Stereochemistry of Polyethylated Aromatic Systems

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Hexaethylbenzene adopts a conformation with the ethyl groups perpendicular to the aromatic ring and oriented in a fully alternated up-down arrangement. The synthesis, stereochemistry and rotational barriers of systems possessing two polyethylaryl rings in spatial proximity (e.g., decaethylbiphenyl, octaethylbiphenylene) are reviewed.
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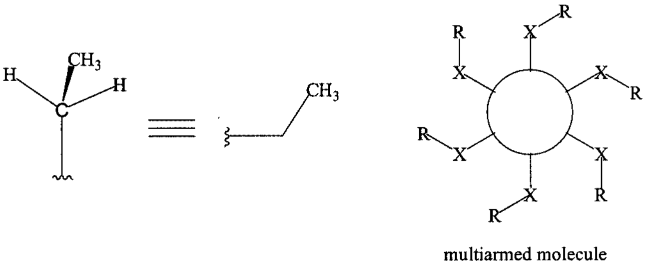
1. The Ethyl Group

The ethyl substituent is the simplest alkyl group of nonconical symmetry.[1] An ethyl group attached to a central frame can be depicted schematically as an "arm" consisting of a CH_3 group protruding from the axis connecting the ethyl group to the central frame. Polyethylated aromatic compounds can be viewed as multiarmed hydrocarbons in which several arms (the ethyl groups) radiate from a central polyatomic core (Scheme 1).[2] Multiarmed compounds (sometimes referred as "octopus molecules")[2b] are of interest inter alia as molecular hosts[3] and as the cores of novel polymeric systems (e.g., dendrimers).

In addition to the synthetic challenge they pose, polyethylated aromatic systems are of interest as sterically crowded compounds. The analysis of their preferred conformations is particularly challenging because of the inherent stereochemical complexity of these conformationally flexible systems.[4] The polyethylated derivatives are capable of existing in a large number of conformations, the relative energies of which are dictated by numerous nonbonded interactions (repulsive and attractive van der Waals interactions)[5] between the ethyl groups. Usually the lowest-energy conformation results from the need to avoid repulsive steric interactions between the groups.



Scheme 1

2. Conformation of Hexaethylbenzene

As shown by Mislow and co-workers, the ethyl groups in the lowest-energy conformation of the prototype of the

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Silvio Biali was born in Buenos Aires in 1957. He completed his PhD thesis under the supervision of Zvi Rappoport at The Hebrew University and spent two years of postdoctoral work in the group of Kurt Mislow (Princeton University). His research interests include calixarenes, sterically crowded compounds, and conformational analysis.

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

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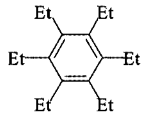
series — hexaethylbenzene (**1**) — are perpendicular to the aromatic ring and are oriented in a fully alternated up-down arrangement (Scheme 2).[6] In this arrangement the ethyl groups on the 1-, 3-, and 5-positions point to one face of the aryl ring while the others are oriented towards the opposite face. This unique conformational feature (sometimes referred as face segregation of the ethyl groups) has been utilized for the design of molecular hosts structurally related to **1**. Most of these systems were obtained formally by replacing three ethyl groups of **1** (those located on the 1-, 3- and 5-positions) by binding groups (see Scheme 3).[7] If the conformational preferences of the host are similar to those of **1**, the up-down alternation of the substituents guarantees that the three binding groups will be pointing to the same face of the aromatic ring, thus enforcing a certain degree of preorganization. By the appropriate modification of the basic skeleton of **1**, other ligand topologies are available.[8] For example, introduction of two binding groups in the 1- and 4-positions of **1**, would result in a derivative with divergent binding groups pointing to opposite faces of the aryl ring.[8]



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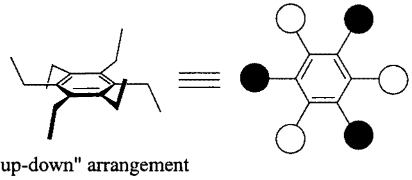
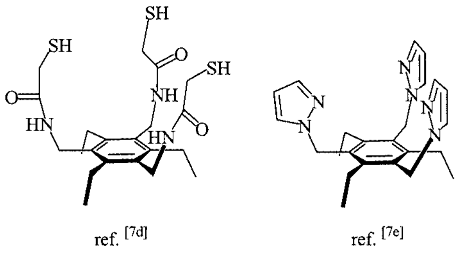


Scheme 2



Scheme 3

The static and dynamic stereochemistry of **1** was analyzed in great detail by Iverson et al.[6] Molecular mechanics calculations indicated that the fully alternated conformation (adopted by **1** in the crystal) indeed corresponds to the lowest in energy.[6,9–11] The arrangement of two *ortho* ethyl groups oriented towards the same face of the aromatic ring is usually designated as a *syn* arrangement, and its associated steric interaction (a *syn* interaction) is repulsive. Assuming that in the conformers of **1** all ethyl groups are perpendicular to the central ring, eight different diastereomeric forms are possible and the calculated relative steric energies of the forms increase roughly with the number of *syn* interactions present (none, two, four or six; Figure 1).[6,9] Although in the crystal **1** adopts the fully alternated conformation, its organometallic derivatives may adopt either the fully alternated arrangement or a conformation in which one or more *syn* arrangements are present. A notable example is the complex **2**, in which — in the crystal — the ethyl groups adopt the all-distal arrangement; i.e., they all point to the same (uncomplexed) face of the ring (in one third of the crystals a single disordered ethyl group points toward the metal atom), to avoid the steric interactions that otherwise would exist with the bulky ligand on the metal atom.[12,13]

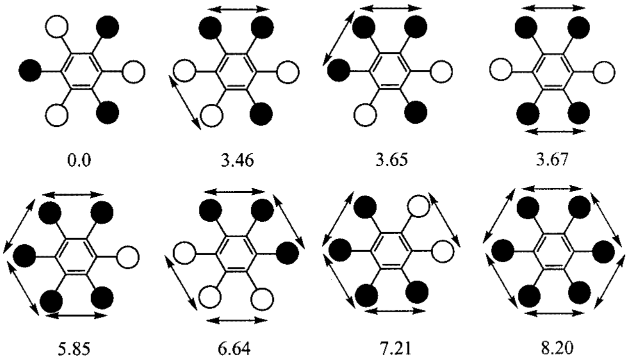
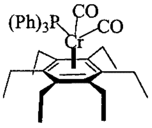
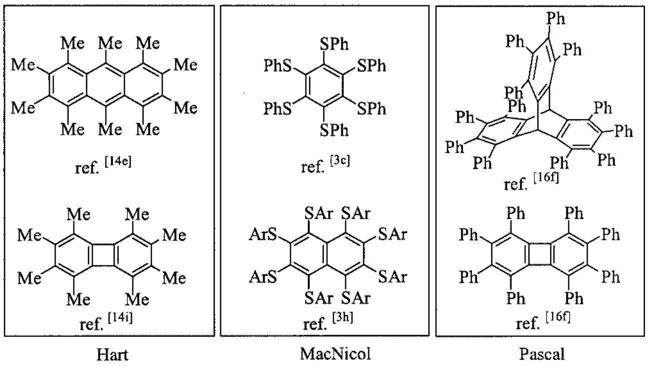


Figure 1. The eight ideal up-down forms of hexaethylbenzene and their calculated (BIGSTRN-2) relative steric energies (from ref.[6]); in all conformations the ethyl groups are oriented perpendicularly (or nearly perpendicularly) to the phenyl ring; filled and empty circles represent ethyl groups pointing to or away from the observer; a double arrow denotes a *syn* arrangement of two *ortho* ethyl groups



2

The polyethylated arene derivatives are structurally related to the polymethylated arenes (studied mainly by Hart in a seminal series of papers),[14,15] and to other polysubstituted arenes such as MacNicol host molecules (e.g., hexaaryloxybenzene and polythiophenoxyarenes)[3] and Pascal's polyphenylarenes[16] (for selected representatives of the families of compounds see Scheme 4). The substituents, however, in the latter case (phenyl groups) possess bilateral symmetry and, in contrast to an ethyl group, no isomerism re-



Scheme 4

sults from a 180° rotation around the bond connecting the substituent to the central frame.[17]

Although **1**, or structurally related compounds[10,18] and their organometallic complexes,[19−22] have been studied extensively, when we started our work we were unaware of any stereochemical study of systems possessing two (or more) polyethylphenyl subunits.

3. Rotational Barriers

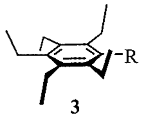
3a. Hexaethylbenzene

When discussing the rotational barrier of polyethylated arenes (which generally are multiconformational systems) the term "rotational barrier" does not usually refer to the rotation of a single ethyl group (a process that in most cases interconverts two diastereomeric conformations), but rather to the overall topomerization barrier determined by NMR spectroscopic methods. This observation is due to the fact that if a single conformation is detected, usually the energy barrier is determined by monitoring the line shape changes of diastereotopic groups that are rendered equivalent by the dynamic process. This topomerization process may involve one or several consecutive ethyl group rotations and/or several intermediate conformers (undetected in the NMR spectrum because of their low populations) along the pathway.

Molecular mechanics calculations indicate that the site exchange of the methylene protons of **1** proceeds through a stepwise (i.e., non correlated) six-step process with a barrier of 11.8 kcal mol^{-1}.[6] A more recent calculation using the MM3 program afforded a value of 12.5 kcal mol^{-1}.[9] The rotational barrier of hexaethylbenzene in solution has not been determined experimentally since, in the lowest-energy, fully alternated conformation, pairs of methylene protons are either homotopic or enantiotopic. Although the rotational barrier of **1** might be determined in principle by monitoring the line shape changes in the NMR spectrum in the presence of a chiral nonracemic additive (which under slow exchange conditions renders the enantiotopic group diastereotopic), this experiment has not been reported so far. The rotational barriers of the side chains of **1** have been measured in the solid state by temperature-dependent magic-angle-spinning NMR spectroscopy by taking advantage of the symmetry nonequivalence of the ethyl groups resulting from the site symmetry of the molecule in the crystal.[23] Surprisingly, the enthalpy of activation of the exchange process is only 50% larger than the calculated barrier for the isolated molecule in the gas phase.[23] Several studies have utilized complexation of the arene ring with a metal atom [e.g., $Cr(CO)_3$, $Mo(CO)_3$, etc.] as a tool for rendering the ethyl groups located "above" and "below" the arene ring symmetry nonequivalent, thus allowing the determination of their rotational barriers.[19−22] In such systems, it has been shown that upon lowering the temperature, the tripodal rotation of the $M(CO)_3$ fragment can be frozen on the NMR spectroscopic timescale and that its rotation is gated by the rotation of the ethyl groups.[21,24]

3b. Pentaethylbenzene Derivatives

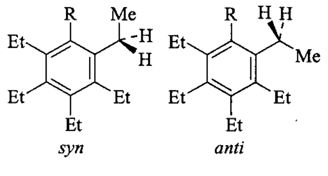
In contrast to the parent **1**, in the pentasubstituted derivatives **3** pairs of methylene protons on the ethyl groups located *ortho* or *para* to the substituent are diastereotopic under the conditions of slow side-chain rotation on the NMR spectroscopic timescale, and their topomerization barrier can be determined readily by dynamic NMR spectroscopy. As shown in Figure 2, the rotational barrier of pentaethylbenzene is lower than the calculated barrier of **1**. During the 180° rotation of an ethyl group, a conformation is reached (ideally, the transition state) in which the CH_2CH_3 bond is coplanar (or nearly coplanar) with the aryl ring. If the two substituents flanking the rotating ethyl group are different, two diastereoisomeric transition states are possible (Scheme 5). In the case when R = H, the *syn* transition state should be favored on steric grounds. Naively, it could be expected (disregarding ground-state effects) that the topomerization barriers of **3c**−**3e** should be similar to that of **1**, since although the substituent R is bulkier than an ethyl group (raising the energy of the *syn* transition state), in the preferred rotational pathway (via the *anti* transition state) the steric interactions should be similar to those found during the ethyl rotations of **1**. Ketone **3c** and esters **3d**,**e**, however, displayed topomerization barriers substantially higher (13.7−16.7 kcal mol^{-1}) than the barrier calculated for **1**.[9] In **3c** the carbonyl group is nearly perpendicular to the aryl plane and two diastereomeric conformations are possible (**3c′** and **3c′′**, Scheme 6). These two conformers may interconvert either by 180° rotation of the five ethyl groups, or by single 180° rotation along the Ar−COR bond. To achieve topomerization of a given form, however, not only must the five ethyl groups rotate, but also the COR group must rotate by 180° and the



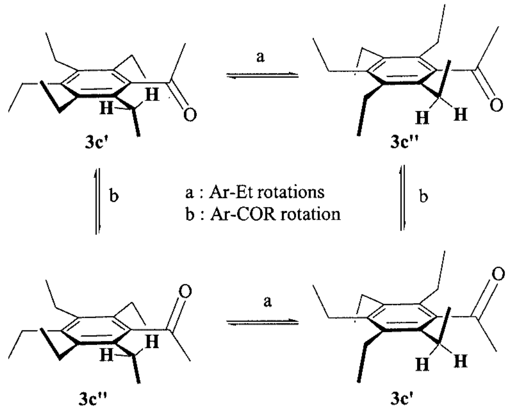
3

	topomerization barrier (kcal/mol)
3a R = H	9.2
3b R = Br	10.2
3c R = $COCH_3$	13.7
3d R = $OCOCH_3$	14.6
3e R = OCOPh	16.7

Figure 2. Experimentally measured topomerization barriers of pentaethylphenyl derivatives; in case of the compounds **3c**−**3e**, topomerization of a pair of protons in an *ortho* or *meta* ethyl group requires 180° rotation of the five ethyl groups around the Ar−Et bonds and 180° rotation of the R substituent (e.g., around the Ar−O bond in the case of **3d**−**3e**)



Scheme 5



Scheme 6

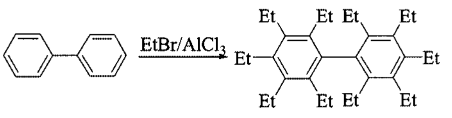
high barrier of the latter process is the one that determines the overall topomerization barrier. Low-temperature NMR spectroscopic data were in agreement with this analysis and, for example, two sets of signals were observed in ^{13}C NMR spectra of **3d** and **3e**.[9]

4. System with Two Mutually Perpendicular Polyethylphenyl Rings: Decaethylbiphenyl

Substituted biphenyls represent one of the classical topics in organic stereochemistry.[25] The polyethylated biphenyl **4**, which can be viewed as formally derived from connecting two pentaethylphenyl rings, is of stereochemical interest since in principle the steric proximity between the *ortho* ethyl groups of the two rings may "relay" conformational information from ring to ring. The structurally related decakis(bromomethyl)biphenyl has been prepared and characterized stereochemically, but unfortunately the slow-exchange low-temperature NMR spectra could not be determined because of the poor solubility of the system.[26]

4a. Synthesis

The molecule was prepared by exhaustive ethylation of biphenyl under Friedel−Crafts conditions using EtBr as both the alkylating reagent and the solvent, and a large excess of $AlCl_3$ [Equation (1)].[27] The reaction demanded several days to reach completion, but good yields of the polyethylated biphenyl were obtained.



4

(1)

Decaethylbiphenyl is more complex stereochemically than hexaethylbenzene, in particular because of the large number of possible arrangements of the ethyl groups. For the analysis of the possible conformations of **4** it was assumed that the two rings are mutually perpendicular and that all ethyl groups are perpendicular to the aryl rings to which they are attached. Under these restrictions, all possible conformations are chiral irrespectively of the "up" or "down" orientation of the ethyl groups. This feature can be rationalized readily since, for example, the two perpendicular *p*-ethyl groups are incompatible with the two σ-planes or the S_4 symmetry operation present in the parent achiral, unsubstituted biphenyl adopting the perpendicular conformation. The configurational matrix method (a "back-of-the-envelope" method for readily calculating the number of ideal conformers in this type of system)[28] gave an estimate of 136 enantiomeric pairs for **4**. This number is substantially larger than the eight diastereomeric forms of **1**, so decaethylbiphenyl is at least one order of magnitude more complex than the parent hexaethylbenzene.

4b. Molecular Mechanics Calculations

To determine the lowest energy conformation, MM3 calculations were conducted on a subset of the 136 theoretical isomers of **4** since it could be safely assumed that some conformers (e.g., those possessing a large number of *syn* interactions) correspond to high-energy forms. The calculations, therefore, were restricted to conformations with at most one *syn* interaction present per ring. The calculations indicated that, in contrast to **1**, the fully alternated conformation lacking any *syn* interaction is not the lowest in energy (conformation a, Figure 3).[29] Granted, a calculated energy gap of 0.7 kcal mol^{-1} is within the margin of error of the MM3 calculations. Notwithstanding this caveat, it could be concluded that according to the calculations, the lowest-energy form possessed one *syn* interaction per ring.

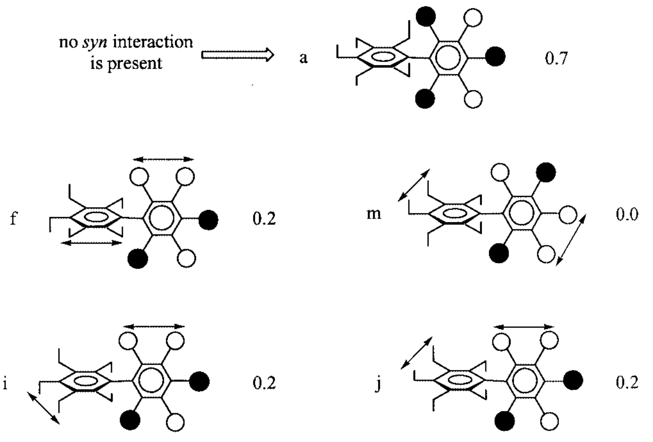


Figure 3. Calculated relative steric energies (MM3, in kcal mol^{-1}) of selected conformers of **4**; in all cases only one of the two enantiomers is depicted; the lowest-energy conformation possesses one *syn* interaction per ring (denoted by a double arrow); according to the calculations, the conformation lacking any *syn* interactions (a) is not the lowest in energy

Three additional conformations (f, i and j, Figure 3), also possessing one *syn* interaction per ring possessed calculated energies just 0.2 kcal mol^{-1} above the global minimum. Viewing the fully alternated conformation along the biphenyl axis was helpful to rationalize why (in contrast to **1**) the fully alternated form "a" is not the global minimum. In this conformation repulsive steric interactions between *ortho* ethyl groups of the two rings are present. If the rings adopt a fully alternated up-down arrangement, the two ethyl groups located *ortho* to the phenyl−phenyl bond should be pointing to the same face, as shown in Figure 4. This arrangement will result in unavoidable "clashing" with one of the *ortho* ethyl groups on the second ring, irrespective of its "up" or "down" orientation (Figure 5). If, on the other hand, each ring adopts a conformation with one or three *syn* arrangements, the two *ortho* ethyl groups on each ring will point to opposite faces of the ring, thus allowing a homodirectional arrangement of the *ortho* ethyl groups, as viewed along the biphenyl axis (Figure 4 and 5). *Introduction of a single syn interaction per ring minimizes the repulsive interactions by allowing a homodirectional arrangement of the ethyl groups.*

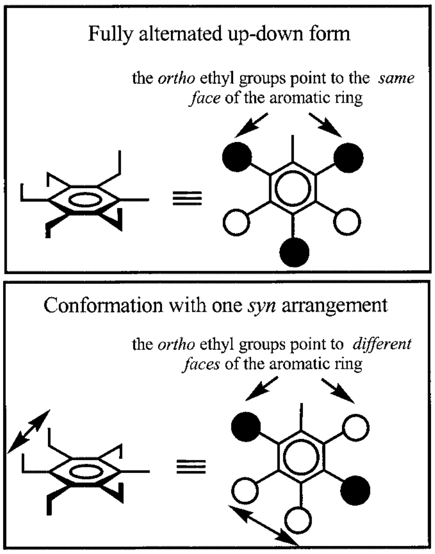


Figure 4. Top: side and top representation of the fully alternated up-down conformation of one pentaethylphenyl subunit of **4**; the two *ortho* ethyl groups are pointing to the same face of the aromatic ring; bottom: conformation with one *syn* orientation (denoted by a double arrow); the two *ortho* ethyl groups point to different faces of the aromatic ring

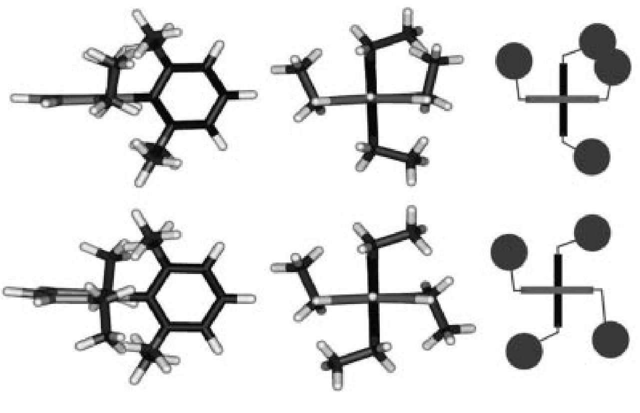


Figure 5. View normal to (left) and along the biphenyl axis (center and right) of biphenyl **4**; for clarity, the *meta* and *para* ethyl groups are replaced by hydrogen atoms; top: When the ethyl groups in each ring are fully alternated, there is a repulsive steric interaction between a pair of *ortho* ethyl groups at different rings; bottom: when a *syn* arrangement is present in each ring the four *ortho* groups can be arranged in a homodirectional fashion

4c. NMR Spectra

The ^{13}C NMR spectrum at 260 K is quite simple, displaying three signals each for the methyl and methylene groups of the *ortho*, *meta* and *para* ethyl residues. The signals were assigned to the different ethyl groups on the basis of their relative intensities and by using 2D NMR methods. Upon lowering the temperature, the signals broadened and decoalesced and at 149 K (in $CDCl_2F$) signals corresponding to at least two different conformers could be distinguished. Notably, the signals that displayed the largest chemical shift difference in the slow-exchange ^{13}C NMR spectrum were those corresponding to the *meta* ethyl groups, while the *ortho* ethyl groups possessed rather similar chemical shifts. To determine the preferred conformation in solution on the basis of the chemical shifts observed it was assumed that the different ethyl groups are sensitive of the environment provided by their immediate neighbors. Two pieces of evidence supported the claim that the major conformer detected in solution indeed corresponds to the lowest-energy conformation "m": (i) The number of signals in the slow-exchange NMR spectrum was consistent with a conformation of C_1 symmetry. (ii) The observed chemical shifts were consistent with conformation "m". In this conformation the *ortho* ethyl groups are oriented in a homodirectional fashion in an arrangement of local S_4 symmetry (disregarding the *para* ethyl groups). Since the *ortho* ethyl groups should mainly "feel" the environment provided by their neighbors at the *meta* positions, and these are also arranged in a homodirectional fashion, the *ortho* ethyl groups should possess very similar chemical shifts. The *meta* ethyl groups reside in different environments since one is *syn* and one is *anti* to the neighboring *para* group, and therefore they should possess different chemical shifts, as observed experimentally.

Notably, according to X-ray diffraction, four independent molecules existing in *three* different conformations were present in a single crystal of **4** grown from ethanol (Figure 6). The calculated lowest energy conformation ("m") was represented twice in the crystal with the two remaining molecules adopting conformations "i" and "j".[27]

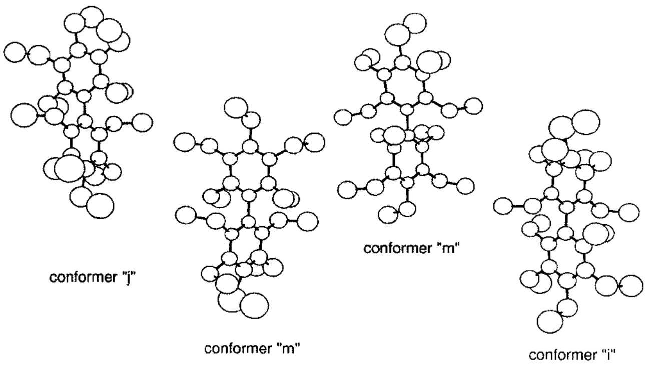


Figure 6. The four crystallographically independent molecules of **4** found in the crystal; two molecules adopt conformation "m" (cf. Figure 3) and the rest conformations "i" and "j"

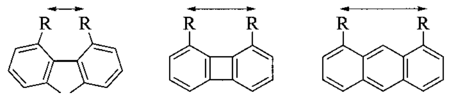
4d. Ethylation of 1,3,5-Triphenylbenzene

The reaction, performed in a similar manner to that described above, was completed overnight, affording mainly the pentadecaethylated product with no substitution of the central ring. NMR spectra consistent with C_{3h} symmetry were obtained both at room temperature and at 160 K, indicating that the ground state is symmetrical, with fully alternated C_6Et_5 substituents.[30a] Since the central ring is not ethyl-substituted, the "clashing" interaction described above cannot occur.

5. Systems with Two Nearly Coplanar Polyethylphenyl Rings

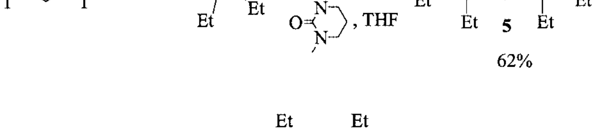
5a. Synthesis

Three different systems (1,2,3,4,5,6,7,8-octaethylanthracene,[30b] octaethylbiphenylene[31] and octaethylfluorene[30b]) were studied containing two tetraethylphenylene units fused in a coplanar (or nearly coplanar) fashion and differing in the distance between *peri* ethyl groups, the shortest being present in the fluorene derivative (Scheme 7).



Scheme 7

Octaethylanthracene **5** has been synthesized by reaction of 1,2,4,5-tetraiodobenzene with a zirconium reagent [Equation (2)].[32] We found, however, that this anthracene derivative could be prepared by ethylation of dihydroanthracene [Equation (3)]. Under the reaction conditions, the ethylated dihydroanthracene aromatized spontaneously eventually providing **5** in 23% yield.[30b] The oxidation of substituted dihydroanthracenes to the corresponding anthracenes in $AlCl_3$-catalyzed alkylations of 9,10-dihydroanthracene has been observed previously.[33]



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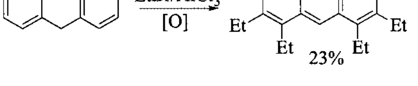
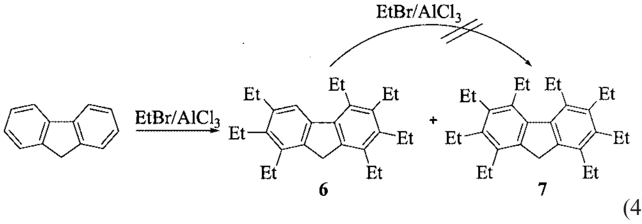


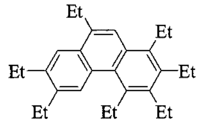
(3)

Octaethylfluorene **7** was prepared by the ethylation of fluorene, but we were unable to obtain the target compound as the major product. Instead, Friedel–Crafts ethylation afforded a mixture of the heptaethyl- and octaethylfluorene derivatives, which were separated by preparative HPLC [Equation (4)].[30b] Attempted ethylation of heptaethylfluorene **6** under the same reaction conditions yielded decomposition products, suggesting that **6** is not an intermediate in the formation of **7**. Apparently, ethylation in the "bay region" positions occurs at an early stage of the reaction.



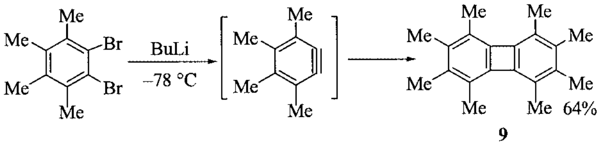
(4)

Similarly, ethylation of dihydrophenanthrene resulted ultimately in 1,2,3,4,6,7,9-heptaethylphenanthrene (**8**).[30a] Interestingly, this product avoids *peri* diethyl interactions as well as double substitution in the bay area.



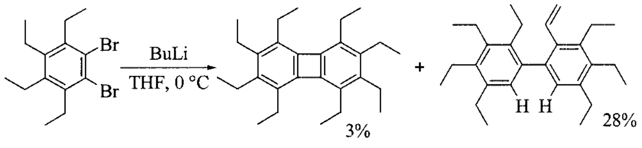
8

The synthesis of octaethylbiphenylene was patterned after the report by Hart and Teuerstein that treatment of 1,2-dibromo-3,4,5,6-tetramethylbenzene with 1 equiv. of BuLi at low temperature affords octamethylbiphenylene **9** in excellent yield [Equation (5)].[14i,35,36] The reaction involves the generation of tetramethylbenzyne, which dimerizes under the reaction conditions.



(5)

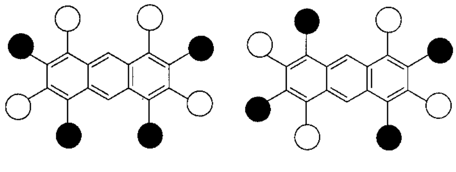
On the basis of this report, the tetraethylbenzene derivative[37] **10** was treated with 1 equiv. of BuLi [Equation (6)]. The yield was very low (about 3%), but fortunately a yellow compound crystallized from the reaction mixture, allowing the facile isolation of pure material. The main product of the reaction was the heptaethyl-monovinylbiphenyl, probably derived from the diradical developed after a σ-bond between two tetraethylbenzyne moieties is formed. It seems likely that the formation of the second σ-bond is a slower process in the polyethylated diradical than in the corresponding polymethylated diradical (probably because of the increase in steric strain) and hydrogen transfer reactions successfully compete with the formation of the four-membered ring.[31]



10 **11** **12** (6)

5b. Calculations and Solution NMR Spectroscopic Data

Two forms with a fully alternated arrangement of the ethyl groups in each ring are possible in octaethylanthracene (**5a** and **5b**, Scheme 8). According to both MM3 and ab initio calculations, and as evidenced by the near identical calculated energies of the two forms, the two tetraethylphenylene subunits do not mutually interact sterically and are conformationally independent.

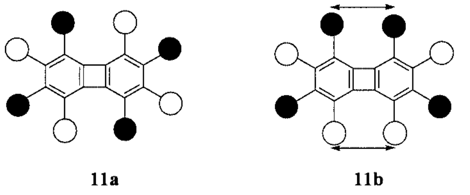


5a **5b**

Scheme 8

Two conformers with similar populations were detected in the ^{13}C NMR spectrum at low temperature (145 K), which were assigned to the forms **5a** and **5b**. Evidently the *syn* arrangement between pairs of *peri* ethyl groups on the same edge of the anthracene scaffold does not affect the energy of the conformation.

According to MM3 and ab initio calculations of biphenylene **11**, the conformation with two pairs of *peri* ethyl groups oriented *syn* is ca. 2 kcal mol^{-1} less stable than the fully alternated form lacking such an interaction (Scheme 9). The closer proximity between the *peri* groups (compared to **5**) allows the two tetraethylphenylene subunits to interact sterically. Both the ^{1}H and ^{13}C NMR spectra were consistent with a fully alternated major conformer. Although a minor conformer could not be detected directly in the low-temperature NMR spectrum, the changes in line shape as a function of temperature were characteristic of the so called "exchange with a hidden partner" (i.e., exchange of the major conformer with a minor form too scarcely populated to be detected in the slow exchange NMR spectrum).[38]



11a **11b**

0.0 2.3 kcal/mol (MM3)
1.7 kcal/mol (MP2(full)/6-31G*//HF/6-31G*)

Scheme 9

Notably, the conformation adopted in the crystal is not the fully alternated but the higher energy conformation **11b** indicating that crystal packing forces are operative (Figure 7). In general, the structural parameters of **11** were very similar to those of biphenylene[39] and octamethylbiphenylene[40] indicating that, although the compound is sterically more crowded, apparently the system is not more strained.

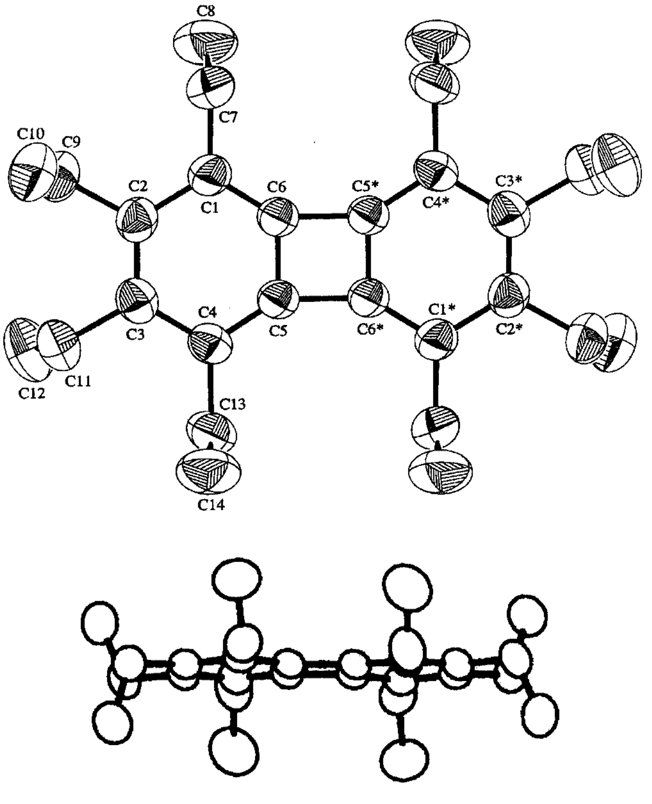


Figure 7. Crystal structure of octaethylbiphenylene **11**

According to X-ray crystallography, in the heptaethyl derivative **6** the fluorene unit is nearly planar. The conformation in the crystal is not the fully alternated one, which according to MM3 calculations is the lowest in energy, but a conformation in which all the ethyl groups in the trisubstituted ring are pointing to the same face of the aromatic ring. This conformation renders one of the faces of the trisubstituted ring sterically more exposed, probably allowing for a more dense packing of the molecules in the crystal. Examination of the crystal packing indicated that the three ethyl groups oriented *syn* are on top of the exposed face of a neighboring ring (Figure 8).

The central core of octaethylfluorene adopts a chiral helical conformation to increase the distance between the ethyl groups in the bay area. The twisted helical nature of the fluorene scaffold of **7** is somewhat reminiscent of the helical twist observed for octamethylnaphthalene **13** which originates from the need to decrease the repulsive steric interactions between pairs of *syn peri* methyl groups.[41]

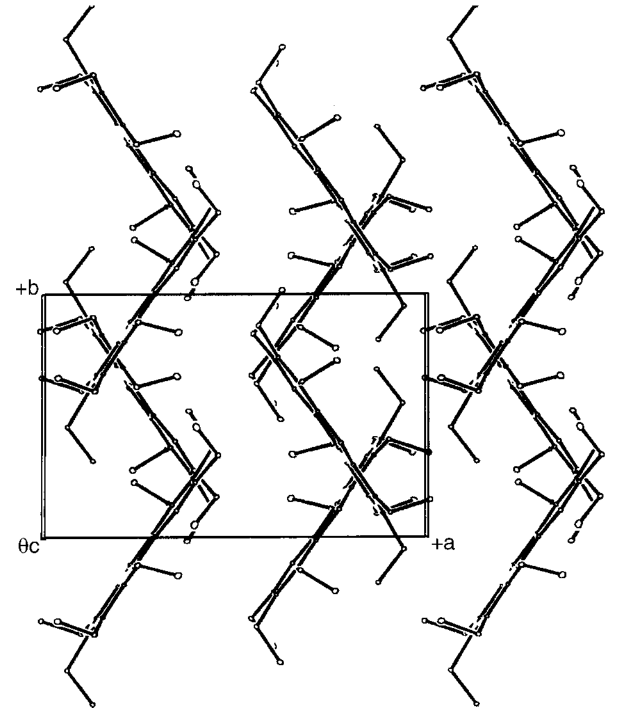
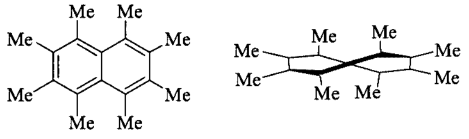


Figure 8. Packing arrangement of heptaethylfluorene **6**



13

The helical deformation of the fluorene core has important stereochemical consequences. In contrast to **1**, independent of the given orientations of the ethyl groups, the two faces of a given aryl subunit are diastereotopic. Two different conformers possessing a fully alternated up-down arrangement of the ethyl groups are possible which have been dubbed "in" and "out" (Figure 9). MM3 calculations indicate that the fully alternated "out" form corresponds to the global minimum, while the "in" form is 8.1 kcal mol^{-1} less stable. MM3 and ab initio RHF 6-31G* calculations predict torsional angles of 34.5 and 29.2°, respectively, for the four aromatic carbon atoms of the bay region of the "out" conformer of **7** (Figure 10). Low-temperature NMR spectra were consistent with the fully alternated "out" conformation of C_2 symmetry. Notably, in the crystal the molecule adopts a conformation with an "out" arrangement of the ethyl group in the bay region, but with a *syn* arrangement between a pair of ethyl groups (Figure 11). This crystal conformation was not the global minimum, but a form lying 1.1 kcal mol^{-1} above the fully alternating "out" form.

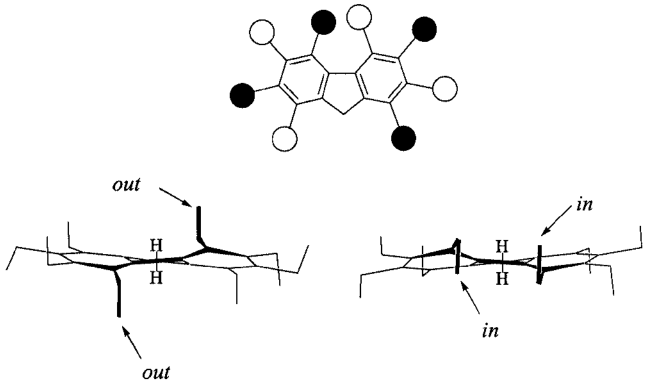


Figure 9. The two diastereomeric fully alternated up-down conformations of octaethylfluorene (in each case only one enantiomer is depicted); depending on the orientations of the ethyl groups in the bay region, the conformations are designated "out" and "in"

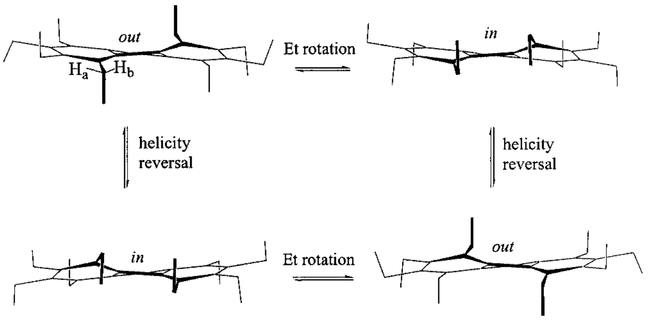


Figure 10. Conformational interconversion of octaethylfluorene **7**; rotation of all ethyl groups interconverts the "out" and "in" conformations; topomerization of the protons of a given methylene group requires both 180° rotations about the Et−Ar bonds and inversion of the helical sense of the fluorene core and results in enantiomerization

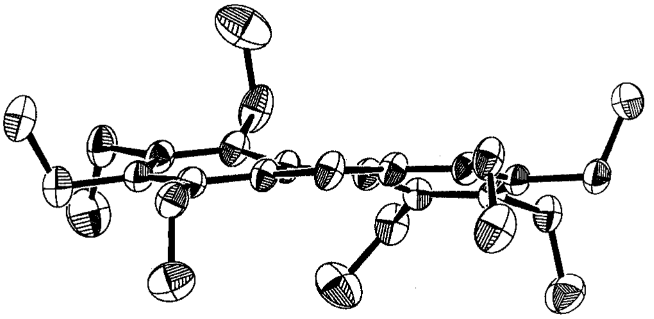
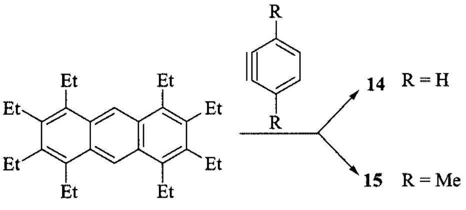


Figure 11. Side view of the conformation of **7** in the crystal; two vicinal ethyl groups adopt a *syn* arrangement

6. Polyethylated Triptycene Derivatives

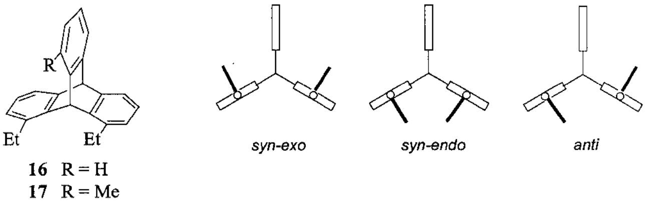
A different stereochemical scenario is present when the two polyethylated rings are arranged in a V-shaped disposition. Such an arrangement exists in the two polyethylated triptycene derivatives (**14** and **15**) that were synthesized by Diels−Alder reaction of the octaethylanthracene **5** with the corresponding benzynes [Equation (7)].



5

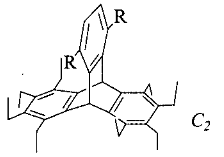
(7)

MM3 calculations were performed initially on the model compounds **16** and **17**. In these compounds, the two faces of a given ethylated ring are diastereotopic and therefore the "up" or "down" arrangements of an ethyl group are not equivalent. Assuming that in the lower energy arrangements the ethyl groups are arranged in a perpendicular fashion, two achiral (*syn-exo* and *syn-endo*) and one chiral conformation (*anti*) are possible (Scheme 10). The MM3 calculations indicated that the *syn-endo* arrangement is intrinsically repulsive and corresponds to a saddle point lying 1.4−0.9 kcal mol^{-1} above the *syn-exo* arrangement.



Scheme 10

Calculations conducted for **14** and **15** indicated that the fully alternated C_2 form (**a**) is the lowest in energy. Conformations possessing a *syn-endo* arrangement of a pair of *peri* ethyl groups were less stable than those lacking this arrangement. The low-temperature ^{13}C NMR spectra displayed a signal pattern consistent with the fully alternated conformation "**a**" as the major conformer. Single crystals of **14** were grown from both chloroform and acetonitrile, and those of **15** from acetonitrile. In all the three structures a conformation with a *syn* interaction between *ortho* ethyl groups was present but lacking *syn-endo* interactions. According to the MM3 data, the crystal conformation is not the lowest in energy.[42]

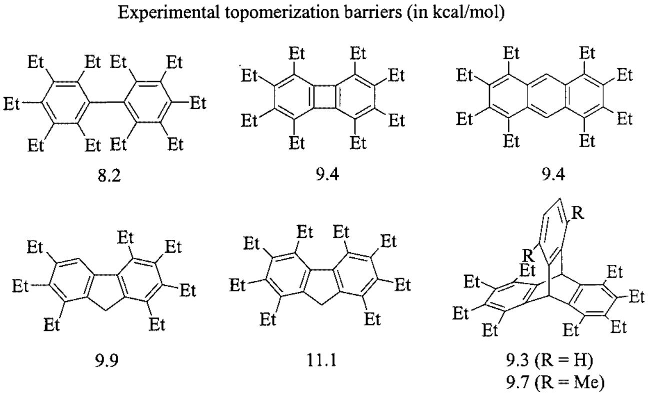


a

7. Rotational Barriers of the Polyethylated Derivatives

From the variable-temperature NMR spectra a topomerization barrier of 8.2 kcal mol^{-1} was determined for **4**. The barrier height clearly rules out rotation around the central phenyl bond since such barriers in biphenyls substituted in the four *ortho* positions by bulky groups are sufficiently high to enable the resolution of properly substituted systems. As discussed in section 3a the main interest was not the "rotational barrier", but rather the threshold topomerization barrier; in other words, the minimum energy pathway (involving one or several individual steps) that result in site exchange of the diastereotopic methylene groups. A full calculation of all possible interconversion pathways was impractical since 136 enantiomeric forms exist, some possessing ten symmetry-nonequivalent ethyl groups. The calculations were therefore restricted to the pathways interconverting (by single ethyl group rotation) conformations possessing at most a single *syn* interaction per ring. The calculations indicated that the topomerization can proceed by a three-step process (with a calculated barrier of 9.1 kcal mol^{-1}) or alternatively by rotation of a single *para* ethyl group.[27]

In general the topomerization barriers measured (summarized in Scheme 11) were quite similar, and were in the 8.2−11.1 kcal mol^{-1} range.[27,30b,31,42] A relatively large barrier was measured for the octaethylfluorene **7** by monitoring the changes in line shape of the methylene proton signals in the ^{1}H NMR specta. In that case, the topomerization process that is monitored involves not only ethyl group rotations, but also a reversal of the helical sense of the fluorene core (Figure 10), since otherwise no exchange would be observed for the methylene protons. Similarly, the barrier for 1,2,3,4,6,7,9-heptaethylphenanthrene (**8**) is very high: 12.5 kcal mol^{-1}.[30a]



Scheme 11

8. Conclusions

Polyethylated aromatic compounds pose a challenge to the chemist both from a synthetic and a stereochemical point of view. These systems provide a unique look into van der Waals interactions since their preferred conformations are dictated by a large array of interactions between proximal ethyl groups on the same or different rings. In these multiconformational systems, several conformations are within a 2 kcal mol^{-1} range of the lowest energy form, and the crystal conformation may not be the lowest in energy, but rather the one that allows for more dense packing. At least in some cases (cf. Figures 8 and 11) conformations with a *syn* arrangement of two neighboring ethyl groups, although higher in energy, are present in the crystal since presumably they allow for a more dense packing of the molecules in the crystal.

Acknowledgments

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[1] For reviews on the conformation of alkyl groups see: [1a] U. Berg, J. Sandström, *Adv. Phys. Org. Chem.* **1989**, *25*, 1−97. [1b] E. L. Eliel, S. H. Wilen, L. N. Mander, *Stereochemistry of Organic Compounds*, Wiley, New York, **1994**, chapter 10. [1c] See also: J. V. Metzger, M. C. Chanon, C. M. Roussel, *Rev. Heteroatom Chem.* **1997**, *16*, 1−45.

[2] [2a] F. M. Menger, *Top. Curr. Chem.* **1986**, *136*, 1−15. [2b] F. Vögtle, E. Weber, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 814−816.

[3] See for example: [3a] D. D. MacNicol, A. D. U. Hardy, D. R. Wilson, *Nature (London)* **1977**, *266*, 611−612. [3b] A. D. U. Hardy, D. D. MacNicol, S. Swanson, D. R. Wilson, *Tetrahedron Lett.* **1978**, 3579−3582. [3c] A. D. U. Hardy, D. D. MacNicol, D. R. Wilson, *J. Chem. Soc., Perkin Trans. 2* **1979**, 1011−1019. [3d] A. Freer, C. J. Gilmore, D. D. MacNicol, D. R. Wilson, *Tetrahedron Lett.* **1980**, *21*, 1159−1162. [3e] C. J. Gilmore, D. D. MacNicol, A. Murphy, M. A. Russell, *Tetrahedron Lett.* **1983**, *24*, 3269. [3f] D. D. MacNicol, P. R. Mallison, A. Murphy, C. D. Robertson, *J. Incl. Phenom.* **1987**, *5*, 233. [3g] D. D. MacNicol, W. M. McGregor, P. R. Mallison, C. D. Robertson, *J. Chem. Soc., Perkin Trans. 1* **1991**, 3380−3382. [3h] G. A. Downing, C. S. Frampton, J. H. Gall, D. D. MacNicol, *Angew. Chem. Int. Ed. Eng.* **1996**, *35*, 1547−1549. [3i] R. K. Henderson, D. D. MacNicol, K. L. McCormack, S. J. Rowan, D. S. Yufit, *Supramol. Chem.* **1998**, *10*, 27−32. [3j] C. S. Frampton, D. D. MacNicol, S. J. Rowan, *J. Mol. Struct.* **1997**, *405*, 169−178.

[4] R. W. Hoffman, *Angew. Chem. Int. Ed. Eng.* **1992**, *31*, 1124−1134.

[5] For examples of conformational phenomena dominated by attractive van der Waals interactions see: [5a] R. E. Carter, B. Nilsson, K. Olsson, *J. Am. Chem. Soc.* **1975**, *97*, 6155−6159. [5b] U. Berg, I. Pettersson, *J. Org. Chem.* **1987**, *52*, 5177−5184. [5c] M. Nishio, M. Hirota, *Tetrahedron* **1987**, *52*, 5177−5184. [5d] J. E. Anderson, V. Bru-Capdeville, P. A. Kirsch, J. S. Lomas, *J. Chem. Soc., Chem. Commun.* **1994**, 1077−1078. [5e] For a review see: R. R. Sauers, *J. Chem. Ed.* **1996**, *73*, 114−116.

[6] D. J. Iverson, G. Hunter, J. F. Blount, J. R. Damewood, Jr., K. Mislow, *J. Am. Chem. Soc.* **1981**, *103*, 6073−6083.

[7] See for example: [7a] Z. Hou, T. D. P. Stack, C. J. Sunderland, K. N. Raymond, *Inorg. Chim. Acta* **1997**, *263*, 341−355. [7b] A. Metzger, V. M. Lynch, M. K. C. Monahan, E. V. Anslyn, *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 649−652. [7c] T. Szabo, B. M. O'Leary, J. Rebek, Jr., *Angew. Chem. Int. Ed. Eng.* **1998**, *37*, 3410−3413. [7d] S.-W. Tam-Chang, J. S. Stehouwer, J. Hao, *J. Org. Chem.* **1999**, *64*, 334−335. [7e] J. Chin, J. Oh, S. Y. Jon, S. H. Park, C. Walsdorff, B. Stranix, A. Ghossoub, S. J. Lee, H. J. Chung, S.-M. Park, K. Kim, *J. Am. Chem. Soc.* **2002**, *124*, 5374−5379. [7f] For a review of facially segregated host molecules structurally related to **1**, see: G. Hennrich, E. V. Anslyn, *Chem. Eur. J.* **2002**, *8*, 2219−2224.

[8] K. V. Kilway, J. S. Siegel, *Tetrahedron* **2001**, *57*, 3615−3627.

[9] H. E. Gottlieb, C. Ben-Ari, A. Hassner, V. Marks, *Tetrahedron* **1999**, *55*, 4003−4014.

[10] For studies on substituted benzenes structurally related to **1**, see for example: M. D. Radcliffe, K. Mislow, *J. Org. Chem.* **1984**, *49*, 2058−2059.

[11] A saturated derivative of **1** (all-*trans*-1,2,3,4,5,6-hexaethylcyclohexane) has been reported in the literature: A. Immirzi, E. Totti, *Atti. Accad. Naz. Lincei, Cl. Sci. Fis., Mat. Nat., Rend.* **1968**, *44*, 98.

[12] G. Hunter, D. J. Iverson, K. Mislow, J. F. Blount, *J. Am. Chem. Soc.* **1980**, *102*, 5942−5943.

[13] Other conformations of complexes of **1** have been observed in the crystal; see Figure 6 in: M. J. McGlinchey, *Can. J. Chem.* **2001**, *79*, 1295−1309.

[14] For studies on the synthesis and reactions of polymethylated aromatic compounds, see: [14a] A. Oku, T. Kakihana, H. Hart, *J. Am. Chem. Soc.* **1967**, *89*, 4554−4554. [14b] H. Hart, A. Oku, *J. Org. Chem.* **1972**, *37*, 4269−4274. [14c] H. Hart, A. Oku, *J. Org. Chem.* **1972**, *37*, 4274−4278. [14d] H. Hart, J. L. Reilly, J. B.-C. Jiang, *J. Org. Chem.* **1977**, *42*, 2684−2689. [14e] H. Hart, B. Ryge, *Tetrahedron Lett.* **1977**, *36*, 3143−3146. [14f] A. Sy, H. Hart, *J. Org. Chem.* **1979**, *44*, 7−9. [14g] E. Dunkelblum, H. Hart, *J. Org. Chem.* **1979**, *44*, 3482−3485. [14h] H. Hart, G. Nwokogu, *J. Org. Chem.* **1981**, *46*, 1251−1255. [14i] For a short synthesis of octamethylnaphthalene, see: H. Hart, A. Teuerstein, *Synthesis* **1979**, 693−695.

[15] For a recent synthesis of decamethylcorannulene, see: T. J. Seiders, E. L. Elliott, G. H. Grube, J. S. Siegel, *J. Am. Chem. Soc.* **1999**, *121*, 7804−7813.

[16] [16a] X. Qiao, M. A. Padula, D. M. Ho, N. J. Vogelaar, C. E. Schutt, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1996**, *118*, 741−745. [16b] X. Qiao, D. M. Ho, R. A. Pascal, Jr, *J. Org. Chem.* **1996**, *61*, 6748. [16c] L. Tong, D. M. Ho, N. J. Vogelaar, C. E. Schutt, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1997**, *119*, 7291−7302. [16d] L. Tong, H. Lau, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **1998**, *120*, 6000−6006. [16e] R. A. Pascal, Jr., L. Barnett, X. Qiao, D. M. Ho, *J. Org. Chem.* **2000**, *65*, 7711−7717. [16f] J. Lu, J. Zhang, X. Shen, D. M. Ho, R. A. Pascal, Jr., *J. Am. Chem. Soc.* **2002**, *124*, 8035−8041.

[17] However, this does not mean that the systems are not conformationally rich since some of the polyphenyl derivatives (particularly those possessing a central core consisting of fused aromatic rings) can adopt a large number of conformations as a result of the different possible distortions of the central frame, induced by the steric interactions between the peripheral rings.

[18] W. Weissensteiner, A. Gutierrez, M. D. Radcliffe, J. Siegel, M. D. Singh, P. J. Tuohey, K. Mislow, *J. Org. Chem.* **1985**, *50*, 5822−5827.

[19] [19a] G. Hunter, J. F. Blount, J. R. Damewood, Jr., D. J. Iverson, K. Mislow, *Organometallics* **1982**, *1*, 448−453. [19b] G. Hunter, W. S. Wadsworth, Jr., K. Mislow, *Organometallics* **1982**, *1*, 968−971. [19c] J. F. Blount, G. Hunter, K. Mislow, *J. Chem. Soc., Chem. Commun.* **1984**, 170−172. [19d] G. Hunter, K. Mislow, *J. Chem. Soc., Chem. Commun.* **1984**, 172−174.

[20] [20a] J. R. Hamon, J. Y. Saillard, A. Le Beuze, M. J. McGlinchey, D. Astruc, *J. Am. Chem. Soc.* **1982**, *104*, 7549−7555. [20b] M. J. McGlinchey, J. L. Fletcher, B. G. Sayer, P. Bougeard, R. Faggiani, C. J. L. Lock, A. D. Bain, C. Rodger, E. P. Kündig, D. Astruc, J.-R. Hamon, P. Le Maux, S. Top, G. Jaouen, *J. Chem. Soc., Chem. Commun.* **1983**, 634−636. [20c] M. J. McGlinchey, P. Bougeard, B. G. Sayer, R. Hofer, C. J. L. Lock, *J. Chem. Soc., Chem. Commun.* **1984**, 789−790. [20d] B. Mailvaganam, B. G. Sayer, M. J. McGlinchey, *Organometallics* **1990**, *9*, 1089−1093.

[21] [21a] K. V. Kilway, J. S. Siegel, *J. Am. Chem. Soc.* **1991**, *113*, 2332−2333. [21b] K. V. Kilway, J. S. Siegel, *Organometallics* **1992**, *11*, 1426−1427. [21c] K. V. Kilway, J. S. Siegel, *J. Am. Chem. Soc.* **1992**, *114*, 255−261.

[22] [22a] G. Hunter, R. L. MacKay, P. Kremminger, W. Weissensteiner, *J. Chem. Soc., Dalton Trans.* **1991**, 3349−3358. [22b] J. A. Chudek, G. Hunter, R. L. MacKay, P. Kremminger, W. Weissensteiner, *J. Chem. Soc., Dalton Trans.* **1991**, 3337−3347. [22c] J. A. Chudek, G. Hunter, R. L. Mackay, G. Farber, W. Weissensteiner, *J. Organomet. Chem.* **1989**, *377*, C69−C72.

[23] J. C. Barnes, J. A. Chudek, G. Hunter, A. J. Blake, P. J. Dyson, B. F. G. Johnson, W. Weissensteiner, *J. Chem. Soc., Faraday Trans.* **1995**, *91*, 2149−2153.

[24] [24a] P. A. Downton, B. Mailvaganam, C. S. Frampton, B. G. Sayer, M. J. McGlinchey, *J. Am. Chem. Soc.* **1990**, *112*, 27. [24b] B. Mailvaganam, C. S. Frampton, S. Top, B. G. Sayer, M. J. McGlinchey, *J. Am. Chem. Soc.* **1991**, *113*, 1177−1185.

[25] See for example: [25a] R. Adams, H. C. Yuan, *Chem. Rev.* **1933**, *12*, 261−338. [25b] E. L. Eliel., S. H. Wilen, L. H. Mander, *Stereochemistry of Organic Compounds*, Wiley, NY, **1994**, p. 1142−1150. [25c]P. Lloyd-Williams, E. Giralt, *Chem. Soc. Rev.* **2001**, *30*, 145−157.

[26] N. Zuaretz, O. Golan, S. E. Biali, *J. Org. Chem.* **1991**, *56*, 2444−2449.

[27] V. Marks, H. E. Gottlieb, S. E. Biali, *J. Am. Chem. Soc.* **1997**, *119*, 9672−9679.

[28] [28a] R. Willem, H. Pepermans, C. Hoogzand, K. Hallenga, M. Gielen, *J. Am. Chem. Soc.* **1981**, *103*, 2297−2306. [28b] See also: S. E. Biali, A. B. Buda, K. Mislow, *J. Org. Chem.* **1988**, *53*, 1289−1294.

[29] The labeling of the conformers of **4** (i.e., "a", "f", etc) in Figure 3 is that used in ref.[27]

[30] [30a] V. Marks, H. E. Gottlieb, S. E. Biali, unpublished results. [30b]V. Marks, H. E. Gottlieb, A. Melman, G. Byk, S. Cohen, S. E. Biali, *J. Org. Chem.* **2001**, *66*, 6711−6718.

[31] M. Taha, V. Marks, H. E. Gottlieb, S. E. Biali, *J. Org. Chem.* **2000**, *65*, 8621−8628.

[32] T. Takahashi, R. Hara, Y. Nishihara, M. Kotora, *J. Am. Chem. Soc.* **1996**, *118*, 5154−5155.

[33] W. Kaim, H. Bock, *Chem. Ber.* **1978**, *111*, 3585.

[34] The anions and cations derived from **9** have been the subject of several studies. See for example: [34a] H. Hart, A. Teuerstein, M. A. Babin, *J. Am. Chem. Soc.* **1981**, *103*, 903−906. [34b] J. W. Bausch, P. S. Gregory, G. A. Olah, G. K. S. Prakash, P. v. R. Schleyer, G. A. Segal, *J. Am. Chem. Soc.* **1989**, *111*, 3633−3640.

[35] In the absence of dienophiles benzyne can dimerize to biphenylene. For a review on the chemistry of benzyne and related compounds see: H. Hart in: *The Chemistry of Functional Groups: Supplement C. The Chemistry of Triple Bonded Functional Groups* (Ed.: S. Patai), Wiley, Chichester, **1994**, chapter 18.

[36] For reviews on biphenylene, see [36a] F. Vögtle, *Fascinating Molecules in Organic Chemistry*, Wiley, Chichester, **1992**, p. 110−125. [36b] M. K. Shepherd, *Cyclobutarenes: The Chemistry of Benzocyclobutene, Biphenylene and Related Compounds*, Elsevier, Amsterdam, **1991**.

[37] [37a] L. I. Smith, C. O. Guss, *J. Am. Chem. Soc.* **1940**, *62*, 2625−2629. [37b] L. I. Smith, C. O. Guss, *J. Am. Chem. Soc.* **1940**, *62*, 2631−2635. [37c] L. I. Smith, C. O. Guss, *J. Am. Chem. Soc.* **1940**, *62*, 2635−2638.

[38] [38a] F. A. L. Anet, V. J. Basus, *J. Magn. Reson.* **1978**, *32*, 339−343. [38b] S. P. Adams, H. W. Whitlock, *J. Am. Chem. Soc.* **1982**, *104*, 1602−1611. [38c] D. Casarini, L. Lunazzi, D. Macciantelli, *J. Chem. Soc., Perkin Trans. 2* **1985**, 1839−1844. [38d] S. E. Biali, V. Böhmer, S. Cohen, G. Ferguson, C. Grüttner, F. Grynszpan, E. F. Paulus, I. Thondorf, W. Vogt, *J. Am. Chem. Soc.* **1996**, *118*, 12938−12949.

[39] [39a] T. C. W. Mak, J. Trotter, *J. Chem. Soc.* **1962**, 1−8. [39b] J. Waser, C. S. Lu, *J. Am. Chem. Soc.* **1944**, *66*, 2035−2042. [39c] J. K. Fawcett, J. Trotter, *Acta Crystallogr.* **1966**, *20*, 87−93. [39d] For an early electron diffraction study of biphenylene, see: J. Waser, V. Schomaker, *J. Am. Chem. Soc.* **1943**, *65*, 1451−1455.

[40] For a study of the crystal structure of octamethylbiphenylene, see: J. B. Jones, D. S. Brown, K. A. Hales, A. G. Massey, *Acta Crystallogr., Sect. C* **1988**, *44*, 1757−1759.

[41] G. A. Sim, *Acta Crystallogr., Sect. B* **1982**, *38*, 623−625. See also: S. Simaan, V. Marks, H. E. Gottlieb, A. Stanger, S. E. Biali, *J. Org. Chem.* **2003**, *68*, 637−640.

[42] V. Marks, M. Nahmany, H. E. Gottlieb, S. E. Biali, *J. Org. Chem.* **2002**, *67*, 7898.

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