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Non-planar aromatic compounds. Part 4: Fine tuning the degree of bend in the pyrene moiety of [7](2,7)pyrenophanes by modifying the nature of the bridge

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Dedicated to Professor Dr Henning Hopf on the occasion of his 60th birthday

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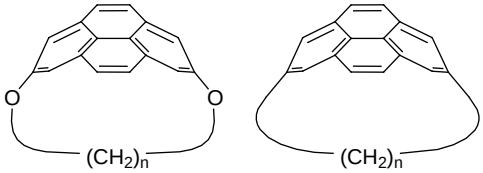
Abstract—Structures for several mono-, di-, tri- and tetraoxa[7](2,7)pyrenophanes were calculated at the AM1 level of theory and the bend angle (θ) of the pyrene system was found to be affected by both the number and the position(s) of the oxygen atom(s). In varying the type of atom X at the 4 position, θ was predicted to decrease with the C–X bond length. Attempted synthesis of 1,4,7-trioxa[7](2,7)pyrenophane gave traces of the target compound as the minor component of a mixture with its recovered precursor. ^{1}H NMR evidence supports the prediction that it possesses a more bent pyrene unit than that of the current record holder. 4-Oxa[7](2,7)pyrenophane was prepared readily in 11% overall yield over ten steps and its crystallographically measured bend angle is 102.9°.

1. Introduction

Hopf has recently discussed ways in which an aromatic system can be caused to adopt a non-planar geometry.[1] Approaches to such systems have fallen, for the most part, into the following three categories: (1) through the judicious incorporation of non-six-membered rings into the aromatic skeleton (e.g. Buckybowls), (2) through the incorporation of an appropriate bridge, or bridges (i.e. cyclophanes), and (3) through non-bonded interactions (e.g. helicenes). Our interest in non-planar aromatic compounds has so far been restricted to the second category,[2–5] but we have recently outlined a strategy for entering category 1 via category 2.[4] To date, we have accomplished the syntheses of two series of [*n*](2,7)pyrenophanes, namely the 1,*n*-dioxa[*n*](2,7)-pyrenophanes **1a**–**f**[2,3,5] and the parent [*n*](2,7)pyrenophanes **2a**–**c**.[4]



1a n=5 **1d** n=8
1b n=6 **1e** n=9
1c n=7 **1f** n=10

2a n=7
2b n=8
2c n=9

Keywords: cyclophanes; polycyclic aromatic compounds; strained compounds.

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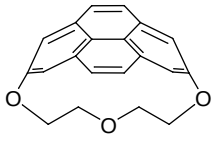

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Comparison of the available X-ray crystal structures and AM1 calculated structures of these compounds led not only to the obvious conclusion that the degree of bend in the pyrene system is influenced strongly by the number of atoms in the bridge, but also that the nature of the bridge exerts a substantial effect. This suggested that the degree of bend in the pyrene unit could be fine tuned by adjustment of the constitution of the bridge and led to the identification of 1,4,7-trioxa[7](2,7)pyrenophane **3** as a synthetic target.[4]

Initial investigations on the reactivity of the pyrenophanes **1** and **2** have also been reported[4] and, at least in the case of cycloadditions, it is clearly dependent upon the degree of bend in the pyrene moiety. As part of ongoing work aimed at the functionalization of **1** and **2** and their eventual conversion into bowl-shaped molecules, it may well become necessary to be able to fine tune the degree of bend and hence the reactivity of the pyrene unit for a specific transformation. We now describe the results of our entrance into the fine tuning process.

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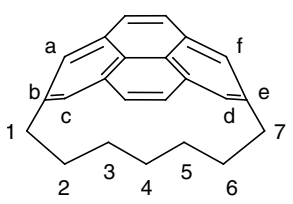
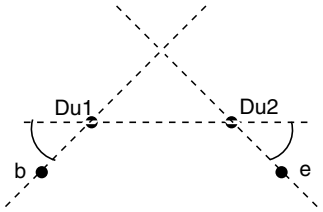
Table 1. AM1 calculated bend angles and heats of formation for some [7](2,7)pyrenophanes





Entry	Heteroatoms in bridge	Compound number	θ (°)	$\theta-\theta_{2a}$ (°)	$\sum(\theta_{n\text{-oxa}})$	$\Delta H_f°$ (kcal mol^{-1})
1	None	**2a**	104.6	0.0		76.35
2	1-Oxa	**4**	108.8	4.2		56.68
3	2-Oxa	**5**	107.0	2.4		51.50
4	3-Oxa	**6**	107.5	2.9		52.92
5	4-Oxa	**7**	108.3	3.7		52.01
6	1,3-Dioxa	**8**	113.1	8.5	7.1	27.23
7	1,4-Dioxa	**9**	112.7	8.1	7.9	32.84
8	1,5-Dioxa	**10**	112.1	7.5	7.1	33.91
9	1,6-Dioxa	**11**	111.3	6.7	6.6	32.06
10	1,7-Dioxa	**1a**	113.3	8.7	8.4	37.41
11	2,4-Dioxa	**12**	111.4	6.8	6.3	24.53
12	2,5-Dioxa	**13**	110.3	5.7	5.3	28.63
13	2,6-Dioxa	**14**	109.4	4.8	4.8	27.17
14	3,5-Dioxa (a)	**15a**	116.0	11.4	5.8	28.22
15	3,5-Dioxa (b)	**15b**	112.4	7.8	5.8	28.18
16	1,4,7-Trioxa	**3**	117.2	12.6	12.1	14.15
17	2,4,6-Trioxa	**16**	114.8	10.2	8.5	−2.17
18	1,3,5,7-Tetraoxa	**17**	125.2	20.6	14.2	−21.71
19	4-Aza	**18**	106.0	1.4		98.45
20	4-Thia	**19**	101.0	−3.7		88.51
21	4-Selena	**20**	97.6	−7.0		95.07

2. Results and discussion

For those pyrenophanes that have had their structures measured crystallographically, the bend angle (θ) was found to be consistently overestimated by AM1 calculations.[4] However, the consistency suggested that AM1 calculations may be used in conjunction with experimental results as a predictive tool with a reasonable degree of confidence. Initial attention was directed toward the [7](2,7)-pyrenophane skeleton because the lowest isolable homologue in each series **1** and **2** has a seven atom bridge. The replacement of carbon with oxygen atoms in the bridge was chosen because some pyrenophanes with oxygen-containing bridges (**1a**–**f**) were already known to be synthetically accessible.

2.1. AM1 predictions

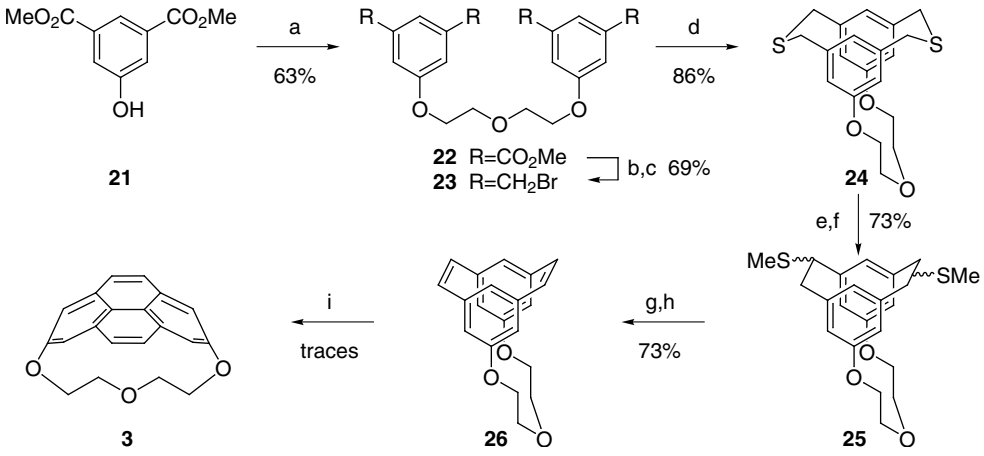
Structures for a number of [7](2,7)pyrenophanes were calculated at the AM1 level of theory (MOPAC, Chem 3D) and the results are given in Table 1. Each structure was constructed from scratch at least three times and virtually identical results (±0.2° in θ and ±0.04 kcal mol^{-1} in $\Delta H_f°$) were obtained for each minimization of a given pyrenophane. The θ values given in Table 1 are averages. With one exception (vide infra), only one bridge conformation was identified for each pyrenophane and, in each case, this closely resembled that observed in the crystal structure determination of **1a**.[3] Attempts to construct new conformations of the other pyrenophanes invariably led to the original conformations upon reminimization. The bend angle θ, which has been defined as an angle formed by the two planes of atoms abc and def,[2–4] for each calculated structure was arrived at by placing dummy atoms (Du1 and Du2) at the ac and df centroids, respectively, measuring the angles (b)-(Du1)–(Du2) and (Du1)–(Du2)–(e) and applying Eq. (1). The two terms on the right hand side of this equation correspond to the two angles indicated in the graphic of Table 1.

$$\theta = \{180 - \text{(b)–(Du1)–(Du2)}\} + 180 - \text{(Du1)–(Du2)–(e)}\} \quad (1)$$

The yardstick against which bend angles were compared was the parent cyclophane **2a**, which was calculated to have a bend angle of 104.6°.[6]

There are four possible oxa[7](2,7)pyrenophanes (**4**–**7**) and it was found that the inclusion of one oxygen atom into the bridge resulted in an increase in θ of 2.4–4.2° (Entries 2–5). As discussed previously,[4] this is consistent with a slight shortening of the effective length of the bridge due to the relative lengths of analogous C–O and C–C bonds. It is interesting to note that the position of the oxygen atom is predicted to have a small, but significant, effect on θ, which increases in steady 0.5–0.8° increments along the series **5** (2-oxa), **6** (3-oxa), **7** (4-oxa), **4** (1-oxa).

There are nine possible dioxa[7](2,7)pyrenophanes that do not contain a peroxide unit (**1a**, **8**–**15**). For those examples that do not contain an acetal (Entries 7–10, 12, 13), the presence of two oxygen atoms in the bridge gave rise to an increase in θ (that was very close (0.0–0.4° larger) to) the sum of those predicted for the two oxa[7](2,7)pyrenophanes with oxygen atoms at positions that correspond to



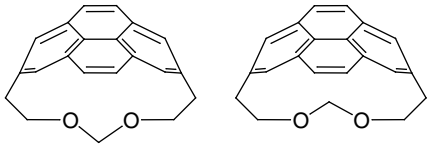
Scheme 1. *Reagents and conditions*: (a) diethylene glycol di-*p*-tosylate, K_2CO_3, DMF, 100°C, 17 h; (b) $LiAlH_4$, THF, rt, 48 h; (c) 4:1 48% HBr/H_2SO_4, rt, 3 h; (d) Na_2S/Al_2O_3, 9:1 CH_2Cl_2/ethanol, rt, 29 h; (e) $(MeO)_2CHBF_4$, CH_2Cl_2, rt, 36 h; (f) *t*-BuOK, THF, rt, 3 h; (g) $(MeO)_2CHBF_4$, CH_2Cl_2, rt, 9 h; (h) *t*-BuOK, 2:1 THF/*t*-BuOK, rt, 4 h; (i) DDQ, benzene, 75°C, 36 h.

those in the dioxapyrenophane in question $\{\sum(\theta_{n\text{-oxa}})\}$. For example, the calculated bend angle for 1,4-dioxa[7](2,7)-pyrenophane **9** (Entry 7) is 112.7°, which exceeds that of **2a** by 8.1°. The two corresponding oxa[7](2,7)pyrenophanes are **4** (1-oxa) and **7** (4-oxa), the bend angles of which are calculated to be greater than that of **2a** by 3.7 and 4.2°, respectively. The sum of these two values $\{\sum(\theta_{n\text{-oxa}})\}$ is 7.9°, which is only 0.2° less than that calculated for **9**. It would thus appear that there is a straight additive effect on θ upon replacing two carbon atoms with oxygen atoms when the positions of replacement are greater than two atoms apart.

For acetal-containing dioxa[7](2,7)pyrenophanes (Entries 6, 11, 14, 15), the calculated bend angles are significantly greater (>0.5°) than would be expected from a simple additive effect. This is attributable to the anomalously low O–C–O bond angles that the software predicts for acetals of formaldehyde.[7] 3,5-Dioxa[7](2,7)pyrenophane **15** (Entries 14 and 15) was unique in that two distinct conformers, **15a** and **15b**, were identified. Their heats of formation were virtually identical, but their calculated θ values differ by 3.6°. Conformer **15b** appears to be the real anomaly, considering that its $\sum(\theta_{n\text{-oxa}})$ value is a full 5.6° less than the calculated θ value. The corresponding difference for **15a** is 2.0°, which is much closer to the analogous differences for **8** (1.4°) and **11** (0.5°).

Structures for only two symmetrical trioxa[7](2,7)pyrenophanes, **3** and **16**, were calculated (Entries 16 and 17) and the effects observed in the dioxa[7](2,7)pyrenophanes were echoed. The predicted bend angle of **3** (117.2°) was 12.6° larger than that of **2a**, which is very close to $\sum(\theta_{n\text{-oxa}})$ (12.1°). The calculated bend angle of the acetal-containing pyrenophane **16** (114.8°) exceeds that of **2a** by 10.2° and exceeds that of $\sum(\theta_{n\text{-oxa}})$ (8.5°) by 1.7°. Acetal-containing 1,3,5,7-tetraoxa[7](2,7)pyrenophane **17** (Entry 18) was calculated to have a bend angle 20.6° greater than that of **2a** and a $\sum(\theta_{n\text{-oxa}})$ value of 14.2°. Despite some effort, no second conformer for this compound could be found.

In order to investigate the effect of other heteroatoms on θ, the structures of a series of 4-heteropyrenophanes **18**–**20** (Entries 19–21) were calculated. Including the parent pyrenophane **2a** and 4-oxapyrenophane **7** in the series, it can be seen that the value of θ decreases in the order O>N>C>S>Se, which mirrors the order of the C–X bond lengths. The θ range for this series (10.7°) is about half the difference between the bend angles measured for **1a**[3] and its next higher homologue **1b**.[2]

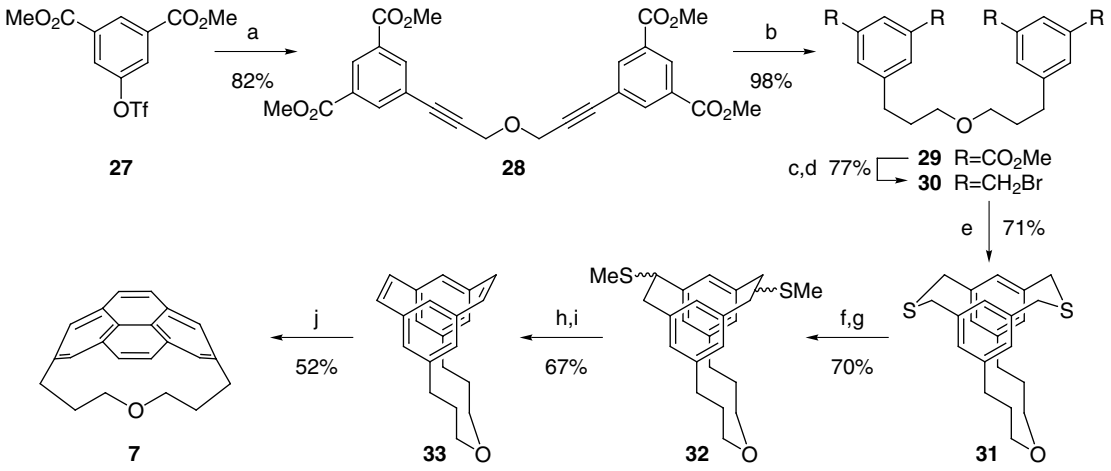


15a **15b**

2.2. Synthesis

Although it would be desirable to have crystal structure determinations of all of the pyrenophanes listed in Table 1, synthetic considerations render this unfeasible. Recalling the ease of cleavage of the strained ether units in **1**,[4] the strained acetal-containing pyrenophanes stand out immediately as problem cases. The N-, S- and Se-containing pyrenophanes **18**–**20** appear to be plausible targets, but will require modification of the established synthetic pathways.[8] Of the remaining oxygen-containing pyrenophanes, the most symmetrical ones are the most attractive synthetically. 4-Oxa[7](2,7)pyrenophane **7** and 1,4,7-trioxa-[7](2,7)pyrenophane **3** were selected for synthesis because they appeared as though they should be accessible via existing synthetic pathways. More importantly, AM1 calculations predict that **3** will have a greater bend angle than the current holder of the record for the highest measured θ value and we were eager to put this prediction to the test.

The planned route to **3** (Scheme 1) was analogous to that employed for the synthesis of pyrenophanes **1a**–**f** and it proceeded uneventfully until the final step. The sequence was initiated by the construction of the eventual seven atom bridge by the reaction of diester **21** with sodium hydride and diethylene glycol di-*p*-tosylate to afford tetra-ester **22** (63%). Reduction of **22** with $LiAlH_4$ and treatment of the crude reaction mixture with HBr/H_2SO_4 led to the



Scheme 2. *Reagents and conditions*: (a) dipropargyl ether, $Pd(PPh_3)_2Cl_2$, CuI, DBU, benzene, rt, 40 h; (b) H_2, Pd(OH)/C, ethyl acetate; (c) $LiAlH_4$, THF, rt, 20 h; (d) 4:1 48% HBr/H_2SO_4, rt, 3 h; (e) Na_2S/Al_2O_3, 9:1 CH_2Cl_2/ethanol, rt, 24 h; (f) $(MeO)_2CHBF_4$, CH_2Cl_2, rt, 16 h; (g) *t*-BuOK, THF, rt, 64 h; (h) $(MeO)_2CHBF_4$, CH_2Cl_2, rt, 20 h; (i) *t*-BuOK, 2:1 THF/*t*-BuOK, rt, 32 h; (j) DDQ, benzene, 75°C, 30 min.

formation of tetrabromide **23** (69%). Dithiacyclophane **24** was then generated (73%) by the reaction of **23** with Na_2S/Al_2O_3.[9] Methylation of the sulfur atoms of **24** with $(MeO)_2CHBF_4$ (Borch reagent)[10] followed by Stevens rearrangement gave rise to a mixture of ring contracted cyclophanes **25** (73%), which were immediately bis-(*S*-methylated) with Borch reagent and then treated with base to produce cyclophanediene **26** (73%).

The key valence isomerization/dehydrogenation step was then attempted by treating **26** with DDQ. As was the case for **1a**, the reaction was slow and, according to tlc analysis, led to the formation of several products. This contrasts with the analogous reactions that led to **1b**–**f** and **2a**–**c**, for which tlc analysis showed essentially spot to spot conversion. Attempted chromatographic separation of the product mixture was unsuccessful. Some decomposition was evident and, for the most part, small amounts of mixtures of unidentified compounds were obtained. However, the ^1H NMR spectrum of the recovered starting material (≈50%) indicated that it was contaminated by a small amount (≈5%) of the desired pyrenophane **3** (vide infra).

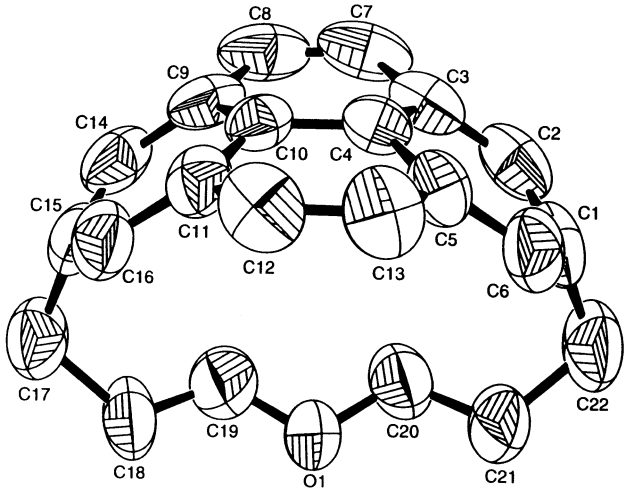


Figure 1. ORTEP representation of **7** (Molecule A) in the crystal. The crystallographic (non-systematic) numbering is shown. Selected distances (Å): C(15)–C(17) 1.502 (4), C(17)–C(18) 1.547 (4), C(18)–C(19) 1.451 (5), C(19)–O(1) 1.386 (4), O(1)–C(20) 1.392 (4), C(20)–C(21) 1.474 (5), C(21)–C(22) 1.552 (5), C(22)–C(1) 1.518 (5). Selected angles (°): C(15)–C(17)–C(18) 108.0 (2), C(17)–C(18)–C(19) 119.6 (4), C(18)–C(19)–O(1) 117.1 (4), C(19)–O(1)–C(20) 115.2 (3), O(1)–C(20)–C(21) 114.3 (3), C(20)–C(21)–C(22) 116.8 (3), C(21)–C(22)–C(1) 107.8 (2).

The synthesis of **7** (Scheme 2) was designed along the lines of those of the parent pyrenophanes **2a**–**c**. Triflate **27**, which is easily prepared from diester **21**,[4] was reacted with dipropargyl ether under Sonogashira conditions[11] to afford diyne-tetraester **28** (82%), hydrogenation of which provided tetraester **29** (98%). A reduction–bromination sequence gave tetrabromide **30** (77%), which was converted into dithiacyclophane **31** (71%) upon reaction with Na_2S/Al_2O_3. Sequential methylation and Stevens rearrangement led to the formation of isomer mixture **32** (70%) and methylation followed by Hofmann elimination delivered cyclophanediene **33** (67%). In contrast to the reaction of **26**, diene **33** reacted cleanly and quickly with DDQ to give pyrenophane **7** in 52% yield.

In the past, the methylation–elimination sequence that is used to generate the cyclophanediene system has proved to be very erratic in the yields it gives. In an attempt to improve the reliability of this transformation, the procedure for the methylation was modified such that the Borch reagent was added very slowly (instead of all at once) to a vigorously stirred solution of the substrates **25** and **32**. Although the yields for the conversions of **25** to **26** (73%) and **32** to **33** (67%) were gratifyingly high, more good results will be required before the modification can be declared a success.

2.3. NMR and structural properties

An X-ray crystal structure determination of **7** (Fig. 1) revealed that there were two independent molecules in the unit cell, the bend angles of which were 103.4° (Molecule A) and 102.4° (Molecule B). The average θ value of 102.9° is 5.4° less than the calculated value of 108 3°. This is in the middle of the range of differences (4.1−7.1°)[4] between

Table 2. Aromatic ^{1}H NMR signals and observed θ values for **1a**–**f** and **3**

Compound	H_a	H_b	θ_{obs} (°)	lit.
3	7.20	7.71		
1a	7.22	7.72	109.2	3
1b	7.44	7.84	87.8	2
1c	7.64	7.91	72.9	5
1d	7.72	7.92	57.7	5
1e	7.83	7.98	39.9	5
1f	7.85	7.96	34.6	5

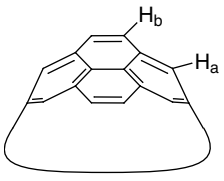
previously measured and calculated θ values. The observation of non-identical θ values for the two molecules of **7** is presumably a consequence of crystal packing forces, which may also play a part in determining the breadth of the range of differences between measured and calculated θ values.

As observed in previous pyrenophane crystal structures, the bond angles about the non-benzylic bridge atoms of **7** are enlarged (range=113.0–119.6°, average=115.8°) and there is no significant elongation of any of the bonds in the bridge. The bond angles about benzylic carbons (range=107.3–108.2°, average=107.8°) are slightly compressed.

The failure to isolate pure **3** immediately ruled out a crystal structure determination. However, an attempt to derive some information about its structure from its ^{1}H NMR spectrum was made. Having observed that the chemical shifts of the aromatic protons of **1a**–**f** move towards higher field as the observed bend angle increases,[5] the aromatic signals of **3** were compared to those of **1a**–**f** (Table 2). Indeed the chemical shifts of H_a and H_b in **3** are observed at slightly higher field than those of **1a**. This is consistent with a slightly larger θ value, assuming that neither the oxygen atom at the 4 position of **3** nor the presence of a large excess of **26** have a significant effect on the chemical shifts of H_a and H_b.

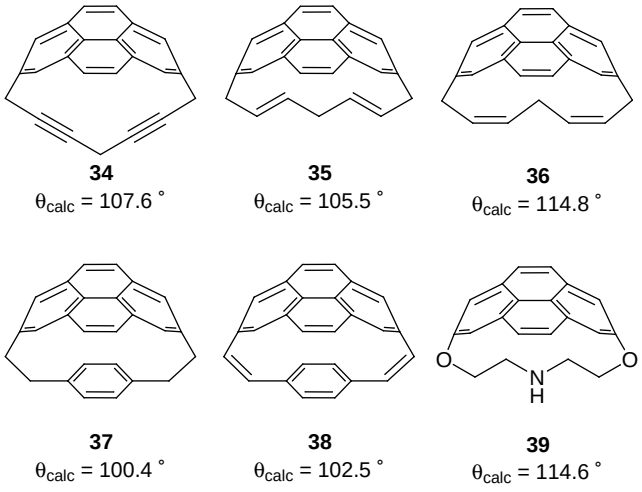
A similar comparison was made between pyrenophanes **2a**–**c** and **7** (Table 3), but the chemical shifts of H_a and H_b of **7** suggest, contrary to AM1 predictions, that it has a less bent pyrene unit than **2a**. Whether this is truly an anomalous case or the NMR method is flawed will only be resolved once X-ray data for **2a** are obtained. Unfortunately, suitable crystals of this compound continue to prove elusive.

Table 3. Aromatic ^{1}H NMR signals and calculated θ values for **2a**–**c** and **7**



Compound	H_a	H_b	θ_{calc} (°)
7	7.40	7.75	108.3
2a	7.34	7.67	104.6
2b	7.59	7.84	87.0
2c	7.75	7.91	70.3

The calculated θ value of **3** (117.2°) is just 3.9° greater than that of **1a** (113.3°), but the reaction of **26** with DDQ afforded only traces of **3**. By comparison, the analogous reaction leading to **1a** proceeded in 35% yield.[3] These observations suggest that the upper limit of an [*n*](2,7)pyrenophane's stability to the conditions currently employed for its formation and isolation lies slightly beyond the θ value of 109.2° observed for **1a**. Future attempts to prepare and isolate a pyrenophane with a greater bend angle than **1a** will thus be directed towards systems with calculated bend angles between those of **1a** and **3**. Two such targets are (*Z*,*Z*)-[7](2,7)pyrenophane-2,5-diene **36** (θ_{calc}=114.8°) and 4-aza-1,7-dioxapyrenophane **39** (θ_{calc}=114.6°). Furthermore, since AM1 calculations continue to show consistency in their overestimation (ca. 4–7°) of θ, we predict that pyrenophanes with calculated bend angles below 110° will be readily accessible using existing methodology. Pyrenophanes such as **34**, **35**, **37** and **38** fulfill this criterion.



3. Conclusions

The most bent pyrene unit measured to date remains that of 1,7-dioxa[7](2,7)pyrenophane **1a**, although AM1 calculations and (somewhat tenuous) ^{1}H NMR evidence suggest that the pyrene unit of 1,4,7-trioxa[7](2,7)pyrenophane **3** is more bent.

From the computational and experimental studies on the [*n*](2,7)pyrenophanes to date, the results indicate that the bend angle can be adjusted most coarsely by changing the number of atoms in the bridge, more finely by changing the constitution of the bridge (replacing one or more C atoms with heteroatoms) and even more finely through the position of atom replacement in the bridge.

4. Experimental

4.1. General

Reactions were performed under air unless otherwise indicated. Those experiments conducted under nitrogen were performed using anhydrous solvents in flame-dried glassware. Solvents for such reactions were dried and

distilled according to standard procedures. All other solvents were used as received. Chromatographic purification was accomplished with 230–400 mesh silica gel. TLC plates were visualized using a short wave (254 nm) UV lamp. Melting points were obtained on a Fisher–Johns apparatus and are uncorrected. IR spectra (cm^{-1}) were recorded on neat samples or nujol suspensions in KBr discs using a Mattson Polaris FT instrument. ^1H NMR spectra were obtained from $CDCl_3$ solutions using a General Electric GE-300 NB instrument operating at 300.1 MHz or a Bruker AVANCE 500 instrument operating at 500.13 MHz. Chemical shifts (δ) are relative to internal TMS standard. Coupling constants are reported in Hz. Reported multiplicities are apparent. ^{13}C NMR spectra were recorded at 75.47 MHz (GE) or 125.77 MHz (Bruker). Chemical shifts are relative to solvent (δ 77.0 for $CDCl_3$). Low-resolution mass spectroscopic data were obtained on a V.G. Micromass 7070HS instrument operating at 70 eV. Combustion analyses were performed by the Microanalytical Services Laboratory, Department of Chemistry, University of Alberta, Edmonton, Alberta.

4.1.1. Bis(3,5-bis(methoxycarbonyl)phenoxyethyl) ether 22. A mixture of diethylene glycol di-*p*-tosylate (10.01 g, 24.1 mmol), dimethyl 5-hydroxyisophthalate **21** (10.66 g, 50.7 mmol), K_2CO_3 (10.02 g, 72.5 mmol) and DMF (150 mL) was stirred magnetically at 100°C (oil bath temperature) for 17 h. The mixture was cooled to rt and poured into a flask containing ethyl acetate (250 mL) and 15% aqueous citric acid solution (250 mL). This mixture was stirred for 10 min, the layers were separated and the organic layer was extracted with 15% aqueous citric acid solution (3×250 mL), water (200 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed (3:3:4 hexanes/ethyl acetate/dichloromethane) to afford **22** (7.46 g, 63%) as a white solid. Mp=125–127°C. ^1H NMR ($CDCl_3$, 300 MHz): δ=8.28 (s, 2H), 7.77 (s, 4H), 4.27–4.24 (m, 4H), 4.00–3.97 (m, 4H), 3.93 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=166.0, 158.7, 131.7, 123.2, 119.8, 69.8, 68.0, 52.4, MS *m/z* (%)=490 (14, M^+), 459 (28), 237 (34), 205 (33), 193 (43), 179 (43), 147 (39), 59 (100). Anal. Calcd for $C_{24}H_{26}O_{11}$: C, 58.77; H, 5.34. Found: C, 58.50; H, 5.25.

4.1.2. Bis(3,5-bis(bromomethyl)phenoxyethyl) ether 23. This reaction was performed under a nitrogen atmosphere. To a 0°C, magnetically stirred slurry of $LiAlH_4$ (6.75 g, 178 mmol) in THF (200 mL) was added a slurry of tetraester **22** (7.06 g, 14.4 mmol) in THF (200 mL) in portions using a Pasteur pipette over 30 min. The mixture was stirred at rt for 48 h, cooled to 0°C and quenched by the careful addition of ethyl acetate (60 mL). After stirring for 2 h, the solvent was removed and the resulting grey residue was dried under high vacuum. To this was added with vigourous stirring 125 mL of a 4:1 mixture of 48% aqueous HBr solution and concentrated H_2SO_4, followed by a further portion of H_2SO_4 (66 mL). Caution: a powerful exotherm occurs upon mixture of the two acids and upon addition of the mixture to the residue. After stirring for 3 h, water (200 mL) and dichloromethane (200 mL) were added and stirring was continued until all solids had dissolved. The layers were separated and the aqueous layer was extracted with dichloromethane (2×100 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ solution (2×200 mL), water (200 mL), saturated aqueous NaCl solution (200 mL) and dried over $MgSO_4$. The solvent was evaporated and the residue was chromatographed (1:1 ethyl acetate/hexanes) to afford **23** (6.24 g, 69%) as a white solid. Mp=98–100°C. ^1H NMR ($CDCl_3$, 300 MHz): δ=7.00 (s, 2H), 6.88 (d, *J*=1.1 Hz, 4H), 4.42 (s, 8H), 4.18–4.15 (m, 4H), 3.95–3.91 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=159.1, 139.6, 122.1, 115.4, 69.8, 67.7, 32.8. MS *m/z* (%)=630 (14, M^+ 2×^{81}Br, 2×^{79}Br), 549 (9), 350 (8), 225 (13), 82 (100). Anal. Calcd for $C_{20}H_{22}Br_4O_3$: C, 38.13; H, 3.52. Found: C, 38.04; H, 3.42.

4.1.3. 1,4,7-Trioxa-15,24-dithia[7.3.3](1,3,5)cyclophane 24. To a vigourously stirred solution of tetrabromide **23** (5.00 g, 7.94 mmol) in 9:1 dichloromethane/absolute ethanol (3000 mL) was added freshly prepared Na_2S/Al_2O_3[9] (6.67 g @ ca. 2.5 mmol g^{-1}, ≈16.7 mmol) in several approximately equal portions over 45 min and stirring was continued for 24 h. Tlc analysis indicated incomplete reaction, so a further portion of Na_2S/Al_2O_3 (2.80 g @ ca. 2.5 mmol g^{-1}, ≈7.0 mmol) was added and stirring was continued for 5 h. The mixture was suction filtered, the solvent was removed under reduced pressure and the residue was chromatographed (1:1:1 ethyl acetate/dichloromethane/hexanes) to afford **24** (2.54 g, 86%) as a white solid. Mp>230°C. ^1H NMR ($CDCl_3$, 300 MHz): δ=6.79 (s, 2H), 6.43 (s, 4H), 4.23–4.20 (m, 4H), 3.89–3.86 (m, 4H), 3.79 (d, *J*=15.0 Hz), 3.75 (d, *J*=14.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=157.4, 139.0, 124.8, 114.1, 68.1, 67.9, 38.8. MS *m/z* (%)=374 (100, M^+), 341 (10), 165 (11), 151 (13), 135 (14), 134 (21). Anal. Calcd for $C_{20}H_{22}O_3S_2$: C, 64.14; H, 5.92. Found: C, 64.06; H, 6.02.

4.1.4. 1,4,7-Trioxa[7.2.2](1,3,5)cyclophane-14,22-diene 26. These reactions were performed under a nitrogen atmosphere. To a vigorously stirred solution of dithiacyclophane **24** (2.03 g, 5.42 mmol)) in dichloromethane (75 mL) was added $(MeO)_2CHBF_4$[10] (1.5 mL, 2.3 g, 14 mmol) and stirring was continued for 36 h. Ethyl acetate (15 mL) was added and the mixture was stirred for 10 min. The mixture was suction filtered and the solids were washed with ethyl acetate and then methanol. Drying under high vacuum afforded a light brown solid (2.91 g), which was slurried in THF (100 mL), and *t*-BuOK (1.70 g, 15.1 mmol) was added. After stirring for 3 h, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (50 mL). This solution was washed with saturated aqueous NH_4Cl solution (50 mL), water (50 mL), saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and concentrated. Filter chromatography (30% ethyl acetate/dichloromethane) afforded a mixture of ring contracted cyclophanes **25** (1.45 g, 73% from **24**) as a sticky yellow solid, which was used immediately in the subsequent step. To a vigourously stirred solution of **25** (1.45 g, 3.60 mmol) in dichloromethane (60 mL) was added $(MeO)_2CHBF_4$ (0.98 mL, 1.5 g, 9.1 mmol) dropwise over 20 min and stirring was continued for 9 h. Methanol (5 mL) was then added and the solvent was removed under reduced pressure and the sticky, dark brown residue was dried under high vacuum for 30 min. The residue was slurried with THF (50 mL) and *t*-butanol (25 mL) and to this well stirred mixture was added *t*-BuOK (2.61 g,

23.3 mmol). After stirring for 4 h, the solvent was removed and to the residue was added ether (100 mL) and saturated aqueous NH_4Cl solution (50 mL). The layers were separated and the organic layer was washed with water (50 mL), saturated aqueous NaCl solution (50 mL) and dried over $MgSO_4$. Chromatography (1:9 ethyl acetate/hexanes) of the residue afforded **26** (0.805 g, 73% from **25**, 53% from **24**) as a pale yellow solid. A small portion was recrystallized from heptane for characterization. Mp=99–102°C (heptane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.12 (s, 4H), 6.77 (s, 2H), 6.13 (d, J=1.2 Hz, 4H), 4.20–4.17 (m, 4H), 3.61–3.56 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=155.4, 136.5, 135.0, 114.3, 69.6, 67.4 (one aromatic signal overlapped). MS *m/z* (%)=306 (37, M^+), 206 (24), 205 (16), 190 (22), 189 (100), 178 (47). Anal. Calcd for $C_{20}H_{18}O_3$: C, 77.40; H, 6.14. Found: C, 77.41; H, 5.92.

4.1.5. 1,4,7-Trioxa[7](2,7)pyrenophane 3. This reaction was performed under a nitrogen atmosphere. To a stirred ca. 75°C solution of cyclophanediene **26** (0.175 g, 0.567 mmol) in benzene (50 mL) was added DDQ (0.130 g, 0.573 mmol) in ca. 10 mg portions over 24 h. After a further 12 h, the mixture was cooled to rt and the solvent was removed. The residue was dissolved in dichloromethane (50 mL) and washed with 1 M aqueous NaOH solution (50 mL), saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (1:19 ethyl acetate/hexanes) of the residue afforded starting material (ca. 50% recovery) that contained, by ^{1}H NMR, a small amount (ca. 5%) of **3**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.71 (s, 4H), 7.20 (s, 4H), 3.31–3.28 (m, 4H), 1.99–1.96 (m, 4H).

4.1.6. Bis(3-(3,5-bis(methoxycarbonyl)phenyl)prop-2-ynyl) ether 28. This reaction was performed under a nitrogen atmosphere. A mixture of dipropargyl ether (2.50 g, 26.6 mmol), $Pd(PPh_3)_2Cl_2$ (0.50 g, 0.71 mmol), CuI (0.62 g, 3.3 mmol), DBU (9.80 g, 64.4 mmol) and triflate **27** (18.47 g, 54.0 mmol) in benzene (175 mL) was stirred at rt for 40 h. The resulting mixture was washed with water (2×100 mL), 1 M aqueous HCl solution (2×100 mL), saturated aqueous $NaHCO_3$ solution (2×100 mL), and saturated aqueous NaCl solution (100 mL). The organic layer was then dried over $MgSO_4$ and the solvent was removed under reduced pressure. Chromatography (2:3:5 dichloromethane/ethyl acetate/hexanes) of the residue afforded some pure (by tlc analysis) **28** and some impure fractions, from which pure **28** was isolated by recrystallization (ethyl acetate/heptane). Diyne **28** was obtained in a total yield of 10.43 g (82%) as a white solid. Mp=153–154°C (ethyl acetate/heptane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.64 (t, J=1.6 Hz, 2H), 8.31 (t, J=1.7 Hz, 4H), 4.58 (s, 4H), 3.96 (s, 12H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=165.5, 136.7, 131.0, 130.4, 123.4, 86.2, 85.0, 57.4, 52.6. MS *m/z* (%)=478 (5, M^+), 447 (14), 414 (32), 214 (10), 43 (100). Anal. Calcd for $C_{26}H_{22}O_9$: C, 65.27; H, 4.63. Found: C, 65.06; H, 4.52.

4.1.7. Bis(3-(3,5-bis(methoxycarbonyl)phenyl)propyl) ether 29. A solution of diyne **28** (5.18 g, 10.8 mmol) in ethyl acetate (400 mL) was purged with nitrogen and Pd(OH)/C (Pearlman's catalyst, 250 mg) was added. Hydrogen (ca. 1 L) was bubbled through the well-stirred solution and then a balloon containing hydrogen was attached to the flask via a needle through a septum. The mixture was stirred at rt for 20 h, filtered though a plug of $MgSO_4$ and the solvent was removed under reduced pressure to afford analytically pure **29** as a white solid. Mp=138–141°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=8.53 (t, J=1.6 Hz, 2H), 8.09 (t, J=1.6 Hz, 4H), 3.94 (s, 12H), 3.42 (t, J=6.4 Hz, 4H), 2.86–2.81 (m, 4H), 1.98–1.92 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=166.4, 142.9, 133.9, 130.6, 130.6, 128.3, 69.6, 52.3, 32.0, 31.0. MS *m/z* (%)=486 (9, M^+), 454 (29), 236 (16), 235 (25), 234 (100), 221 (34), 207 (53), 203 (53), 189 (36) 177 (39), 175 (37), 149 (62). Anal. Calcd for $C_{26}H_{30}O_9$: C, 64.19; H, 6.22. Found: C, 63.98; H, 6.16.

4.1.8. Bis(3-(3,5-bis(bromomethyl)phenyl)propyl) ether 30. This reaction was performed under a nitrogen atmosphere. To a 0°C, magnetically stirred slurry of $LiAlH_4$ (4.75 g, 125 mmol) in THF (200 mL) a solution of tetraester **29** (4.96 g, 10.2 mmol) in THF (200 mL) was added dropwise from a dropping funnel over 1 h. The mixture was stirred at rt for 20 h, cooled to 0°C and quenched by the careful addition of ethyl acetate (40 mL). After stirring for 2 h, the solvent was removed and the resulting grey residue was dried under high vacuum for 5 h. To this was added with vigourous stirring 125 mL of a 4:1 mixture of 48% aqueous HBr solution and concentrated H_2SO_4, followed by a further portion of H_2SO_4 (65 mL). Caution: a powerful exotherm occurs upon mixture of the two acids and upon addition of the mixture to the residue. The resulting orange solution was stirred for 3 h, water (200 mL) and dichloromethane (200 mL) were added and stirring was continued until all solids had dissolved. The layers were separated and the aqueous layer was extracted with dichloromethane (100 mL). The combined organic layers were washed with water (200 mL), saturated aqueous $NaHCO_3$ solution (200 mL), saturated aqueous NaCl solution (200 mL) and dried over $MgSO_4$. The solvent was evaporated under reduced pressure and the residue was chromatographed (1:4 ethyl acetate/hexanes) to afford **30** (5.02 g, 77%) as a white solid. Mp=65–67°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.25 (s, 2H), 7.16 (d, J=1.7 Hz, 4H), 4.45 (s, 8H), 3.42 (t, J= 6.3 Hz, 4H), 2.73–2.68 (m, 4H), 1.93–1.88 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=143.4, 138.3, 129.3, 127.1, 69.7, 33.1, 32.0, 31.0. MS *m/z* (%)=M^+ not observed, 467 (4), 465(8), 463 (4), 385 (4), 383 (4), 306 (27), 304 (54), 302 (27), 279 (10), 277 (18), 275 (9), 225 (100), 223 (93), 199 (34), 197 (37). Anal. Calcd for $C_{22}H_{26}Br_4O$: C, 43.29; H, 4.11. Found: C, 43.18; H, 4.12.

4.1.9. 4-Oxa-15,24-dithia[7.3.3](1,3,5)cyclophane 31. To a vigourously stirred solution of tetrabromide **30** (4.75 g, 7.44 mmol) in 9:1 dichloromethane/absolute ethanol (3000 mL) was added freshly prepared Na_2S/Al_2O_3 (6.24 g, ca. 2.5 mmol g^{-1}, ≈15.6 mmol) in several approximately equal portions over 4 h and stirring was continued for 20 h. Tlc analysis indicated incomplete reaction, so a further portion of Na_2S/Al_2O_3 (2.68 g @ ca. 2.5 mmol g^{-1}, ≈6.7 mmol) was added and stirring was continued for 4 h. The mixture was suction filtered, the solvent was removed under reduced pressure and the residue was chromatographed (2:3:15 ethyl acetate/dichloromethane/hexanes) to afford **31** (1.95 g, 71%) as a white solid. Mp>230°C. ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.11 (s, 2H), 6.67 (d, J=0.7 Hz, 4H), 3.81 (s, 8H), 3.22–3.18 (m, 4H), 2.48–2.44 (m, 4H),

1.89–1.83 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=141.5, 137.4, 129.1, 126.9, 68.1, 39.2, 30.3, 28.7. MS *m/z* (%)=371 (27), 370 (100, M^+), 239 (14), 207 (18), 177 (30), 176 (67), 175 (29), 146 (45), 145 (60), 144 (57). Anal. Calcd for $C_{22}H_{26}OS_2$: C, 71.30; H, 7.07. Found: C, 71.15; H, 6.79.

4.1.10. 4-Oxa[7.2.2](1,3,5)cyclophane-14,22-diene 33. These reactions were performed under a nitrogen atmosphere. To a vigorously stirred solution of dithiacyclophane **31** (1.63 g, 4.39 mmol) in dichloromethane (50 mL) was added $(MeO)_2CHBF_4$[10] (1.4 mL, 2.1 g, 13 mmol) dropwise over 20 min and stirring was continued for 16 h. Ethyl acetate (15 mL) was added and the mixture was stirred for 10 min. The mixture was suction filtered and the solids were washed with ethyl acetate and then methanol. Drying under high vacuum afforded a light brown solid (2.58 g), which was slurried in THF (100 mL), and *t*-BuOK (1.21 g, 10.8 mmol) was added. After stirring for 16 h, remaining pieces of solid were crushed with a spatula and a further portion of *t*-BuOK (1.00 g, 8.9 mmol) was added. Stirring was continued for 48 h, the solvent was removed under reduced pressure and the residue was dissolved in dichloromethane (100 mL). This solution was washed with saturated aqueous NH_4Cl solution (50 mL), saturated aqueous NaCl solution (2×50 mL), dried over $MgSO_4$ and concentrated. Filter chromatography (20% ethyl acetate/dichloromethane) afforded a mixture of ring contracted cyclophanes **32** (1.20 g, 70% from **31**), which was used immediately in the subsequent step. To a vigourously stirred solution of **32** (1.20 g, 3.08 mmol) in dichloromethane (30 mL) was added $(MeO)_2CHBF_4$ (0.83 mL, 1.3 g, 7.7 mmol) dropwise over 30 min and stirring was continued for 20 h. Methanol (5 mL) was then added and the solvent was removed under reduced pressure and the sticky, dark brown residue was dried under high vacuum for 30 min. The residue was slurried with THF (50 mL) and *t*-butanol (25 mL) and to this well stirred mixture was added *t*-BuOK (2.22 g, 19.8 mmol). After stirring for 16 h, tlc analysis indicated incomplete reaction and a second portion of *t*-BuOK (1.10 g, 9.80 mmol) was added. Stirring was continued for 16 h, the solvent was removed under reduced pressure and to the residue were added ether (100 mL) and saturated aqueous NH_4Cl solution (50 mL). The layers were separated and the organic layer was washed with water (50 mL), saturated aqueous NaCl solution (50 mL) and dried over $MgSO_4$. Chromatography (dichloromethane) of the residue afforded **33** (0.620 g, 67% from **32**, 47% from **31**) as a pale yellow solid. A small portion was recrystallized from heptane for characterization. Mp=129–131°C (heptane). ^{1}H NMR ($CDCl_3$, 300 MHz): δ=7.39 (s, 2H), 7.23 (s, 4H), 6.41 (s, 4H), 2.93–2.87 (m, 4H), 2.33–2.28 (m, 4H), 1.76–1.66 (m, 4H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ=137.3, 135.8, 133.3, 125.6, 67.3, 30.4 (one aromatic signal overlapped). MS *m/z* (%)=302 (58, M^+), 257 (37), 243 (36), 241 (24), 230 (79), 229 (55), 228 (42), 216 (48), 215 (100), 202 (42), 114 (30). Anal. Calcd for $C_{22}H_{22}O$: C, 87.38; H, 7.33. Found: C, 87.53; H, 7.37.

4.1.11. 4-Oxa[7](2,7)pyrenophane 7. This reaction was performed under a nitrogen atmosphere. To a stirred ca. 75°C solution of cyclophanediene **33** (0.530 g, 1.75 mmol) in benzene (100 mL) was added DDQ (0.400 g, 1.76 mmol) in two equal portions with a 10 min interval. After a further 15 min, another portion of DDQ (0.040 g, 0.18 mmol) was added, 5 min after which tlc analysis indicated the starting material had been completely consumed. The mixture was cooled to rt, suction filtered and the solvent was removed under reduced pressure. The residue was dissolved in dichloromethane (100 mL) and washed with 1 M aqueous NaOH solution (50 mL), water (50 mL), saturated aqueous NaCl solution (50 mL), dried over $MgSO_4$ and concentrated under reduced pressure. Chromatography (9:1 dichloromethane/hexanes) of the residue afforded **7** (0.271 g, 52%) as a white solid. A small sample was recrystallized from heptane. Mp=132–133°C (heptane). ^{1}H NMR ($CDCl_3$, 500 MHz): δ=7.75 (s, 4H), 7.40 (s, 4H), 2.39–2.35 (m, 4H), 0.78–0.60 (m, 4H), 0.58–0.55 (m, 4H). ^{13}C NMR ($CDCl_3$, 125 MHz): δ=135.4, 132.1, 131.3, 130.0, 126.5, 68.1, 33.0, 32.0. MS *m/z* (%)=301 (24), 300 (100, M^+), 255 (18), 242 (38), 241 (71), 230 (28), 229 (29), 228 (58), 215 (31), 114 (28). Anal. Calcd for $C_{22}H_{22}O$: C, 87.96; H, 6.71. Found: C, 87.49; H, 6.77.

4.2. Crystal structure determination of 7

Colorless prism (0.30×0.25×0.42 mm^3) from heptane, $C_{20}H_{20}O$, M=300.40, triclinic, P-1 (#2), Z=4, a=12.984 (2), b=15.017 (2), c=9.120 (2) Å, α=100.79 (1), β=107.602 (9), γ=93.33 (1), V=1652.4 (5) Å^3, D_c=1.207 g cm^{-3}, $F(000)$=640, μ(Cu–Kα)=5.56 cm^{-1}. Data collection with a Rigaku AFC6S diffractometer at 26°C with graphite monochromated Cu–Kα radiation (λ=1.54178 Å), $\omega-2\theta$ scan type with ω scan width=$(1.73+0.14\tan\theta)°$, ω scan speed 4.0° min^{-1} (in ω) (up to five rescans for weak reflections), 5161 reflections measured, 4910 unique (R_{int}= 0.031), Lorentz-polarization, empirical absorbtion (max., min. corrections=1.000, 0.964) and secondary extinction (coefficient: 2.00227×10^{-5}) corrections, giving 3869 with $I>2.00\sigma(I)$. Solution and refinement by direct methods (SHELX97) using the teXsan package of the Molecular Structure Corporation; all non-hydrogen atoms were refined anisotropically; full matrix least squares refinement with 536 variable parameters led to R=0.054 and R_w=0.053, GOF=3.45.

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