

Nonplanar Aromatic Compounds. 9. Synthesis, Structure, and Aromaticity of 1:2,13:14-Dibenzo[2]paracyclo[2](2,7)- pyrenophane-1,13-diene

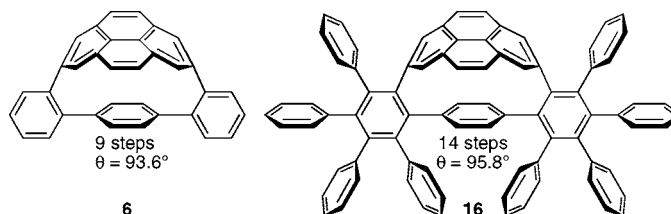
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ABSTRACT



Pyrenophane (**6**) and an octaphenyl derivative (**16**) were synthesized using two different routes. Both cyclophanes contain a severely bent pyrene unit (**6**: $\theta = 93.6^\circ$ and **16**: $\theta = 95.8^\circ$, according to DFT-calculations (B3LYP/6-311G**)), which was generated at room temperature by a valence isomerization/dehydrogenation (VID) reaction. HOMA and NICS indicate 92–98% retention of aromaticity of the highly distorted pyrene systems compared to planar pyrene.

Cyclophanes constitute a very broad class of compounds, which overlaps with various other classes of compounds. For example, cyclophanes consisting solely of arylene units, can also be viewed as cyclic oligoarylenes. Larger representatives of such systems, e.g., hexa-*m*-phenylene (**1**) and related systems,¹ are usually categorized as shape-persistent macrocycles,² whereas smaller systems, e.g., **2**³ and **3**,⁴ usually attract attention from the cyclophane perspective.⁵ Exactly how such systems are perceived is, of course, entirely viewer-dependent. Whatever the perspective, there has been no previous report of an oligoarylene cyclophane that contains an arylene unit as large as a 2,7-pyrenylene unit,⁶ let alone a severely bent one. We report here two synthetic approaches to such a system.

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(1) For example, see: (a) Staab, H. A.; Binnig, F. *Tetrahedron Lett.* **1964**, 319. (b) Fujitaka, Y. *Bull. Chem. Soc. Jpn.* **1984**, 57, 3494. (c) Hensel, V.; Schlüter, A. D. *Eur. J. Org. Chem.* **1999**, 451. (d) Hensel, V.; Schlüter, A. D. *Chem. Eur. J.* **1999**, 5, 421.

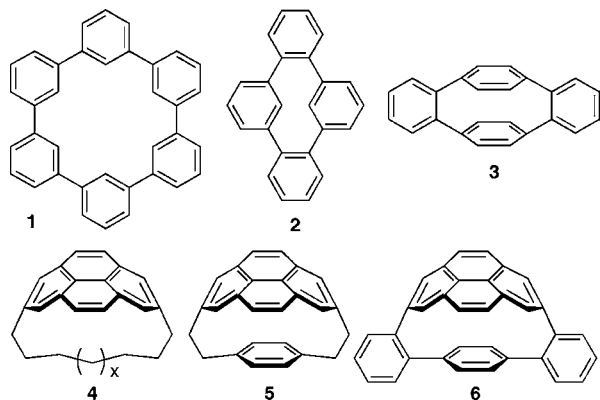
Our group has synthesized several (2,7)pyrenophanes by exploiting a valence isomerization/dehydrogenation (VID) reaction of tethered [2.2]metacyclophane-1,9-dienes.⁷ As part of an effort to apply this methodology more broadly, pyrenophane **6** was identified as an attractive target. This was arrived at through a process of incremental structural modification, which commenced with the parent [*n*](2,7)pyrenophanes **4**⁸ ($x = 1-4$) and progressed through [2]paracyclo[2](2,7)pyrenophane **5**⁹ and then to **6**. Pyreno-

(2) Grave, C.; Schlüter, A. D. *Eur. J. Org. Chem.* **2002**, 3075.

(3) (a) Williams, R. V.; Edwards, W. D.; Mitchell, R. H.; Robinson, S. G. *J. Am. Chem. Soc.* **2005**, 127, 16207. (b) Mitchell, R. H.; Iyer, V. S.; Mahadevan, R.; Venugopalan, S.; Zhou, P. *J. Org. Chem.* **1996**, 61, 5116.

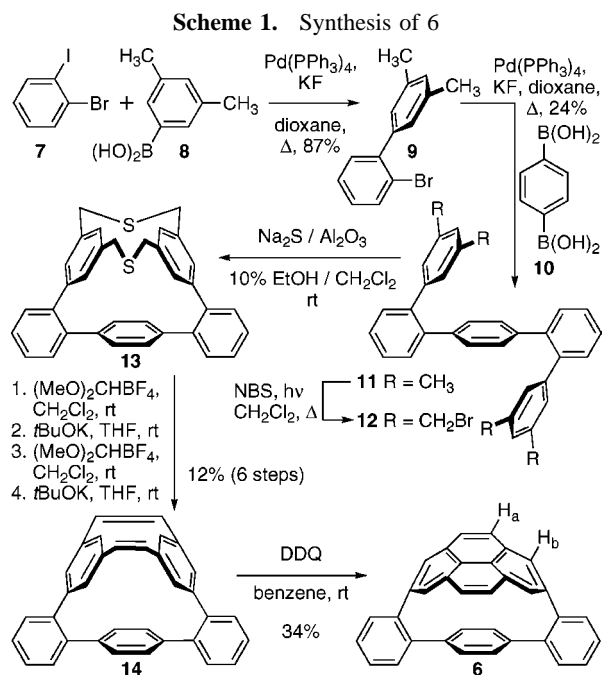
(4) (a) Reiser, O.; König, B.; Meerholz, K.; Heinze, J.; Wellauer, T.; Gerson, F.; Frim, R.; Rabinovitz, M.; de Meijere, A. *J. Am. Chem. Soc.* **1993**, 115, 3511. (b) de Meijere, A.; Heinze, J.; Meerholz, K.; Reiser, O.; König, B. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 1418. (c) Chan, C. W.; Wong, H. N. C. *J. Am. Chem. Soc.* **1988**, 110, 462. (d) Reiser, O.; Reichow, S.; de Meijere, A. *Angew. Chem., Int. Ed. Engl.* **1987**, 26, 1277. (e) Wong, H. N. C.; Chan, C. W.; Mak, T. C. W. *Acta Crystallogr.* **1986**, C42, 703. (f) Chan, C. W.; Wong, H. N. C. *J. Am. Chem. Soc.* **1985**, 107, 4790.

phanes **4** and **5**, which have clearly identifiable aromatic and aliphatic moieties, are quintessential cyclophanes. By com-



parison, pyrenophane **6**,¹⁰ which has no sp^3 -hybridized atoms, can also be viewed as a cyclic oligoarylene.¹¹ Either way, the system contains a highly distorted pyrene moiety. Before embarking on synthetic work, the bend angle (θ)¹² of the pyrene system was calculated at the AM1 level of theory. The calculated value of 100.6° , although quite high, was well within what the VID methodology had been able to deliver in other systems.¹³

A more important consequence of having only sp^2 -hybridized atoms is that the general Sonogashira-based synthetic strategy⁸ employed for the syntheses of **4** and **5** is not applicable to **6**. In view of the three biaryl bonds present in **6**, a new strategy based on the Suzuki–Miyaura reaction was devised (Scheme 1).



The synthesis began with the Suzuki–Miyaura coupling of 1-bromo-2-iodobenzene (**7**) with (3,5-dimethylphenyl)boronic acid (**8**) to afford biphenyl **9** (87%).¹⁴ Suzuki–Miyaura coupling of **9** with 1,4-phenylenebis(boronic acid) (**10**) resulted in the formation of several compounds, from which quinquephenyl **11** was isolated in 24% yield. An alternative approach to **11** involving Suzuki–Miyaura coupling of **8** with 2,2''-dibromoterphenyl or 2,2''-diiodoterphenyl gave inferior results. Reaction of **11** with NBS under irradiation with visible light afforded a mixture of brominated products, ca. 70% of which (¹H NMR analysis) was tetrabromide **12**. Attempts to isolate **12** by crystallization and chromatography failed, so the crude product was treated with Na_2S/Al_2O_3 .¹⁵ Again, the majority of the crude mixture appeared to be the desired compound (**13**), but attempted separations failed. The product mixture was then carried through to cyclophanediene **14** without purification of the intermediates via bis(*S*-methylation) with Borch reagent,¹⁶ thia-Stevens rearrangement, another bis(*S*-methylation) and Hofmann elimination. Cyclophanediene **14** was obtained, but it was contaminated with ca. 10% of pyrenophane **6**. Treatment of the mixture with DDQ in benzene at room temperature gave, after chromatography, pure **6** (3% over seven steps). The most significant losses were suffered during the Hofmann elimination and VID reaction. The overall yield of **6** from **4** was 0.8% (nine steps).

Although there was much room for improvement in the synthesis of **6**, the prospect of working primarily with compound mixtures made this unattractive. Attention was therefore turned to an alternative synthesis leading to an

(5) (a) *Modern Cyclophane Chemistry*; Gleiter, R., Hopf, H., Eds.; Wiley-VCH: Weinheim, 2004. (b) Hopf, H. *Classics in Hydrocarbon Chemistry*; Wiley-VCH: Weinheim, Germany, 2000. (c) Bodwell, G. J. In *Organic Synthesis Highlights*; Schmalz, H. G., Ed.; Wiley-VCH: New York, 2000; Vol. IV, pp 289–300. (d) de Meijere, A.; König, B. *Synlett* **1997**, 1221. (e) Bodwell, G. J. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2085. (f) Kane, V. V.; de Wolf, W. H.; Bickelhaupt, F. *Tetrahedron* **1994**, *50*, 4575. (g) *Top. Curr. Chem.* **1994**, *172*. (h) Vögtle, F. *Cyclophane Chemistry*; Wiley: New York, 1993. (i) Diederich, F. *Cyclophanes*; Royal Society of Chemistry: London, UK, 1991. (j) *Top. Curr. Chem.* **1983**, *113*, 115. (k) *Cyclophanes*; Keehn, P. M., Rosenfeld, S. M., Eds.; Academic Press: New York, 1983; Vols. 1 and 2.

(6) To date, the largest arylene units that have been incorporated in an oligoarylene-type cyclophane are 1,6-naphthalenyl and 2,8-(1,9-phenanthrolyl). See (a) Schafer, L. L.; Tilley, T. D. *J. Am. Chem. Soc.* **2001**, *123*, 2683. (b) Velten, U.; Rehahn, M. *Macromol. Chem. Phys.* **1998**, *199*, 127.

(7) For the original applications of this methodology, see: (a) Bodwell, G. J.; Bridson, J. N.; Houghton, T. J.; Kennedy, J. W. J.; Mannion, M. R. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1320. (b) Bodwell, G. J.; Bridson, J. N.; Houghton, T. J.; Kennedy, J. W. J.; Mannion, M. R. *Chem. Eur. J.* **1999**, *5*, 1823.

(8) (a) Bodwell, G. J.; Fleming, J. J.; Mannion, M. R.; Miller, D. O. *J. Org. Chem.* **2000**, *65*, 5360. (b) Aprahamian, I.; Bodwell, G. J.; Fleming, J. J.; Manning, G. P.; Mannion, M. R.; Merner, B. L.; Sheradsky, T.; Vermeij, R. J.; Rabinovitz, M. *J. Am. Chem. Soc.* **2004**, *126*, 6765.

(9) Bodwell, G. J.; Miller, D. O.; Vermeij, R. *J. Org. Lett.* **2001**, *3*, 2093.

(10) We prefer the name 1:2,13:14-dibenzo[2]paracyclo-[2](2,7)pyrenophane-1,13-diene.

(11) The cyclic system is shape-persistent, but the size of the cycle (16 atoms) and the small cavity (4.0 Å between the centroid of the central benzene ring and the centroid of the C(10b)–C(10c) bond of the pyrene system) make categorizing it as a macrocycle questionable.

(12) Bodwell, G. J.; Fleming, J. J.; Miller, D. O. *Tetrahedron* **2001**, *57*, 3577.

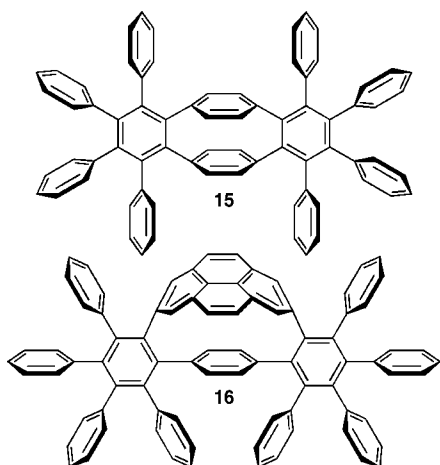
(13) Pyrenophanes with an AM1-calculated bend angle (θ) greater than this (up to 113.4°) had already been isolated. (a) Reference 7b. (b) Reference 8. (c) Reference 12.

(14) The product arising from Suzuki–Miyaura coupling of **8** and **10** was obtained in 13% yield.

(15) Bodwell, G. J.; Houghton, T. J.; Koury, H. E.; Yarlagadda, B. *Synlett* **1995**, 751.

(16) Borch, R. F. *J. Org. Chem.* **1969**, *34*, 627.

octaphenyl derivative, **16**, which was inspired by de Meijere's [2.2]paracyclophane derivative **15**^{4b} and Müllen's work on polyphenylenes¹⁷ and nanographenes.¹⁸



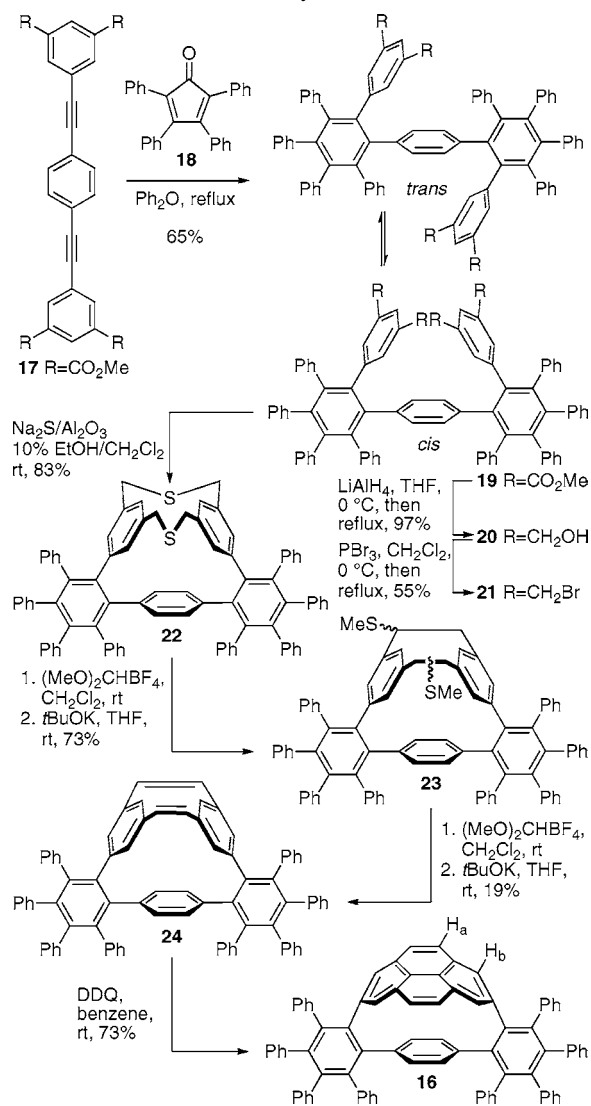
The synthesis of **16** (Scheme 2) started with the construction of tetraesterdiyne **17** in five steps from 5-hydroxyisophthalic acid according to our previously published procedures.⁸ Heating **17** with tetraphenylcyclopentadienone (**18**) in diphenyl ether at reflux (bp = 260 °C) gave tetraester **19** in 65% yield. Reduction of **19** with LiAlH₄ afforded tetraol **20** (100%), which was reacted with PBr₃ to generate tetrabromide **21** (55%). Compounds **19**–**21** were obtained as slowly equilibrating mixtures of *cis* and *trans* isomers.¹⁹ Reaction of **21** with Na₂S/Al₂O₃ yielded dithiacyclophane **22** in 83% yield, which is the highest yield yet obtained for a dithiacyclophane using this reagent. Bridge contraction to give **23** (73%) and double bond formation to give **24** (19%) was achieved as for **13**→**14**. The 14-step synthesis of pyrenophane **16** (1.6% overall yield) was then completed upon VID reaction (73%) of **24**, again under remarkably mild conditions (room temperature). The poor yield of **24** is yet another indication that there is a need for the development of superior methodology for the conversion of dithiacyclophanes into cyclophanedienes.

In the ¹H NMR spectra of **6** and **16** (Figure 1) the chemical shifts of the protons on the *p*-phenylene ring were observed at δ 5.67 and 5.54, respectively, which are not significantly different from the corresponding protons in **5** (δ 5.54). The protons of the pyrene systems of **6** and **16** appeared at δ 7.72 (H_a) and 7.47 (H_b), and δ 7.60 (H_a) and 7.44 (H_b). The analogous protons of **5** resonate at δ 7.67 (H_a) and 7.40 (H_b). The similarity of these chemical shifts suggests that neither the “benzannulation” of **5** nor the addition of eight phenyl groups to **6** results in significant changes in the structure of the pyrene system.

Despite many attempts to grow crystals of **6** and **16**, none that were suitable for an X-ray crystal structure determination were obtained. Their structures were therefore calculated.

(17) Grimsdale, A. C.; Müllen, K. *Adv. Polym. Sci.* **2006**, *199*, 1.
 (18) (a) Wu, J. S.; Pisula, W.; Müllen, K. *Chem. Rev.* **2007**, *107*, 718.
 (b) Watson, M. D.; Fechtenkötter, Müllen, K. *Chem. Rev.* **2001**, *101*, 1267.
 (19) The conformational behavior of these and related compounds will be addressed in a future publication.

Scheme 2. Synthesis of 16



A series of geometry optimization and frequency calculations at B3LYP/6-311G** level of theory²⁰ found a C_s-symmetric

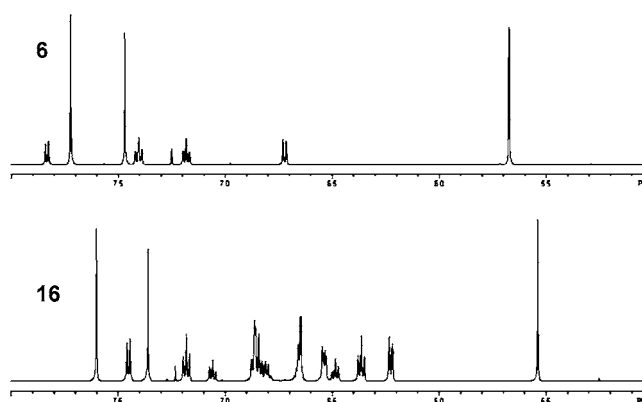


Figure 1. ¹H NMR spectra of **6** and **16**.

minimum energy conformation for compound **6** in which the *p*-phenylene ring is twisted by 74.4° relative to the neighboring *o*-phenylene units. Degenerate C_s minima interconvert via a C_{2v} -symmetric transition-state structure (in which the *p*- and *o*-phenylenes are orthogonal), which is calculated to be only 0.07 kcal/mol higher in energy. This implies that the central fragment librates easily. This is supported by the calculated lowest vibrational frequency for the C_s conformer, which corresponds to libration of the *p*-phenylene fragment and has an intensity of 46.8 cm⁻¹.

In **16**, unlike in **6**, the lowest-energy structure has C_2 symmetry, which results from the minimization of a close nonbonded interaction between the “*para*” H atoms of the two phenyl groups that point toward one another (see Figure 2). This H···H distance is 3.199 Å, which compares to

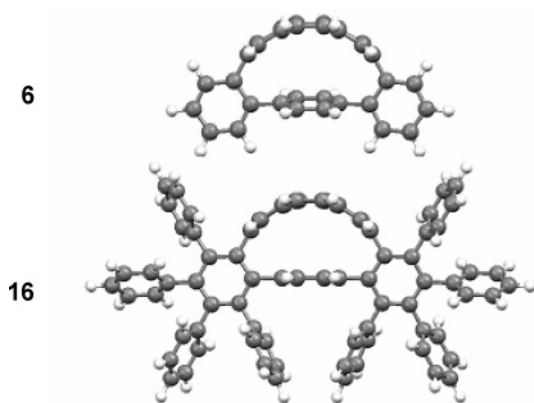


Figure 2. Lowest-energy geometries of **6** and **16**.

distances of 2.651 Å and 2.698 Å in higher energy (up to 1.4 kcal/mol) geometries having C_{2v} or C_s symmetry, respectively. In the C_2 -symmetric conformation, the macrocyclic oligoarylene framework is somewhat twisted. The twist of the *p*-phenylene ring with respect to the *o*-phenylene fragments is 84.8°, whereas the two *o*-phenylene rings are twisted with respect to each other by 10.4°. In turn, the peripheral phenyl rings are twisted with respect to the *o*-phenylene units by 67.6–78.9°.

The degree of distortion from planarity of the pyrene moieties of **6** and **16** is similar. The bend angle (θ)¹² for the

(20) Frisch, M. J.; et al. Gaussian, Inc.: Wallingford CT, 2004. See Supporting Information for full citation.

lowest-energy conformers of **6** and **16** is 93.6° and 95.8°, respectively. By comparison, the crystallographically determined value for **5** is 89.7°.⁹

Despite the large distortion from planarity, the π -electron delocalization is highly preserved. The geometry-based HOMA index²¹ for the pyrene system in **6** and **16** is 0.714 and 0.719, respectively. For planar pyrene, HOMA is 0.742, which implies a 96–97% retention of aromaticity in the pyrene systems of **6** and **16**. The magnetism-based nucleus independent chemical shift, NICS²² (computed at GIAO/B3LYP/6-311G**), leads to an almost identical conclusion. NICS for the central rings of both **6** and **16** is –4.5 ppm, which compares to –4.4 ppm for planar pyrene (98% retention of aromaticity). For the apical rings, NICS is –11.1 (**6**) and –11.0 ppm (**16**), which compares to –11.9 ppm for planar pyrene (92–93% retention).

In summary, two syntheses of the 1:2,13:14-dibenzo-[2]-paracyclo[2](2,7)pyrenophane-1,13-diene system have been developed. The addition of eight phenyl groups (i.e., **6** to **16**) does not significantly influence the geometry or the aromaticity of the severely bent pyrene moiety. However, it does offer the potential to gain access to pyrenophane–graphene hybrids via cyclodehydrogenation.

Acknowledgment. G.J.B. gratefully acknowledges the Natural Sciences and Engineering Research Council (NSERC) of Canada. The ICM computer center, Warsaw (Poland) is acknowledged for computational facilities.

Supporting Information Available: Experimental procedures, characterization data, and NMR spectra (¹H and ¹³C) for all pure compounds, total energies and Cartesian coordinates at B3LYP/6-311G** for the geometries of **6** and **16**, and the full citation for reference 20. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(21) (a) Krygowski, T. M. *J. Chem. Inf. Comput. Sci.* **1993**, *33*, 70. (b) Review: Krygowski, T. M.; Cyrański, M. K. *Chem. Rev.* **2001**, *101*, 1385. (c) Harmonic oscillator model of aromaticity is defined as: $HOMA = 1 - \frac{\alpha}{N} \sum (R_{opt} - R_i)^2$, where N is the number of bonds taken into the summation; α is an empirical constant fixed to give HOMA = 0 for a model nonaromatic system and HOMA = 1 for a system with all bonds equal to an optimal value R_{opt} , assumed to be realised for fully aromatic systems. R_i stands for a running bond length.

(22) (a) Schleyer, P. v. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; van Eikema Hommes, N. J. R. *J. Am. Chem. Soc.* **1996**, *118*, 6317. (b) Review: Chen, Z.; Wannere, C. S.; Corminboeuf, C.; Puchta, R.; Schleyer, P. v. R. *Chem. Rev.* **2005**, *105*, 3842. (c) NICS was originally defined as the negative value of the absolute shielding computed at the geometric centre of a ring system. Rings with negative NICS values qualify as aromatic, and the more negative the value of NICS become, the more aromatic the rings are.