Nonplanar Aromatic Compounds. 5.[1] A Strategy for the Synthesis of *cis*-10b,10c-Dimethyl-10b,10c-dihydropyrenes. First Crystal Structure of a *cis*-10b,10c-Dimethyl-10b,10c-dihydropyrene

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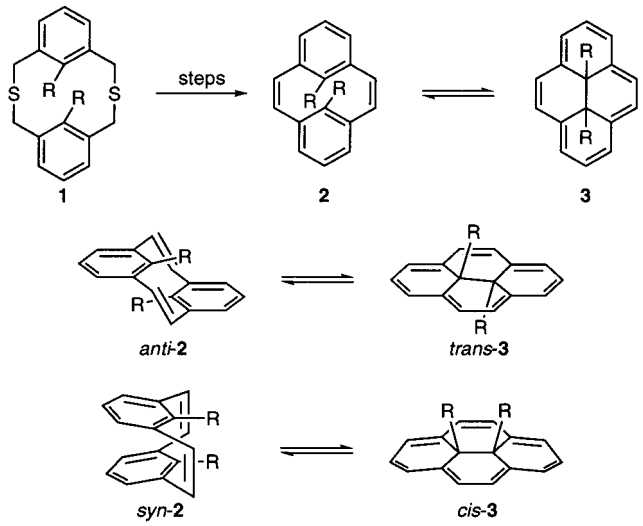
Abstract: Through the use of a potentially removable tether, a heavily substituted 10b,10c-dimethyl-10b,10c-dihydropyrene (DMDHP), **20**, was synthesized exclusively as the *cis*-isomer. It exists as the major component (20:1) in an equilibrium with its valence isomer *syn*-[2.2]metacyclophanediene **19**. An X-ray crystal structure determination of **20**, a *cis*-(2,7)-10b,10c-dihydropyrenophane, provided the first experimental measurements of the *cis*-DMDHP skeleton. The observed bond alternation in the [14]annulene was found to be larger than that of the corresponding *trans*-DMDHP framework. Prior MMPI calculations, on which previous discussion of the structure of the *cis*-DMDHP system had been based, are in very good agreement with the experimental results. Our own DFT calculations predict a more symmetric and more bond equalized structure than was observed in **20**.

Introduction

By virtue of its 14π electron perimeter, the 10b,10c-dihydropyrene framework has been the subject of considerable experimental and theoretical interest.[2,3] The best studied members of this class of compounds are the *trans*-10b,10c-dimethyl-10b,10c-dihydropyrenes (*trans*-DMDHPs), the internal methyl groups of which have been used to great effect as probes for aromaticity.[3] The most widely used synthetic approach to 10b,-10c-dihydropyrenes is the "cyclophane route",[4] which involves the synthesis of a 2,11-dithia[3.3]metacyclophane **1**, its conversion to a [2.2]metacyclophane-1,9-diene **2**, and the thermally and/or photochemically driven valence isomerization thereof to the corresponding dihydropyrene **3** (Scheme 1). In most cases, the dihydropyrene is the thermodynamically favored isomer.[2,3]

The majority of known DMDHPs are *trans* isomers, and this has its origin in the general preference for the *anti* conformation of their progenitors, the [2.2]metacyclophane-1,9-dienes **2**. Owing to the difficulty of preparing synthetically useful amounts of the corresponding *syn*-[2.2]metacyclophane-1,9-dienes, the corresponding *cis*-DMDHPs are comparatively rare entities.[5]

Scheme 1



Structural details of the *trans*-DMDHP skeleton have been measured crystallographically,[3c,6,7] and these are in good agreement with those generated from computational studies,[3a,7,8] provided that electron correlation[9] is employed. Important structural features of the *trans*-DMDHP system are the high degree of bond equalization and relative planarity of the [14]-annulene unit.

Until now, there has been no X-ray crystallographic structure determination of a *cis*-DMDHP[10] and all previous discussion

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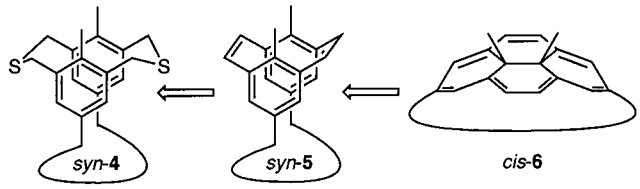
Scheme 2



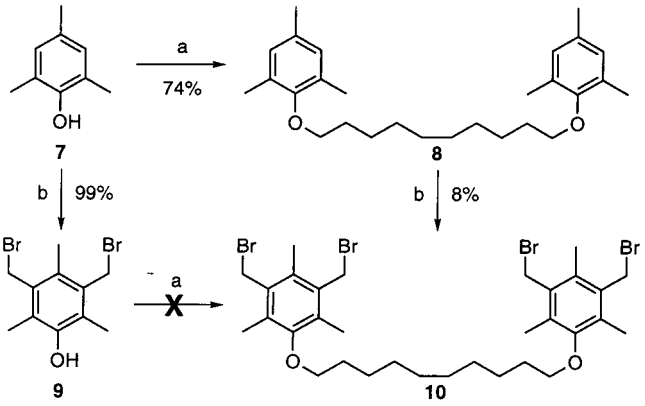
of their structures has been based on computational work. A bowl, or saucer, shaped [14]annulene with greater bond alternation than that of the *trans*-DMDHP system has been calculated.[11] Thus the original goals of this work were the development of a reliable synthetic route to *cis*-DMDHPs and the X-ray crystallographic characterization of the *cis*-DMDHP skeleton. We now present our initial findings.

Synthesis of *cis*-20. The chief problem with existing synthetic routes to *syn*-[2.2]metacyclophane-1,9-dienes is the strong preference for the adoption of the *anti* conformation during the formation of the 2,11-dithiacyclophane **1** (in the case of internally substituted systems[5,12]) or the subsequent bridge contraction to a [2.2]metacyclophane.[13] To circumvent this problem, the use of a temporary third bridge, a tether, in the cyclophane system was envisaged (Scheme 2). An important consideration was that the tether be short enough to ensure that dithiacyclophane **4** forms and remains exclusively in the *syn* conformation but long enough to permit valence isomerization of *syn*-**5** to *cis*-**6**, during which the attachment points of the tether move away from one another substantially. In related work,[14] we observed that a 13-atom tether between the 5 and 13 positions of the [2.2]metacyclophane skeleton is long enough to allow *syn/anti* isomerism at room temperature, but a 12-atom tether is not. Thus a 12-atom tether was chosen for initial investigation.

For the sake of synthetic simplicity, 2,4,6-trimethylphenol **7** was chosen as the starting material, despite the presence of extraneous methyl groups. The original synthetic plan (Scheme 3) commenced with the alkylation of **7** to afford **8** (74%). Attempted bromomethylation gave only 8% of the desired tetrabromide **10**, extensive tether cleavage having occurred during this reaction. Indeed the major product was the dibromide **9** (86%). Reversing the order of these reactions proved to be no more successful. Bromomethylation of **7** gave dibromide **9** in 99% yield, but attempted introduction of the tether to give **10** afforded only intractable material. It had been hoped that the hindered nature of both the benzylic bromides and the hydroxy group of **9** would disfavor self-alkylation reactions, but this was clearly not the case.

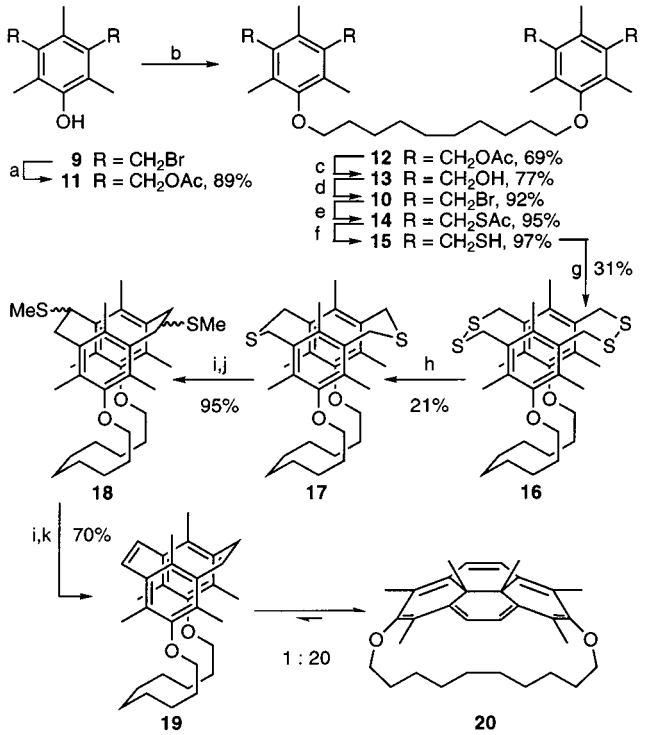
The successful route (Scheme 4) involved the protection of the benzylic bromides prior to the introduction of the tether. Dibromide **9** was first treated with potassium acetate to provide diacetate **11** (89%) and the tether could now be installed satisfactorily (69%). $LiAlH_4$ reduction of the resulting tetraacetate **12** provided tetraol **13** (77%) and reaction with PBr_3 then furnished tetrabromide **10** (92%).

Scheme 3[a]



[a] Key: (a) $Br(CH_2)_{10}Br$, K_2CO_3, DMF, 80 °C; (b) 1,3,5-trioxane, 35% HBr/HOAc, reflux.

Scheme 4[a]



[a] Key: (a) KOAc, CH_3CN, reflux, 22 h; (b) $Br(CH_2)_{10}Br$, K_2CO_3, DMF, 80 °C, 19 h; (c) $LiAlH_4$, THF, r.t., 21 h; (d) PBr_3, CH_2Cl_2, r.t., 14 h; (e) KSAc, CH_3CN, reflux, 23 h; (f) KOH, DMF, 60 °C, 4 h; (g) I_2, pyridine, CH_2Cl_2/EtOH, r.t., 5 d; (h) $(Me_2N)_3P$, benzene, reflux, 31 h; (i) $(MeO)_2CHBF_4$, CH_2Cl_2, 0 °C to rt, 11−12 h; (j) *t*-BuOK, THF, rt, 3 h; (k) *t*-BuOK, 1:1 THF:*t*-BuOH, 0 °C to rt, 1 h.

At this point, the crucial step of ring closure of **10** to give dithiacyclophane **17** had to be addressed. Attempts to accomplish this transformation using Na_2S/Al_2O_3,[15] which we had found to be a very effective reagent in related systems,[1,14,16,17] afforded none of the desired product. This is presumably due to the congested environment of the benzylic bromides in **10**. To negotiate this obstacle, the oxidative coupling of thiols to disulfides,[18] which can be converted into thioethers,[19] was then considered. This approach was attractive because the closure

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of the bridges involves reaction at homobenzylic sulfur atoms, as opposed to sterically encumbered benzylic carbon atoms. In addition, there is precedent for the use of this methodology in the synthesis of metacyclophanes.[20]

The required tetrathiol **15** was prepared from tetrabromide **10** by treatment with potassium thioacetate to afford **14** (95%) and hydrolysis of **14** with KOH/DMF (97%). Reaction of **15** with iodine and pyridine under high dilution conditions gave tetrathiacyclophane **16** (31%) along with a dimeric product in 28% yield.[21] Desulfurization of **16** with HMPT then afforded the desired dithiacyclophane **17** (21%). No other nonpolar products were obtained from this reaction.

All that remained now was the bridge contraction and formation of the double bonds. Fortunately the standard protocol did not present any problems. Methylation of the sulfur atoms of **17** with $(MeO)_2CHBF_4$ (Borch reagent) followed by Stevens rearrangement afforded the ring-contracted products **18** (95%) as a mixture of isomers. Finally, after 2-fold *S*-methylation of **18** with Borch reagent, Hofmann elimination led to the formation of a ca. 1:20 mixture (^{1}H NMR) of the cyclophanediene **19** and its valence isomeric *cis*-DMDHP **20** in a combined yield of 70% from **18**. The overall combined yield of **19** and **20** for the 13-step sequence starting from **7** was 1.7%, the majority of the losses having been suffered during the conversion of **15** to **17** (7% yield over two steps).

Discussion

^{1}H NMR Spectrum of 20. The ^{1}H NMR spectrum of **20** exhibits singlets at δ 8.66 and -1.78 for the external protons and internal methyl protons, respectively. By comparison, the corresponding protons of the parent *cis*-DMDHP **21** are observed at δ 8.74 and -2.06, respectively.[5d,e] The chemical shift difference between the internal methyl protons of **20** and those of *cis*-**21** is $\approx$0.3 ppm, which is much the same as that ($\approx$0.4 ppm) between those of the parent *trans*-DMDHP *trans*-**21**[22] and **22**,[23] the closest known *trans*-DMDHP analogue of **20**. In light of the sensitivity of the internal methyl protons' chemical shifts to physical changes in the dihydropyrene skeleton,[2] these observations suggest that the presence of the bridge in **20** does not significantly affect the geometry of the *cis*-DMDHP moiety. Analysis of the chemical shifts of the external aromatic protons leads to the same conclusion.

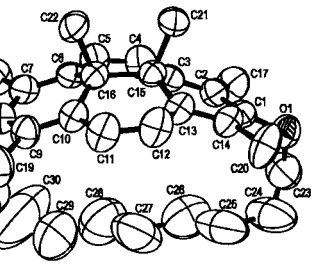
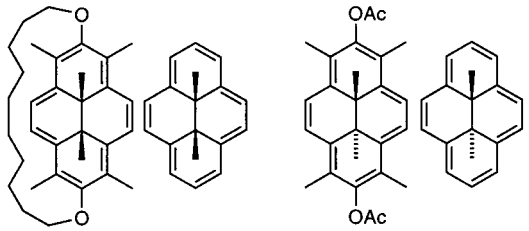


Figure 1. ORTEP representation of *cis*-**20** in the crystal.



	20	*cis*-**21**	**22**	*trans*-**21**
δ (Me_{int})	−1.78	−2.06	−3.88	−4.25
δ (H_{ext})	8.66	8.74	8.66	8.67
ref.		5d,5e	22	23

The external methyl protons of **20** (δ 3.02) are deshielded by 1.05 ppm from those of cyclophanediene **19** (δ 1.93). The bridge protons of **20** appear as a series of 4H multiplets centered at δ 4.11, 1.17, -0.09, -0.39, and -0.83. Although the observation of high field shifted protons was fully expected, it is the first instance of NMR active nuclei being held directly under the concave face of a *cis*-DMDHP. Interestingly, the chemical shifts of the bridge protons of **20** are very similar to those of the [*n*](2,7)pyrenophane with the same tether, 1,12-dioxa[12](2,7)pyrenophane **24**: δ 4.31 (4H), 1.41 (4H), -0.14 (8H), -0.63 (4H).[24]

X-ray Crystal Structure of 20 and DFT-Calculated Structure of *cis*-21. Prior to this work, all structural data for the *cis*-DMDHP skeleton was derived from MMPI calculations. Fortunately, slow evaporation of a deep emerald green solution of **19** and **20** in dichloromethane/heptane afforded dark red-green birefringent crystals of **20**, which were of suitable quality for an X-ray crystal structure determination. The crystal structure (Figure 1) was solved with ease, but a disorder problem of some kind in the tether was evident. This did not appear to be a case of two alternate conformations, but rather a high degree of "looseness", which could not be modeled with any degree of confidence. For comparison purposes, the structure of *cis*-**21** was optimized at the B3LYP/6-31G(d) level of theory using Gaussian 94.[25] Selected structural data are presented in Figure 2 and Tables 1−4 along with previously calculated (MMPI) data for *cis*-**21**.

The prediction of a bowl-shaped [14]annulene moiety in the *cis*-DMDHP skeleton by the MMPI and DFT calculations is

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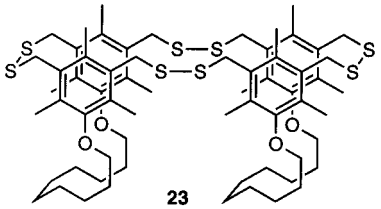
(21) A similar byproduct was obtained in the oxidative self-coupling of a lower homologue of **15**, the structure of which was determined crystallographically. By analogy, structure **23** is assigned to the dimer of **16**.



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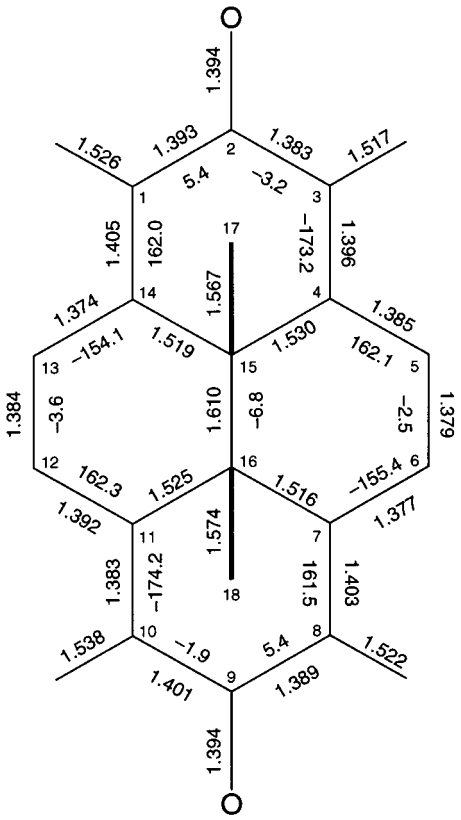

Figure 2. Bond lengths (Å) and torsion angles (deg) in *cis*-**20**.

Table 1. Measured and Calculated Dihydropyene Bond Lengths[a]

	20	*cis*-**21**	
bond[b]	X-ray	MMPI	B3LYP/6-31G(d)
C(1)−C(2)	1.393(4)	1.398	1.398
C(2)−C(3)	1.383(3)	1.398	1.398
C(3)−C(4)	1.396(3)	1.402	1.397
C(4)−C(5)	1.385(4)	1.405	1.398
C(5)−C(6)	1.379(4)	1.389	1.392
C(6)−C(7)	1.377(4)	1.405	1.398
C(7)−C(8)	1.403(3)	1.402	1.397
C(8)−C(9)	1.389(4)	1.398	1.398
C(9)−C(10)	1.401(4)	1.398	1.398
C(10)−C(11)	1.383(3)	1.402	1.397
C(11)−C(12)	1.392(4)	1.405	1.398
C(12)−C(13)	1.384(4)	1.389	1.392
C(13)−C(14)	1.374(4)	1.405	1.398
C(14)−C(1)	1.405(3)	1.402	1.397
C(4)−C(15)	1.530(3)	1.519	1.534
C(7)−C(16)	1.516(3)	1.519	1.534
C(11)−C(16)	1.525(3)	1.519	1.534
C(14)−C(15)	1.519(3)	1.519	1.534
C(15)−C(16)	1.610(3)	1.572	1.630
C(15)−C(17)	1.567(3)	1.555	1.571
C(16)−C(18)	1.574(3)	1.555	1.571

[a] Bond lengths in angstroms. [b] Numbering as shown in Figure 2.

confirmed by the crystallographic results. The origin of the nonplanarity of the [14]annulene system can be traced back to the geometric requirements of the central ethano moiety. A planar [14]annulene skeleton would force the internal methyl groups to well within van der Waals contact and impose severe angle strain about the two central carbon atoms. Adoption of a bowl shape relieves these forms of strain but still leaves the ethano moiety in an eclipsed conformation. Torsional strain in the ethano unit can be relieved by rotation about the central C−C bond, but it is counterbalanced by an increase in torsional strain of the peripheral [14]annulene system. By comparison,

Table 2. Bond Angles[a]

	20	*cis*-**21**	
angle[b]	X-ray	MMPI	B3LYP/6-31G(d)
C(4)−C(15)−C(14)	111.9(2)	109.1	111.0
C(4)−C(15)−C(16)	114.6(2)	113.7	114.0
C(4)−C(15)−C(17)	102.0(2)	104.0	102.8
C(14)−C(15)−C(16)	113.3(2)	113.7	114.0
C(14)−C(15)−C(17)	102.7(2)	104.0	102.8
C(16)−C(15)−C(17)	111.2(2)	112.9	111.2
C(7)−C(16)−C(11)	111.9(2)	109.1	111.0
C(7)−C(16)−C(15)	113.5(2)	113.7	114.0
C(7)−C(16)−C(18)	102.2(2)	104.0	102.8
C(11)−C(16)−C(15)	115.0(2)	113.7	114.0
C(11)−C(16)−C(18)	102.1(2)	104.0	102.8
C(15)−C(16)−C(18)	110.7(2)	112.9	111.2

[a] Bond angles in degrees. [b] Numbering as shown in Figure 2.

Table 3. Observed and Calculated Torsion Angles[a]

	20	*cis*-**21**	
bond[b,c]	X-ray	MMPI	B3LYP/6-31G(d)
C(1)−C(2)−C(3)−C(4)	−3.2(4)	7	4.7
C(2)−C(3)−C(4)−C(5)	−173.3(2)	−176	−167.7
C(3)−C(4)−C(5)−C(6)	162.1(2)	160	160.1
C(4)−C(5)−C(6)−C(7)	−2.5(4)	−3	0.0
C(5)−C(6)−C(7)−C(8)	−155.4(3)	−155	−160.1
C(6)−C(7)−C(68)−C(9)	161.5(2)	164	167.7
C(7)−C(8)−C(9)−C(10)	5.4(4)	3	4.7
C(8)−C(9)−C(10)−C(11)	−1.9(4)	7	4.7
C(9)−C(10)−C(11)−C(12)	−174.2(2)	−176	−167.7
C(10)−C(11)−C(12)−C(13)	162.3(3)	160	160.1
C(11)−C(12)−C(13)−C(14)	−3.6(4)	−3	0.0
C(12)−C(13)−C(14)−C(1)	−154.1(3)	−155	−160.1
C(13)−C(14)−C(1)−C(2)	162.0(2)	164	167.7
C(14)−C(1)−C(2)−C(3)	5.4(4)	3	4.7
C(17)−C(15)−C(16)−C(18)	−6.8(2)	8	0.0

[a] Bond angles in degrees. [b] The sign is positive if, when looking from atom 2 to atom 3, a clockwise motion of atom 1 superimposes it on atom 4. [c] Numbering as shown in Figure 2.

the ethano unit of the *trans*-DMDHP skeleton is held in a staggered conformation and the [14]annulene moiety is not far from being perfectly planar.[7] Thus it is not surprising that the unusual structural features observed in the crystal structure of **20** are all associated with the ethano unit.

The crystal structure of **20** revealed that the central ethano unit is not fully eclipsed, the C(17)−C(15)−C(16)−C(18) torsion angle being 6.8°. This is very close to the angle predicted by MMPI calculations (8°). On the other hand, the DFT calculations predict a symmetric structure for *cis*-**21** containing two planes of symmetry and a corresponding torsion angle of 0°. To verify that this structure was a true energy minimum, frequencies were calculated at the B3LYP/6-31G(d) level of theory and no imaginary frequencies were found.

In the crystal structure of **20**, the bond between the two central sp^3 carbon atoms {C(15)−C(16)} is quite long (1.610 Å). This is significantly longer than the MMPI-calculated value (1.572 Å) and slightly shorter than the DFT-calculated value (1.630 Å). The bonds between the quaternary sp^3 carbons and their attached internal methyl carbon atoms (1.567 and 1.564 Å) are also observed to be somewhat elongated and quite close to their calculated values (MMPI, 1.555 Å; DFT, 1.571 Å).

The bond angles about the central carbon atoms of **20** are all distorted from the tetrahedral angle. For C(15), the angles C(4)-C(15)−C(17) (102.0°) and C(14)C(15)−C(17) (102.7°) are substantially compressed and the remaining four angles are in the range 111.2−114.6° (Table 2). A similar situation exists around C(16), where the angles C(7)C(16)−C(18) (102.2°) and

Table 4. Structural Data for **20**, *cis*-**21**, and *trans*-**21**

	20	*cis*-**21**		*trans*-**21**		
	X-ray	MMPI		X-ray[a]	MMPI	AM1/CI4
range	1.374−1.405	1.389−1.405	1.392−1.398	1.389−1.398 1.388−1.397	1.400−1.405	1.393−1.397
$\bar{d}$	1.389	1.400	1.397	1.393 1.392	1.402	1.396
$\bar{\Delta}\,\bar{d}$	0.008	0.003	0.001	0.003 0.003	0.002	0.001
$\Delta\,\bar{d}_{max}$	0.016	0.011	0.005	0.004 0.005	0.004	0.003
$\bar{\tau}$	11.2	11	10.5	2.5 2.7	6	n.a.
τ_{max}	25.9	25	19.9	4.1 5.0	11	n.a.
ref		2a		7	2a	7

[a] The unit cell contains two crystallographicaly independent molecules.

C(11)C(16)−C(18) (102.1°) are compressed and the other four angles lie in the range 110.7−115.0°. These distortions are consistent with a steric repulsion between the nearly eclipsed internal methyl groups. Both the MMPI and DFT calculations predict this distortion, although the DFT results are much closer to the observed data.

Another consequence of the proximity of the internal methyl groups is that all of their attached hydrogens were located from a difference map at an early stage of the refinement, which suggests a higher than normal barrier to rotation at room temperature in the solid state. However, the signals of the internal methyl groups are no broader than those of the external methyl groups in the ambient temperature ^{1}H NMR spectrum and only slightly broader at −90 °C. This suggests that rotation is not significantly restricted in solution, even at low temperature.

A particularly unusual feature of the crystal structure was the set of four independent regions of lower than expected electron density observed on the final difference map. These were located beneath the four bonds C(3)−C(4), C(7)−C(8), C(10)−C(11), and C(14)−C(1). The origin of this phenomenon is unclear.

Structural features of the peripheral [14]annulene systems of both *cis*- and *trans*-DMDHPs have been used to comment on the aromatic character of the system.[2] Key structural parameters associated with the [14]annulene moiety of **20** are summarized in Table 4 along with the corresponding data for *cis*-**21** and *trans*-**21**. The bond lengths of **20** range from 1.374 to 1.405 Å, and their average length ($\bar{d}$) is 1.389 Å. The computational methods tend to overestimate the bond lengths of both the *cis*- and *trans*-DMDHP skeleton. The average deviation from $\bar{d}$ ($\bar{\Delta}\,\bar{d}$) is 0.008 Å, and the largest deviation from $\bar{d}$ ($\Delta\,\bar{d}_{max}$) is 0.016 Å. Both the MMPI and our DFT calculations predict a significantly more bond equalized [14]annulene system than was observed in **20**, especially the DFT calculations. The actual degree of bond equalization in the *cis*-DMDHP skeleton of **20** is considerably lower than that observed in the crystal structure of *trans*-**21**, which is what was predicted by MMPI calculations on the two systems.

The average deviation of the torsional angles from 0 or 180° ($\bar{\tau}$) (a coplanar arrangement) is 11.2°, and the maximum deviation from coplanarity (τ_{max}) is 25.9°. This is in excellent agreement with the MMPI calculations (Tables 3 and 4). The DFT calculations afford lower numbers (a less distorted annulene), primarily due to the prediction of a symmetric structure containing a fully eclipsed central ethano unit. As mentioned earlier, rotation about the central bond causes a twist in the [14]-annulene system, and this necessarily results in an increase in $\bar{\tau}$ and τ_{max}.

Having established a viable synthetic route to the *cis*-DMDHP skeleton, we are now in the process of investigating whether the bridge of **20** and its homologues can be cleaved to afford free *cis*-DMDHPs and how the length of the tether affects the valence isomerization between a tethered *syn*-[2.2]metacyclophanediene and the corresponding *cis*-dimethyldihydropyrenophane.

Conclusions

Dimethyldihydropyrenophane **20** was synthesized exclusively as its *cis* isomer by using a 12-atom tether to ensure formation and maintenance of only the *syn* conformation of the metacyclophanes that preceded it. A crystal structure determination of **20** revealed that the *cis*-DMDHP skeleton is indeed less bond equalized and more distorted from planarity than the corresponding *trans*-DMDHP skeleton. The structure predicted for *cis*-**21** by the MMPI calculations is in excellent agreement with the observed *cis*-DMDHP moiety of **20**, right down to the twist of the central ethano unit. DFT calculations predict a more symmetric and more bond equalized *cis*-DMDHP structure.

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Supporting Information Available: Full experimetal details and characterization data for all new compounds. ^{1}H NMR spectra for **8**−**20** and **23**. ^{13}C NMR spectra for all **8**−**17**, **19**, **20**, and **23**. X-ray structural data for **20**. This material is available free of charge via the Internet at http://pubs.acs.org.

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