Molecular “Iron Maidens”: Ultrashort Nonbonded Contacts in Cyclophanes and Other Crowded Molecules

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Ultrashort nonbonded interactions involving aromatic rings should be the sole province of cyclophane chemists, but it is not always so. In this review, the structures, syntheses, and properties of molecules exhibiting the closest nonbonded contacts of various atoms and functional groups with the faces of aromatic rings are discussed and illustrated.

The purpose of this review is to examine the structures, and to a lesser extent the syntheses and properties, of molecules that exhibit extremely tight, nonbonded contacts between various functional groups and carbocyclic aromatic rings. Enforced proximity of less reactive or normally unreactive functional groups with benzene rings has been a persistent theme in cyclophane chemistry,[1] and the synthesis of *in*-cyclophanes for this purpose, one of my own research interests, is highlighted to some degree. Of course, similar levels of molecular congestion can be attained in other classes of compounds, and this review attempts to cover any and all well characterized organic molecules possessing the very closest intramolecular nonbonded interactions involving benzene rings (metal-containing structures have been excluded). Such molecules present serious synthetic challenges, but once these are overcome, their X-ray structures provide not only confirmation of the synthetic achievements, but also vitally important checks on the accuracy of modern computational methods.[2] For this reason, the molecular structure of each compound of interest, provided that its coordinates are available in the Cambridge Structural Database (CSD),[3] is illustrated below its conventional chemical depiction, and its CSD refcode is appended to the reference for its crystal structure determination.

An enzymologist by training, I had only a passing interest in strained organic molecules when I joined the Princeton faculty in 1982. However, Princeton University requires at least a year of laboratory research from its undergraduate chemistry majors, and I soon discovered that the schedules of these students were incompatible with multi-step protein

Robert A. Pascal, Jr., was born in New Orleans in 1954. He attended Louisiana State University where he ran track (primarily the long sprints: 440 y and 600 y) and ultimately received his B.S. in 1976 (Biochemistry). Entering Rice University on an NSF Predoctoral Fellowship, he studied demethylation reactions in cholesterol biosynthesis under the direction of George Schroepfer, Jr., and he received his Ph.D. in 1980 (Biochemistry). Joining Christopher Walsh’s group at MIT as an NIH Postdoctoral Fellow, he spent two years on the isolation and mechanistic studies of dihydroorotate oxidase from parasitic protozoa. He joined the Chemistry faculty at Princeton in 1982, and, due to circumstances outlined in this review, soon began the synthesis of strained organic molecules as a diversion from biochemical research. Professor Pascal’s principal research interests have been in the areas of biochemistry (enzyme mechanisms, design of enzyme inhibitors, and natural product biosynthesis) and physical organic chemistry (strained aromatic molecules, kinetic isotope effects, molecular association, and crystal engineering) with a recent emphasis on the latter. His chief pastimes are reading, running, cycling, shooting, photography, and amateur astronomy.

MICROREVIEWS: This feature introduces the readers to the author's research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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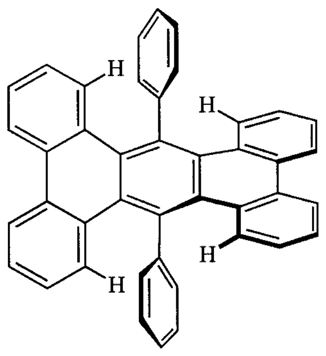
purification. Accordingly, the undergraduates who joined my research group were chiefly employed in the chemical synthesis of enzyme substrates, substrate analogues, and inhibitors. This was a satisfactory arrangement, but there is always the temptation (a *good* temptation) to commit "free" resources to especially risky projects, and I was soon persuading my students to attempt very short, but perhaps dubious, syntheses of exotic molecules. In this way, our practical experience with the chemistry of crowded molecules began with the one-step preparation of polycyclic aromatic hydrocarbon **1** in 1986.[4,5]

Compound **1** is obviously very twisted, by 66° end-to-end in fact, in order to accommodate the benzo hydrogens and phenyl groups between the relatively rigid phenanthrene termini of the polycycle. We naturally wondered whether these hydrogen-to-arene nonbonded contacts were especially short; they are not. We then asked, though, how closely could a carbon-bound hydrogen approach an aromatic ring from above − that is, within an imaginary hexagonal prism above the ring (**2**)[6] − or, indeed, how closely could a hydrogen approach the *center* of an aromatic ring?



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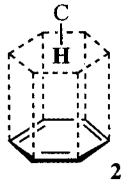

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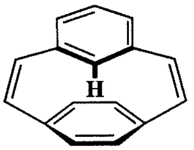

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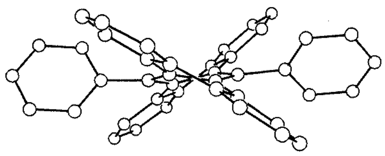
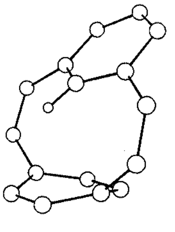
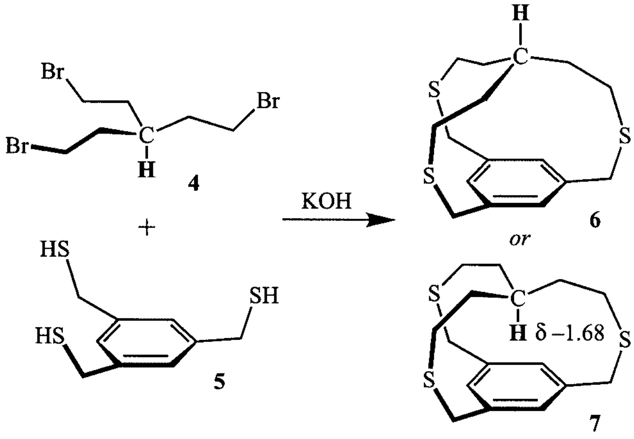


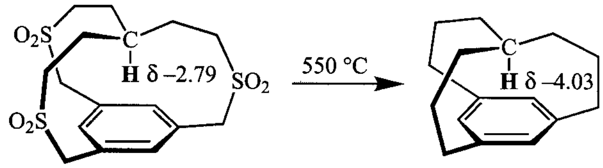


The X-ray structures of cyclophanes were exhaustively reviewed in 1983,[7] and from this compendium it was clear that the "world record" for close hydrogen-arene nonbonded contacts was to be found in Boekelheide's metaparacyclophane **3**.[8,9] In this molecule, the illustrated hydrogen is only 2.11 Å from the center of the opposing benzene ring. (Hereafter, this distance, to the center of the ring, is called the H---Ar contact,[10] but nonbonded distances to specific carbon atoms are designated H---C contacts. Furthermore, in this review, "improved" C-H covalent bond lengths[11,12] are used for the calculation of all nonbonded contacts involving hydrogen atoms.) In compound **3**, however, the hydrogen atom is neither directly above nor pointed directly at the center of the opposing benzene, because the upper ring is not held perpendicular to the lower. It is easy to imagine structures that would force the C-H bond to be orthogonal to the ring, but how might they be made?

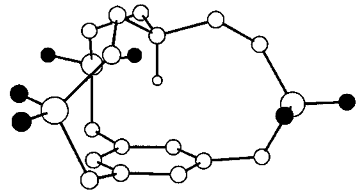
The answer was most surprising: such compounds had already been made, but they had not been recognized! In 1976, Ricci et al. reported the synthesis of cyclophane **6** by condensation of tribromide **4** and trithiol **5**.[15] That the structure of **6** might have been misassigned would never have occurred to us save for a rare example of editorial largesse: the actual 60 MHz ^{1}H NMR spectra of this and related cyclophanes were reproduced in a figure in Ricci's paper. These spectra covered the region from 0 to 8 ppm (δ), but it was clear that the apical proton resonance for **6** was missing. It must have been shifted far upfield, but if so, then the cyclophane had to be the *in* isomer **7**, rather than the *out* isomer **6**.[16] We reproduced the synthesis, and to our delight the ^{1}H NMR spectrum of the product displayed a septet at $\delta = -1.68$ ppm.[17] It was indeed the *in* isomer!



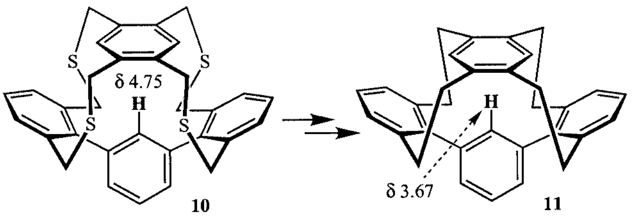
The final ring closure to form **7** functions as a molecular "Iron Maiden" ("an iron frame in human form hinged to admit a victim, who, as the frame closed, was impaled on the spikes which stud the interior" − *Webster's New International Dictionary*, 2nd ed.), and such C_3 symmetric cyclophanes are ideally suited to project a functional group toward the center of an aromatic ring. The *in* isomers appear to be preferred in such molecules because of a high degree of angle strain in the *out* isomers. Nine years were to pass before the crystal structure of **7** was to be obtained,[18] but its trisulfone derivative **8**, formed by boiling **7** in hydrogen peroxide and acetic acid, gave single crystals immediately.[19] Its X-ray structure yields an H---Ar distance of 2.13 Å: close, but not the record. However, brief pyrolysis[20] of **8** at 500−600 °C gave the *in*-cyclophane **9** in 11% yield.[19] This unique hydrocarbon displays an exceptionally high-field methine resonance ($\delta = -4.03$, due to the diamagnetic anisotropy of the benzene ring), a very small ^{13}C-^{1}H coupling constant ($J_{C,H} = 120$ Hz, indicating a high degree of *p*-character in the C-H bond), and a 400 cm^{-1} frequency enhancement (due to steric compression) of the methine C-H stretch in its IR spectrum ($\nu_{CH} = 3325$ cm^{-1}). Obviously the H---Ar contact is extremely tight, but the X-ray structure of this waxy solid has yet to be determined.



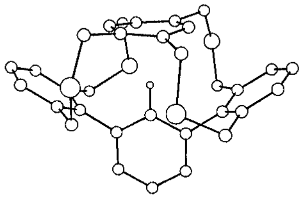
8 **9**



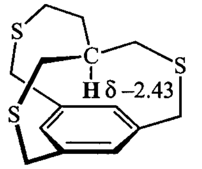
Unbeknown to us, Vinod and Hart had been pursuing the synthesis of more complex, but equally tight *in*-cyclophanes. One year later they reported the preparation of the "cappedophanes" **10** and **11**.[21] The crucial ring-forming and ring-contraction steps were similar to those described above: compound **10** was made by condensation of a tetrabromide with a tetrathiol, and oxidation and flash vacuum pyrolysis (FVP) gave the hydrocarbon **11**. The X-ray structure of compound **10** gave an H---Ar distance of 2.00 Å, the shortest yet observed, but no crystal structure of the much more congested **11** was forthcoming.



10 **11**



Although FVP methods had been used to form the very tight cyclophanes **9** and **11**, molecular mechanics calculations [MM2(85)] clearly indicated that *in*-cyclophanes even as tight as **9** are more stable than their *out* isomers, and so the direct condensation of smaller trithiols and tribromides might provide such compounds. This proved to be the case, and in 1989 we obtained cyclophanes **12** and **13** in 15% and 3% yields, respectively, from the appropriate acyclic precursors.[22] Their X-ray structures placed the *in*-hydrogen atoms much closer to the arenes than previously observed, with H---Ar distances of 1.86 Å and 1.68 Å, respectively. Furthermore, compound **13** displays many of the same spectral phenomena as **9**, but to a less extreme degree ($\delta_{\text{in-H}} = -2.84$ ppm, $J_{\text{C,H}} = 128$ Hz, and $\nu_{\text{CH}} = 3260\ \text{cm}^{-1}$).



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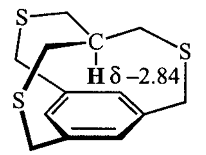

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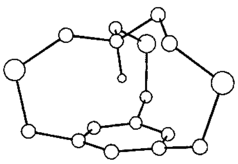
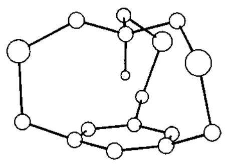
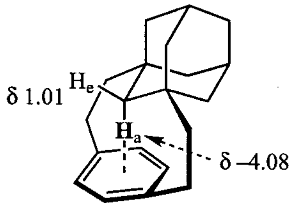




Subsequent attempts to prepare *in*-cyclophanes with three-armed bridges even shorter than in **9** proved unsuccessful, but a few years later Vögtle and co-workers found a new way to force hydrogens into aromatic rings. Simple [*n*]paracyclophanes[23] do not display particularly short H---Ar contacts, because their bridging polymethylene chains arch above the ring. Through the incorporation of a bulky adamantyl group into the bridge of [7]paracyclophane to form **14**, however, it was found that one of the hydrogens (H_a) is tipped toward the center of the basal ring.[24] This proton displays an ^{1}H NMR resonance at δ = −4.08 ppm, and the X-ray structure of **14** reveals an H---Ar distance of only 1.64 Å, which remains the closest such contact so far observed.



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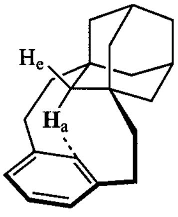

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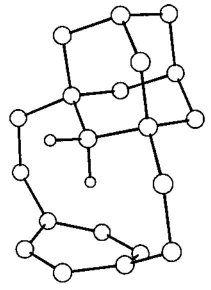
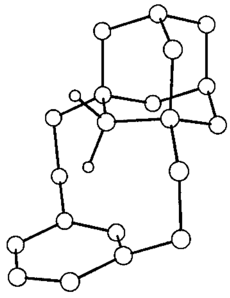
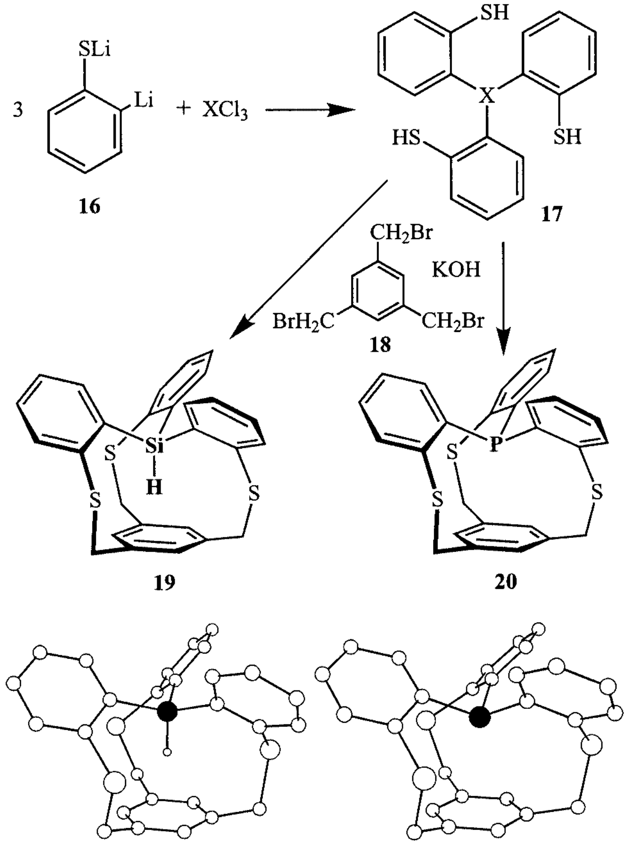




In each of the cyclophanes so far mentioned, the *in*-hydrogen is projected toward the center of the opposing aromatic ring, and so there are short H---C contacts with all of the carbon atoms in the ring. However, in order to achieve the single, shortest possible H---C contact, the *in*-hydrogen must be moved toward one side of the ring. Vögtle and co-workers achieved this with the metacyclophane **15**,[25] in which the H---Ar distance is "only" 2.02 Å, but there is one exceptionally short H---C contact of 1.98 Å! It is notable that compounds **14** and **15**, like **9** and **11**, were prepared by the FVP of sulfone precursors, which is, of course, a specialty of Prof. Vögtle.[20]

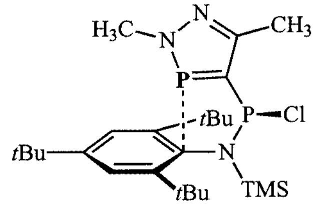
In compounds as congested as these, one must wonder whether there has been a significant shortening of the C-H covalent bond lengths. Unfortunately, there exist no neutron diffraction data for any of these cyclophanes. However, recent computational studies of compounds **13** and **14**[2] suggest that there is real bond compression. Most convincing are comparisons of the C-H_a and C-H_e distances in **14** at various levels of theory: MP2/6-31G(d), 1.06 and 1.10 Å, respectively; B3LYP/6-31G(d), 1.06 and 1.10 Å; B3LYP/cc-pVTZ, 1.06 and 1.09 Å. Thus a bond compression of about 0.04 Å seems to be likely in this molecule. It must be noted that some weakly *attractive* interactions of C-H groups with benzene rings exist. They are not so tight as the repulsive interactions considered above, but they are described in some detail by Desiraju and Steiner.[26]

In order to extend the chemistry of the *in*-cyclophanes to include functional groups other than alkanes, we sought a short, versatile preparation of suitable three-armed caps. This was found in the chemistry of Block, who employed a dilithium derivative of thiophenol (**16**) for the synthesis of the triarylelement trithiols **17**.[27] Conventional condensation reactions with tribromide **18** gave the *in*-silane **19** and the *in*-phosphane **20**.[28] Compound **19** exhibits the shortest H_{Si}---Ar (1.86 Å[29]) and H_{Si}---C (2.32 Å) contacts in the CSD, and its spectroscopic properties parallel those of the *in*-cyclophanes **9** and **13**: $\delta_{\text{in-H}} = 1.04$ (5 ppm upfield from an acyclic model) and $\nu_{\mathrm{SiH}} = 2457\ \mathrm{cm}^{-1}$ ($280\ \mathrm{cm}^{-1}$ higher than an acyclic model).



Cyclophane **20**, not surprisingly, possesses the shortest known P---Ar contact (2.90 Å), and this interaction is intimate enough that the ^{13}C NMR spectrum of **20** shows substantial spin-spin coupling between the phosphorus atom and the basal aromatic ring [$J_{\mathrm{P,C(methine)}} = 7.5$ Hz and $J_{\mathrm{P,C(quaternary)}} = 3.5$ Hz].[28] The phosphane of **20** is exceptionally unreactive: it is not protonated by anhydrous HBr, and even heating in refluxing hydrogen peroxide and acetic acid gives only the corresponding trisulfone with no formation of a phosphane oxide. Several derivatives of **20** with basal rings bearing halogen, nitro, and amino substituents have also been prepared and crystallographically characterized.[31] The mono- and dinitro compounds are brightly colored, due to strong charge-transfer absorptions in their UV spectra, and the nitro derivative was resolved into stable enantiomers, which exhibit extremely high ellipticities in their circular dichroism spectra.[31]

The phosphane of **20** is directly above the center of the opposing ring, and it has three very short P---C contacts of about 3.2 Å. However, the shortest known single P---C contact, of 3.00 Å, belongs to the crowded phosphadiazole **21**,[32] which, surprisingly, is nonmacrocyclic. In this compound, the heterocyclic phosphorus atom is nestled in the face of a tri-*tert*-butylbenzene. As is the case for several structures highlighted in this review, the authors were unaware of (or at least did not comment on) the exceptionally close approach of the phosphorus atom to the aromatic ring!



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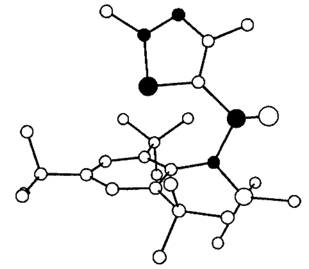
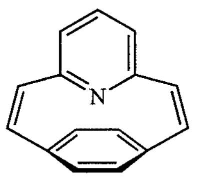


The forced interaction of lone-pair electrons with aromatic rings is a characteristic shared by a variety of heterophanes[33] containing elements other than phosphorus. The tightest contacts are found in Boekelheide's pyridinophanes, of which **22** is the most exceptional example.[34,35] In this molecule, unlike in the structurally related cyclophane **3**, the upper ring is perpendicular to the bottom. This gives rise to an N---Ar contact of 2.44 Å, and two N---C contacts of only 2.67 Å, almost 0.6 Å less than the sum of the van der Waals radii of nitrogen and carbon. The N---Ar distances in the doubly capped phane **23** are scarcely longer (2.51 Å and 2.52 Å),[36,37] and the near perpendicular orientation of rings in this molecule clearly indicates that the orthogonal relationship of the rings in **22** is not an effect of crystal packing forces. Unlike cyclophane **20** and its relatives, **22** retains sufficient flexibility for the nitrogen to react: it forms salts with ordinary acids and a complex with boron trifluoride, and it can be converted into the *N*-oxide.[34]



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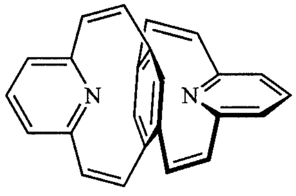

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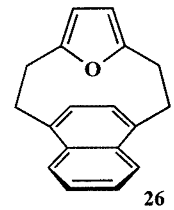

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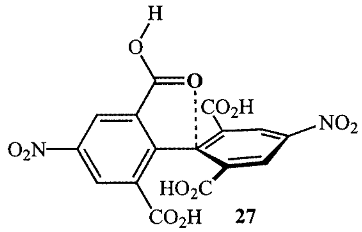

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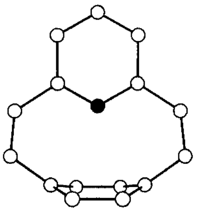
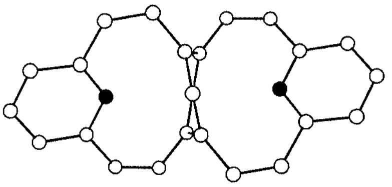
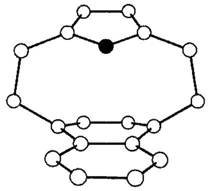
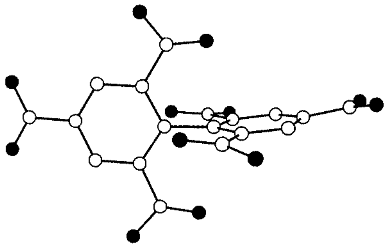
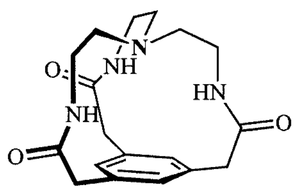








It has been 30 years since the preparation of **22**, but it will be difficult to surpass the close N---Ar contacts achieved in **22** and **23**. For example, it is not obvious that the nitrogen analogue of **9** would choose an *in* conformation. The one *in*-trialkylamino cyclophane in the CSD, compound **24**, does not have a particularly short N---Ar distance (4.21 Å),[38] and the comparably sized aminophane **25** adopts an *out* conformation.[39]



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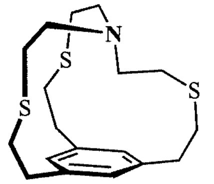

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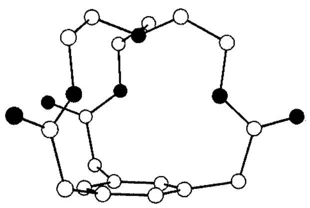
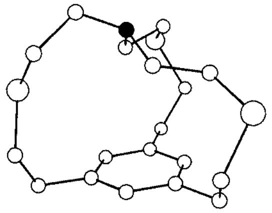
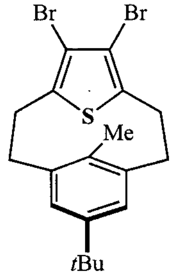




The most congested cyclophanes containing oxygen atoms are perhaps not so remarkable as the pyridinophanes above. The shortest O---Ar distance to be found in the CSD is 2.55 Å, in the furanophane **26**,[40,41] but this is 0.1 Å longer than the N---Ar distance in **22**, even though oxygen is smaller than nitrogen. More surprising is the fact that the closest O---C contact (2.66 Å) is found in another non-macrocyclic structure (**27**).[42] In very crowded biphenyls, one or both rings frequently adopt a shallow boat conformation,[43] and in **27** that distortion brings the carbonyl oxygen into the imaginary prism above the benzene (**2**). It is possible that this "nonbonded" contact is electronically enhanced, however; the opposing ring contains three strong electron-withdrawing groups. Could this be a case of incipient nucleophilic addition akin to those described by Bürgi and Dunitz?[44]

A similar situation exists for sulfur. The shortest S---Ar distance is 2.90 Å, in Takeshita and Tashiro's thiophenophane **28**[45] (the same as the P---Ar distance in **20**), and once again the shortest S---C contact (2.97 Å) is in a non-macrocycle: compound **29**.[46] It should be noted that several shorter sulfur-to-arene contacts exist, but these are invariably in sulfur-containing radical cations, in which the interaction with the ring must have a significant attractive component, and thus are excluded from consideration as nonbonded contacts. The short S---C contact in **29** may itself conceivably benefit from a slight electron deficiency in the sulfur atom due to induction from the adjacent imine and carbonyl groups.



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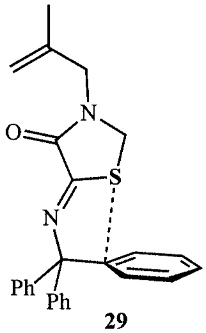

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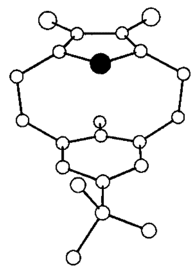
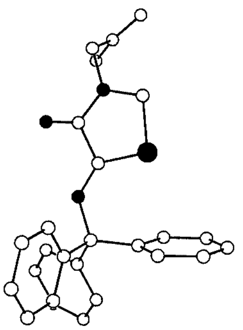
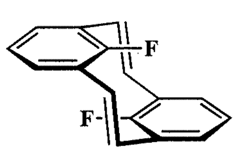




Close hydrogen-to-arene contacts involving halogens are more difficult to achieve, due to the fact that there is only one bond to restrain the atom. Thus the tightest F---Ar and F---C distances, both 2.70 Å, are found in Boekelheide's metacyclophane **30**,[47,48] but even these are longer than the shortest oxygen and nitrogen contacts. The F---Ar distance is long because the fluorine atoms in **30** are not near the centers of the opposing rings. It would seem that the *in*-cyclophane strategy used to drive down the H---Ar distance could be employed to make an ultrashort F---Ar contact, since an *in*-fluorine would be directly over the ring center. A good start is the *in*-fluorosilaphane **31**, prepared as usual by the condensation of a trithiol with a tribromide, which has an F---Ar distance of 2.81 Å.[49,50] However, the abysmally low yield of **31**, 0.4% for the final cyclization and 0.02% from commercial starting materials, has so far precluded any serious attempt to extrude the sulfur atoms.



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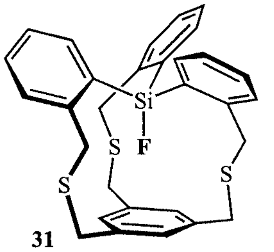

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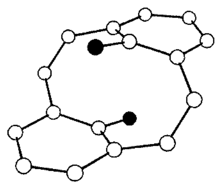
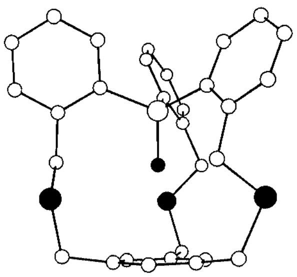
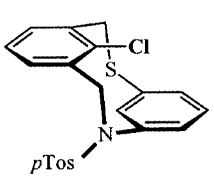




Chlorine-containing cyclophanes are relatively rare, but the shortest Cl---Ar distance in the CSD (3.10 Å) is found in one of them (**32**).[51] The shortest Cl---C contact (2.99 Å) appears to be in the congested porphyrin **33**.[52] It should be possible to improve on these relatively long values.



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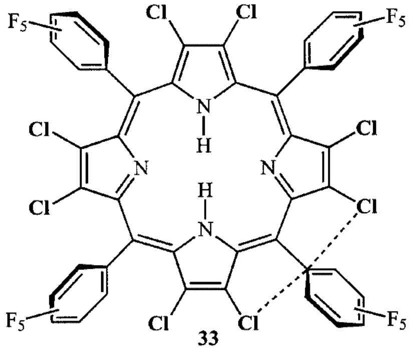

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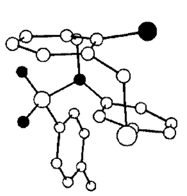
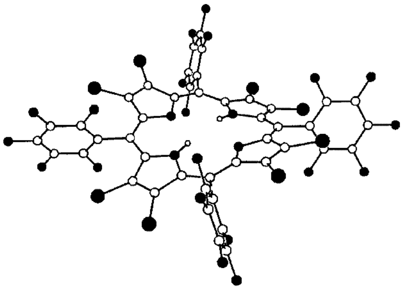
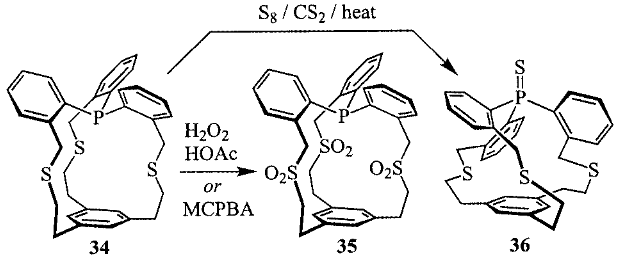
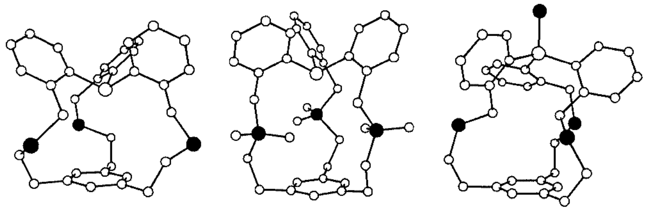


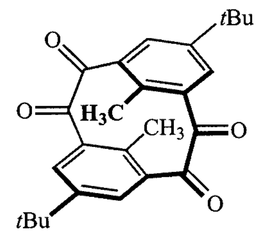


The preparation of the *in*-fluorophane **31** led us to wonder if pendant oxygen or sulfur atoms could be placed in a similar environment. Unlike **31**, the macrocyclization leading to *in*-phosphane **34** proceeds in 51% yield,[50] and the cavity of **34** is clearly large enough to accommodate a phosphane oxide. Unfortunately, numerous attempts to condense a triarylphosphane oxide cap with an aromatic base failed to give any *in*-cyclophanes at all.[50] Alternatively, the arms of **34** are long enough to allow it to distort so that the phosphane might react with electrophiles, but the results of such reactions were surprising. Oxygenation of **34** by various reagents led only to the trisulfone **35**; perhaps the sulfones form rapidly, rigidify the linking arms, and block access to the phosphorus.[50] Sulfuration should not display this problem, but although triphenylphosphane itself reacts with sulfur in seconds at room temperature, the reaction of **34** requires high enough temperatures that phosphorus inversion ($\Delta G^{\ddagger}$ = 35 kcal/mol) and sulfuration lead to the *out* isomer **36**![53]





Let us return now to carbon-containing functional groups. Every chemist has wondered how closely a methyl group can be forced into an aromatic ring, but putting it there is another matter. For the present, the tetraketone **37** reported by Tsukamoto et al. presses a methyl closest to the center of a benzene ring, with a C_{methyl}---Ar distance of 3.00 Å.[54] This very unusual metacyclophane was prepared by further oxidation and fragmentation of an oxygenated 10*b*,10*c*-dimethyl-10*b*,10*c*-dihydropyrene, which had itself been generated by oxidative ring closure of a tetrahydroxy metacyclophane. The methyl proton resonances of **37** are not especially far upfield (δ = 0.92 ppm), but the high degree of distortion in the aromatic rings suggests that bringing methyl groups closer to benzene rings will be difficult. No *in*-cyclophane with a sterically congested methyl group has yet been prepared.[50] The tightest C_{methyl}---C contact probably belongs to the hexahelicene **38**,[55] in which the indicated distance is only 2.97 Å. However, there are numerous crowded porphyrins, akin to compound **33** but with methyl groups in place of chlorines, which have comparable contacts, but those methyl groups seem always to lie just outside of the ring face.



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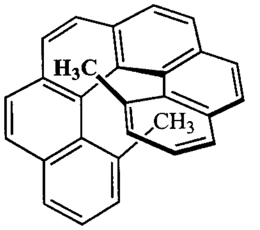

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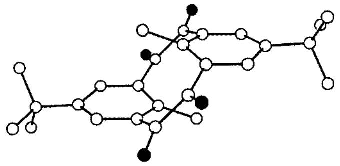
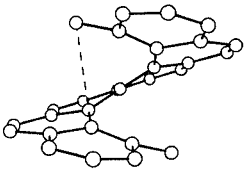
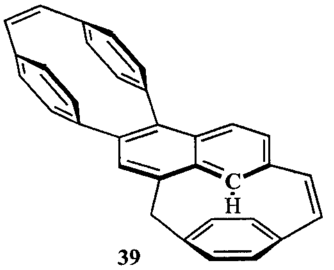




Finally, what is the closest approach of *any* carbon atom to an aromatic ring? For this we must return to the start of this review and Boekelheide's compound **3**. The close approach of the hydrogen atom in **3** has been most often noted in the literature, but it is the attached carbon atom that is directly over the center of the opposing ring, with a C---Ar distance of only 2.64 Å. This has been surpassed only once − barely − in the related double cyclophane **39** reported by Buchholz and de Meijere[56] with a C---Ar distance of 2.62 Å. In this molecule the naphthalene moiety is even more restrictive of bond angle distortions than the simpler olefinic bridges of compound **3**.



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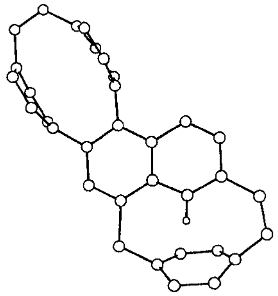
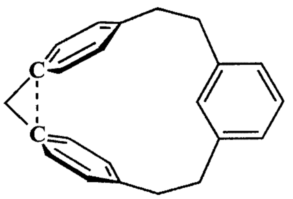


The closest C---C contacts involving aromatic rings belong to cyclophanes with carbons very near to the edge of the opposing ring. [1,*n*]Cyclophanes such as **40** may have extraordinarily close C---C contacts (in this case, 2.38 Å[57]), but because the two benzene rings are not parallel, the most closely contacting carbon in one ring does not lie within the imaginary prism above the opposing ring (**2**), and thus is not "above" it.[6] The closest contact to meet our definition in a reasonably well determined structure is found in the metacyclophane **41**, with a C---C distance of 2.61 Å,[58] but there are in fact many cyclophanes with contacts nearly as close.

One example is "superphane" **42**,[59,60] which contains six (!) C---C contacts of 2.62−2.63 Å. However, the desymmetrization of such multiarmed cyclophanes in order to bring two carbons together, as in **43** (the illustrated contact is 2.50 Å),[61] once again tilts the rings so that the close-contacting carbon is no longer above the opposing ring.



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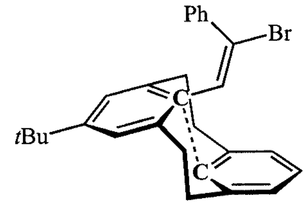

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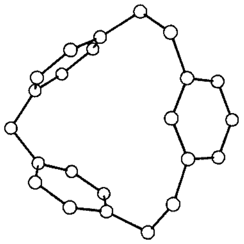

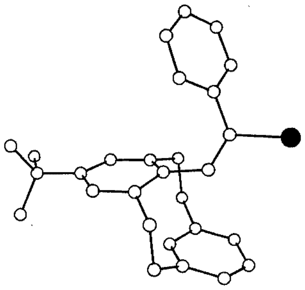

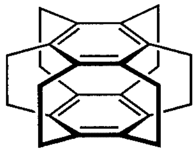

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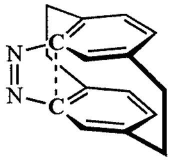

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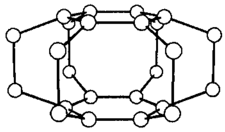

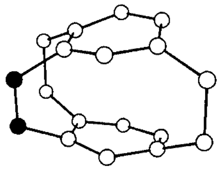

As mentioned above, the most highly strained cyclophanes provide numerous challenges for synthetic chemists as well as excellent tests of the performance of computational methods. With regard to the latter, I have reported a fairly extensive computational study of seven molecules highlighted in this review: compounds **7**, **13**, **14**, **19**, **20**, **22**, and **31**.[2] The chief result was that calculations at the HF/3-21G(*) and MP2/6-31G(d) levels of theory gave geometric data in excellent agreement with the experimentally determined structures, but all of the most popular HDFT methods systematically overestimated the transannular nonbonded contact distances in these molecules, usually by more than 0.05 Å, and sometimes by more than 0.1 Å.[2] This should be borne in mind by those who wish to take up the synthetic challenge: your actual results may be better than anticipated if you employ HDFT methods to guide your research. And what might be the best targets for synthesis? The shortest crystallographically characterized contacts discussed in this review are summarized in Table 1. Since aromatic rings have less electron density in the center than on the rim, the closest X---Ar distances should generally be shorter than the corresponding X---C contacts. Where this is not true − for carbon, fluorine, and chlorine atoms − there is certainly room for improvement. Indeed,

Table 1. The closest crystallographically characterized contacts of various elements and functional groups with the faces of benzene rings

Contact[10]	Compound	Distance (Å)	Contact[10]	Compound	Distance (Å)
H---Ar	**14**	1.64[11]	H---C	**15**	1.98[11]
$\mathrm{H_{Si}}$---Ar	**19**	1.86[29]	$\mathrm{H_{Si}}$---C	**19**	2.32[29]
C---Ar	**39**	2.62	C---C	**41**	2.61
$\mathrm{C_{methyl}}$---Ar	**37**	3.00	$\mathrm{C_{methyl}}$---C	**38**	2.97
N---Ar	**22**	2.44	N---C	**22**	2.67
O---Ar	**26**	2.55	O---C	**27**	2.66
F---Ar	**30**	2.70	F---C	**30**	2.70
P---Ar	**20**	2.90	P---C	**21**	3.00
S---Ar	**28**	2.90	S---C	**29**	2.97
Cl---Ar	**32**	3.10	Cl---C	**33**	2.99

none of the heterophanes, except perhaps the nitrogen-containing examples **22** and **23**, seem to approach any sort of limit for close contacts, and thus there are many opportunities for the construction of new "world record" molecules in the future!

Acknowledgments

The author's own *in*-cyclophanes are the products of undergraduate students Robert B. Grossman, Charles G. Winans, Anthony P. West, Jr., Meredith L. Carter, Mark R. Johnson, and Yen Ting Chen, graduate student Steven Dell, and postdoctoral Robert P. L'Esperance, and the crystal structures of these molecules reflect the efforts of Donna Van Engen, Douglas M. Ho, and Nancy J. Vogelaar; their contributions are most appreciated. Thanks are also due to the National Science Foundation for many years of continuous support.

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[1] J. F. Liebman, *The Conceptual Chemistry of Cyclophanes.* In *Cyclophanes* (Eds.: P. M. Keehn, S. M. Rosenfeld), Academic Press: New York, **1983**; vol. 1, pp. 23−68.

[2] R. A. Pascal Jr., *J. Phys. Chem. A* **2001**, *105*, 9040−9048.

[3] F. H. Allen, O. Kennard, R. Taylor, *Acc. Chem. Res.* **1983**, *16*, 146−153.

[4] R. A. Pascal Jr., W. D. McMillan, D. Van Engen, *J. Am. Chem. Soc.* **1986**, *108*, 5652−5653 (refcode: **FACPEE**).

[5] R. A. Pascal Jr., W. D. McMillan, D. Van Engen, R. G. Eason, *J. Am. Chem. Soc.* **1987**, *109*, 4660−4665.

[6] The extensive CSD searches performed for this review clearly show that it is much easier for functional groups to approach an aromatic ring from the side (and thus away from the π-cloud). All contacts cited in this work involve atoms that lie above the ring, as defined strictly by this imaginary prism whose edges are *normal to the mean plane* of the aromatic ring.

[7] P. M. Keehn, *Crystal Structures of Cyclophanes*, In *Cyclophanes* (Eds.: P. M. Keehn, S. M. Rosenfeld), Academic Press: New York, **1983**, vol. 1, pp. 69−238.

[8] V. Boekelheide, P. H. Anderson, T. A. Hylton, *J. Am. Chem. Soc.* **1974**, *96*, 1558−1564.

[9] A. W. Hanson, *Acta Crystallogr., Sect. B* **1971**, *27*, 197−202 (refcode: **MPCYLP10**).

[10] In order to keep the typography simple, triple hyphens will indicate nonbonded contacts between groups (e.g. H---Ar, O---C), but short hyphens will be used for covalent bonds (e.g. C-H, C-O).

[11] C-H bond lengths are systematically underestimated by X-ray crystallography because hydrogen atoms have no core electrons, and the peak of the hydrogen electron density in a covalent C-H bond is displaced slightly toward the carbon.[13] For this reason, C-H bond lengths are often observed to be about 0.96 Å in X-ray structures, and in cases where the hydrogen positions are not refined, riding models which employ similar distances are used. In this review, in order to give more nearly accurate nonbonded distances involving hydrogen atoms, the C-H bond lengths have been "improved"; that is, the bond has been lengthened along the observed C-H bond vector to the standard values observed for that type of bond in neutron diffraction experiments: 1.083 Å for aromatic C-H, 1.092 Å for methylene C-H, and 1.099 Å for methine C-H.[14]

[12] Nonbonded distances involving aromatic rings have been reported in a variety of ways, some of which I illustrate for compound **3**. In Hanson's original report[9] of the crystal structure, in which a C-H bond length of 0.98 Å was observed for the critical hydrogen, he says, "... C(8) lies only 2.71 Å, and H(8) only 2.16 Å, from the plane of the unsubstituted atoms of the *para*-bridged ring." This was mistranslated into Keehn's review of cyclophane structures[7] as "... 2.71 and 2.16 Å, respectively, from the mean plane of the *para*-bridged ring." In fact, when the mean plane of the ring is used (all six carbons, not just the unsubstituted ones), the distance is calculated to be 2.08 Å. When an improved[11] C-H bond length of 1.083 Å is also used, the distance to the mean plane drops to 2.03 Å. Finally, the distance of the (improved) hydrogen from the center (or, more properly, the centroid) of the benzene ring is 2.11 Å. This last measure is perhaps the least ambiguous, and it is the distance most often quoted in this review.

[13] M. R. Churchill, *Inorg. Chem.* **1973**, *12*, 1213−1214.

[14] F. H. Allen, O. Kennard, D. G. Watson, L. Brammer, A. G. Orpen, R. Taylor, *J. Chem. Soc., Perkin Trans. 2* **1987**, S1−S19.

[15] A. Ricci, R. Danieli, S. Rossini, *J. Chem. Soc., Perkin Trans. 1* **1976**, 1691− 1693.

[16] For an excellent review of *in, out* isomerism, see: R. W. Alder, S. P. East, *Chem. Rev.* **1996**, *96*, 2097−2111.

[17] R. A. Pascal, Jr., R. B. Grossman, *J. Org. Chem.* **1987**, *52*, 4616.

[18] R. A. Pascal, Jr., M. L. Carter, M. R. Johnson, D. M. Ho, *Tetrahedron Lett.* **1996**, *37*, 8125−8128 (refcode: **RAZZIB**).

[19] R. A. Pascal, Jr.; ,. B. Grossman, D. Van Engen, *J. Am. Chem. Soc.* **1987**, *109*, 6878−6880 (refcode: **FOXXAR**).

[20] For a review of syntheses via sulfone pyrolysis, see F. Vögtle, L. Rossa, *Angew. Chem. Int. Ed. Eng.* **1979**, *18*, 515−529.

[21] [21a] T. K. Vinod, H. Hart, *J. Am. Chem. Soc.* **1988**, *110*, 6574−6575 (refcode: **VAGFIS**). [21b] T. K. Vinod, H. Hart, *J. Org. Chem.* **1990**, *55*, 881−890.

[22] R. A. Pascal, Jr., C. G. Winans, D. Van Engen, *J. Am. Chem. Soc.* **1989**, *111*, 3007−3010 (refcodes: **VAMMAX, VAMMEB**).

[23] For recent reviews of [*n*]cyclophanes, see: [23a] F. Bickelhaupt, W. H. de Wolfe, *J. Phys. Org. Chem.* **1998**, *11*, 362−376 and [23b] Y. Tobe, *Top. Curr. Chem.* **1994**, *172*, 1−40.

[24] L. Lemmerz, M. Nieger, F. Vögtle, *J. Chem. Soc., Chem. Commun.* **1993**, 1168−1170 (refcode: **WAPWIT**).

[25] F. Vögtle, J. Dohm, K. Rissanen, *Angew. Chem. Int. Ed. Eng.* **1990**, *29*, 902−904 (refcode: **VETZEZ**).

[26] G. R. Desiraju, T. Steiner, *The Weak Hydrogen Bond*, Oxford University Press: Oxford, **1999**, pp. 152−158.

[27] [27a] E. Block, V. Eswarakrishnan, M. Gernon, G. Ofori-Okai, C. Saha, K. Tang, J. Zubieta, *J. Am. Chem. Soc.* **1989**, *111*, 658−665. [27b] E. Block, G. Ofori-Okai, J. Zubieta, *J. Am. Chem. Soc.* **1989**, *111*, 2327−2329.

[28] [28a] R. A. Pascal, Jr., A. P. West, Jr., D. Van Engen, *J. Am. Chem. Soc.* **1990**, *112*, 6406−6407 (refcode: **KEZTIS**). [28b] R. P. L′Esperance, A. P. West, Jr., D. Van Engen, R. A. Pascal Jr., *J. Am. Chem. Soc.* **1991**, *113*, 2672−2676 (refcode: **VIWFAI**).

[29] The Si−H bond length was improved to the standard value of 1.48 Å.[30]

[30] E. Lukevics, O. Pudova, R. Sturkovich, *Molecular Structure of Organosilicon Compounds*, Ellis Horwood Limited: Chichester, **1989**; p. 12.

[31] A. P. West, Jr., N. Smyth, C. M. Kraml, D. M. Ho, R. A. Pascal Jr., *J. Org. Chem.* **1993**, *58*, 3502−3506 (refcodes: **EACWUA, EACXAH**).

[32] V. D. Romanenko, V. L. Rudzevich, A. O. Gudima, M. Sanchez, A. B. Rozhenko, A. N. Chernega, M. R. Mazieres, *Bull. Soc. Chim. Fr.* **1993**, *130*, 726−732 (refcode: **PICKOB**).

[33] W. W. Paudler, M. D. Bezoari, *Synthesis and Properties of Heterophanes*, in *Cyclophanes* (Eds.: P. M. Keehn, S. M. Rosenfeld), Academic Press: New York, **1983**, vol. 2, pp. 359−441.

[34] V. Boekelheide, K. Galuszko, K. S. Szeto, *J. Am. Chem. Soc.* **1974**, *96*, 1578−1581.

[35] L. H. Weaver, B. W. Matthews, *J. Am. Chem. Soc.* **1974**, *96*, 1581−1584 (refcode: **PYPCPE**).

[36] I. D. Reingold, W. Schmidt, V. Boekelheide, *J. Am. Chem. Soc.* **1979**, *101*, 2121−2128.

[37] A. W. Hanson, *Acta Crystallogr., Sect. B* **1977**, *B33*, 2657−2659 (refcode: **PBPSUP**).

[38] T. H. Kim, S. Y. Yang, S. S. Lee, J. S. Kim, J. Kim, *Acta Crystallogr., Sect E* **2001**, *57*, o1200−o1202 (refcode: **CACBEO**).

[39] J. M. Baumeister, R. Alberto, K. Ortner, B. Spingler, P. A. Schubiger, T. A. Kaden, *J. Chem. Soc., Dalton Trans.* **2002**, 4143−4151 (refcode: **AHEBUK**).

[40] H. H. Wasserman, P. M. Keehn, *Tetrahedron Lett.* **1969**, 3227−3230.

[41] M. Corson, B. M. Foxman, P. M. Keehn, *Tetrahedron* **1978**, *34*, 1641−1649 (refcode: **FURNOP**).

[42] P. Holy, J. Zavada, J. Zezula, I. Cisarova, J. Podlaha, *Collect. Czech. Chem. Commun.* **2001**, *66*, 820−832 (refcode: **QUJGIL**).

[43] L. Tong, H. Lau, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 6000−6006.

[44] H. B. Bürgi, J. D. Dunitz, *Acc. Chem. Res.* **1983**, *16*, 153−161.

[45] M. Takeshita, M. Tashiro, *J. Org. Chem.* **1991**, *56*, 2837−2845 (refcode: **SIZKUH**).

[46] A. C. Kaura, C. D. Maycock, R. J. Stoodley, B. Beagley, R. G. Pritchard, *J. Chem. Soc., Perkin Trans. 1* **1988**, 2259−2269 (refcode: **GIKJUF**).

[47] V. Boekelheide, P. H. Anderson, *J. Org. Chem.* **1973**, *38*, 3928−3931.

[48] A. W. Hanson, *Acta Crystallogr., Sect. B* **1975**, *B31*, 2352−2354 (refcode: **AFMCPD**).

[49] S. Dell, N. J. Vogelaar, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 6421−6422 (refcode: **HAKQOZ**).

[50] S. Dell, D. M. Ho, R. A. Pascal Jr., *J. Org. Chem.* **1999**, *64*, 5626−5633 (refcodes: **CIPSID, CIPSUP, HAKQOZ01**).

[51] M. Nieger, S. Bartram, F. Vögtle, private communication to the CSD, **2000** (refcode: **DIXQAC**).

[52] E. R. Birnbaum, J. A. Hodge, M. W. Grinstaff, W. P. Schaefer, L. Henling, J. A. Labinger, J. E. Bercaw, H. B. Gray, *Inorg. Chem.* **1995**, *34*, 3625−3632 (refcode: **ZALHUP**).

[53] Y. T. Chen, K. K. Baldridge, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1999**, *121*, 12082−12087 (refcodes: **GOFWON, GOFYOP**).

[54] K. Tsukamoto, D. A. Sahade, M. Taniguchi, T. Sawada, T. Thiemann, S. Mataka, *Tetrahedron Lett.* **1999**, *40*, 4691−4692 (refcode: **XEFLUP**).

[55] T. E. M. van den Hark, J. H. Noordik, *Crystal Struct. Commun.* **1973**, *2*, 643 (refcode: **DMHXIC**).

[56] H. Buchholz, A. de Meijere, *Synlett* **1993**, 253−255 (refcode: **WAJZOW**; there are some errors in the CSD coordinates; however, Prof. de Meijere kindly provided correct coordinates for this work).

[57] T. Lahtinen, E. Wegelius, K. Rissanen, *New J. Chem.* **2001**, *25*, 905−911 (refcode: **EBUREY**).

[58] T. Ishi-i, T. Sawada, S. Mataka, M. Tashiro, *J. Org. Chem.* **1996**, *61*, 5103−5108 (refcode: **TIWBIK**).

[59] A. W. Hanson, T. S. Cameron, *J. Chem. Res. Synop.* **1980**, 336−337 (refcode: **CLOPNA**).

[60] Y. Sekine, V. Boekelheide, *J. Am. Chem. Soc.* **1981**, *103*, 1777−1785.

[61] K. El Shaieb, V. Narayanan, H. Hopf, I. Dix, A. Fischer, P. G. Jones, L. Ernst, K. Ibrom, *Eur. J. Org. Chem.* **2003**, 567−577 (refcode: **LUSNIW**).

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