

Novel Synthesis and Structures of Tris-Annulated Benzene Donors for the Electron-Density Elucidation of the Classical Mills–Nixon Effect

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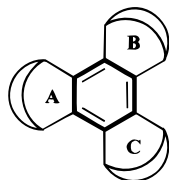
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Abstract: A versatile method for the high-yield synthesis of various tris-, bis-, and mono-annulated benzenes (as well as cyclooctatetraene) is based on the Pd-catalyzed coupling of three (or four) ethylenic units comprised of α,β -dibromoalkenes and α' -alkenyl Grignard reagents—all carried out in a single pot. The particular application to tris(bicyclopentyl)-annulated benzene yields the syn isomer **1s** in high purity; X-ray diffraction analysis confirms the aromatic bond alternation relevant to the Mills–Nixon effect. Most importantly, the efficient synthesis of **1s** crystals of extraordinary quality allows us (for the first time) to make precise electron-density measurements of the “banana-type” distortion and the ellipticity (π -character) of the various aromatic C–C bonds—sufficient to identify the electronic origin of the classical Mills–Nixon effect. The unique electron-donor properties of tris-annulated benzenes also relate to their highly reversible one-electron oxidation potentials even in nonpolar solvents.

Introduction

The annulation of benzene by small rings induces a significant bond alternation of the type originally proposed by Mills and Nixon to explain the enhanced positional selectivities in electrophilic aromatic substitutions.^{1,2} Recently, such a bond fixation has become a subject of considerable theoretical as well as experimental scrutiny;^{3,4} particularly noteworthy is the use of benzenoid hydrocarbons which are tris-annulated by small bicyclic rings,⁵ as represented in the generic structure I (**GS**) below



- (1) (a) Mills, W. H.; Nixon, I. G. *J. Chem. Soc.* **1930**, 2510. (b) Also, see: Vaughan, J.; Welch, G. J.; Wright, G. J. *Tetrahedron* **1965**, 21, 1665. (2) Taylor, R. *Electrophilic Aromatic Substitution*; Wiley: New York, 1990. (3) (a) Baldrige, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1992**, 114, 9583. (b) Gadre, R. S.; Pundlik, S. S. *J. Am. Chem. Soc.* **1995**, 117, 9559. (c) Faust, R.; Glendening, E. D.; Streitwieser, A.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1992**, 114, 8263. (d) Dewar, M. J. S.; Holloway, U. K. *J. Chem. Soc., Chem. Commun.* **1984**, 1188. (e) Mahanti, M. K. *Indian J. Chem.* **1980**, 19B, 149. (f) Eckert-Maksic, M.; Hodoseck, M.; Kovacek, D.; Mitic, D.; Maksic, Z. B.; Poljanec, K. *J. Mol. Struct.* **1990**, 206, 89. (g) Thummel, R. P. *Acc. Chem. Res.* **1980**, 13, 70. (h) Jemmis, E. D.; Kiran, B. *J. Org. Chem.* **1996**, 61, 9006. (4) (a) Diercks, R.; Vollhardt, K. P. C. *J. Am. Chem. Soc.* **1986**, 108, 3150. (b) Durr, R.; Lucchi, O. D.; Cossu, S.; Lucchini, V. *J. Chem. Soc., Chem. Commun.* **1996**, 2447. (c) Durr, R.; Cossu, S.; Lucchini, V.; Lucchi, O. D. *Angew. Chem., Int. Ed. Engl.* **1997**, 36, 2805. (d) Cossu, S.; Lucchi, O. D.; Lucchini, V.; Valle, G. *Tetrahedron Lett.* **1997**, 38, 5319. (5) (a) Bürgi, H.-B.; Baldrige, K. K.; Hardcastle, K.; Frank, N. L.; Gantzel, P.; Siegel, J. S.; Ziller, J. *Angew. Chem., Int. Ed. Engl.* **1995**, 34, 1454. (b) Frank, N. L.; Baldrige, K. K.; Gantzel, P.; Siegel, J. S. *Tetrahedron Lett.* **1995**, 36, 4389. (c) Cardullo, F.; Giuffrida, D.; Kohnke, F. H.; Raymo, F. M.; Stoddart, J. F.; Williams, D. J. *Angew. Chem., Int. Ed. Engl.* **1996**, 35, 339. (d) Also see, Rouhi, A. M. *Chem. Eng. News* **1996**, 74 (14), 27.

In addition to the increased interest in such tris-annulated benzenes arising from the Mills–Nixon debate,⁶ we recently noted that the structural modification of benzene with a bicycloalkane framework also leads to the remarkably effective stabilization of reactive intermediates associated with electrophilic aromatic substitution, such as the Wheland intermediates,⁷ cation radicals,⁸ etc. Moreover, the trigonal symmetry of these annulated aromatic hydrocarbons will also provide the nucleus for the synthesis of three-dimensional (highly carbon-rich) dendrimeric materials.⁹

The notable lack of an efficient and versatile general method of the synthesis of tris-annulated benzenes has unfortunately hampered the exploration of the interesting chemistry of these novel hydrocarbons—especially those in which the benzene ring is completely entombed within the bicycloalkane framework.¹⁰ Heretofore, the cyclotrimerization of alkynes using a variety of transition metal catalysts has been extensively utilized for the synthesis of a variety of substituted benzene derivatives,¹¹ but its application to the trimerization of highly strained and transient “norbornyne” leads to unpredictable results.^{12,13} A similar

- (6) (a) Stanger, A. *J. Am. Chem. Soc.* **1991**, 113, 8277. (b) Frank, N. L.; Siegel, J. S. In *Advances in Theoretically Interesting Molecules*, Volume 3; Thummel, R. P., Ed.; JAI Press: London, 1995, and references therein. (c) Siegel, J. S. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 1721. (d) Apeloig, Y.; Karni, M.; Arad, D. In *Strain and Its Implications in Organic Chemistry*; de Meijere, A.; Blechert, S., Eds.; Kluwer Academic: Dordrecht, The Netherlands, 1989. (e) Mo, O.; Yanez, M.; Eckert-Maksic, M.; Masic, Z. B. *J. Org. Chem.* **1995**, 60, 1635 and references therein. (7) Rathore, R.; Loyd, S. H.; Kochi, J. K. *J. Am. Chem. Soc.* **1994**, 116, 8414. (8) Rathore, R.; Kochi, J. K. *J. Org. Chem.* **1995**, 60, 4399. (9) (a) Frechet, J. M. J. *Science* **1994**, 263, 1710. (b) Tomalia, D. A.; Durst, H. D. *Top. Curr. Chem.* **1993**, 165, 193. (c) Tomalia, D. A.; Naylor, A. M.; Goddard III, W. A. *Angew. Chem., Int. Ed. Engl.* **1990**, 29, 138. (10) See: Rathore, R.; Lindeman, S. V.; Kochi, J. K. *J. Am. Chem. Soc.* **1997**, 119, 9393. (11) (a) Hoffman, R. W. *Dehydrobenzenes and Cycloalkynes*; Academic: New York, 1967; 350pp. (b) Bannett, M. A.; Wenger, E. *Chem. Ber.* **1997**, 130. (c) Vollhardt, K. P. C. *Acc. Chem. Res.* **1977**, 10, 1 and references therein. (d) Stanger, A.; Ashkenazi, N.; Boese, R.; Bläser, D.; Stellberg, P. *Chem. Eur. J.* **1997**, 3, 208. (e) Stanger, A.; Ashkenazi, N.; Boese, R. *J. Org. Chem.* **1998**, 63, 247. (12) Gassman, P. G.; Gennick, I. *J. Am. Chem. Soc.* **1980**, 102, 6863.

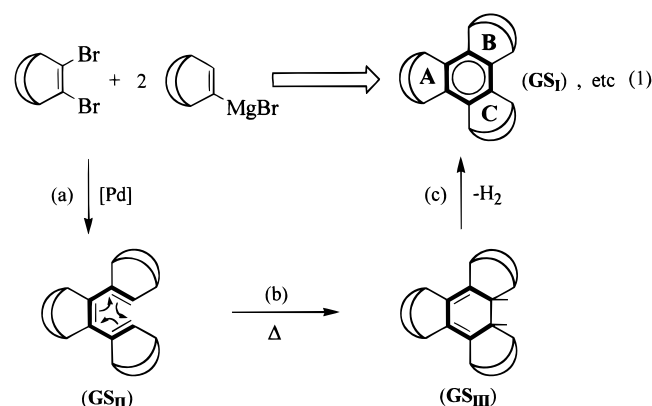
cyclotrimerization of the putative “bicyclo[2.1.1]hexyne” and “bicyclo[2.2.2]octyne” affords only a 1 and 4% yield, respectively, of the corresponding tris-annulated benzene derivatives.^{14,15} Moreover, the cyclotrimerization of stable alkynes can only be practically applied to symmetrically annulated benzenes.

A new and general synthetic method for tris-annulated benzenes is clearly required—especially one which is sufficiently versatile to allow the construction in high yields of unsymmetrically substituted benzene derivatives in which the annulations A, B, and C (vide supra) are different. Accordingly, we now report an efficient (one-pot) synthesis of various symmetrically and unsymmetrically annulated benzenes (as well as a novel cyclooctatetraene), the molecular structures of which are unambiguously established by X-ray crystallography, and the donor (redox) properties quantitatively assessed by cyclic voltammetry. Importantly, the ready availability of various tris-annulated benzenes allows the judicious selection of high-quality single crystals for precise electron-density measurements relevant to the identification of the electronic origin of the Mills–Nixon effect.

Results and Discussion

The synthetic methodology for the tris-annulated benzenes (**GS_I**, vide supra) is based on the direct conversion of a 1,2-dibromoalkene with 2 equiv of a vinylic Grignard reagent, as schematically represented in eq 1. In practice, the procedure is initiated by (a) the coupling of the (2:1) components with a palladium catalyst to afford the linear 1,3,5-triene (**GS_{II}**), followed by (b) the spontaneous sigmatropic rearrangement in situ to the dihydrobenzene **GS_{III}**, which in turn (c) can be easily aromatized to **GS_I**—all carried out in one pot, as outlined in Scheme 1.

Scheme 1



Synthesis of Various Tris-, Bis-, and Mono-Annulated Benzenes via the Sequential Coupling of Three Ethylenic Units. To illustrate the versatility of the methodology depicted in Scheme 1, we considered the typical synthesis of a series of symmetrical and unsymmetrical tris-, bis-, and mono-annulated benzenes as follows.

I. Symmetrical Tris-Annulated Benzenes with the Rings A = B = C. A solution of 2,3-dibromonorbornene in anhydrous tetrahydrofuran containing a catalytic amount of bis(triphenylphosphine)palladium(II) chloride [hereinafter referred to as

(13) Loyd, S. H. Master's Thesis, University of Houston, Houston, Texas, 1996.

(14) Frank, N. L.; Baldrige, K. K.; Siegel, J. S. *J. Am. Chem. Soc.* **1995**, *117*, 2102.

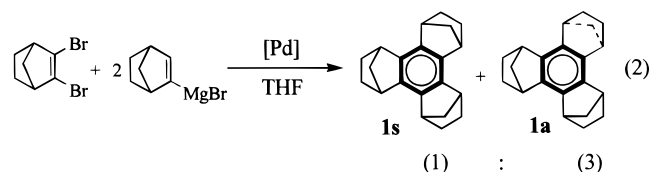
(15) Komatsu, K.; Aonuma, S.; Jinbu, Y.; Tsuji, R.; Hirose, C.; Takeuchi, K. *J. Org. Chem.* **1991**, *56*, 195 and references therein.

Table 1. Catalytic Synthesis of Various Annulated Benzenes According to Scheme 1^a

Dibromoalkene	Vinyl Grignard	Products	Yield ^b
		1s (25) 1a (75)	94
		2	97
		3s (50) 3a (50)	93
		4	92
		5s (50) 5a (50)	84
		6	76 ^c
		7	84 ^c

^a See Experimental Section for a general procedure. ^b Isolated yields. ^c See text.

the palladium catalyst]¹⁶ was treated with a freshly prepared solution of the Grignard reagent from 2-bromonorbornene to afford a 1:3 mixture of syn and anti isomers of tris-norbornabenzene **1s** and **1a**, respectively, in excellent yields, i.e.¹⁷



In a similar manner, 2,3-dibromobicyclooctene and the Grignard reagent from 2-bromobicyclo[2.2.2]octene afforded a single isomer of tris-bicyclo[2.2.2]octanobenzene **2** in close to quantitative yields (see Table 1); it was found to be identical with that previously synthesized in very low yields.¹⁸

II. Unsymmetrical Tris-Annulated Benzenes with Ring A ≠ B = C. The catalytic coupling of a pair of dissimilar bicyclic frameworks is illustrated by the synthesis of the tris-annulated homologues **3** (with one ethano/two methano bridges) and **4** (with two ethano/one methano bridges) in excellent yields from the dibromobicycloalkenes and Grignard reagents listed in Table 1 (entries 3 and 4). The dimethano analogue **3** was

(16) Kumada, K. *Pure Appl. Chem.* **1980**, *52*, 669. Also, see: Rathore, R.; Weigand, U.; Kochi, J. K. *J. Org. Chem.* **1996**, *61*, 5246.

(17) (a) Note that the ratio of syn and anti isomers of tris-norbornabenzene **1** was found to be identical to that obtained by Gassman and Gennick¹² by the trimerization procedure. (b) The 3:1 molar ratio of **1a**/**1s** derives from a statistical coupling of a pair of *R,S*-norbornenyl Grignard moieties in eq 2. It is interesting to note that the use of a pure enantiomer should result in only the anti isomer.

(18) Tris-bicyclooctanobenzene **2** was the same (mp, GC-MS, and NMR) as an authentic sample prepared by the trimerization of bicyclooctyne (via 2,3-dibromobicyclooctene) in the presence of nickelocene (~10% yield).¹³

formed as an equimolar mixture of analytically pure syn and anti isomers, which always cocrystallized as rather sharp-melting (eutectic) crystals. However, X-ray diffraction analysis revealed sufficiently severe disorder to preclude the structure determination (see Experimental Section). Importantly, the higher homologue **4** consists of a single isomer, and the molecular structure was established by X-ray crystallography (Figure S1, Supporting Information). It is noteworthy, however, that the loose packing of the tris-annulated benzene **4** in the crystal was coupled with the partial (1:4) disorder arising from the relatively similar size and shape of the ethano and methano bridges. The latter is undoubtedly related to the severe crystallographic disorder noted when *two* methano bridges are present, as in **3** (vide supra).

The same methano/ethano distinction was potentially inherent to the yellow fluoranthrene derivative **5** prepared in good yields as a 50:50 mixture of syn/anti isomers from the catalytic coupling of dibromoacenaphthylene with 2 equiv of norbornenyl Grignard reagent in Table 1 (entry 5). However, the simple crystallization of this equimolar mixture from dichloromethane/ethanol at $-23\text{ }^{\circ}\text{C}$ spontaneously resulted in a mixture of yellow prismatic crystals of pure **5s** and pure **5a** that were morphologically indistinguishable. The crystallographic purity was readily established by X-ray diffraction analysis, and the structure of the syn isomer **5s** is illustrated in Figure 1. We tentatively attribute such an unusual behavior of the fluoranthrene derivative **5** during the crystallization process to the presence of a rather large (planar) aromatic chromophore that induced a tighter crystal packing relative to that obtained with the tris-annulated benzenes **3** and **4** (vide supra).

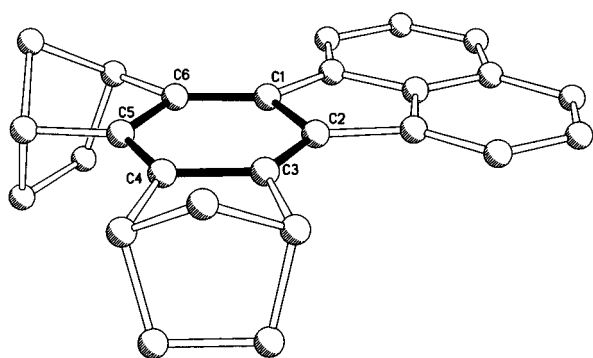
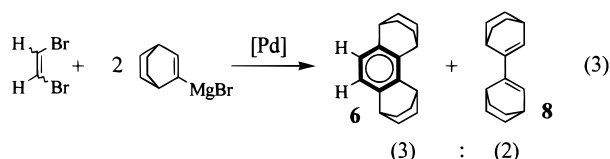


Figure 1. Molecular structure of the syn isomer **5s** of the bis-annulated fluoroanthrene. Hydrogens omitted for clarity.

III. Bis-Annulated Benzenes with no Ring A. The synthesis of bis-annulated benzenes utilized a 1,2-dibromoalkene to obviate ring A. For example, a tetrahydrofuran solution of the Grignard reagent derived from 2-bromobicyclooctene was added to a solution of 1,2-dibromoethylene (as a 60:40 mixture of cis and trans isomers) and Pd catalyst, and the mixture was refluxed for 12 h. An aqueous workup afforded a roughly 3:2 mixture of the bis-annulated benzene **6** (51%) together with the diene **8** (32%), i.e.



However, the coupling of pure *cis*-dibromoethylene with a Grignard solution of 2-bromobicyclooctene yielded only the bis-annulated benzene **6** in 76% yield. GC and GC-MS analysis

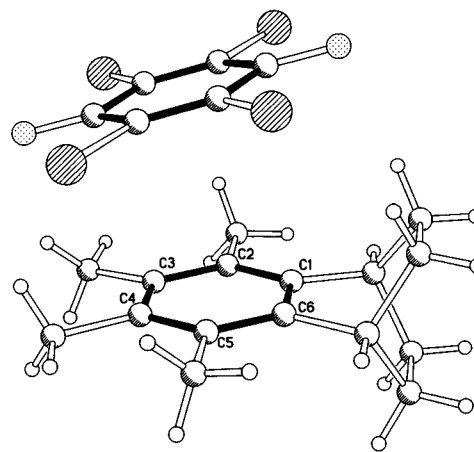
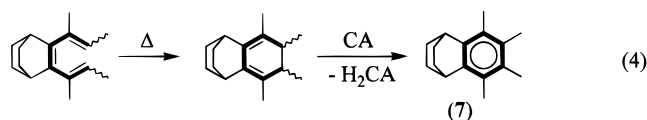


Figure 2. The 1:1 electron donor-acceptor complex of chloranil (CA) with the mono-annulated benzene **7** showing the tilt (and lateral displacement) of CA induced by the presence of the bicyclohexyl annulation.¹⁹

of the crude mixture showed that no diene was present. When equimolar amounts of bromobicyclooctene and its Grignard reagent were treated with the palladium catalyst under identical conditions, the coupled diene **8** was formed in 93% yield. We thus deduced that some of the bicyclooctenyl Grignard reacted with *trans*-dibromoethylene to regenerate 2-bromobicyclooctene (by the loss of acetylene), which in turn reacted with the Grignard reagent to yield the diene **8** found in eq 3.

IV. Mono-Annulated Benzenes with no Rings B and C.

The synthesis of mono-annulated benzenes could be based on alkenylmagnesium bromides to obviate rings B and C (see Scheme 1). For example, a solution of the Grignard reagent derived from 2-bromo-2-butene (as a *cis/trans* mixture) was treated with 2,3-dibromobicyclooctene, and an aqueous workup afforded a mixture of trienes (compare **GS_{II}** in Scheme 1). The crude mixture was readily cyclized in refluxing xylene, and then aromatized with added chloranil, i.e.



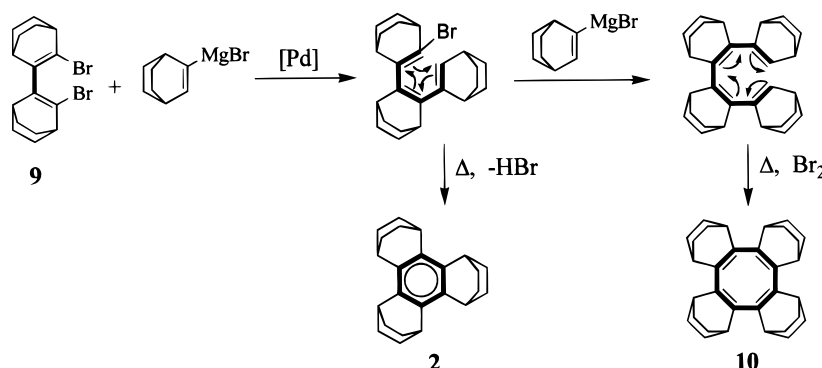
The mono-annulated benzene **7** was contaminated with a small amount of the molecular complex of **7** with the unreacted chloranil, the structure of which was established by X-ray crystallography (see Figure 2).¹⁹

The slightly altered procedure required for the synthesis of the mono-annulated benzene **7** (described above) indicated that the steps involving the electrocyclic conversion of the linear triene to the dihydroaromatic intermediate as well as its subsequent dehydrogenation (i.e., **GS_{II}** \rightarrow **GS_{III}** \rightarrow **GS_I** in Scheme 1) were both substantially slower than those pertaining to the synthesis of the tris- and bis-annulated benzenes **1–6**. As such, it appeared that step (b) as well as (c) was facilitated by the presence of bicyclic annulation at the terminal carbon sites. Nonetheless, the high yields of **7** that were ultimately obtained in Table 1 encourage the more general use of this catalytic procedure, especially for the synthesis of other mono-annulated benzenes.

Catalytic Synthesis of Annulated Cyclooctatetraene via the Sequential Coupling of Four Ethylenic Units. Extension of the catalytic coupling procedure to the fully annulated cyclooctatetraene **10**, as the “vinylogue” of the tris-annulated benzene

(19) Compare with analogous structures of molecular complexes described by Rathore, R. et al. in ref 10.

Scheme 2



2, was readily performed by utilizing a dibromobutadiene unit. Thus diene **8** was converted to the bis-annulated 1,4-dibromobutadiene **9** via a standard bromination/dehydrobromination. The subsequent catalytic coupling of **9** with 2 equiv of bicyclooctenylmagnesium bromide led to a readily separable (3:1) mixture of the tetrakis-annulated cyclooctatetraene **10** and the tris-annulated benzene **2** in ~90% overall yield. [By comparison, the recently reported synthesis of this novel and highly reducing cyclooctatetraene was achieved in only a very poor yield.]²⁰ The relative amounts of **2** and **10** doubtlessly arose via the stepwise coupling first to the trimeric intermediate and then to the tetrameric intermediate in Scheme 2. As such, competition was established by the rate of the sigmatropic cyclization of the trimeric intermediate (followed by rapid loss of HBr and aromatization) which was comparable to the rate of the second alkenylation to the tetrameric intermediate. We anticipate that the adjustment of the concentration of the catalyst and/or Grignard reagent as well as a systematic temperature variation will eventually lead to suitably higher selectivities.

Electron-Density Elucidation of the Mills–Nixon Effects in Tris-Annulated Benzene. We searched extensively among the various annulated benzenes for that hydrocarbon yielding single crystals of sufficient quality to carry out precise X-ray diffraction measurements. Eventually, our best choice was a single crystal of the syn isomer of the tris-cycloC₅-annulated **1s**, the crystallographic quality of which was indicated by its ability at –155 °C to diffract the Mo–K α radiation up to relatively high (2 θ) angles. Since this hydrocarbon was the same as that measured earlier by Siegel and co-workers²¹ at –75 °C, the two sets of only the relevant (aromatic) bond distances are listed in Figure 3.²² Indeed, both sets of crystallographic results show substantial aromatic bond alternations to exist between 1.422(1) Å for the annulated *endo* bonds (a) and 1.379(1) Å for the *non*-annulated *exo* bonds (b). Such a bond alternation is clearly associated with the decrease of the *endo* (ac) angle by 13 deg upon the bicyclic C₅-annulation—as qualitatively predicted by the Mills–Nixon effect when recast in contemporary terminology.²³

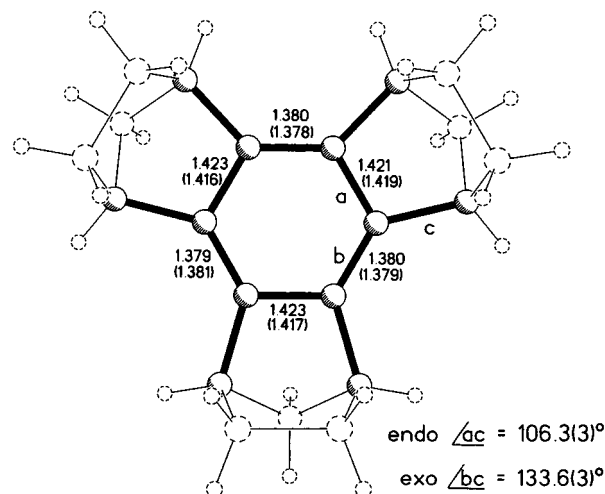


Figure 3. The aromatic bond alternation in the syn isomer **1s** of the tris-annulated benzene with C_{3v} local symmetry. The bond lengths in parentheses are taken from Siegel et al.^{5b}

I. Electronic Nature of the Bond Alternation in Annulated Benzenes. The electronic origin of the aromatic bond alternation in Figure 3 was probed by the precise measurement of the (valence) electron distribution in the syn isomer **1s** that was allowed by the growth of an exceptionally high quality single crystal.²⁴ The multipole data refinement was performed with the XD program package²⁵ at the hexadecapole level for all carbon atoms and the dipole level for the hydrogens.²⁶ The cross-sectional cut of the three-dimensional grid of the deforma-

(23) (a) In the context of their times, Mills and Nixon⁶ formulated the bond fixation to favor one of the pair of Kekule forms in which the single bond was included in the annulation,^{1,2} e.g.



and not



We believe that the present-day depiction qualitatively calls for *less* double-bond character in the annulated (*endo*) bond and *more* double-bond character to the nonannulated (*exo*) bond in measure with the magnitude of the Mills–Nixon effect. (b) However, the term “Mills–Nixon effect” is seriously questioned by Siegel,^{6b,c} who prefers the concept of strain-induced bond localization as suggested by Stanger et al. (*J. Organomet. Chem.* **1987**, 542, 19).

(24) See Experimental Section for details.

(25) Koritsanszky, T.; Howard, S.; Mallinson, P. R.; Su, Z.; Richter, T.; Hansen, N. K. *XD, a Computer Program Package for Multipole Refinement and Analysis of Electron Densities from Diffraction Data; Beta Test Version 2++ 1995*; for Int'l. Union Crystallographers, Commission on Charge, Spin and Momentum Densities, Free University, Berlin.

(20) Komatsu, K.; Nishinaga, T.; Aonuma, S.; Hirosawa, C.; Takeuchi, K.; Lindner, H. J.; Richter, J. *Tetrahedron Lett.* **1991**, 32, 6767. Also see, Nishinaga, T.; Komatsu, K.; Sugita, N. *J. Am. Chem. Soc.* **1993**, 115, 11642.

(21) (a) The sample of the tris-annulated benzene **1s** which we prepared for Siegel et al.^{5b} was obtained as the minor isomer in very low yields via the rather laborious procedure described by Gassman et al.^{12,13} On the other hand, the high yields of **1** obtained in Table 1 enabled sufficient amounts of **1s** to be readily isolated for extensive purification. (b) Single crystals of the major component obtained as the pure anti isomer **1a** could not be grown without some crystallographic disorder.

(22) The slightly greater precision of $\sigma = 0.1$ pm (compared to $\sigma = 0.2$ pm)^{5b} was attributed to the lower temperature and the collection of more diffraction data allowed by the CCD detector in the Siemens SMART diffractometer.

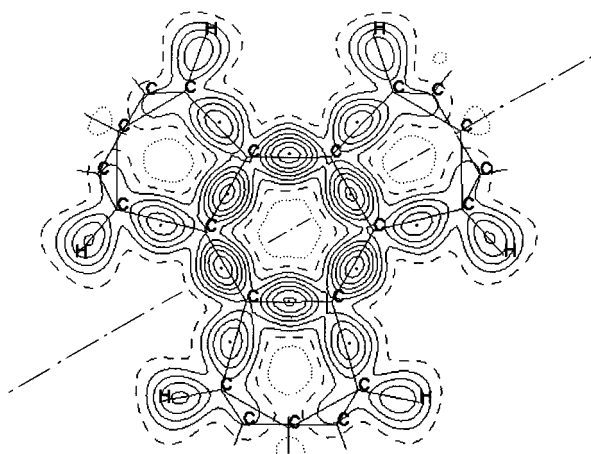


Figure 4. Deformation electron density (multipole static map) in the aromatic plane of **1s** drawn in contour steps of $0.1 \text{ e}/\text{\AA}^3$ progressively increasing from the zero level (---). For comparison, the negative contour (-0.1e) is indicated by the dotted lines. The mirror plane drawn through the *endo* and *exo* bonds is denoted as (---). The location of the critical point for each C–C bond is indicated by a filled dot (●).

tion electron-density taken through the aromatic plane is presented in Figure 4.

Two features of the electron-density contours (Figure 4) were immediately apparent relative to the location and magnitude of the critical point (CP, denoted by filled dots ●) representing the point of highest compression of the electron density between the pair of carbon centers. *First*, the critical point CP_a for the *endo* bond lies more or less along the bond length (d , the straightline between carbon centers), whereas CP_b lies off the *exo* bond length.²⁷ The latter results in a decreased bond length (d) and increased bond bulge (δ), which are quantitatively evaluated in Table 2, columns 2 and 4, respectively. Such a shortening of d and bulging of δ in the *exo* bond corresponds to a “banana” bond distortion of the type previously described by Boese and others.²⁸ *Second*, the electron density (ρ) at the critical point of the *exo* bond is significantly larger than that of the *endo* bond (see Table 2, column 5). Moreover, the Laplacian (i.e., second derivative) of the electron density at the critical point of the *exo* bond is also larger (more negative) than that of the *endo* bond, as given by the values of $\nabla^2\rho$ in Table 2, column 6.²⁹ In chemical terms, the latter translates into a stronger com-

Table 2. Structural and Electron-Density Parameters for the Carbon Bonds of the Tris-Annulated Benzene **1s**

	d (Å)	p (Å)	δ (Å)	ρ ($\text{e}/\text{\AA}^3$)	$\nabla^2\rho$ ($\text{e}/\text{\AA}^5$)	ϵ
(a) Endo						
C1–C2	1.4233(3)	1.425	+0.008	2.68(2)	−31.70(5)	0.17
C3–C4	1.4232(2)	1.425	+0.004	2.61(2)	−30.02(5)	0.16
C5–C6	1.4227(2)	1.428	+0.008	2.64(2)	−31.48(5)	0.18
(b) Exo						
C2–C3	1.3809(2)	1.386	−0.028	2.86(2)	−34.89(6)	0.19
C4–C5	1.3826(3)	1.385	−0.023	2.85(2)	−35.06(6)	0.18
C6–C1	1.3803(2)	1.383	−0.022	2.85(2)	−34.85(5)	0.19
$\text{CH}_2\text{--CH}_2$ (for comparison)						
C8–C9	1.5616(3)	1.570	0.020	2.06(2)	−22.21(5)	0.03
C13–C14	1.5636(3)	1.566	0.025	2.04(2)	−21.65(6)	0.01
C18–C19	1.5627(3)	1.564	0.009	2.01(2)	−21.11(6)	0.04

pression (i.e., localization) of the negative charge in the *exo* bond (relative to that of the *endo* bond) to facilitate electrophilic attack in accord with the expectations of the Mills–Nixon effect.

II. Change in the π -Character of Aromatic Bonds upon Annulation. The electron densities along the *endo* and *exo* bonds can also be considered in terms of their axial distribution at the critical point. Thus Figure 5 shows a cross-sectional cut of the electron-density contours above and below the aromatic plane along the mirror plane (---) shown in Figure 4. To quantify the difference in these electron-density distributions, we employ the ellipticity ϵ as the ratio of the orthogonal components (λ_x and λ_z) of the gradient, i.e., $\epsilon = \lambda_x/\lambda_z - 1$, the critical-point values of which are tabulated in Table 2, column 7.³⁰ By taking the ellipticity of a pure σ bond as $\epsilon_\sigma = 0$ and the π -bond in benzene as $\epsilon_\pi \approx 0.2$,^{28b} we interpret the larger

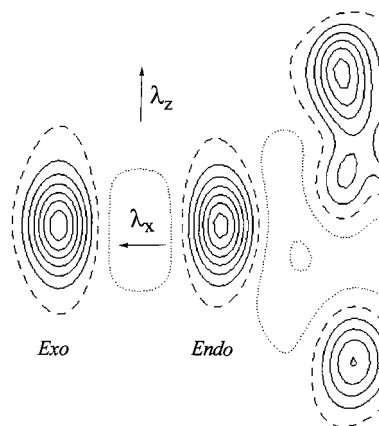
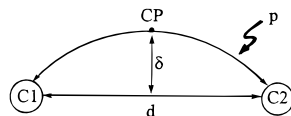


Figure 5. Cross-sectional cut of the electron-density map along the mirror plane in Figure 4 showing the ellipticity of the *endo* and *exo* bonds (above and below the aromatic plane) of **1s**, with the gradients λ_x and λ_z as indicated.

(26) All C–H bond lengths were normalized to the standard neutronographic values of 1.095 and 1.097 Å at tertiary and secondary centers, respectively.

(27) The distinction between bond length (d , the straightline between carbon centers) and bond path (p , the separation based on maximum electron density) is depicted as:



and the bond bulge is evaluated by δ in Table 2. The critical point (CP) has chemical meaning as the center of the C–C bond at which the gradient of the electron density $\nabla^2\rho(r) = 0$, and p is the gradient path of maximum electron density.

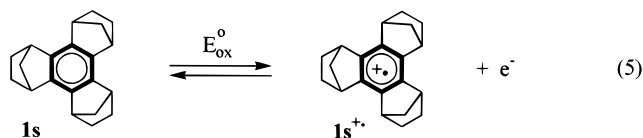
(28) (a) Boese, R.; Bläser, D.; Billups, W. E.; Haley, M. M.; Maulitz, A. H.; Mohler, D. L.; Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1994**, 33, 313 and references therein. (b) Koritsanszky, T.; Buschmann, J.; Luger, P. *J. Phys. Chem.* **1996**, 100, 10547. (c) Yufit, D. S.; Mallinson, P. R.; Muir, K. W.; Kozhushkov, S. I.; DeMeijere, A. *Acta Crystallogr.* **1996**, 852, 668. (d) Note that the “banana-type” distortions in annulated benzene **1s** extends to the ring-contracted σ bonds—the most severe being the six $\text{C}_{ar}\text{--C}_\alpha$ bonds, typically with $\delta \approx 0.04$ Å.

(29) For a physical significance, the magnitudes of $\nabla^2\rho < 0$ identify areas of charge compression, and $\nabla^2\rho > 0$ identify areas of charge decompression to denote nucleophilic and electrophilic reactivity, respectively.

value of ϵ_{exo} in Table 2 as an indication of its greater π -character relative to that of ϵ_{endo} .^{30b} In other words, the aromatic *exo* bond has more π -character than that of the *exo* bond by about 10%.

III. Electronic Origin of the Mills–Nixon Effect. The precise location of the critical points for the *endo* and *exo* bonds (a) and (b), respectively, provides a structural basis for the Mills–Nixon distortion based on the valence shell electron pair repulsion (VSEPR) theory.³¹ Thus the separation between the critical point CP_c of the annelating bond and the CP_a of the *endo* bond (i.e., CP_c – CP_a) is significantly less (by 9%) than the corresponding separation from the critical point CP_b of the *exo* bond (i.e., CP_c – CP_b).³² As such, VSEPR theory would predict a roughly 13% transfer of the π -component of the *endo* bond to that of the *exo* bond in accord with the Mills–Nixon formulation.³³

Annulated Benzenes as Electron Donors. The intrinsic electron-donor properties of aromatic hydrocarbons were conveniently evaluated as their reversible oxidation potentials by cyclic voltammetry. Accordingly, the various annulated benzenes in Table 1 were oxidized electrochemically at a platinum electrode as 5 mM solutions in dichloromethane containing 0.2 M tetra-*n*-butylammonium hexafluorophosphate (TBA⁺PF₆[−]) as the supporting electrolyte. The typical cyclic voltammograms (CV) in Figure S2 (see Supporting Information) showed that the tris-annulated benzene **1s** was reversibly oxidized at a scan rate as slow as 25 mV s^{−1}, with a theoretical anodic/cathodic peak current ratio $i_a/i_c = 1.0$ at 25 °C. The potential calibration of the CV peaks with a ferrocene internal standard provided the reversible oxidation potential for the (1e[−]) production of the aromatic cation radical, i.e.



(30) (a) We employ the ellipticity parameter ϵ as defined by Coppens, P. *X-ray Charge Density and Chemical Bonding*, Oxford: London, 1997. For measurements of ellipticity see refs 28b and c. (b) Such a change of π -character accompanying annelation differs from Boese's interpretation,^{28a} since the increase in the bond bulge δ for the *exo* bonds relative to the *endo* bulge is not accompanied by a significant decrease in the corresponding bond length relative to the bond path, as shown by the comparison of (d) and (p) in Table 2.

(31) (a) Gillespie, R. J.; Nyholm, R. S. *Q. Rev. (London)* **1957**, *11*, 339. (b) Meckenna, A. G.; Meckenna, J. F. *J. Chem. Ed.* **1984**, *61*, 771. (c) Gillespie, R. J. *Molecular Geometry*; Reinhold: New York, 1972.

(32) The average separation for CP_c–CP_a (*endo*) is 1.213 Å (1.229, 1.202, 1.203, 1.213, 1.212, and 1.218 Å), and for CP_c–CP_b (*exo*) the average separation is 1.319 Å (1.326, 1.315, 1.300, 1.334, 1.330, and 1.311 Å).

(33) (a) The 9% difference between CP_c–CP_a (*endo*) and CP_c–CP_b (*exo*) described in footnote 32 should result in a corresponding difference of their Coulombic repulsion energies (if the valence electrons are simply considered to be localized at the CP). The latter can be leveled (to accommodate VSEPR) by an obvious increase in the charge by 0.13 e[−] at CP_b and a corresponding decrease at CP_a so that the electron-density ratio $\rho_b/\rho_a \approx 1.09$, which is rather close to the experimental value of 1.08. The resulting bond orders of 1.565 (*exo*) and 1.435 (*endo*) are equivalent to the π -bond character of 113 and 87%, respectively, relative to that in benzene. Interestingly, these bond orders correspond to calculated bond lengths of 1.394 and 1.422 Å (based on Pauling's bond order/bond length relationship)³⁴ which compare favorably with the experimental values of 1.381 and 1.423 Å, respectively, despite the highly qualitative formulation. (b) We disfavor an alternative explanation of the bond alternation in annulated benzenes based on the repulsive interactions of C–H and C–C Walsh orbitals of the bicyclic framework (Shurki, A.; Shiak, S. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2205), since it does not include the experimentally observed angular distortion of the C_{Ar}–C_α Walsh orbital, as described in this study. (We thank Professor R. Boese for bringing this recent paper to our attention.)

Table 3. Electrochemical (Anodic) Oxidation of Annulated Benzene Donors in Dichloromethane^a

benzene donor	E_{ox}^p (V vs SCE) ^b	E_{ox}^o (V vs SCE)	benzene donor	E_{ox}^p (V vs SCE) ^b	E_{ox}^o (V vs SCE)
1s	1.55	1.50	6	1.74	<i>c</i>
1a	1.56	1.50	7	1.62	<i>c</i>
2	1.61	1.55	11	1.64	<i>c</i>
4	1.58	1.53			

^a In anhydrous dichloromethane containing 0.2 M *n*-tetrabutylammonium hexafluorophosphate at $\nu = 200$ mV s^{−1} and 25 °C. ^b Anodic peak potentials. ^c Irreversible cyclic voltammograms at $\nu = 200$ mV s^{−1}.

The highly reversible anodic oxidation of the tris-annulated benzene **1** strongly contrasts with the irreversible oxidation of the acyclic analogue hexamethylbenzene (**11**), the cyclic voltammogram of which is highly *irreversible* at a scan rate as high as 10 V s^{−1} even in a more polar solvent such as acetonitrile.³⁵ The latter is due to the enhanced reactivity of the cation radical (**11**^{•+}), largely owing to the facile loss of an α -proton.³⁶ Thus the reversible CV behavior of the tris-annulated benzenes **1–4** in Table 3 can be attributed to the generation of cation-radicals **1**^{•+}–**4**^{•+} that are not prone to proton loss owing to their location more or less in the aromatic (nodal) phase.³⁷ It is particularly interesting to note that the electron-donor properties of all the tris-annulated benzenes were singularly constant within ± 30 mV (irrespective of the ring size of the annelation) and essentially the same as those of the *non*-annulated hexamethylbenzene and the mono-annulated tetramethylbenzene **7**. The results in Table 3 thus confirm the notion that the intrinsic electron-donor properties of benzenoid hydrocarbons are largely determined by the *number* of carbon-centered substituents and not on their size or (α) branching.³⁸ We hope that the efficient synthesis of various annulated benzenes will allow their (one-electron) conversion to cation radicals (compare eq 5) and lead to the isolation of crystalline paramagnetic salts for further X-ray diffraction scrutiny of the Mills–Nixon effect.

Summary and Conclusions

The Pd-catalyzed coupling to afford the linear triene (**GS_{II}** in Scheme 1), followed by its spontaneous cyclization and ready dehydrogenation, represents the novel strategy for the efficient (one-pot) synthesis of different tris, bis, and mono-annulated benzenes (and cyclooctatetraene). Indeed, the excellent yields and purities of the tris-annulated benzenes that are obtained by this procedure is exploited for the preparation of single crystals of very high quality for precise X-ray diffraction analysis. As applied to the bicyclopentyl-annulated benzene **1s**, the electron-density distributions in the various aromatic C–C bonds can be used to directly identify the interesting electronic origin of the Mills–Nixon effect.³⁹ The ready synthesis of the various aromatic hydrocarbons (**1–7** in Table 1) also provides the basis

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(35) Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 3968.

(36) Schlesener, C. J.; Amatore, C.; Kochi, J. K. *J. Am. Chem. Soc.* **1984**, *106*, 7472.

(37) Onopchenko, A.; Schulz, J. G. D. *J. Org. Chem.* **1972**, *37*, 1414. Compare also Rathore, R. et al. in ref 8.

(38) Steric hindrance arising from the enhanced van der Waals thickness of these tris-annulated benzenes also discourages nucleophilic attack by solvents, etc. See Rathore, R. et al. in refs 7 and 8.

(39) The versatility of the catalytic procedure in Scheme 1 will allow us to prepare a variety of strained benzenes to examine the general effects of different numbers/types of annelation on the Mills–Nixon Effect. [Unfortunately, the crystallographic disorder in **4**, **5s**, and **7** precludes an extensive discussion at this juncture.]

for the unique electron-donor properties of tris-annelated benzenes, as indicated by their highly reversible oxidation potentials that can be measured by cyclic voltammetry even at slow scan rates and in nonpolar solvents.

Experimental Section

Materials. 2-Bromobicyclo[2.2.1]hept-2-ene,^{40a} 2,3-dibromobicyclo[2.2.1]hept-2-ene,^{40b} 2-bromobicyclo[2.2.2]oct-2-ene,¹⁸ 2,3-dibromobicyclo[2.2.2]oct-2-ene,¹⁸ and 1,2-dibromoacenaphthylene⁴¹ were synthesized via the literature procedures. 2-Bromobutene and 1,2-dibromoethylene were commercially available (Aldrich) and further purified by distillation. Bis(triphenylphosphine)palladium(II) dichloride (Aldrich) was stored under an argon atmosphere. Tetrahydrofuran (Mallinckrodt analytical reagent) was refluxed over lithium aluminum hydride for 12 h, distilled under an argon atmosphere, and stored in a Schlenk flask equipped with a Teflon valve fitted with Viton O-rings. The ¹H and ¹³C NMR spectra were obtained on a General Electric QE-300 FT NMR spectrometer. The electrochemical procedures for the determination of oxidation potentials have been described previously.⁴²

General Procedure for the Catalytic Synthesis of the Annelated Benzenes. A 200-mL flask equipped with a Schlenk adaptor, reflux condenser, and a dropping funnel was charged with purified magnesium turnings⁴³ (1.06 g, 44 mmol) and anhydrous tetrahydrofuran (10 mL) under an argon atmosphere. A small crystal of iodine was added and the mixture refluxed. A solution of 2-bromonorborene (3.81 g, 22 mmol) in tetrahydrofuran (40 mL) was added dropwise via a dropping funnel at a rate to maintain gentle reflux. After the addition was complete, the reaction mixture was refluxed for 2 h and cooled to room temperature. The Grignard solution as obtained above was transferred via a cannula to a Schlenk flask containing a solution of 2,3-dibromonorborene (2.52 g, 10 mmol) and a catalytic amount of bis(triphenylphosphine)palladium(II) dichloride (70 mg) in anhydrous tetrahydrofuran (25 mL), under a flow of argon. The resulting pale yellow reaction mixture was refluxed for 8–12 h and cooled to room temperature. It was then poured into a mixture of saturated aqueous ammonium chloride (40 mL) and dichloromethane (100 mL), and the organic layer was separated. The aqueous layer was further extracted with dichloromethane (3 × 25 mL). The combined organic extracts were washed with water and dried over anhydrous magnesium sulfate. Evaporation of the solvent yielded a pale yellow residue which upon GC and GC-MS analysis (using an internal standard method) indicated the presence of 3:1 mixture of anti and syn isomers of tris-norborene benzenes (>70%) together with small quantities of unaromatized products. The crude residue was redissolved in dichloromethane (50 mL) and treated with bromine (480 mg, 3 mmol). The orange mixture was stirred for 5 min and quenched with 5% aqueous sodium thiosulfate solution (25 mL). The organic layer was washed with water and dried over anhydrous magnesium sulfate. Removal of solvent and flash chromatography on silica gel with hexane as an eluant yielded a 3:1 mixture of anti and syn isomers (**1a** and **1s**) in an excellent yield (2.6 g, 94%).

Separation of Anti/Syn Isomers. Typically a purified mixture of anti/syn isomers of **1** (1.5 g) was loaded on a column which was made up of silica gel (ICN silica 32–63, 60 Å) overlaid with 30 g of

Celite (Celite 545, Baker). With pentane as the eluant, the fractions (approximately 10 mL each) were collected and serially analyzed by GC. The pure anti isomer (**1a**) eluted first, followed by the syn isomer **1s** (contaminated with ~5% of anti isomer), but further recrystallization from ethanol afforded both isomers in pure form.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,4:5,8:9,12-trimethanoriphenylene (syn isomer **1s).** Yield: 19%; recrystallized from a mixture of dichloromethane and ethanol, mp 193–194 °C (lit.¹² mp 175–180 °C); ¹H NMR (CDCl₃) δ 0.99–1.05 (m, 6H), 1.47–1.52 (m, 3H), 1.60–1.66 (m, 3H), 1.79–1.87 (m, 6H), 3.34–3.35 (m, 6H); ¹³C NMR (CDCl₃) δ 27.54, 41.58, 49.36, 136.67. GC-MS *m/z* 276 (M⁺), 276 calcd for C₂₁H₂₄.

1,2,3,4,5,6,7,8,9,10,11,12-Dodecahydro-1,4:5,8:9,12-trimethanoriphenylene (anti isomer **1a).** Yield: 60%; recrystallized from a mixture of dichloromethane and ethanol, mp 166–167 °C (lit.¹² mp 165–168 °C); ¹H NMR (CDCl₃) δ 1.01–1.14 (m, 6H), 1.47–1.52 (m, 3H), 1.56–1.63 (m, 3H), 1.85–1.87 (m, 6H), 3.34–3.35 (m, 6H); ¹³C NMR (CDCl₃) δ 27.67, 28.03, 41.71, 41.77, 48.00, 49.28, 136.87, 137.06, 137.28. GC-MS *m/z* 276 (M⁺), 276 calcd for C₂₁H₂₄.

X-ray Crystallography of the Annelated Benzenes. The intensity data were collected with the aid of a Siemens SMART diffractometer equipped with a CCD detector using Mo-Kα radiation (λ = 0.71073 Å), at –150 °C unless otherwise specified. The structures were solved by direct methods⁴⁴ and refined by full matrix least-squares procedure with IBM Pentium and SGI O₂ computers. The X-ray crystallography of the single crystals of **1s**, **3**, **4**, **5s**, and [7, chloranil] are described in detail in the Supporting Information. [Note that the X-ray structure details of various compounds mentioned here are on deposit and can be obtained from Cambridge Crystallographic Data Center, U.K.]

Determination of Electron-Density Distributions by High Angle Diffraction of Annelated Benzene **1s and Multipole Refinement.** The high angle diffraction data were accumulated for 6 days at –155 °C on a very high quality single crystal. Ten sets of 606 frames each were collected using the ω-scan mode (scan range 0.3°) at different orientations of the crystal in φ with the detector positioned at 2θ = 31, 62, and 93° (exposition times of 40, 80, and 160 s/frame, respectively) to ensure the multiple (complete) coverage of the entire reciprocal sphere up to 2θ ≈ 124°. Integration and the Lorentz and polarization corrections were performed (using SAINT) and 69 664 reflections were collected with *R*(int) = 0.0340. No significant time decay was detected. After application of the SADABS procedure (in the standard mode but without Savitsky-Golay smoothing) on all the reflections, values of *R*(int) decreased up to 0.0235, and 20 108 symmetrically independent reflections were merged, 19 802 of which with θ_{max} = 62° were put into the refinement, and 14 736 reflections had *I* ≥ 2σ(*I*). For further details see Supporting Information.

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Supporting Information Available: The detailed procedures for the preparation of benzene **7**, dibromobutadiene **9**, and cyclooctatetraene **10**, the spectral data for benzenes **2–7** and cyclooctatetraene **10**, the X-ray crystal structure data for **1s**, **4**, **5s**, and [7, CA], the experimental details of electron-density distribution and multipole refinement, and Figures S1 and S2 (35 pages, print/PDF). See any current masthead page for ordering information and Web access instructions.

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