conformer (either *syn* or *anti*). A combination of steric crowding in the *syn* conformers of **28b-c** and CH–π interactions between the internal substituents the π cloud of the pyrene system in the *anti* conformers was invoked to explain the preference of these cyclophanes for the *anti* conformation. Oxidation of **23a-e** to the corresponding sulfones followed by flash vacuum thermolysis (FVT) afforded the [2]metacyclo[2](1,3)pyrenophanes **24a-e**, all of which were obtained exclusively as *anti* conformers.



Scheme 5 Synthesis of (1,3)pyrenophanes **24a-e** and reactions of **24b**

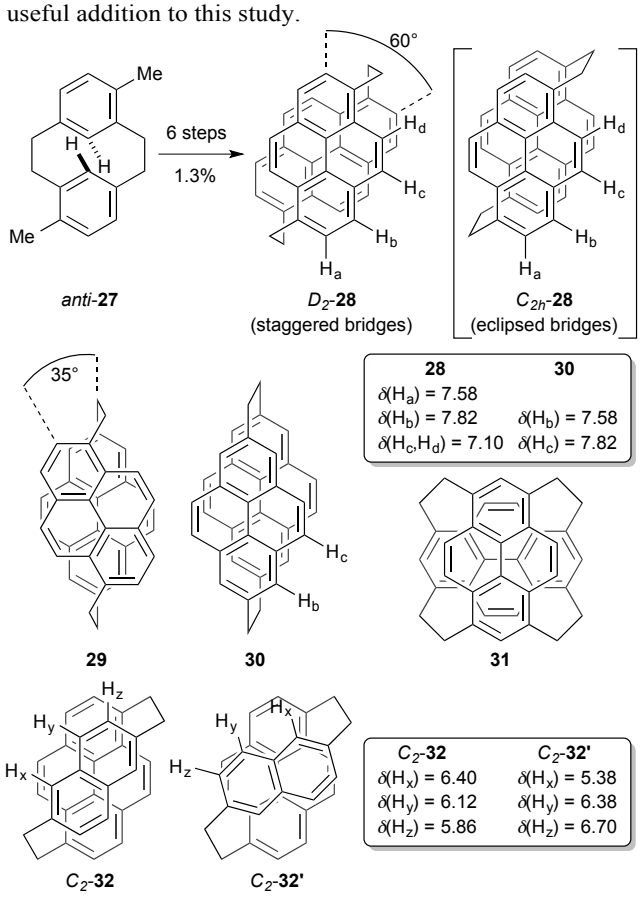
The synthesis of pyrenophanes **24a-e** delivered enough material (0.5 g of **24b**) for a brief investigation of their chemistry. Just two reactions were reported, but this was enough to produce thought-provoking results. Whereas [2.2]metacyclophanes usually afford tetrahydropyrenes when subjected to most electrophilic aromatic substitution reactions,[32] pyrenophane **24b** underwent completely regioselective nitration on the pyrene system *ortho* to the *t*-butyl group to afford **25**. Clearly, the electronic preference of pyrene to undergo substitution at the 1, 3, 6 and 8 positions is very strong. In contrast, bromination occurred exclusively in the K region to afford **26**. The same reactions of a model compound (7-*t*-butyl-1,3-dimethylpyrene, the direct synthetic precursor of **21**) were much slower and both resulted in substitution only adjacent to the *t*-butyl group. The faster rate of reaction for **24b** was explained as being due to a through-space electron donation from the benzene system to the pyrene pi system. Although a mechanism starting with the addition of Br_2 to the K region of the pyrene system of **24b** can account for the formation of **26**, it is not at all clear why this should be the case for **24b** and not for the model compound.

3.1.2 (1,6)Pyrenophanes.

In 1978, Misumi reported the synthesis of [2.2](1,6)pyrenophane (**28**) and [2.2](1,6)(2,7)pyrenophane (**29**) using chemistry similar to that described above.[33] This involved conversion of synthetic intermediate *anti*-4,12-dimethyl[2.2]metacyclophane **27**[34] into **28** through a six-step sequence (Scheme 6). At 1.3%, the overall yield of **28** from **27** punctuates the need for better synthetic methodology, not just for these systems, but for short-bridged cyclophanes as a whole. The marked upfield shift of protons H_c and H_d relative to H_a and H_b in the ^{1}H NMR spectrum of **28** was used to conclude that it prefers the D_2-symmetric structure in solution rather than the alternative C_{2h}-symmetric conformer. This is presumably due largely to staggering in the bridges of D_2-**28** as opposed to eclipsing in those of C_{2h}-**28**. Mixed pyrenophane **29** was synthesized by an analogous route, again in very low overall yield. [2](2,6)Naphthaleno[2](1,6)pyrenophane (**32**), which was also synthesized according to a Type I strategy, likewise has two available conformers (both having C_2 symmetry), but in this case both of them were formed (18:82 ratio of **32**:**32'**).[35] As with **28**, ^{1}H NMR spectroscopy was used to assign the structure of the major isomer as **32'**.

Along with [2.2](2,7)pyrenophane **30** (see Section 3.1.6), pyrenophanes **28** and **29** form an interesting series of compounds, in which two essentially parallel pyrene systems are held in an increasingly twisted orientation relative to a perpendicular axis: 0° (**30**), 35° (**29**) and 60° (**28**). The fluorescence spectrum of **30** (0° twist) consists of a single strong band (λ_{max}=540 nm), which is characteristic of excimer emission. Excimer emission (λ_{max}=500 nm) is still observed for **29** (35° twist), but its intensity is lower (a weak and structureless band is observed). On the other hand, the fluorescence spectrum of **28** (60° twist) consists of a relatively intense band at λ_{max}=440–450 nm, which corresponds to monomer emission. Evidently, the face-to-face orientation (0°) is the most favourable for excimer fluorescence over the range of 0–60° of twist. It would be most interesting to see whether excimer emission returns as the twist angle is increased beyond 60°, but this will require the synthesis of an appropriate cyclophane, *e.g.* **31**, which has 90° of twist.

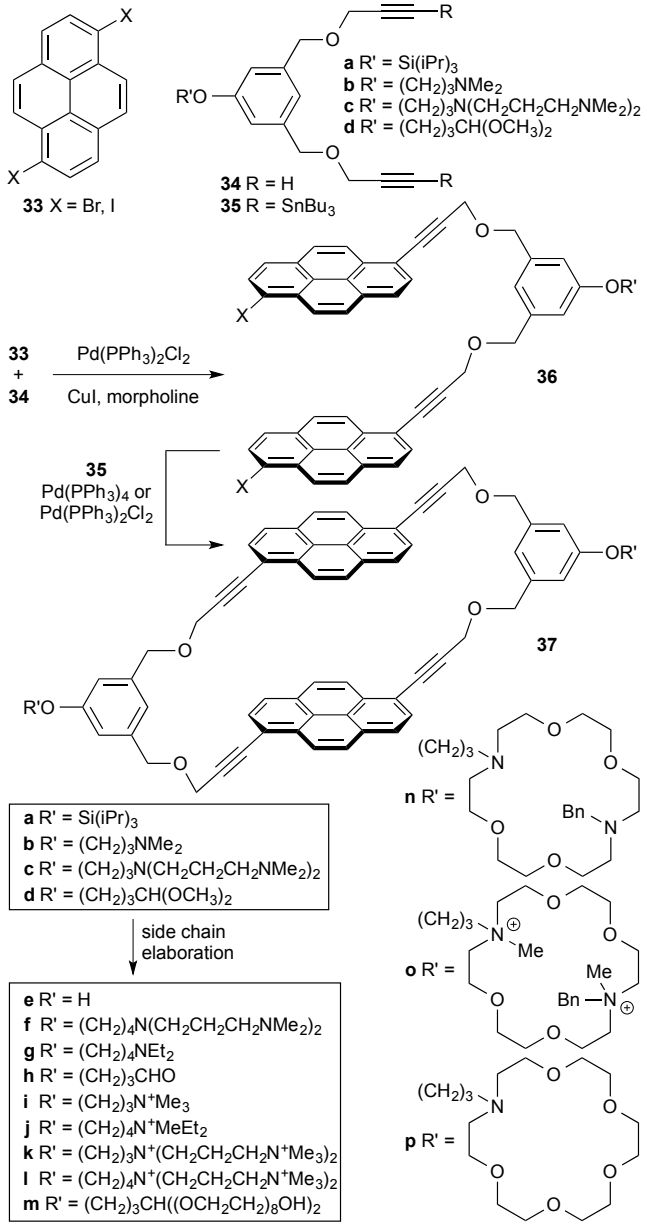
The effect of twisting two pyrene units relative to one another on the stabilization energy and spin distribution in the pyrenophane cation radicals was studied by ESR, ENDOR and CV.[36] As the degree of twist increases from 0°, the resonance integral β'_{1-u} undergoes changes that manifest themselves in a loss of resonance stabilization and a redistribution of spin. In other words, the bonding orbital ψ_- and antibonding orbital ψ_+, which result from the combination of the HOMOs of the two pyrene units, become closer in energy. At a twist angle of 30°, the orbital energies cross over and again reach a maximum energy difference at 60°, whereby resonance stabilization is regained. As before, a system with a 90° twist would have been a useful addition to this study.



Scheme 6 (1,6)Pyrenophanes **28**-**30** and **32**.

The (1,6)pyrenophanes **37a**–**p**,[37] several of which are water-soluble, are the largest and most elaborate pyrenophanes to have been reported to date. These systems were designed to have moderately rigid, side-chain-bearing frameworks that would encompass a neutral cavity and thereby resemble the hydrophobic areas of double helical DNA for the purpose of recognizing planar (aromatic) molecules in water. The pyrene systems not only provided a hydrophobic environment to the interior space, but also brought with them their distinct photophysical properties, which enabled the study of their molecular recognition abilities through UV/Vis and fluorescence spectroscopy. The cationic or amphiphilic side chains promoted water solubility while leaving the cavity uncharged. The calculated cavity of **37e** (R'=H) in the conformation shown in Scheme 7 (an "open" conformation) was calculated to have dimensions (0.46×0.95×1.31 Å), which should allow for the recognition of planar molecules as large as porphyrins. Although closed (collapsed) forms are likely to be

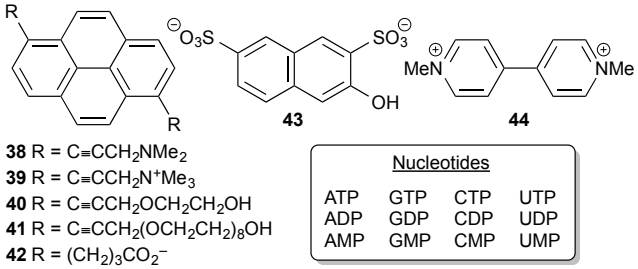
more stable than the open form in the absence of a guest, the systems have enough flexibility to receive a guest through an induced fit mechanism.



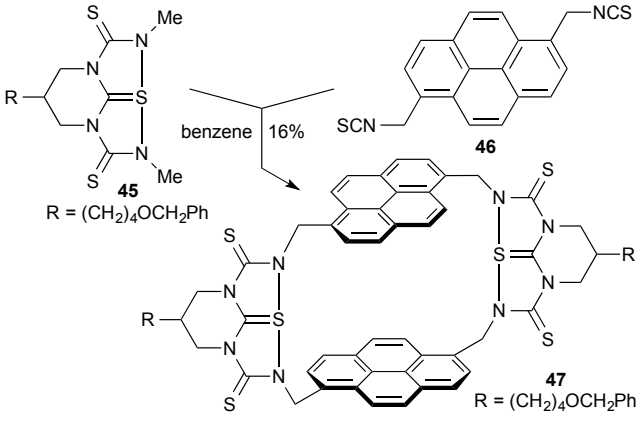
Scheme 7 Macrocyclic (1,6)pyrenophanes **37a-p**

The synthesis of pyrenophanes **37a-p** was conducted using a Type II strategy (Scheme 7). Sonogashira reaction of **33** (X=Br or I) with diynes **34a-d** afforded dihalodiynes **36a-d**. The key macrocyclizations were then achieved using Stille couplings of **36a-d** with distannanes **35a-d**. Elaboration of the side chains then afforded pyrenophanes **37e-p**, which include some positively charged, water-soluble systems. Hydrogenation of the alkynes in **37b** and **37i** afforded two saturated analogs (not shown). Not surprisingly, the pyrenophanes **37i** and **37m** showed only excimer emission (λ_{max}=520 nm) at any concentration in their fluorescence spectra.

A series of model and host molecules (**38**–**44** and a set of twelve nucleotides) were chosen to study the complexation behaviour of certain pyrenophanes. UV/Vis and fluorescence spectroscopy were used to establish that pyrenophane **37i** formed strong complexes (K_{assoc} = 9.0×10^3 – $\geq1.0\times10^6$) with anionic (**43** and the four nucleotide monophosphates) and cationic guests (**44**). The strong binding constants for the cationic guests were taken as evidence that the binding affinities were governed mainly by hydrophobic and/or pi stacking rather than electrostatic interactions. The macrocyclic nature of the pyrenophanes was also shown to be indispensable for complex formation. The neutral, polyether-substituted pyrenophane **37m** showed the greatest affinity for 1,6-disubstituted pyrenes (**39**, **41**, **42**), regardless of the charge on the substituents, whereas hexaammonium pyrenophanes **37k**,**l** and bis(diazoniacrown)pyrenophane **37o** exhibited the best affinity for aromatic species with negatively charged substituents, (**43** and the twelve nucleotides). Interestingly, the K_{assoc} values for the triphosphates (2.6×10^5 – 1.3×10^6) were about two orders of magnitude greater than those of the corresponding diphosphates (4.0×10^3 – 2.2×10^4) and monophosphates (1.9×10^3 – 4.0×10^3). This was ascribed to superior co-operative binding of the end phosphate group to the crown ether unit and the aromatic moiety to the pyrenophane.



A related, less flexible and decidedly unusual (1,6)pyrenophane (**47**) was reported at about the same time as **37a-p**.[38] A Type I synthetic strategy was employed, the key step of which was the very unusual cyclophane-forming reaction between tetraazathiapentalene **45** and 1,6-bis(isothiocyanatomethyl)-pyrene (**46**) (Scheme 8).

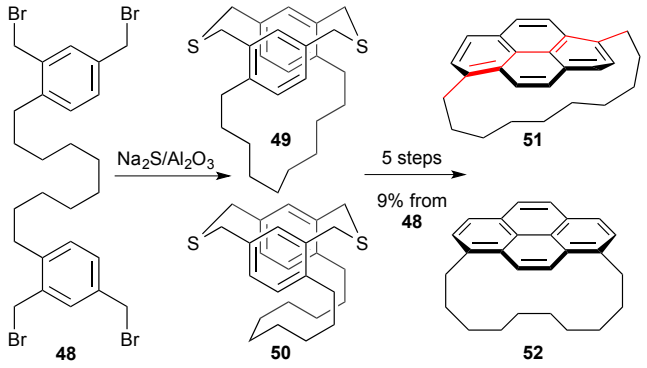


Scheme 8 Synthesis of (1,6)pyrenophane **47**

Semi-empirical calculations predicted a structure akin to the D_2-symmetric conformer of **28** (Scheme 6). In contrast to the relatively flexible pyrenophanes **37a-p**, which were calculated to have a face-to-face orientation of the two pyrene units and exhibited only excimer fluorescence, the fluorescence spectrum of **47** contained monomer (λ_{max}=408 nm) and excimer (λ_{max}=480 nm) fluorescence bands of roughly equal intensity. Evidently, the conditions for excimer formation (distance and

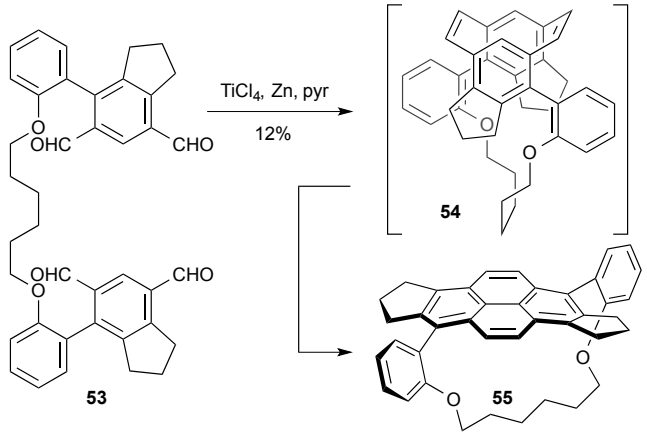
mutual orientation) in **47** are not optimal, but also not prohibitive.

Two very different [*n*](1,6)pyrenophanes have been recently added to the (1,6)pyrenophane family. What makes these systems interesting is that they are inherently chiral. [10](1,6)pyrenophane (**51**), a bare bones [*n*](1,6)pyrenophane, was obtained as the minor component of a 4:7 mixture with [10](1,8)pyrenophane (**52**).[39] The pyrenophane mixture was the end product of a low-yielding (9%) six-step sequence that started with the conversion of tetrabromide **48** into dithiacyclophane mixture **49**/**50** upon treatment with Na_2S/Al_2O_3 (Scheme 9). Pyrenophanes **51** and **52** could not be separated chromatographically or by crystallization, but crystal structures were obtained by fishing out two different-looking crystals from one batch of crystals. Short intermolecular CH–π contacts (2.64–2.76 Å) between the bridge of one molecule and the pyrene system of a neighbouring molecule of like chirality gave rise to single enantiomer columns in the crystal. The pyrene system of **51** was observed to have a gentle end-to-end bend along with a significant longitudinal twist. The degree of twist was quantified by the dihedral angles along the pathway (shown in red) that connects the two benzylic carbon atoms through the middle of the pyrene system. 10–20° deviations from the 180° angles in a planar pyrene system were observed. The enantiomers of **51** were separated using chiral phase HPLC, which allowed the measurement of their CD spectra and specific rotations. The more interesting question of how these properties change with increasing twist will have to wait until other (hopefully lower) homologues of **51** can be synthesized.



Scheme 9 Synthesis of [10](1,6)pyrenophane **51** and [10](1,8)pyrenophane **52**

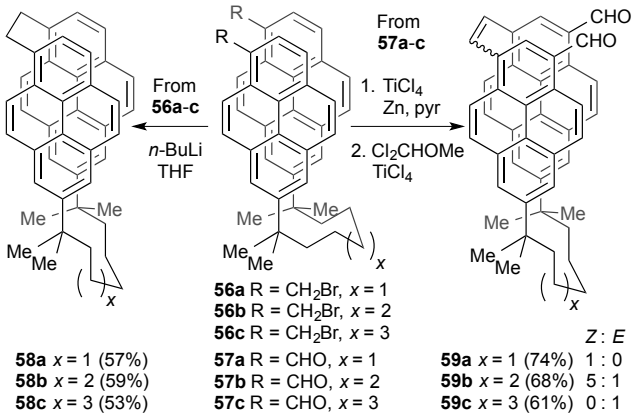
The much more elaborate [12](1,6)pyrenophane **55** was synthesized in just five (!) steps.[40] The first step (not shown) was a very productive multicomponent reaction that assembled all of the skeletal atoms except for the $(CH_2)_6$ chain. The final step was a domino double intramolecular McMurry / valence isomerization / dehydrogenation reaction of tetraaldehyde **53** (Scheme 10). The 12% yield of this reaction is actually quite impressive when one considers how much it accomplishes. The conversion of the presumed [2.2]metacyclophanediene intermediate **54** to the pyrenophane **55** under reductive conditions (oxidative conditions are usually employed for such transformations) is quite remarkable. As with **51**, the two enantiomers of **55** were separated by chiral HPLC and their CD spectra and specific rotations were recorded, but the absence of other homologues precluded the investigation of how the chiroptical properties change with incremental distortion of the pyrene system.



Scheme 10 Synthesis of highly decorated (1,6)pyrenophane **55**

3.1.3 (1,7)Pyrenophanes.

[*n*.2](7,1)Pyrenophanes **58a-c** and pyrenophane-monenes **59a-c** were reported as synthetic intermediates *en route* to the [*n*](2,11)teropyrenophanes described in Section 3.8.[41,42] Both were synthesized according to Type I strategies, whereby the two-atom bridges were installed directly from dibromides **56a-c** and dialdehydes **57a-c** in decent yield using intramolecular Wurtz couplings and McMurry reactions, respectively (Scheme 11). The avoidance of thiacyclophanes saved several synthetic steps. The unusual 1,7 substitution pattern of the pyrene systems in **56a-c** and **57a-c** was obtained through a combination of Friedel-Crafts *tert*-alkylation (high 2,7 selectivity) and other electrophilic aromatic substitution reactions (high 1,3,6,8 selectivity). The crude McMurry products were subjected to Rieche formylation to facilitate purification. The olefination reactions are noteworthy in that the stereochemical outcome was strongly dependent upon the length of the long bridge. In going from **59a**, (7-atom bridge), to **59c** (9-atom bridge) the geometry of the newly-formed alkene went from 100% *Z* to 100% *E*.

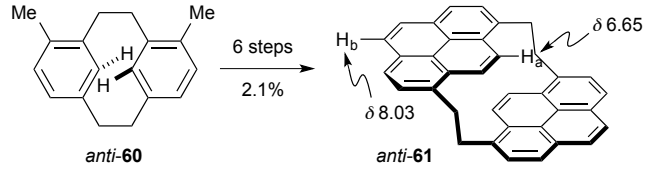


Scheme 11 Synthesis of (1,7)pyrenophanes **58a-c** and **59a-c**

3.1.4 (1,8)Pyrenophanes.

Only two (1,8)pyrenophanes have been reported, namely [2.2](1,8)pyrenophane **61** and [10](1,8)pyrenophane **52**. The former cyclophane was synthesized from *anti*-4,14-dimethyl[2.2]metacyclophane **60** by way of a very low-yielding (2.1%) six-step sequence (Scheme 12) that mirrored the synthesis of **28** (Scheme 6).[33] The adoption of an *anti* conformation (staggered bridges) was inferred from the high

field shift of H_a compared to H_b in the ^1H NMR spectrum of **53**. The absorption spectrum of *anti*-**64** was red shifted (*ca*. 40 nm) from that of pyrene (**1**), but not nearly as much as those of **36** and **41** (*ca*. 120 nm), which is consistent with a lesser degree of interaction between the pyrene systems. The fluorescence spectrum of *anti*-**64** (λ_{max}=410 nm) resembles that of monomeric pyrene, which further supports the notion that pyrene excimers have a limited range of favorable geometries. Looking forward, the recent development of a highly selective method for accessing 1,8-dihalopyrenes offers opportunities for the synthesis of further (1,8)pyrenophanes.[43]



Scheme 12 Synthesis of (1,8)pyrenophane **61**

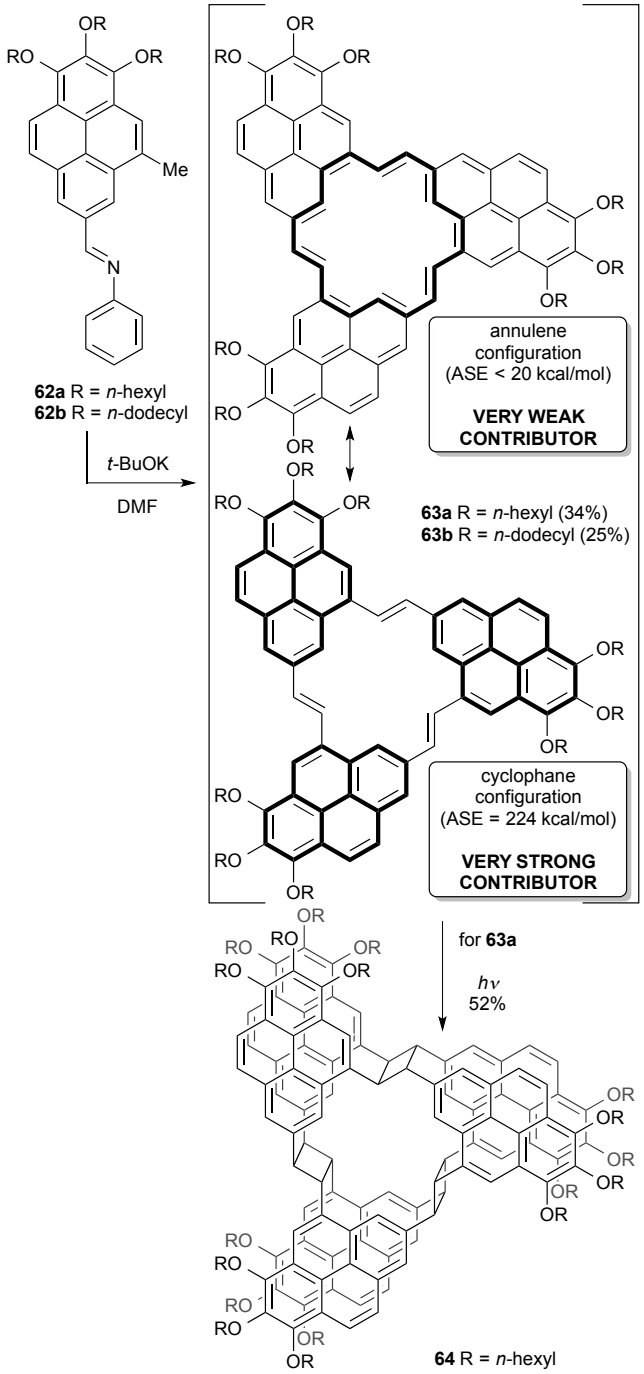
(1,8)Pyrenophane **52** (Scheme 9) undergoes a conformational process in which the bridge flips from one side of the pyrene system to the other.[39] The energy barrier to this process was determined to be 14.9 ± 0.2 kcal/mol using dynamic NMR experiments.

3.1.5 (2,4)Pyrenophanes.

The synthesis of the only known (2,4)pyrenophanes (**63a-b**) was accomplished using a rather unusual Type I strategy.[44] The uncommon substitution pattern on the pyrene system in pyrenophane precursors **62a-b** was established through a multistep sequence that included two separate photochemically-driven electrocyclic ring-closing reactions to generate the two central rings of the pyrene system. The cyclophane-forming reaction (**62a-b** to **63a-b**) was a rare example of the Siegrist reaction (Scheme 13). As before, the modest yield (25-34%) should be considered in the context of what is accomplished.

These rather large pyrenophanes are prime examples of how diffuse the boundaries between cyclophanes and other classes of designed pi systems can be. Although **63a-b** were named as annulenes, *i.e.* "tripyreno[2,3,4-*abc*:2,3,4-*ghi*:2,3,4-*mno*][18]annulenes", no evidence was found for the existence of a macrocyclic ring current. Accordingly, they were described as consisting of "aromatic 'islands' which are combined by *trans* configured 'bridges'," *i.e.* as cyclophanes! In fact, the annulene configuration and the cyclophane configuration are simply different resonance contributors to a resonance hybrid. The cyclophane configuration consists of three intact pyrene systems, each of which has a large amount of aromatic stabilization energy (ASE) (74.6 kcal/mol).[45] On the other hand, the annulene configuration consists of an [18]annulene unit with three completely bond-fixed pyrene units having no cyclic π electron delocalization at all. Different types of stabilization energies for [18]annulene have been calculated[46] and measured[47] to be quite small (16-28 kcal/mol), which pales in comparison to the contribution of three times the ASE for pyrene (224 kcal/mol).

Although the lowest energy conformation of the macrocyclic core of **63a-b** is not perfectly planar, the overall shape of the molecules is reasonably flat, or disc-like. This, in conjunction with the nine alkoxy side chains, led to the formation of aggregates in solution, as indicated by concentration-dependent NMR experiments. Conversely, there was only a small concentration effect on the fluorescence spectrum and fluorescence lifetime, which appeared to be due to almost undisturbed monomer. A rapid collapse of excited aggregates was proposed to explain this behaviour. Nevertheless, short-lived excimers were thought to be responsible for the regio- and stereoselective photodimerization of **63a**, which afforded belt-like pyrenophane **64** in an impressive 52% yield (Scheme 13).[48]



Scheme 13 Synthesis of (2,4)pyrenophanes **63a-b** and **64**.

3.1.6 (2,7)Pyrenophanes.

The (2,7)pyrenophanes are easily the most populous class of pyrenophanes. They are especially interesting because the 2 and 7 positions are the maximally separated pair of skeletal

atoms in pyrene. Consequently, any distortion from planarity of the pyrene system is distributed over the full length of the pyrene framework. Two different bend angles (θ[49] and α[50]) and a bowl depth parameter (h)[51] have been used to quantify such end-to-end bend. The angle θ (Fig 2), which is the smallest angle between the planes defined by C1-C2-C3 and C6-C7-C8 (pyrene numbering), will be used here.

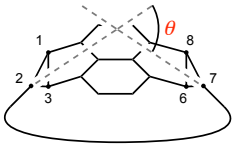
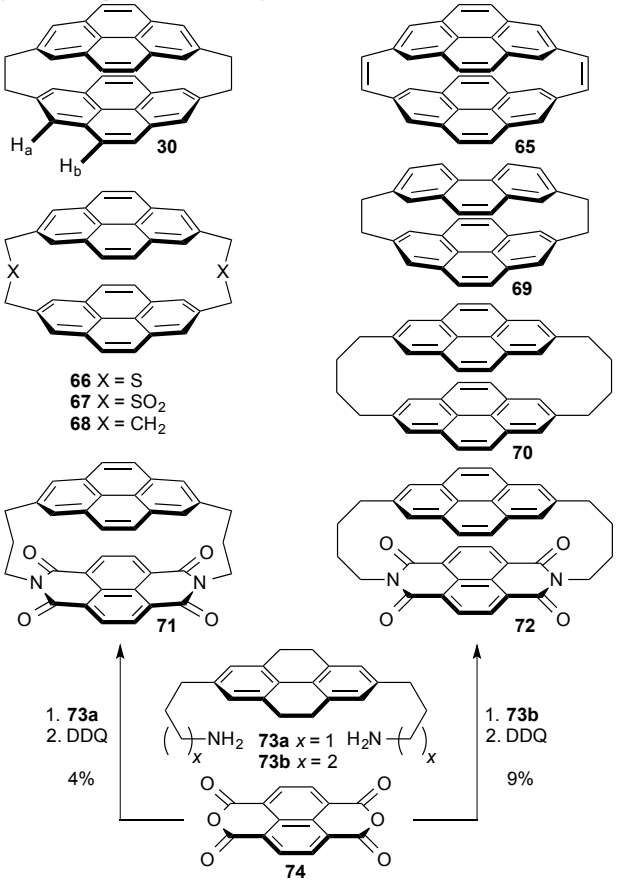


Figure 2 Definition of the bend angle θ

(2,7)Pyrenophanes **30** and **65-72**, which were reported over a *ca*. two-decade period starting in the mid 1970s, feature a pyrene system that is held in a face-to-face orientation with respect to either a second pyrene system or a different aromatic system of similar size.[33,35,52–57] The only notable departure from the standard Type I cyclophane chemistry was with the synthesis of **71** and **72**.[57] Here, the key cyclophane-forming reactions took place between naphthalene 1,4,5,8-tetracarboxcylic dianhydride (**74**) and bis-2,7-(ω-aminoalkyl)-4,5,9,10-tetrahydropyrenes **73a-b** (Scheme 14). Dehydrogenation of the resulting tetrahydropyrenophanes (not shown) with DDQ afforded pyrenophanes **71** and **72**. Although the approach to **71** and **72** was unique, it certainly didn't offer any advantages in terms of yield.

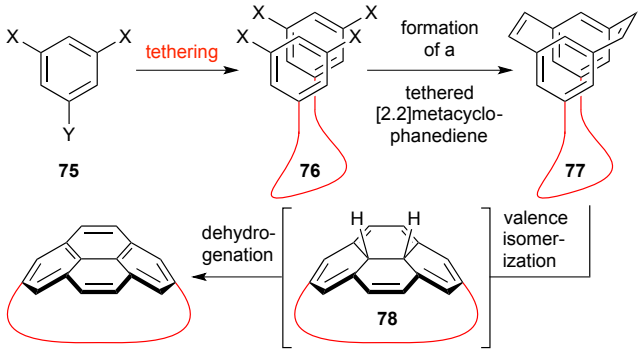


Scheme 14 (2,7)Pyrenophanes **30** and **65-72**.

The pyrenophanes **30**, **68** and **70** form an interesting series, in which the two pyrene systems are increasingly bent, albeit not over a particularly large range (θ = 0°, 19.0° and 37.9° for **70**, **68** and **30**, respectively).[52,56,58,59] In the absorption spectra of these three compounds, the shortening of the bridges is accompanied by a red shift and loss of vibronic fine structure of the lowest energy bands, which was explained as being due to increasing interactions between the two pi systems as they are forced closer to one another. All three pyrenophanes exhibit pure excimer fluorescence (λ_{max} = 556, 515, 469 nm for **30**, **68** and **70**, respectively) with Stokes shifts close to that of pyrene (5050 cm^{-1}). Transannular interactions between the pyrene systems were studied by various groups.[60]

As in many other cyclophanes with face-to-face oriented aromatic rings, the chemical shifts of the aromatic protons of **30**, **68** and **70** (H_a and H_b in structure **30** in Scheme 14) are observed at substantially higher field than those of an appropriate model compound, in this case 2,7-dimethylpyrene (δ 7.97 and 7.98).[61] The influence of increasing distortion on the chemical shifts of the aryl protons is, however, ambiguous. As the pyrene systems become more distorted (**30** to **68** to **70**), H_b moves to progressively to lower field (δ 7.33 to 7.41 to 7.45), whereas H_a has a less clear trend (δ 7.32 to 7.39 to 7.20). The problem here is that the way in which the two pyrene systems affect one another magnetically changes not only with their shape, but also with their relative positions in space.

To meaningfully address the effects of increasing bend in the pyrene (or any aromatic) system on its properties (spectroscopic, physical, chemical), it would be more useful to have access to series of cyclophanes containing not two, but just one aromatic system, *i.e.* [*n*]cyclophanes. Thus, a more instructive set of compounds is the [*n*](2,7)pyrenophanes **79a-d**,[62,63] 1,*n*-dioxa[*n*](2,7)pyrenophanes **80a-f**[51,64,65] and 4-oxa[7](2,7)pyrenophane (**81**),[49] which were synthesized using a Type III strategy (Scheme 15). An appropriately trisubstituted aromatic compound **75** was tethered to afford a bis(difunctionalized) species **76**. This was then converted into a [*n*.2.2](1,3,5)cyclophane (tethered [2.2]metacyclophanediene) **77**. Heating the dienes in the presence DDQ brought about a valence isomerization / dehydrogenation (VID) reaction to afford the respective pyrenophanes **79a-d**, **80a-f** and **81**. Some of the dienes with longer bridges underwent VID reaction under the conditions of their formation.[51]



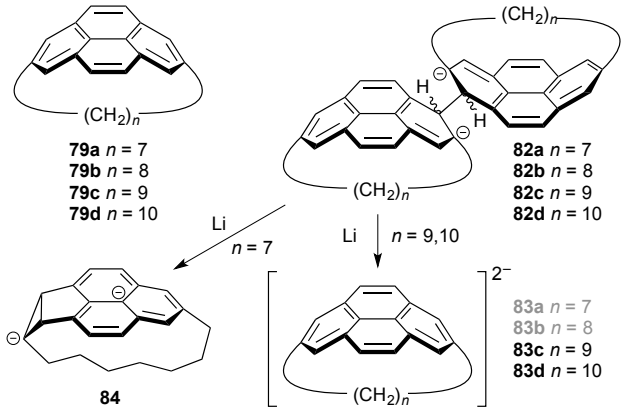
Scheme 15 General strategy for the synthesis of [*n*](2,7)pyrenophanes **79a-d**, 1,*n*-dioxa[*n*](2,7)pyrenophanes **80a-f** and 4-oxa[7](2,7)pyrenophane (**81**).

The VID reaction in the synthesis of (2,7)pyrenophanes has been discussed in detail elsewhere,[66] but a couple of key points are worth mentioning here. Although it resembles the [2.2]metacyclophane to 4,5,9,10-tetrahydropyrene transformation that has featured prominently up to now, the VID reaction is far more powerful when it comes to the generation of more highly distorted pyrene systems. To a large extent, this is because it goes directly to the pyrene system. Apart from obviating the need for a separate (and often low-yielding) dehydrogenation step, the large ASE of the pyrene system (74.6 kcal/mol)[45] plays a major role in offsetting developing strain as the innately bent and relatively unstrained [2.2]metacyclophanediene **77** goes through (presumably) a *cis*-10b,10c-dihydropyrenophane **78** to the pyrenophanes **79a-d**, **80a-f** and **81**.

The bend in the pyrene system in pyrenophanes **79a-d** and **80a-f** spans a very broad range (θ=34.6° for **80f**, to 109.2° for **80a**). Interestingly, the smallest θ value in this series rivals that of the pyrene systems in **30** (37.5°), which were originally considered to be highly distorted. At the other end of the scale, the pyrene system in **80a** is more bent that the one that can be identified in the equator of D_{5h} C_{70}.[65] The most important conclusion from the study of these compounds was that the aromaticity of the pyrene system (as measured by geometric (HOMA), magnetic (NICS) and energetic (ASE) criteria) is affected only weakly by bending out of planarity.[50,51] Gently to quite substantially bent pyrenes retain well over 90% of the aromaticity of planar pyrene. When the very most distorted systems are reached, the retention of aromaticity is still 65-80%, depending upon the criterion that is used to measure it.

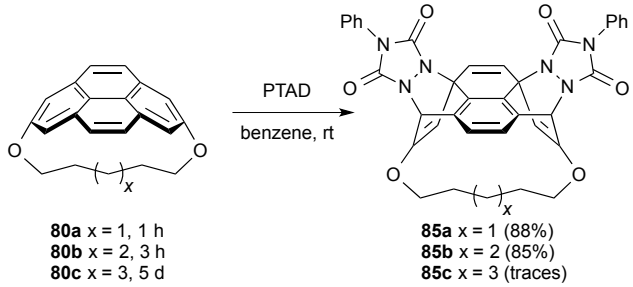
The ^{1}H NMR spectra of **79a-d** and **80a-f** show a consistent upfield shift of both H_a and H_b with increasing bend. As expected, some of the bridge protons are observed at very high field (*e.g.* as high as δ –2.10 for **79a**). In the absorption spectra, the longest wavelength signals (*p* bands) do not shift significantly over the full range of bend, but their intensity drops off with increasing bend. Fluorescence spectra have only been recorded for **79a**, **79d** and **81**,[67] but the substantial difference in θ values does allow for conclusions to be drawn about the effect of bend. Only monomer emission is observed in all cases, even at concentrations as high as 1 mM. A red shift and a drop in the quantum yield were observed in going from **79d** (θ=46.4°, λ_{max}=397 nm, Φ=0.54) to **79a** (θ=97.5°,[68] λ_{max}=423 nm, Φ=0.37) to **81** (θ=102.9°, λ_{max}=429 nm, Φ=0.19). Interestingly, the fluorescence spectrum of **79a** showed small (vibrational?) bands at 380 and 390 nm, which hints at the emergence of unusual behaviour as the pyrene system reaches the higher end of the bend range. Electrogenerated chemiluminesce in the presence of dibenzoyl peroxide resulted in both monomer and excimer emission for **79d** (λ_{max}=420, 589 nm), **79a** (λ_{max}=439, 603 nm) and **81** (λ_{max}=444, 607 nm). Again, there was a consistent red shift as the bend in the pyrene moiety became larger.

The increase in bend in the pyrene system upon going from **79d** to **79a** is accompanied by intriguing changes in behaviour upon reduction by alkali metals (Scheme 16).[63,69,70] All four pyrenophanes were found to accept an electron to give a radical anion, which dimerized to afford dianions **82a-d** as single (but unassigned) diastereomers. For the two least strained systems, further reduction with Li metal resulted in the formation of formally antiaromatic dianions **83c-d**, thus mirroring the behaviour of pyrene and 2,7-dimethylpyrene. The situation was then observed to change as the bridge became shorter. Dianion **82b** was completely resistant to further reduction and **82a** rearranged to afford rearranged dianion **84**. The reluctance of **82b** to undergo further reduction was explained as being due to the unfavourability of forming a strained antiaromatic system (**83b**). Of course, the formation of **83a** should be even more unfavourable. Here, it was surmised that the additional strain in **83a** provided it with access to the strain-relieving rearrangement leading to **84**. The formation of a bicyclo[3.1.0]hexane framework at the expense of a benzene ring would normally be expected to be energetically costly, but in the case of **84** it neatly avoided the formation of a strained antiaromatic system by kinking the (former) pyrene system and generating an aromatic phenalenyl anion. The odd man out is the system with the eight-carbon bridge. Dianion **83b** is apparently too strained to form, but not strained enough for the sacrificial rearrangement to be a viable escape route.



Scheme 16 Reduction of pyrenophanes **79a-d**

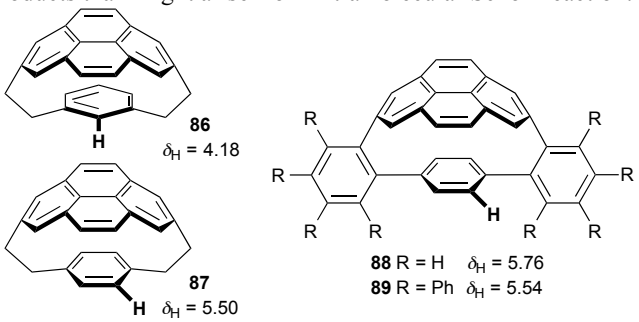
A rather limited amount of chemistry has been performed on the [*n*](2,7)pyrenophanes. Some of the more strained cyclophanes undergo Diels-Alder reactions across the 1 and 3a positions of the pyrene system with reactive dienophiles such as TCNE and PTAD (Scheme 17).[62,65] For example, **80a** and **80b** react with PTAD to afford 1:2 adducts **81a-b.** Pyrenophane **80c** is virtually unreactive under the same conditions, which again indicates that a certain amount of strain relief is needed to compensate for the loss in ASE. Electrophilic aromatic substitution reactions of **79a-d** and **80a-f** could be very useful starting points for the synthesis of larger aromatic systems, but nothing has been reported on this front other than unsuccessful attempts to electrophilically brominate **80d**,[62] which afforded either addition or bridge-cleaved products.



Scheme 17 Diels–Alder reactions of **80a-c** with PTAD

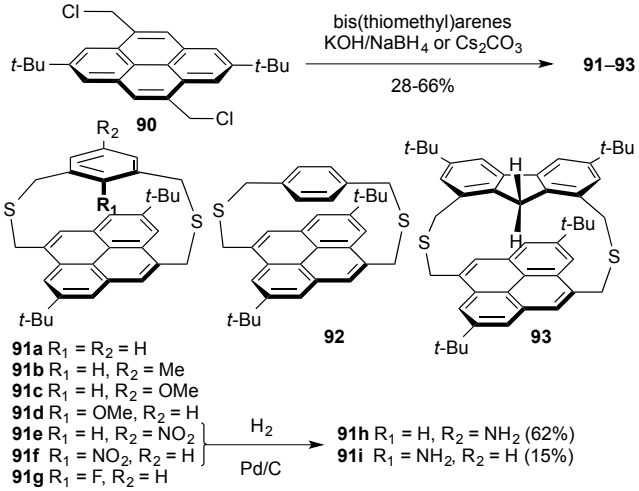
A handful of mixed [2.2]cyclophanes of benzene and pyrene (**86**–**89**) have been synthesized using the same general approach as for the [*n*](2,7)pyrenophanes.[71–73] All four cyclophanes

exhibit high field-shifted aryl protons on the benzene deck. Pyrenophane **86** undergoes a conformational flipping of the *meta*-substituted ring ($\Delta G^{\ddagger}$=18.9 kcal/mol), whereas **87** features very wide bond angles (*ca*. 125°) at the benzylic carbon atoms adjacent to the benzene ring. For **88** and **89**, the lines between cyclophanes and other classes of designed pi systems are once again blurry. They could just as easily be viewed as cyclic oligoarylenes or benzannulated cyclophanedienes. Octaphenylpyrenophane **89** is intriguing because of the products than might arise from intramolecular Scholl reaction.



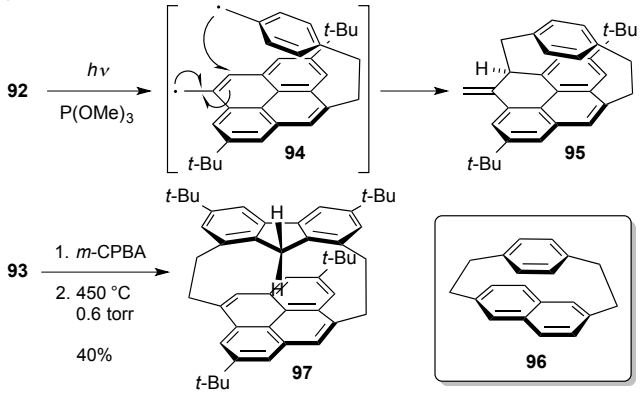
3.1.7 (4,9)Pyrenophanes.

All of the known (4,9)pyrenophanes have been synthesized according to Type I strategies that proceeded through 2,7-di-*t*-butyl-4,9-bis(chloromethyl)pyrene (**90**, 6 steps from pyrene, 30%).[74] The functionalization of pyrene on the 4 and 9 positions through electrophilic aromatic substitution was enabled by the presence of the *t*-butyl groups at the 2 and 7 positions. In this case, the bulk of these groups provided enough steric hindrance to the neighbouring 1, 3, 6 and 8 positions to disfavour substitution at these sites. Reaction of dichloride **90** with various bis(thiomethyl)arenes afforded dithia(4,9)pyrenophanes **91-93** in modest to moderate yield (Scheme 18).[74–77] A macrocyclic cyclophane (not shown was obtained in low yield from the reaction between **90** and 1,2-bis(thiomethyl)benzene.[75] The S_N2 transition state leading to the desired dithia[3.3]cyclophane is presumably too strained.



Scheme 18 Synthesis of (4,9)pyrenophanes **91-93**

Strain is surely also responsible for the failure of attempts to ring contract pyrenophanes **91a** and **92** using either photolytic desulfurization or sulphone pyrolysis. Indeed, a most unusual cyclophane, phenanthrenophane **95**, was obtained from the attempted photolytic desulfurization of **92** (Scheme 19). The formation of **95** can be explained easily enough from the presumed diradical intermediate **94**, but what makes the result interesting is that the analogous ring contraction leading to naphthalenophane **96** was successful (9%).[78] The difference in the outcome of these two reactions again highlights the importance of the interplay between strain and aromaticity. The unusual pathway (leading to **91**) leads to the formation of a less strained product than the usual pathway (leading to **92**), but at the cost of the ASE of one six-membered ring. It is reasonable to assume that that the amount of strain relief is approximately the same in the two reactions, so the difference is reactivity is a reflection of the lower aromaticity in one ring of naphthalene (HOMA=0.802) than the "central" ring of pyrene (HOMA=0.572).[79]



Scheme 19 Synthesis of phenanthrenophane **95** and (4,9)pyrenophane **97**

For the [3]metacyclo[3](4,9)cyclophanes **91a-g**,[76,77] those systems lacking an internal substituent (**91a-c**, and **91e**) exhibit two AB systems for the bridge protons in their ^{1}H NMR spectra as low as –100 °C. This was interpreted as being due to a "perpendicular conformation", but is also consistent with a rapid conformational equilibrium between two degenerate face-to-face conformers. On the other hand, the ^{1}H NMR spectra of those systems having an internal substituent (**91d**, **91f** and **91g**) exhibit four AB systems, which indicates that these systems are conformationally rigid.

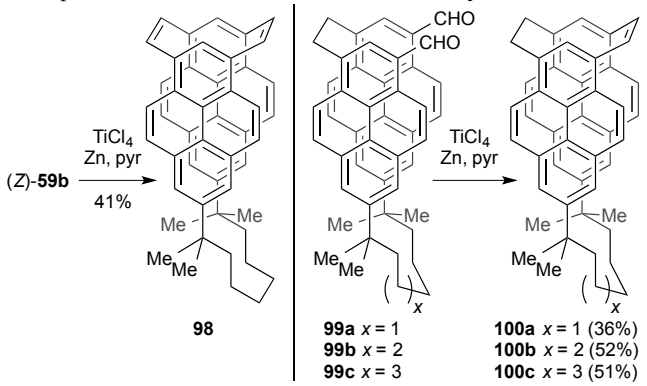
Reduction of **91e** and **91f** afforded the corresponding amines **91h** and **91i**, the latter of which is especially interesting owing to its internal amino substituent. The NH stretching frequencies in its infrared spectrum are observed at 3438 and 3298 cm^{-1}, which are at significantly lower frequencies than those of pyrenophane **91h** (3480 and 3380 cm^{-1}) and 2,6-dimethylaniline (3484 and 3400 cm^{-1}). The significant shift to lower frequency in **91i** was ascribed to NH–π bonding. Further evidence to support this conclusion was obtained from the much lower stability constant of the 1:1 charge transfer complex of **91i** (1.25 L/mol) with TCNE than that of **91h** (8.58 L/mol). It was reasoned that the participation of the π cloud of the pyrene moiety in hydrogen bonding with the amino group rendered the pyrene unit less π basic, which weakened its charge transfer complex.

Unlike **91a** and **92**, dithia[3](1,8)fluoreno[3](4,9)pyrenophane **93** was successfully ring-contracted to afford the corresponding [2.2]cyclophane **97**. The success of this ring contraction is due to the greater span of the (1,8)fluorenylene unit than the (1,3)- and (1,4)phenylene units. Both **93** and **97** are conformationally locked up to 150 °C, with the C-9 methylene group sitting over

the pyrene system. Not only are these protons at very much higher field than those of an appropriate model compound (δ = 3.95), but one of the protons at this site (the "inner" protons) points towards the pyrene system and consequently resonates at significantly higher field than those pointing away from it (the "outer" protons). Upon going from **93** (δ_{inner} = –0.48, δ_{outer} = 1.40) to **97** (δ_{inner} = –0.80, δ_{outer} = 1.59) the inner proton moves to higher field, as one might expect from bringing the two aromatic systems closer together. In fact, this proton has the largest $\Delta\delta$ value (4.75 ppm) of any pyrenophane proton. Perhaps counterintuitively, the "outer" proton moves to lower field. The fluorescence of **97** was observed to be *ca*. 35% more intense than that of **93** and this was ascribed to intramolecular energy transfer from the fluorene system to the pyrene component.

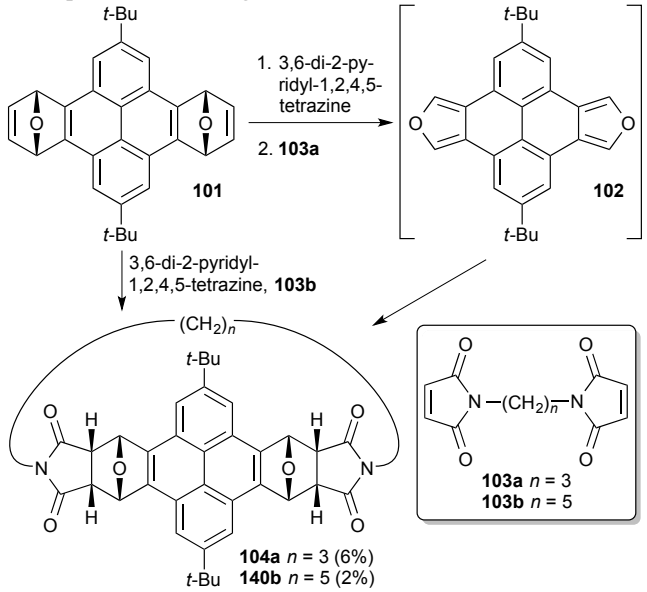
3.1.8 Multibridged Pyrenophanes.

Until recently, there were no examples of pyrenophanes with more than two bridging points. The first such system to be reported was [8.2.2](7,1,3)pyrenophanediene **98**, which was synthesized in 41% yield by the intramolecular McMurry reaction of (*Z*)-**59b** (Scheme 20).[41] Subsequently, it was reported that dialdehydes **99a-c**, which were obtained from the formylation of **58a-c**, also underwent McMurry reactions to afford [*n*.2.2](7,1,3)pyrenophanemonoenes **100a-c**.[42] The success of these McMurry reactions contrasts numerous earlier reports that the McMurry reaction was generally ineffective for the formation [2.2]metacyclophanes with unsaturation in one or both of the bridges.[80] It may be that π–π interactions between the two pyrene systems in the starting dialdehydes and/or increased preorganization due to the presence of two bridges are responsible for the success of the McMurry reactions.



Scheme 20 Synthesis of [*n*.2.2](7,1,3)pyrenophanes **98** and **100a-c**

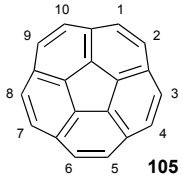
The most highly bridged pyrenophanes reported to date are the two homologous (4,5,9,10)pyrenophanes **104a-b**. The Type 1 synthetic strategy involved the exploitation of Warrener's "dipytet" methodology for the synthesis of isobenzofurans,[81] which are especially reactive Diels-Alder dienes (Scheme 21). Application of this chemistry to diether **101** (a double Diels-Alder adduct obtained from the reaction of 4,5,9,10-tetrabromo-2,7-di-*t*-butylpyrene with *n*-BuLi in furan) afforded relatively unstable bis(isobenzofuran) **102** in very low yield (2%). The synthesis of cyclophanes **104a-b** was achieved by double Diels-Alder reactions of **102** with bis(maleimide)s **103a-b**, either using a sequential one-pot procedure to give **104a** (6%) or *in situ* generation of **102** to afford **104b** (2%). The central bridge protons of **104a** and **104b** lie over the center of the pyrene system and are consequently observed at very high field (δ –2.46 ppm and δ –2.1, respectively). Whereas the pyrene system in **104b** is essentially planar, the pyrene system in **104a** is gently bent in an end-to-end fashion (θ =18.5°) with the *convex* face exposed to the bridge.



Scheme 21 Synthesis of (4,5,9,10)pyrenophanes **104a-b**

3.2 Corannulenophanes.

Corannulene (**105**) is the smallest innately bowl-shaped fullerene fragment. The nonplanar geometry renders the construction of corannulenophanes especially interesting. The relatively high symmetry and the presence of only one type of non-quaternary peripheral carbon atom mean that there are only five possible basic bridging motifs ((1,3), (1,4), (1,5), (1,6) and (1,8)).



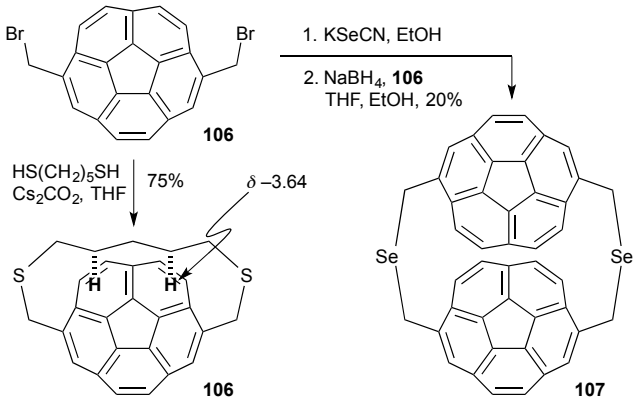
- 6 rings
- 20 total carbon atoms
- 10 non-quaternary atoms on the periphery
- 5 basic bridging motifs are available
- 2 basic bridging motifs are known

3.2.1 (1,6)Corannulenophanes.

The two known (1,6)corannulenophanes (**107** and **108**) were arrived at *via* Type I approaches,[82] both of them proceeding through 1,6-bis(bromomethyl)corranulene (**106**) (6 steps from 2,7-dimethylnaphthalene). Reaction of **106** with 1,5-pentanedithiol under basic conditions efficiently afforded "basket" **107** (2,8-dithia[9](1,6)corannulenophane) (Scheme 22). "Basket ball" **108** (2,15-diselena[3.3](1,6)corannulenophane) was obtained by conversion of **106** to the corresponding bis(selenacyanide) (not shown) followed by reduction in the presence of more **106**. The unusual choice of a diselenacyclophane arose from unsuccessful attempts to form the analogous dithiacyclophane.

Like the [*n*](2,7)pyrenophanes, the bridge in **107** is held in an *all-anti* conformation across the concave face of the aromatic system. Whereas a bridge flip in the [*n*](2,7)pyrenophanes is degenerate, the lower symmetry of **107** means that there are

two possible *all-anti* conformations. Based on its ^{1}H NMR spectrum, one of them is dominant. On the NMR timescale, the rapid bowl-to-bowl inversion of the corannulene system is arrested and there is no jump-rope motion of the bridge from one face of the corannulene system to the other. Two of the bridge protons are observed at very high field shifts (δ –3.64), a full 5 ppm upfield from those of the corresponding protons in 1,5-pentanedithiol. The observation of such an extraordinarily large $\Delta\delta$ value for a simple [*n*]corannulenophane suggests that corannulene exerts a considerably stronger magnetic anisotropic effect than pyrene (*cf.* $\Delta\delta$ values of up to 3.3 ppm for the [*n*](2,7)pyrenophanes).



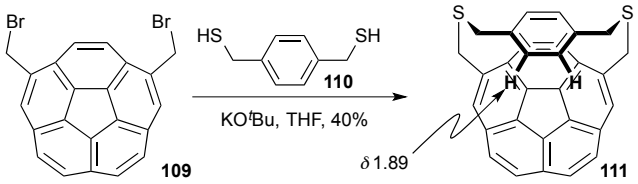
Scheme 22 Synthesis of (1,6)corannulenophanes **107** and **108**

Ab initio calculations predicted that the bowl depth of the corannulene moiety in **107** is 0.96 Å, which significantly exceeds that of corannulene (**105**) (0.88 Å). This corresponds to a *ca*. 5 kcal/mol increase in strain in the corannulene moiety (and likely more in the whole cyclophane). Attempts to extrude the S atoms from the bridge to afford [7](1,6)corannulenophane were unsuccessful. This is not at all surprising because the methods that were employed (photolysis in $P(OEt)_3$ and oxidation to the corresponding disulfone followed by flash vacuum thermolysis) typically fail when called upon to deliver more highly strained products. The bowl depth calculated for the bridge-contracted cyclophane (1.20 Å) corresponds to a *ca*. 30 kcal/mol increase in strain in the corannulene moiety alone.

"Basket ball" corannulenophane **108** was formed as a 10:1 mixture of two isomers (^{1}H NMR analysis). The major isomer was shown to have an *anti* arrangement of the two corannulene units by nOe difference experiments. This *anti*-face-to-face orientation mirrors that of opposing corannulene units in C_{60}, although the two arenes are much closer to one another in **108**. In the calculated structure of the sulphur analog of **108**, the edges of two arenes are separated by only 3.3 Å. This proximity is likely why the sulphide coupling failed and the selenide coupling succeeded (C–Se = 1.98 Å vs. C–S = 1.81 Å).

3.2.2 (1,8)Corannulenophanes.

"Covered basket" **111** (2,15-dithia[3.3](1,8)corannulenophane) was synthesized in 40% yield by the coupling of 1,8-bis(bromomethyl)corannulene (**109**) (5 steps from 3,8-dimethyl-1,2-acenaphthylenedione, 9%) with 1,4-bis(thiomethyl)benzene (**110**) (Scheme 23).[83] This compound was originally named as a (2,5)corannulenophane, but it has been changed here to (1,8) to give the lowest possible number to the first point of substitution on the corannulene system.

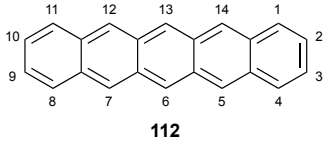


Scheme 23 Synthesis of (1,8)corannulenophane **111**.

The calculated bowl depth of the corannulene moiety in **111** is 0.87 Å (*cf.* 0.89 Å for corannulene (**105**)), which suggests that this cyclophane has considerably less strain than **108**. The calculated lowest energy conformation of **111** has both CH_2SCH_2 bridges pointing away from the corannulene system and this places two of the protons of the benzene ring almost directly over the centre of the corannulene bowl, *ca*. 2.5 Å over the best plane of the rim carbon atoms and 3.4 Å above the plane of the five-membered ring. As in the case of (1,6)corannulenophane **107**, the very strong anisotropic effect of corannulene causes these protons to be observed at remarkably high field (δ 1.89), a whopping 5.4 ppm upfield from the corresponding protons of **110**. No conformational processes (benzene ring twirl or skipping rope motion of the benzene ring from one face of the corannulene system to the other) were observed up to 148 °C.

3.3 Pentacenophanes.

Pentacene (**112**) is a tremendously important aromatic system because of its prevalence in the field of molecular electronics, most notably as a hole-transporting material in organic field-effect transistors (OFET). In contrast to the large body of literature on pentacene and its derivatives, there is but a single report of a pentacenophane.[84]

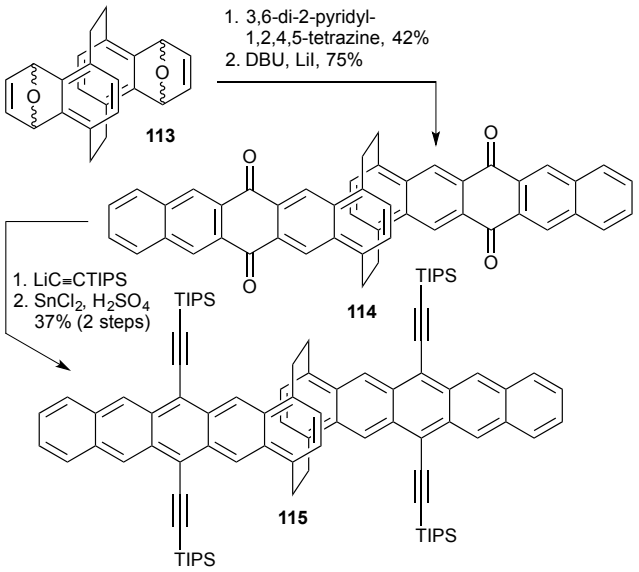


- 5 rings
- 22 total carbon atoms
- 14 non-quaternary atoms on the periphery
- 24 basic bridging motifs are available
- 1 basic bridging motif is known

3.3.1 (1,4)Pentacenophanes.

Reminiscent of the syntheses of pyrenophanes **104a-b**, the six-step synthesis of *anti*-[2.2](1,4)pentacenophane **115** relied on Diels-Alder reactions of isobenzofurans (Scheme 24). Diether **113** (two steps from [2.2]paracyclophane) was reacted with dipytet in the presence of 1,4-anthraquinone, to afford (after subsequent aromatization) *anti*-[2.2]cyclophane **114**. Acetylide addition and reductive aromatization then delivered the blue pentacenophane **115**. This is a Type III strategy in which the quinone systems in **114** serve as pre-arenes for the pentacene systems in **115**.

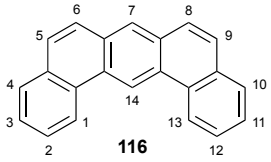
The face-to-face overlap of the two pentacene systems had the effect of red-shifting the longest wavelength *p* band by about 20 nm compared to an appropriate model compound. This was explained as arising from a coupling of the two pentacene systems and a consequent splitting of the two sets of frontier molecular orbitals akin to Davydov splitting in organic crystals. Recall that similar orbital mixing between face-to-face-oriented pyrene systems arose in pyrenophanes **28-30** (Scheme 6). The HOMO-LUMO gap for **115** was determined to be *ca*. 1.9 eV both computationally and experimentally (CV, UV-vis).



Scheme 24 Synthesis of *anti*-[2.2](1,4)pentacenophane **115**.

3.4 Dibenzo[*a,j*]anthracenophanes.

Dibenzo[*a,j*]anthracene (**116**) is a far less important PAH than its constitutional isomer pentacene (**112**), but it has made more appearances in the cyclophane literature.

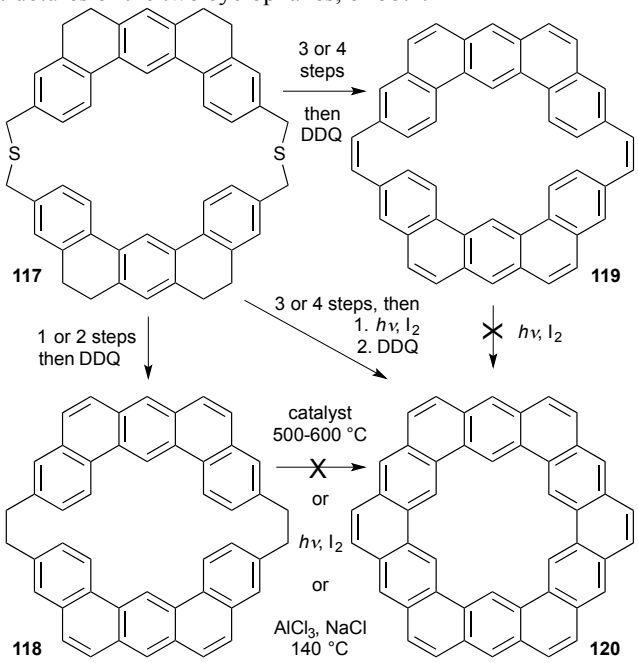


- 5 rings
- 22 total carbon atoms
- 14 non-quaternary atoms on the periphery
- 42 basic bridging motifs are available
- 2 basic bridging motif are known

3.4.1 (3,11)Dibenzo[*a,j*]anthracenophanes.

[2.2](3,11)Dibenzo[*a,j*]anthracenophanes **118** and **119** were synthesized in connection with Staab's landmark synthesis of kekulene (**120**).[85] They were obtained in a few steps from dithiacyclophane **117**, which contains partially saturated (tetrahydrodibenzo[*a,j*]anthracene) aromatic systems (Scheme 25). The use of such a heavily hydrogentated dithiacyclophane was necessary because the precursors to the corresponding fully aromatic cyclophane were not sufficiently soluble. For both **118** and **119**, classic cyclophane chemistry was used to bring about ring contraction and the dibenzo[*a,j*]anthracene systems were installed in the final step by dehydrogenation with DDQ (a Type III strategy). Attempts to generate kekulene (**120**) from **118** by thermal, photochemical and wet chemical methods afforded a mixture of "extremely insoluble" compounds, starting material and a "black solid", respectively. Prolonged irradiation of cyclophanediene **119** was also unsuccessful, although MS analysis of the product mixture did show a (presumably small) signal corresponding to kekulene (**120**). In any event, the successful route to kekulene (**120**) ultimately avoided dibenzo[*a,j*]anthracenophanes altogether. A hydrogenated version of **119** (not shown) was smoothly cyclodehydrogenated photochemically and the resulting octahydrokekulene was then dehydrogenated using DDQ.

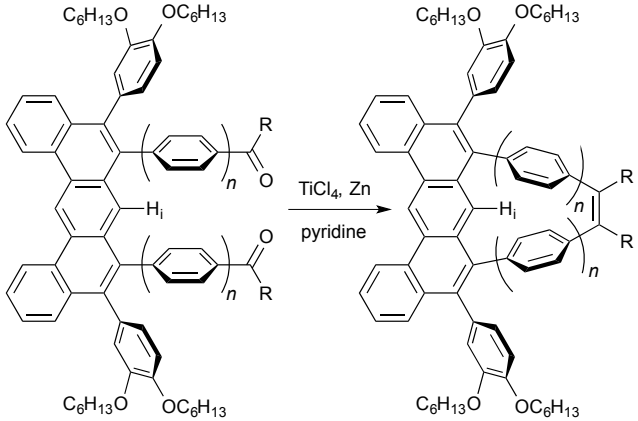
The ease of the photochemical cyclodehydrogenation leading to kekulene (**120**) compared to that of **119** is noteworthy, considering that both reactions were expected to be unfavourable (the sum of the free valence indices (ΣF^*) of the carbon atoms involved in bond formation in the first excited state is well below 1.0 for both compounds). The observed difference in behaviour may be a consequence of differences in the nature of the two chromophores, differences in the structures of the two cyclophanes, or both.



Scheme 25 Synthesis of kekulene (**120**).

3.4.2 (6,8)Dibenzo[*a,j*]anthracenophanes.

A set of four (6,8)dibenzo[*a,j*]anthracenophanes **122a-d** was synthesized using McMurry reactions of **121a-d** (Scheme 26).[86] Considering that the products are not insignificantly strained, especially **122a-b**, the yields of these reactions are very good.



121a *n*=1, R=H
121b *n*=1, R=Me
121c *n*=2, R=H
121d *n*=2, R=Me

122a *n*=1, R=H (63%)
122b *n*=1, R=Me (53%)
122c *n*=2, R=H (67%)
122d *n*=2, R=Me (71%)

Scheme 26 Synthesis of (6,8)dibenzo[*a,j*]anthracenophanes **122a-d**

It is interesting to note that no products arising from intermolecular reaction were observed. The crumpling of the bridging arylene-ethenylene units that occurs upon formation of the cyclophanes has the effect of shifting the internal proton (H_i) on the dibenzo[*a,j*]anthracenophane systems to significantly higher field. For example, in going from **121a** to

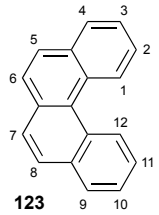
122a, H_i moves from δ 7.25 to δ 5.91. Due to the orthogonality of the dibenzo[*a,j*]anthracene systems to the bridging arylene-ethenylene units, the absorption spectra of **122a-d** all show lowest energy absorption maxima at 312 nm, which corresponds to the absorption of the dibenzo[*a,j*]anthracene moiety.

3.5 Helicenophanes.

Helicenes are very attractive aromatic systems for the construction of cyclophanes, due not only to their innate nonplanarity, but also their chirality and exceptionally high specific rotations.[87]

3.5.1 [4]Helicenophanes.

Although [4]helicene (**123**) is formally the fourth member of the helicene family, it is the smallest one to have a lowest energy conformation that is nonplanar (helical) and thus deserve consideration as a *bona fide* helicene. It does have very low configurational stability, but this situation can be effectively remedied by substitution at the 1 and 12 positions. To find examples of [4]helicenophanes, one must look to other classes of aromatic compounds and then make the case for membership in the cyclophane club. This is not a difficult task, but it does require one to make decisions about how far one is comfortable in going with the cyclophane concept.

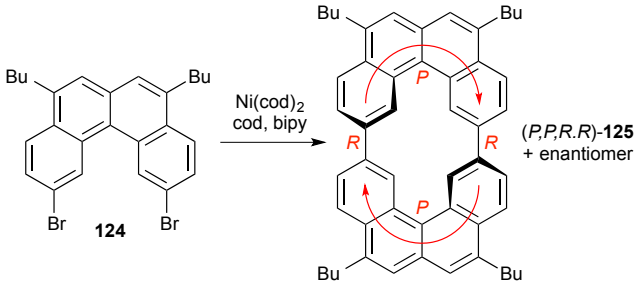


- 4 rings
- 18 total carbon atoms
- 12 non-quaternary atoms on the periphery
- 29 basic bridging motifs are available
- 3 basic bridging motifs are known

3.5.1.1 (2,11)Helicenophanes.

It is certainly debatable whether bridge lengths in cyclophanes should start at zero or one atom. If one accepts that a zero-atom bridge (a biaryl bond) is valid, then compound **125** is indeed a cyclophane, and a fascinating one at that. Originally named cyclobis[4]helicene (*i.e.* as a cyclic oligoarylene), [0.0](2,11)[4]helicenophane (**125**) was synthesized *via* a Type II synthetic strategy that culminated with a Yamamoto coupling of 2,11-dibromo[4]helicene **124** (Scheme 27).[88]

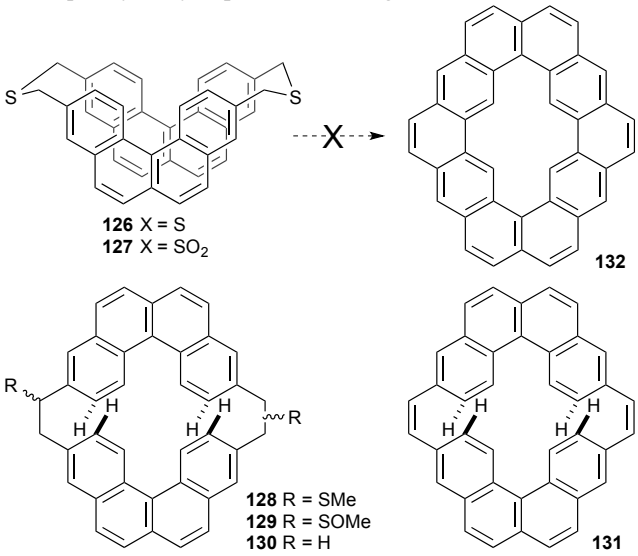
A crystal structure determination revealed that individual molecules of **125** are comprised of two helicene units of the same configuration. Akin to (1,6)pyrenophane **51**, the enantiomers of **125** recognize one another and form alternating single-enantiomer columns in the crystal. Calculations predicted that the corresponding *meso* isomer is 7.5 kcal/mol higher in energy and that interconversion of the two enantiomers requires an activation energy of just 10.1 kcal/mol. Interconversion in solution is therefore rapid at room temperature. Upon initial examination of the representation of (*P,P,R,R*)-**125** in Scheme 27, it would appear as though tracking a circle (red arrows) around the two helicene moieties results in a perpetual downward motion, which is reminiscent of a well-known impossible object, the Penrose stairs. Since a molecule of (*P,P,R,R*)-**125** is a real object, there must be something missing from or flawed in the initial analysis. The flaw is that the axial chirality associated with the biaryl bonds has been overlooked. When the notation of the chirality of the biaryl bonds is converted to helicene notation, the description goes from (*P,P,R,R*) to (*P,P,M,M*). Thus, each biaryl "bridge" corresponds to a step up between two descending staircases.



Scheme 27 Synthesis of [0.0](2,11)[4]helicenophane **125**

3.5.1.2 (3,10)[4]Helicenophanes.

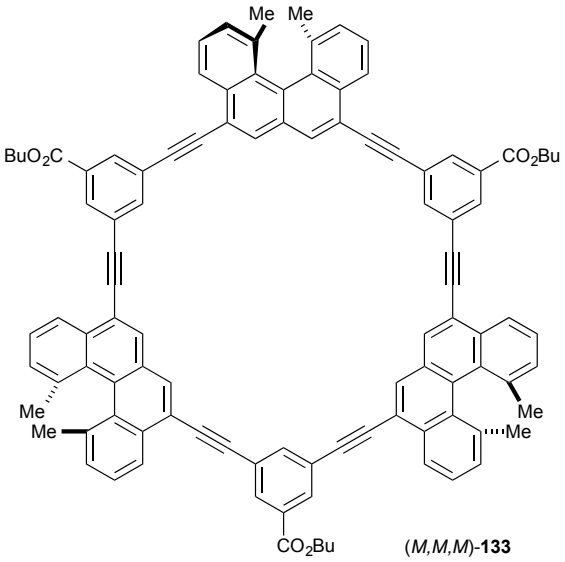
The family of (3,10)[4]helicenophanes **126-131** was synthesized in conjunction with work aimed at the synthesis of "cycloarene" **132** (a relative of kekulene (**120**)), but the Type I strategy only proceeded as far cyclophanes **130** and **131** (Scheme 28).[89] Attempts to convert these two cyclophanes into **132** were unsuccessful, giving instead the large [*n*]cyclophanes shown in Section 3.10. The synthesis of **132** was ultimately achieved using hexahydro[4]helicene-based cyclophanes, which do not qualify as cyclophanes with large PAHs.[90]



Scheme 28 (3,10)[4]Helicenophanes **126-131**

3.5.1.3 (5,8)[4]Helicenophanes.

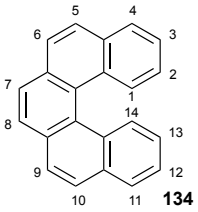
The overlap between cyclophanes and shape-persistent macrocycles is sizeable and several systems with large PAHs lie in this grey area. A good example is shape-persistent arylene-ethynylene macrocycle (*M,M,M*)-**133**, which can be easily viewed as a "polyunsaturated cyclophane",[91] *i.e.* a [2.2.2.2.2.2]cyclophanehexayne. A Type II strategy involving Sonogashira chemistry was used to prepare all possible stereoisomers of **133**, in which the [4]helicene units are configurationally stable due to the presence of the two cove-region methyl groups. The (*M,M,M*) isomer of **133** was found to self-associate in solution at significantly lower concentration that the other isomers.



(*M,M,M*)-**133**

3.5.2 [5]Helicenophanes.

[5]Helicene (**134**) has a racemization barrier of 24.9 kcal/mol (at 196 °C),[92] which means that it has only limited configurational stability at room temperature (*ca*. 14 h half life). Substitution, especially at the 1 and 14 positions, can significantly increase the barrier to inversion, as can bridging.

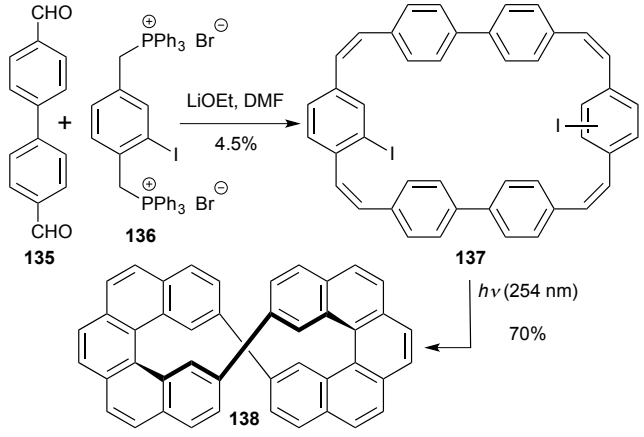


134

- 5 rings
- 22 total carbon atoms
- 14 non-quaternary atoms on the periphery
- 41 basic bridging motifs are available
- 1 basic bridging motif is known

3.5.2.1 (2,13)[5]Helicenophanes.

The first [5]helicene to be reported was [0.0](2,13)[5]helicenophane **138**.[93] It has the same D_2 symmetry as a two-bladed propeller and was thus dubbed "propellicene". It is structurally homologous to **125** in that it is a cyclic bi[*n*]helicene connected through its symmetry-related 2 and 2*n*+3 positions.

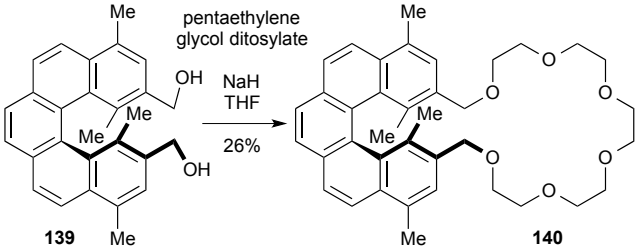


135 **136** **137** **138**

Scheme 29 Synthesis of [0.0](2,13)[5]helicenophane (**138**)

In contrast to the synthesis of **125**, the synthesis of **138** relied upon a "one-two punch" of reactions that has been used extensively for the synthesis helicenes: Wittig reaction followed by Mallory reaction (also referred to as stilbene-phenanthrene photocyclization or photochemical cyclodehydrogenation). Thus, the reaction of dialdehyde **135** with the ylide derived from bis(triphenylphosphonium bromide) **136** afforded cyclophanetetraene **137** as a mixture of isomers (Scheme 29). The two [5]helicene systems of **134** were then generated upon irradiation of **137**. This is a Type III strategy, in which the diarylalkene units serve as "pre-arenes" for the helicene systems. As in the case of **125**, the two helicene moieties in **138** are of the same configuration. Configurational stability was expected for this molecule, but no resolution of the enantiomers was reported and this could not be confirmed. No evidence of significant interaction between the two aromatic systems in **138** was evident from the analysis of its absorption and emission spectra.

The only other known [5]helicenophane is 1,4,10,14-tetramethyl-2,5,8,11,14,17-hexaoxa[18](2,13)[5]helicenophane (**140**).[94] This chiral, crown ether-like compound was synthesized using a Type 1 strategy that involved the construction of 2,13-bis(hydroxymethyl)[5]helicene **139** (using Wittig and Mallory reactions) and its double *O*-alkylation with pentaethylene glycol ditosylate to give **140** (26%) (Scheme 30).



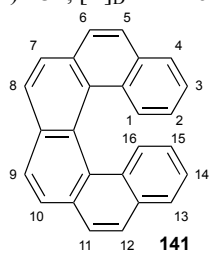
139 **140**

Scheme 30 Synthesis of [18](2,13)[5]helicenophane **140**

The methyl groups at the 1 and 14 positions (fjord region) of **140** ensured configurational stability and the enantiomers were separated using chiral HPLC. Upon mixing with methyl (±)-phenylglycinate hydrochloride, (*M*)-(–)-**140** ($[\alpha]_D^{25}$ = –754, MeOH) was found to selectively complex the *S* enantiomer (8:1). Based on this selectivity, (*M*)-(–)-**140** could be used to selectively transport (6.0% transport) the same guest across a bulk liquid membrane in 75% *ee*.

3.5.3 [6]Helicenophanes.

[6]Helicene (**141**) has a substantially higher racemization barrier ($\Delta G^{\ddagger}$ = 37.4 kcal/mol at 200 °C)[95,96] than its lower congener **134**. As such, it is configurationally much more stable at room temperature and strategically placed substituents are not needed to prevent racemization at room temperature. Also worthy of note is that its specific rotation ((*M*)-(–)-**141**, $[\alpha]_D^{22}$ = –3570, $CHCl_3$)[97] is more than double that of **134** ((*M*)-(–)-**134**, $[\alpha]_D^{26}$ = –1670, isooctane).[92]

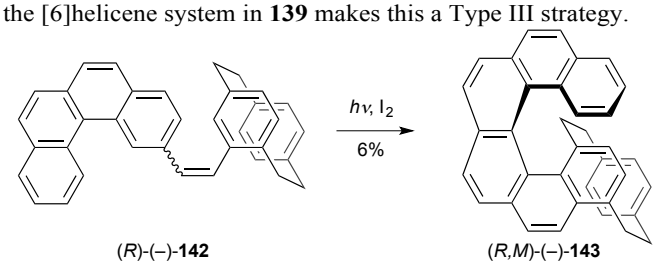


141

- 6 rings
- 26 total carbon atoms
- 16 non-quaternary atoms on the periphery
- 55 basic bridging motifs are available
- 3 basic bridging motifs are known

3.5.3.1 (1,4)[6]Helicenophanes.

Enantiomerically pure (*R,M*)-(–)-[2]paracyclo[2](1,4)[6]helicenophane (**143**) was obtained from the Mallory reaction of enantiomerically pure diarylalkene **142** (Scheme 31).[98] As before, the elaboration of the diarylalkene system in **138** into the [6]helicene system in **139** makes this a Type III strategy.

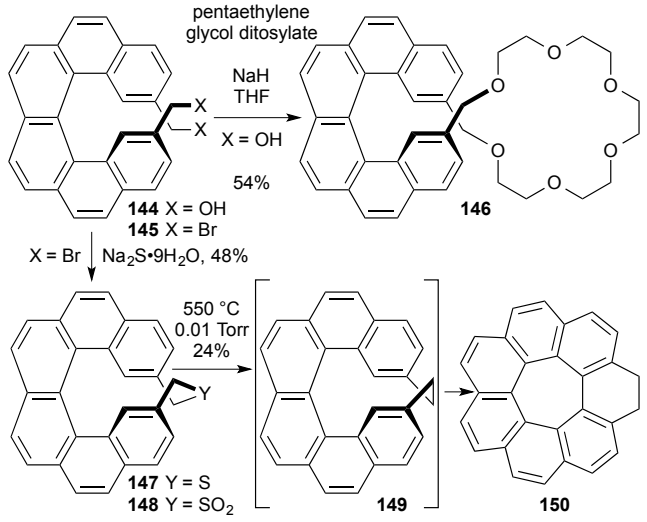


Scheme 31 Synthesis of [2]paracyclo[2](1,4)[6]helicenophane (**143**)

The origin of the asymmetry in **143** was the resolution of [2.2]paracyclophane-4-carboxylic acid. The significance of having a single enantiomer of **142** ($[\alpha]_D^{25}$ = –220) was that, due to steric reasons, the Mallory reaction could only afford the *M*-configured [6]helicene. The observation of a very large negative specific rotation for **143** ($[\alpha]_D^{25}$ = –2716) and the similarity of the ORD spectra of [6]helicene (**141**) and **143** provided the first chemical confirmation of earlier X-ray diffraction studies that (–)-[6]helicene (**141**) has the *M* (left-handed) configuration.

3.5.3.2 (2,15)[6]Helicenophanes.

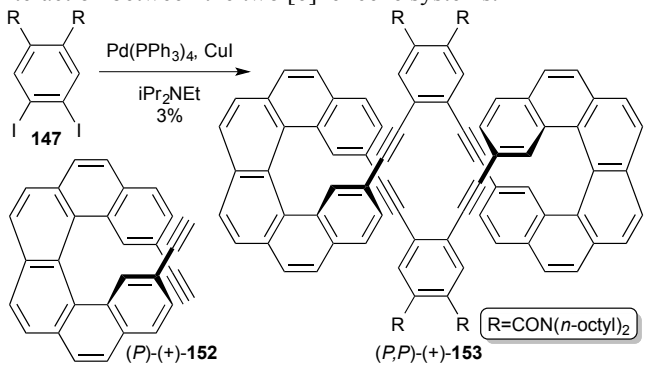
2,5,8,11,14,17-Hexaoxa[18](2,15)[6]helicenophane (**146**) was reported together with **140** (Scheme 32).[94] In going to the larger helicene, the relative spatial orientation of the bridgehead positions on the aromatic system changes significantly and this alters the chiral environment of crown ether-like host. These changes are presumably responsible for the considerably higher yield of the cyclophane-forming reaction leading to **146** and also for the reversal of (and decrease in) the observed selectivity of individual enantiomers of **146** (separated by chiral HPLC, (*M*)-(–)-**146**, $[\alpha]_D^{25}$ = –1269, MeOH) for chiral guests.



Scheme 32 Synthesis of (2,15)[6]helicenophanes **146-149**

The same group later reported the synthesis of 2-thia[3](2,15)[6]helicenophane (**147**) using a standard Type 1 approach, *i.e.* sulphide coupling of dibromide **145** (Scheme 32).[99] In this case, the helicenophane was not the object of interest, but rather a stepping stone on the way to a more interesting target. Thus, thioether **147** was oxidized to the corresponding sulfone **148** and then subjected to FVT to afford 1,2-dihydro[7]circulene (**150**), presumably from cyclodehydrogenation of [2](2,15)[6]helicenophane (**149**). Dehydrogenation of **150** gave [7]circulene. The success of this synthesis can be attributed to the two-atom bridge in **149**, which not only introduces additional strain to the [6]helicene system, but also holds the carbon atoms involved in the key bond-forming step in proximity.

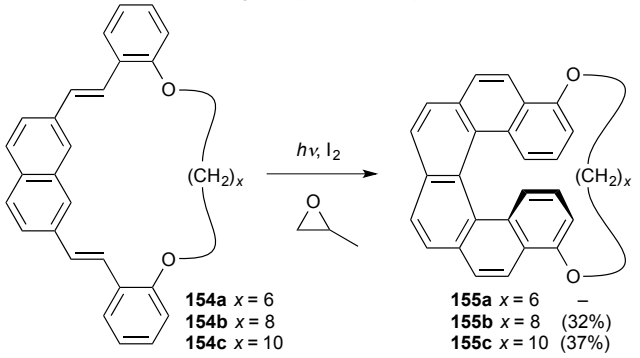
A larger (2,15)[6]helicenophane was obtained using a Type II strategy.[100] Sonogashira reaction between (*P*)-(+)-2,15-diethynyl[6]helicene **152** and diiodide **151** gave rise to a mixture of cyclic oligomers (FAB-MS analysis shows dimer, trimer and tetramer) (Scheme 33). The cyclic dimer, (*P,P*)-(+)-[6]helicenophane **153**, was isolated by preparative TLC and HPLC, albeit in very low yield. The very small amount of material (0.3 mg) presumably precluded determination of the specific rotation. The similarity of the absorption spectrum of **153** to that of **152** led to the conclusion that there is very little interaction between the two [6]helicene systems.



Scheme 33 Synthesis of (*P,P*)-(+)-[6]helicenophane **153**

3.5.3.3 (4,13)[6]Helicenophanes.

1,*n*-Dioxa[*n*](4,13)[6]helicenophanes **155b-c** were synthesized using a Type III approach, which culminated with the Mallory reaction of macrocycles **154b-c** (Scheme 34).[101] Interestingly, the lower homolog **154a** did not afford helicenophane **155a**, but rather a dimer resembling **64** (Scheme 13).



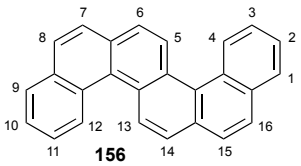
Scheme 34 Synthesis of 1,*n*-dioxa[*n*](4,13)[6]helicenophanes **155b-c**

Partial separations of the enantiomers of **155b-c** were achieved by chromatography on silica gel doped with Newman's reagent

((*R*)-(–)-TAPA). This enabled the determination of the racemization barriers (at 200 °C). In going from [6]helicene (**141**) to **155c** to **155b**, $\Delta G^{\ddagger}$ was found to drop from 37.4 to 35.3 to 32.8 kcal/mol. Here, the bridge plays a decisive role. Bridging the 4 and 13 positions of [6]helicene, even with the twelve-atom bridge in **155c**, serves to strain the C_2-symmetric ground state relative to the C_s-symmetric transition state and thus lowers the activation energy. As the bridge is shortened to ten atoms, *i.e.* **155b**, the effect becomes more pronounced. Upon further shortening of the bridge to eight atoms, *i.e.* **155a**, there is evidently enough additional strain in the helicenophane, or intermediates leading to it, that an alternative reaction pathway (photodimerization) becomes favoured.

3.6 Dibenzo[*c.l*]chrysenophanes.

Dibenzo[*c.l*]chrysene (**156**) is an S-shaped PAH, which means that it has two prochiral faces. As a result, cyclophane formation by many of the 56 available basic bridging motifs will have stereochemical consequences.



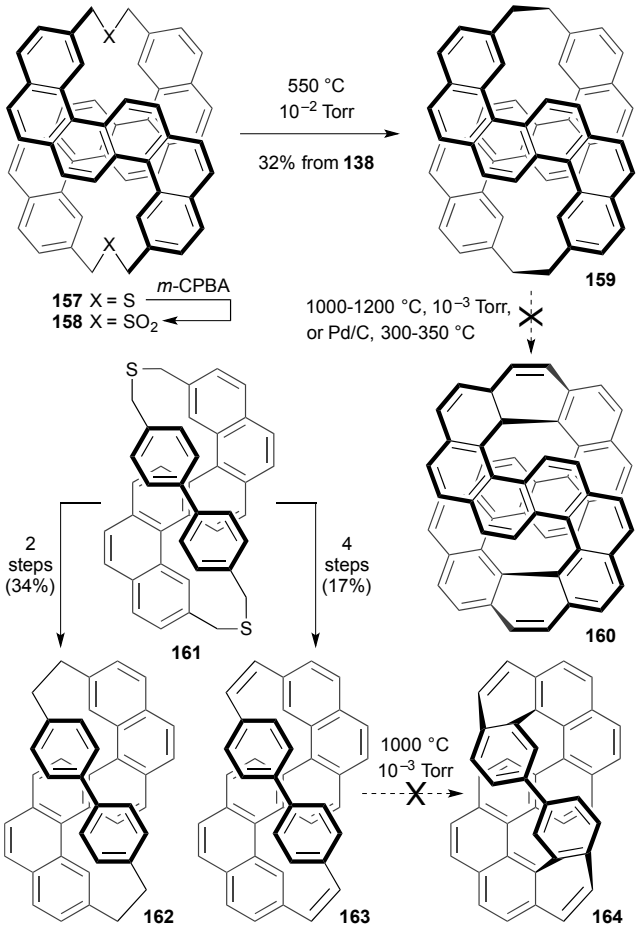
156

- 6 rings
- 26 total carbon atoms
- 16 non-quaternary atoms on the periphery
- 56 basic bridging motifs are available
- 1 basic bridging motif is known

3.6.1 (3,11)Dibenzo[*c.l*]chrysenophanes.

In connection with an unsuccessful attempt to synthesize a very unusual, figure-8-shaped PAH ([14]circulene **160**), a small set of structurally interesting (3,11)dibenzo[*c.l*]chrysenophanes was constructed.[102] Dithiacyclophane **157**, the product of a classic thiol-bromide coupling, has two possible diastereomers – the chiral D_2-symmetric structure shown in Scheme 35 and an achiral C_{2h}-symmetric structure (not shown) in which the two aromatic systems are superimposed when viewed perperdicular to their planes. They are effectively a *dl* pair (D_2 isomer) and a *meso* compound (C_{2h} isomer). Only the D_2 structure was formed, as evidenced by the significant upfield shifts ($\Delta\delta$ up to 0.90 ppm) of some, (but not others) of the protons attached to the dibenzo[*c.l*]chrysene system. The C_{2h} isomer would be expected to exhibit similar $\Delta\delta$ values for all of the aryl protons. An oxidation/FVT sequence afforded the bridge-contracted [2.2]cyclophane **159**, which was unambiguously determined to be a D_2-symmetric isomer by crystallography. Attempts to convert **159** into **160** (*cf.* **149** to **150**), even under very forcing conditions, resulted in the formation of "a polymer".

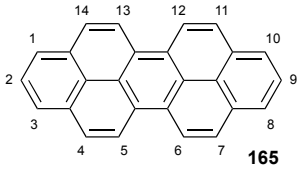
The biphenyl-contaning dibenzo[*c.l*]chrysenophane **161** was obtained in a similar fashion to **157**, but in addition to ring contracting it to the corresponding [2.2]cyclophane **162**, it was also converted into [2.2]cyclophanediene **163**. Subjection of [2.2]cyclophane **162** to FVT again failed to deliver any cyclodehydrogenated products. Although FVT of **163** at 1000 °C was also not successful in generating the highly interesting self-biaryl **164** (a new case of a snake biting its own tail?), it did deliver the very unusual cyclophane shown in Section 3.9. Considering that the use of cyclophanediene **163** led to a better result than its saturated counterpart **162**, it would seem that the cyclophanediene corresponding to **159** might have been worth investigating as a substrate for the synthesis of **160**.



Scheme 35 Synthesis of (3,11)dibenzo[*c.l*]chrysenophanes **157**-**159** and **161**-**163**

3.7 Peropyrenophanes.

Peropyrene (**165**) is the third member of a series of aromatic ribbons that starts with benzene and then moves to pyrene (**4**). This series of compounds can be viewed as capped rylenes.

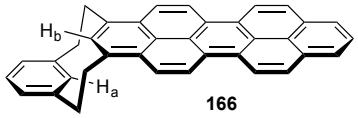


165

- 7 rings
- 26 total carbon atoms
- 14 non-quaternary atoms on the periphery
- 24 basic bridging motifs are available
- 1 basic bridging motif is known

3.7.1 (1,3)Peropyrenophanes.

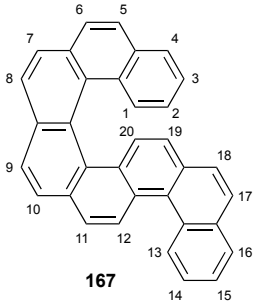
A byproduct of the chemistry leading to the synthesis of *u,u*-**8** and *u,d*-**8** (Scheme 3) was [2]metacyclo[2](1,3)peropyrenophane (**166**).[22] The interesting thing about this cyclophane is that the chemical shifts of the internal protons H_a (δ 3.66) and H_b (δ 5.27) are very close to those observed for the corresponding protons in **7**, *u,u*-**8** and *u,d*-**8**. This implies that the peropyrene system does not exert a stronger magnetic anisotropic effect than the pyrene system, at least in the environment of H_a. In light of how pronounced the change was in moving from benzene to pyrene, one might have expected to see a further (perhaps smaller) change in the same direction.



166

3.8 Naphtho[2,1-*c*][6]helicenophanes.

Naphtho[2,1-*c*][6]helicenophane (**167**) is the least symmetric of all of the large PAHs that have been incorporated into a cyclophane. As such, it has a very large number (170) of basic bridging motifs available to it.

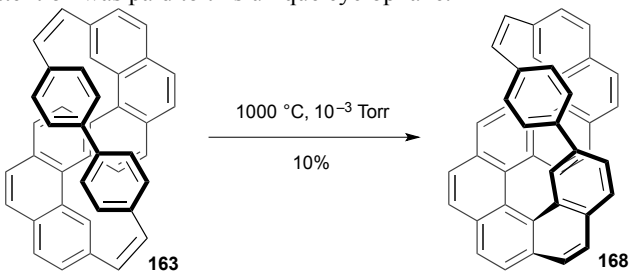


167

- 8 rings
- 34 total carbon atoms
- 20 non-quaternary atoms on the periphery
- 170 basic bridging motifs are available
- 1 basic bridging motif is known

3.8.1 (2,14)Naphtho[2,1-*c*][6]helicenophanes.

As described earlier, the attempted conversion of dibenzo[*c.l*]chrysenophane **163** into **164** by FVT at 1000 °C did not give the desired product, but it did lead to the formation of mono-cyclodehydrogenated product **168** in 10% yield (Scheme 36).[102] This most remarkable compound is a mixed [2.0]cyclophane of benzene and naphtho[2,1-*c*][6]helicene. As an unwanted product, it is understandable that not much attention was paid to this unique cyclophane.

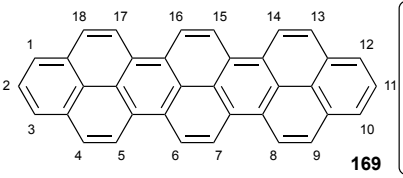


163 168

Scheme 36 Synthesis of (2,14)naphtho[2,1-*c*][6]helicenophane **168**

3.9 Teropyrenophanes.

Teropyrene (**169**) follows peropyrene in the capped rylene series. Until the synthesis of the small set of teropyrenophanes described below, the only teropyrene that had been synthesized was the parent hydrocarbon **169**, which was accessed through layered metacyclophanes (*cf.* **7**, *u,u*-**8** and *u,d*-**8** and **162**).[103] Due to its very low solubility, the only characterization of **169** to be reported was a UV-vis spectrum.

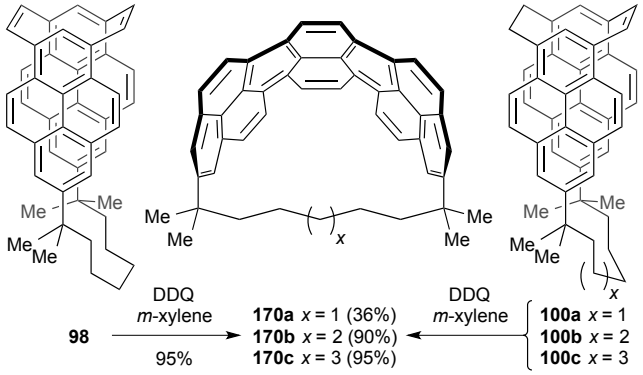


169

- 10 rings
- 36 total carbon atoms
- 18 non-quaternary atoms on the periphery
- 55 basic bridging motifs are available
- 1 basic bridging motif is known

3.9.1 (2,11)Teropyrenophanes.

By direct analogy to the Type III strategy used for the conversion of tethered [2.2]metacyclophanedienes **77** to the [*n*](2,7)pyrenophanes **79**-**81**, tethered pyrenophanediene **98** was converted into [8](2,11)teropyrenophane **170b** upon reaction with DDQ (Scheme 37).[41] The formation of **170b** under the conditions used to synthesize the (2,7)pyrenophanes (benzene, reflux) was sluggish, so a higher boiling solvent (*m*-xylene) was employed. The pyrenophanemonoenes **100a-c** were also found to be viable substrates for the VID reaction leading to teropyrenophanes **170a-c**.[42] The smallest teropyrenophane **170a** formed more slowly than the others, required a greater excess of DDQ and did not result in the complete consumption of **100a**. This is attributable to the higher strain energy of **170a**.



98 → **170a** *x* = 1 (36%), **170b** *x* = 2 (90%), **170c** *x* = 3 (95%) ← **100a** *x* = 1, **100b** *x* = 2, **100c** *x* = 3

Scheme 37 Synthesis of [*n*](2,11)teropyrenophanes **170a-c**

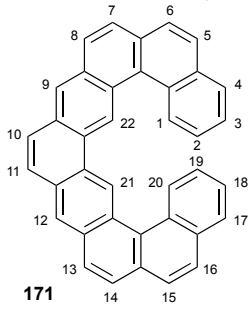
Remarkably, the (2,11)teropyrenophanes **170a-c** have the same bridge lengths at the (2,7)pyrenophanes **79a-c**, even though teropyrene is much longer than pyrene. Consequently, the end-to-end bend of the aromatic systems in **170a-c** is much larger than in **79a-c**. The crystallographically determined θ value for **170c** is 154.3° and it increases to 167.0° in **170b**. A crystal structure has not yet been reported for **170a**, but its calculated θ value is 178.7°, just a hair short of a 180° bend. As in the [*n*](2,7)pyrenophanes, all of the aromatic protons move upfield at the teropyrene system becomes more bent. However, a small blue shift in the absorption and emission spectra of **149a-c** is observed as the aromatic system becomes more bent. This contrast what was observed in the pyrenophanes and may point to complexity in the relationship between distortion from planarity and photophysical properties in PAHs.

Teropyrenophanes **170a-c** exhibit good solubility in common organic solvents, which means that opportunities exist for the investigation of the chemistry of the teropyrene system. The only obstacle at this time is the availability of larger quantities of the teropyrenophanes. The roughly semi-circular shape of the aromatic systems in **170a-c** means that they can be viewed as segments of armchair single-walled carbon nanotubes (SWCNT). Thus, a study of the chemistry of these systems may well have implications for the armchair edge functionalization of both nanographenes and open-ended carbon nanotubes. The presence of a sizeable cavity points to the possibility of interesting host-guest chemistry. Ultimately, the achievement of almost 180° of bend is cause for optimism that the general approach will be applicable to the synthesis of a full aromatic belt.[104]

3.10 Dinaphtho[1,2-*a*;2',1'-*o*]pentaphenophanes.

Two dinaphtho[1,2-*a*;2'1'-*o*]pentaphenophanes have been reported. Contrary to the claim that teropyrene (C_{36}) is the

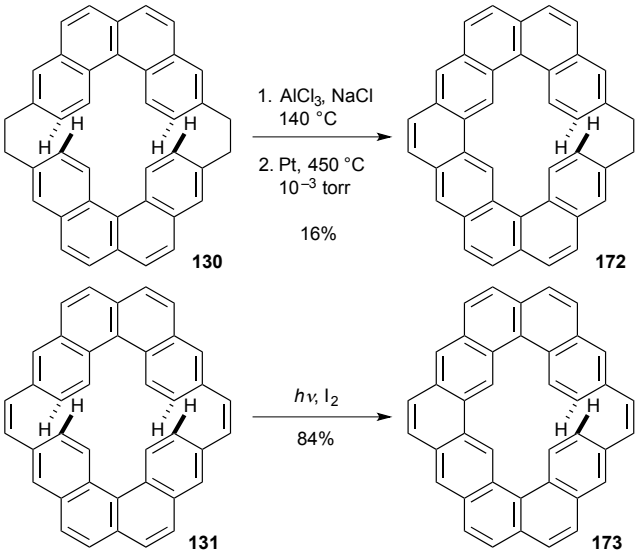
largest aromatic system to have been incorporated into an [*n*]cyclophane,[41] dinaphtho[1,2-*a*;2'1'-*o*]pentaphenophane (**171**, C_{38}) is actually the record-holder.



- 9 rings
- 38 total carbon atoms
- 22 non-quaternary atoms on the periphery
- 107 basic bridging motifs are available
- 1 basic bridging motif is known

3.10.1 (3,18)Dinaphtho[1,2-*a*;2',1'-*o*]pentaphenophanes.

[2](3,8)Dinaphtho[1,2-*a*;2'1'-*o*]pentaphenophane **172** and its unsaturated analog **173** were obtained from the attempts to convert [4]helicenophanes **130** and **131** into cycloarene **132**.[89] Scholl reaction of **130** (followed by sublimation through a platinum catalyst) led to the formation of **172** in poor yield (16%), whereas Mallory reaction of **131** afforded **173** in excellent yield (84%) (Scheme 38). The failure of **172** and **173** to proceed to **132** under the conditions of their formation was ascribed to "molecular rigidity". The inference here is that the rigidity of the cyclophane structures prevents the two ends of the helical aromatic system from orienting themselves in a way that is amenable to further reaction. This starkly contrasts the successful conversion of [6]helicenophane **149** into dihydro[7]circulene **150**, where the molecular rigidity was postulated to facilitate ring closure.

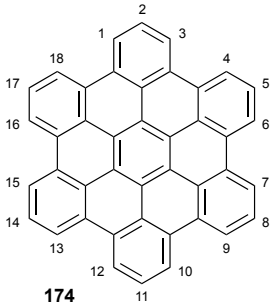


Scheme 38 Synthesis of [2](3,8)dinaphtho[1,2-*a*;2'1'-*o*]pentaphenophanes **172** and **173**

Despite the unprecedented size of the aromatic systems in the [*n*]cyclophanes **172** and **173**, which has not been improved upon for over 30 years, these two cyclophanes were essentially consolation prizes and they didn't garner the attention that they may have deserved.

3.11 Hexabenzo[*bc,ef,hi,kl,no,qr*]coronenophanes.

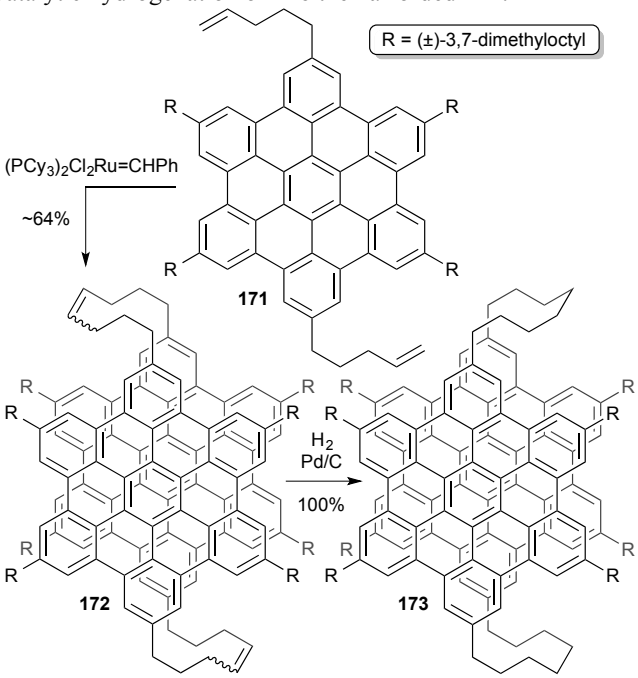
Hexabenzo[*bc,ef,hi,kl,no,qr*]coronene (**174**, HBC) is the largest PAH to have been built into a cyclophane of any type. Owing largely to the numerous contributions by the Müllen group,[105] this "super-sized benzene" has figured prominently in the fields of organic materials and organic electronics since the mid 1990s. The high symmetry (D_{6h}) and low number of unique non-quaternary peripheral carbon atoms (2) means that there are very few basic bridging motifs (16) for a PAH of its size.



- 13 rings
- 42 total carbon atoms
- 18 non-quaternary atoms on the periphery
- 16 basic bridging motifs are available
- 1 basic bridging motif is known

3.11.1 (2,11)Hexabenzocoronenophanes.

Two [8.8](2,11)hexabenzocoronenophanes, **176** and **177** have been reported.[106] The synthesis of the first of these king-size cyclophanes was accomplished by the self-RCM reaction of 2,11-bis(pent-4-enyl)HBC **175** (a Type I strategy), which afforded cyclophanediene **176** in "~64%" yield (Scheme 39). Catalytic hydrogenation of **176** then afforded **177**.



Scheme 38 Synthesis of (2,11)hexabenzocoronenophanes **172** and **173**.

Both **176** and **177** are mixtures of several diastereoisomers by virtue of a stereorandom asymmetric centre in each of the eight side chains. Since RCM is known to be ineffective in providing strained cyclophanes,[80] it is entirely unsurprising that the presumably quite strained [8](2,11)hexabenzocoronenophane arising from intramolecular reaction of **175** was not observed. The impressively high yield of **176** is probably due to some extent to π-π stacking between the two HBC systems. The use of pentenyl side chains appears to have been a wise choice

because it imparted enough flexibility to the system to allow for cyclophane formation regardless of the stereochemical outcome of the first olefin-forming reaction. It would be interesting to see if butenyl or allyl side chains would give rise to the corresponding [6.6]- and [4.4]cyclophanes, respectively. On the other hand, it would be just as interesting to investigate how much longer the side chains would need to be in order for an [*n*]cyclophane to form.

Solution phase studies (^{1}H NMR, absorption, emission) of **176** and **177** led to the conclusion that the two HBC systems are arranged in a close face-to-face fashion, but that they are laterally offset from one another on average. In other words, the two discs aggregrate, leaving no cavity. With regard to their bulk properties, DSC, optical microscopy and WAXD measurements indicated that **176** and **177** behave like their monomeric analogues (*e.g.* **175**) in that they self-assemble to form thermotropic columnar liquid crystal phases. At a solid-liquid interface, STM was used to visualize self-assembled two-dimensional crystals. According to scanning tunnelling spectroscopy (STS), single molecules of **176** and **177** exhibited diode-like behaviour resembling that of single-molecule monomeric HBCs. Subsequent STM and STS studies of **177** and double layers of HBC (**174**) revealed that the lateral offset between layers has a very strong influence on the electron transport.[107] Such orientational dependence on arene-arene interactions is reminiscent of pyrenophanes **28**-**30** and pentacenophane **115**, and was attributed also to HOMO and LUMO splittings in the stacks.

Conclusions

The niche of cyclophane chemistry that encompasses PAHs with four or more rings is relatively very small, but is especially interesting and instructive. This is because the large PAHs bring interesting/unusual structural characteristics and physical properties to the range of existing features that have been responsible for keeping cyclophane chemistry vibrant for over several decades.

In total, only thirteen large PAHs have ever been built into a cyclophane and, with the exception of the smallest of them (pyrene), only a low number of examples of each has been reported. Even so, virtually all of these cyclophanes have played some part in a story that offers useful lessons about synthesis, properties, structure, fundamental concepts and function. Looking forward, opportunities abound for the construction of new structures that will certainly lead to further insights and discoveries.

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Notes and references

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§ Dedicated to Prof. Dr. Henning Hopf on the occasion of his 75th birthday.

Electronic Supplementary Information (ESI) available: Analyses of basic bridging motifs available for PAHs **4**, **105**, **112**, **116**, **123**, **134**, **141**, **156**, **165**, **167**, **169**, **171** and **174**. See DOI: 10.1039/b000000x/

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