Total Syntheses and Structures of Angular [6]- and [7]Phenylene: The First Helical Phenylenes (Heliphenes)**

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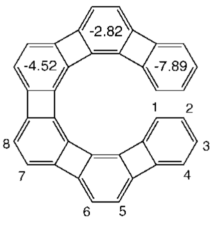
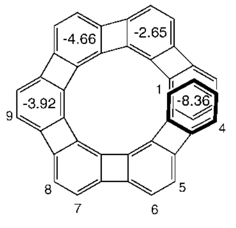
Helically extended conjugated π systems are of great interest in the design and synthesis of novel molecules and materials with a variety of unusual properties and applications.[1] The [*N*]phenylenes,[2] comprised of alternating *N* benzene units fused to $N-1$ cyclobutadiene rings, can be regarded as highly σ- and π-activated "spacer" polycyclic benzenoid hydrocarbons, long arrays of which may furnish interesting structures endowed with small band gaps.[3] Among their various topologies, the angular variant is unusual, in as much as it becomes helical for $N > 5$, a feature that has attracted the attention of theoretical chemists.[4] So far, unbranched phenylenes could be synthesized only up to $N = 5$.[2,5] We disclose herein the synthesis of the next two higher members of the series, the first helical phenylenes (heliphenes), **1a**, $N = 6$, and **2a**, $N = 7$ [nucleus-independent chemical shift (NICS)(0) values are given inside the rings], their X-ray structures (and comparison with the structure of angular [5]phenylene, **11**), and their ease of enantiomerization.

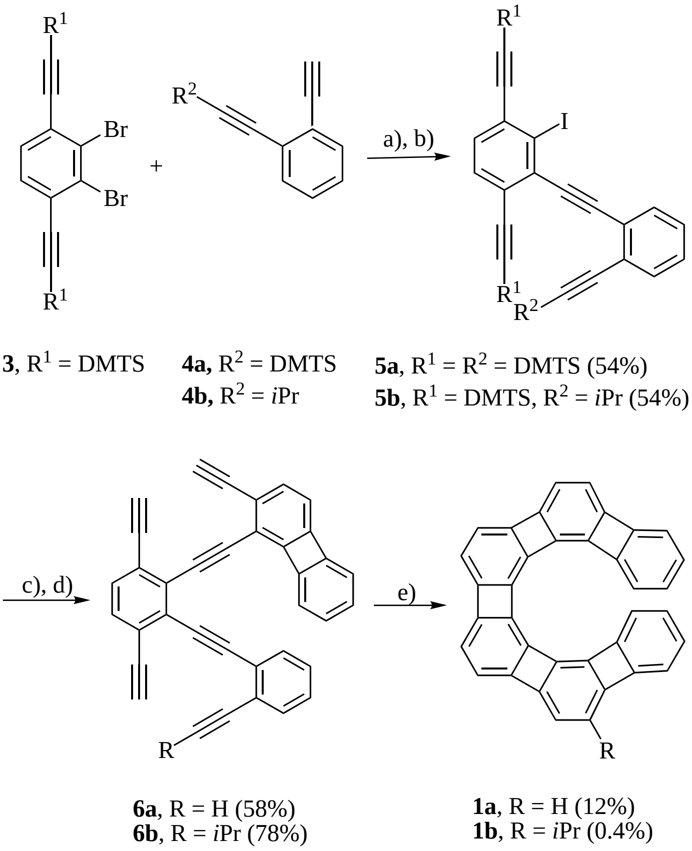


1a



2a

Consideration of a cobalt-based cyclization strategy[2a,5,6] to the target molecules ruled out an adaptation of the single-cyclotrimerization approach used in the construction of their lower benzocyclobutadienologues, because of the absence of suitably functionalized angular [3]phenylene derivatives. Instead, a double-cyclization protocol was followed, in which the requisite hexaynes were derived by judicious Pd-catalyzed alkynylations of the readily available central core building block **3**.[7] For **1** (Scheme 1), appendages **4a** and **7** had been made previously,[2a,5b] and **4b** was prepared by employing 3-methyl-1-butyne as one of the alkyne units (78% from 1-bromo-2-iodobenzene). For **2** (Scheme 2), **8**[7] and **9a**[5b] were known, **9b** was constructed using 3-methoxy-1-propyne (77%), and **9c** and **9d** were the end result of the same sequence of steps that lead to **9a**, but starting from commercial 1,2-dibromo-4,5-dimethylbenzene (seven steps, 4.6% and 3.9% yield, respectively). The assembly of **10e** by the method used for **10b** failed. A modified protocol was successful in which the first biphenylene appendage was introduced by coupling silyl-protected 1,2,4-triethynyl-3-iodobenzene[7] with 1-ethynyl-2-(2-DMTS-ethynyl-6,7-dimethylbiphenylene (made in two steps from **9c**, 74%) in 72% yield, and reacting the product (after desilylation) with **9d** as in Scheme 2 (three



Scheme 1. a) 4–6% $[Pd(PPh_3)_2Cl_2]$, 4–6% CuI, Et_3N, 70–85 °C, 14–22 h; b) 1) BuLi, Et_2O, −78 °C, 2) I_2, Et_2O, −78 °C; c) 1-ethynyl-2-(2-DMTS-ethynyl)biphenylene (**7**), 10% $[Pd(PPh_3)_2Cl_2]$, 10% CuI, Et_3N, 85 °C, 22 h; d) $Bu_4N^+F^-$ (5–7 equiv), THF, 23 °C, 40 min; e) $[CpCo(CO)_2]$ (2.5–3.5 equiv), *m*-xylene, *hν*, △, 30 min. DMTS = $SiMe_2(CMe_2CHMe_2)$ (dimethylthexylsilyl).

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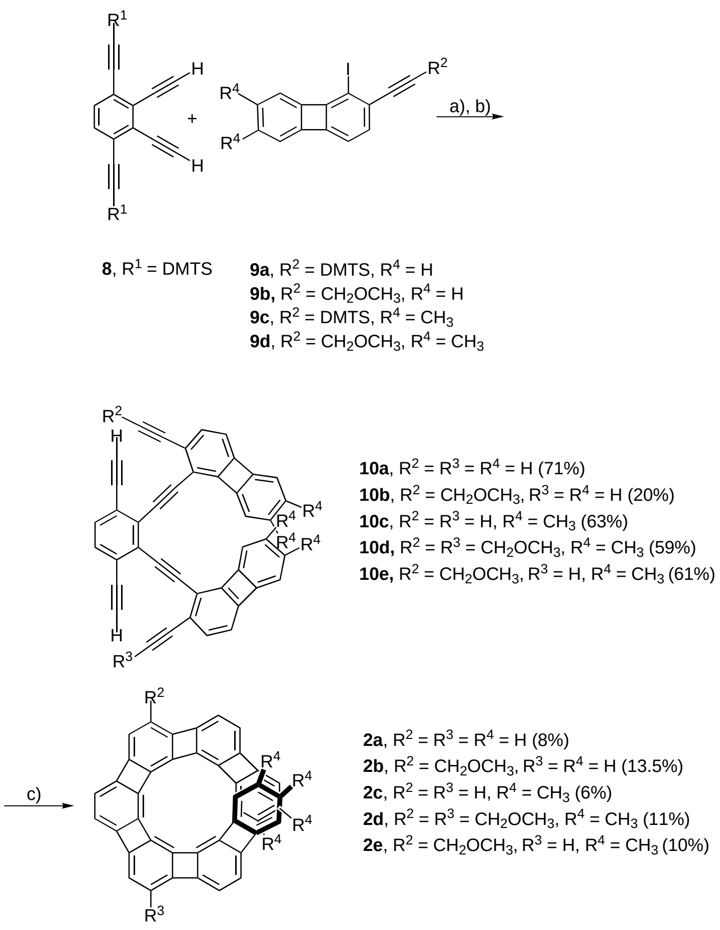

Scheme 2. a) For **10a**, **c**, and **d**: **9** (2 equiv), 5–16% $[Pd(PPh_3)_2Cl_2]$, 5–20% CuI, Et_3N, 50–75 °C, 5–22 h; for **10b**: same conditions, but 1) **9a** (1 equiv), 2) **9b** (1 equiv); for **10e**: see text; b) $Bu_4N^+F^-$ (5–7 equiv), THF, 23 °C, 40 min; c) $[CpCo(CO)_2]$ (4–15 equiv), *m*-xylene, *hν*, △, 30 min.

Table 1. Selected physical data for **1a**, **2a**, and **2c**.[8][a]

1a: light orange solid; MS (70 eV): *m/z* (%): 448 ([M^+], 100), 446 (46), 444 (25); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 7.00$–6.95 (m, 2H, H3), 6.88 (td, $J = 7.2$, 0.8 Hz, 2H, H1), 6.84–6.82 (m, 4H, H2, H4), 6.49 (s, 4H, H7, H8), 6.34 ppm (s, 4H, H5, H6); ^{1}H NMR (400 MHz, C_6D_6): $\delta = 6.74$–6.66 (m, 4H), 6.61–6.54 (m, 4H), 6.20 (d, $J = 6.8$ Hz, 2H), 6.16 (d, $J = 6.8$ Hz, 2H), 6.09 ppm (s, 4H); UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 236 (sh, 4.46), 272 (sh, 4.43), 281 (4.66), 309 (4.35), 321 (4.32), 350 (4.19), 374 (4.02), 444 (3.61), 470 (3.57), 491 nm (sh 3.40). High-resolution MS calcd for $C_{36}H_{16}$: 448.1252; found: 448.1240.

2a: orange solid; MS (70 eV): *m/z* (%): 522 ([M^+], 100); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 6.77$ (dt, $J = 6.8$, 0.8 Hz, 2H, H1), 6.64 (m, 2H, H3), 6.63 (m, 2H, H4), 6.54 (m, 2H, H2), 6.49 (s, 4H, H7, H8), 6.42 (s, 2H, H9), 6.32 (d, $J = 6.8$ Hz, 2H, H6), 6.27 ppm (d, $J = 6.8$ Hz, 2H, H5); UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 247 (5.03), 292 (sh, 4.95), 306 (5.16), 367 (4.44), 389 (4.39), 430 (3.99), 457 (3.99), 485 (3.86), 503 nm (sh, 3.48). High-resolution MS calcd for $C_{42}H_{18}$: 522.1408; found: 522.1403.

2c: orange solid; MS (70 eV): *m/z* (%): 578 ([M^+], 100); ^{1}H NMR (400 MHz, CD_2Cl_2): $\delta = 6.62$ (s, 2H, H1), 6.45 (s, 4H, H7, H8), 6.42 (s, 2H, H4), 6.37 (s, 2H, H9), 6.24 (d, $J = 6.8$ Hz, 2H, H6), 6.11 (d, $J = 6.8$ Hz, 2H, H5), 1.91 (s, 6H), 1.87 ppm (s, 6H); UV/Vis (CH_2Cl_2): λ_{max} (lgε) = 253 (5.11), 266 (sh, 5.06), 291 (5.04), 312 (5.15), 377 (4.56), 393 (4.49), 459 (4.08), 486 (3.91), 505 nm (sh, 3.70); High-resolution MS calcd for $C_{46}H_{26}$: 578.2034; found: 578.2049.

[a] For the labeling of the protons see the structural formulae.

steps, 64%). Noteworthy is the desymmetrization of the ultimate starting material, 1,2,3,4-tetrabromobenzene, to the hexaalkynyl systems **6** and **10**. Angular [5]phenylene (**11**) was resynthesized[5b] according to the double-cyclization strategy in Scheme 1 starting from **3** and **4a** (three steps, 18%).

Systems **1** and **2** are orange solids,[8] moderately stable to air (except in solution, but sufficiently stable to be isolable by column chromatography on silica with hexane/CH_2Cl_2 gradient), and moderately soluble in ordinary organic solvents. The spectral data (Table 1) highlight some of their extraordinary features. Thus, in the EI mass spectra of **1a** (and **1b**) diagnostic single and double dehydrogenations [M^+, M^+-2, M^+-4] are evident (unique for the entire series), suggesting potentially facile annealing to antikekulene.[7] The electronic spectra reveal the same characteristic patterns as those of the lower phenylene homologues[2a] but shifted to increasingly longer wavelengths. Thus, the longest wavelength peaks along the series angular [3]- to [6]phenylene are displaced by relatively constant increments of about 20–22 nm. Interestingly, this value is approximately halved (12 nm) when going from **1a** to **2a**, perhaps an indication of convergence with the effective conjugation length in polyheliphene.[9]

The ^{1}H NMR spectra could be assigned by comparison with those of the lower angular phenylenes[2a,5b] and calculated spectra,[4,10,12] and utilizing the simplifying effects of substitution in the alkylated derivatives (Schemes 1 and 2). Two observations are noteworthy. First, as in all angular phenylenes, the terminal six-membered rings are the most diatropic (aromatic), the penultimate rings the most cyclohexatrienic. However, while the proximity of the former in **1** ($\delta_{avg} = 6.88$ ppm; cf. **11**, $\delta_{avg} = 6.95$ ppm) has an almost negligible effect on chemical shifts (pointing to the presence of a nonplanar structure), in **2** all terminal hydrogens are significantly shielded ($\delta_{avg} = 6.64$ ppm) due to the overlap stacking of the corresponding rings, as in the helicenes.[11] Second, we had noted previously[2a,5] that the internal benzene units reveal attenuated ring currents, the degree of which seems to alternate, in agreement with NICS data.[10,12] A didactically useful interpretation takes recourse to Clar's notion of the electron sextet.[13] Thus, to maximize aromaticity in the six- and minimize antiaromaticity in the four-membered rings, the extent of bond localization should alternate, starting from a minimum value at the termini. This picture explains why angular [3]phenylene has the most shielded internal (cyclohexatrienic) hydrogens in the series ($\delta = 6.18$ ppm), why in **11** the hydrogens of the central ring resonate at lower field ($\delta = 6.51$ ppm) than their neighbors ($\delta = 6.29$ ppm), and why the internal hydrogens in angular [4]phenylene have chemical shifts that are intermediate ($\delta = 6.31$ ppm). Gratifyingly, this simple model is consistent with the data for **1** and **2** (Table 1). Perhaps most impressive is that in **2** (as opposed to **11**) the central benzene ring hydrogens are *shielded* (for **2a**: $\delta = 6.42$ ppm) relative to their neighbors ($\delta = 6.49$ ppm).

The X-ray crystal structures of **1a**, **2a**, and **11** are shown in Figure 1.[14] The compounds exhibit bond parameters that are in excellent agreement with calculations.[4,10] Visually most dramatic is the sudden topological change from relatively planar to helical on going from **11** to **1a** and then **2a**. The phenylenes are readily deformed[15] and, consequently, the calculated "helical strain" in **1a** (BLYP/6-31G*,

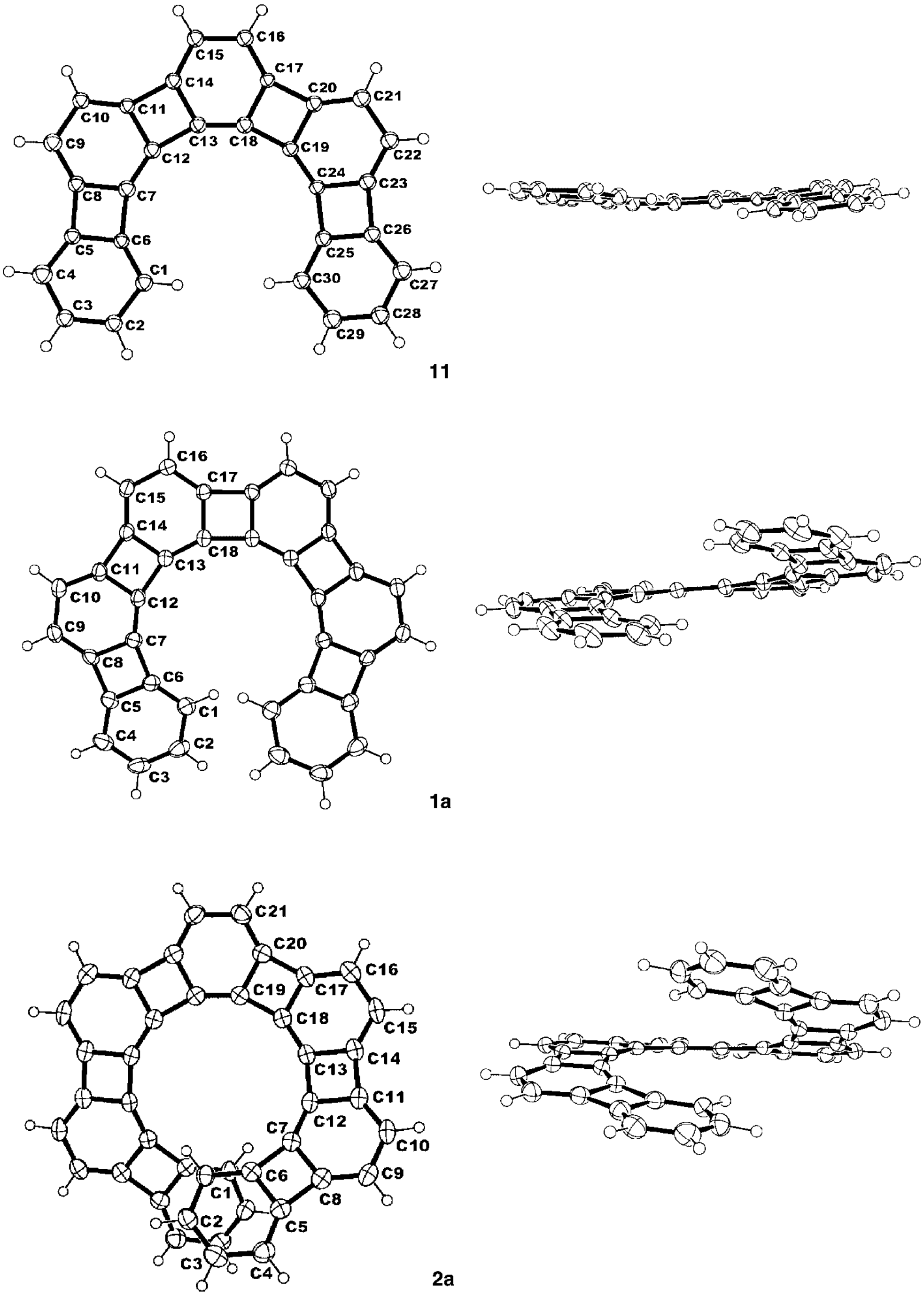

Figure 1. X-ray crystal structures of **11** (from CH_2Cl_2/*m*-xylene by diffusion), **1a** (from CH_2Cl_2/benzene by diffusion), and **2a** (from CH_2Cl_2/benzene by diffusion); views from above (left) and the side (right).

3.2 kcal mol^{-1}) and **2a** (5.4 kcal mol^{-1}) is small.[4] In agreement with the NMR data, the extent of bond localization alternates. Using 1,2-dimethylenecyclobutene as a 100% reference,[16] the percent bond fixations in the six-membered rings (starting from the terminus) amount to (for **11**) 31, 68, 48% [shortest bond 1.33(1) Å, longest bond 1.46(1) Å], (for **1a**) 15, 55, 51% [1.346(4), 1.449(3) Å], and (for **2a**) 23, 53, 47, and 50% [1.348(3) Å, 1.460(3) Å]. In **11**, the distance between H1 and H30 (numbering in Figure 1) is 2.68 Å, beyond van der Waals contact, yet the molecule is not completely planar but adopts a prehelical conformation with dihedral angles between the planes of adjacent rings ranging from 0.82° to 5.18°. The calculated lowest-frequency vibrational mode is $a_2 = 18\,\mathrm{cm}^{-1}$,[10] hence this observed distortion is certainly due to crystal packing forces.[15] The terminal ring centroids are separated by 7.41 Å, the corresponding interplanar angle is 14.3°. Taking the central six-membered ring as a reference, the inner prehelix (C1, C6, C7, C12, C13, etc.) climbs 0.64 Å and turns in plane by 305.9°.

Helical **1a** has twofold symmetry and crystallizes as stacked pairs of each enantiomer. The closest contact is between H1 and H1′ at 2.36 Å (calculated 2.42 Å),[10] considerably more than that in the planar structure (calculated 1.85 Å).[4] The terminal ring centroids are separated by 5.62 Å (5.87 Å),[10] and the corresponding interplanar angle is 22.8° (27.2°; cf. these values for [6]helicene: 4.44 Å, 58.5°[17]). The interplanar angles between consecutive six- and four-membered rings are 1.49, 3.35, 2.41, 3.28, and 3.28°, describing a slightly uneven helical turn. Taking the central four-membered ring as a reference, the inner helix climbs 2.16 Å (2.30 Å) and turns in plane by 337.3° (332.4°) (for [6]helicene: 3.20 Å, 314.3°).[17]

Heliphene **2a** is centrosymmetric and crystallizes as alternating right- and left-handed helices. The closest contact is between C1 and C1′ [3.31 Å (3.64 Å)] with a terminal ring centroid distance of 4.07 Å (4.54 Å) and corresponding interplanar angle of 30.1° (40.6°; cf. [7]helicene, 3.83 Å, 32.3°[18]). The interplanar angles between consecutive six- and four-membered rings are 2.25, 2.99, 4.01, 6.66, 4.50, and 3.88 Å, more uneven and larger in size than those in **1a**. Taking the central six-membered ring as a reference, the inner helix climbs 3.29 Å (3.64 Å) and turns in plane by 361.3° (361.6°; [7]helicene 3.75 Å and 380.8°[18]).

The unusual electronic nature of the heliphenes suggests exceptional chiroptical properties of the enantiomers.[1,11,19] Therefore, the feasibility of resolving **1a** and **2a** was probed.

While the barriers to enantiomerization in the related [6]- (36.2 kcal mol^{-1}) and [7]helicene (41.7 kcal mol^{-1})[11] are relatively high, the bond length patterns in the angular phenylenes are distorted from perfect symmetry in such a way as to spread the termini (Figure 1).[7] That effect, in conjunction with the phenylenes' flexible frames,[15] suggests lesser configurational stability. Indeed, the calculated inversion barrier for **1a** (BLYP/6-31G*) is low—3.6 kcal mol^{-1}.[4] For **2a**, AM1 calculations, which reproduce experimental findings well in the helicenes,[20] gave a more encouraging 17.0 kcal mol^{-1} (C_s symmetry). To obtain experimental numbers, the heliphene backbones were decorated with substituents bearing potentially diastereotopic units for ^{1}H NMR experiments (Schemes 1 and 2). In accord with the theoretical estimate above, the two methyl groups in **1b** did not decoalesce at the (solubility) limiting temperature of −75 °C (400 MHz, [D$_8$]toluene). We then turned to the more promising [7]phenylene derivative incorporating a synthetically more readily accessible methoxymethyl group. Heliphene **2b** showed decoalescence of the methylene hydrogen signals to an AB quartet at −27 °C (400 MHz, $\Delta\nu_{max} = 13.5$ Hz, [D$_8$]toluene), corresponding to $\Delta G^{\ddagger} = 12.6 \pm 0.4$ kcal mol^{-1}, a surprisingly low value (cf. [6]- and [7]helicene: $\Delta G^{\ddagger}_{-27\,^{o}\mathrm{C}} = 36.2$ and 41.7 kcal mol^{-1}, respectively),[11c] obviating attempts to resolve the molecule.

Helicenes with methyl substituents on the terminal rings exhibit higher barriers to enantiomerization than the parent systems.[11,20] Consequently, the tetramethylated **2c** and, subsequently, its methoxymethyl derivatives **2d** and the less symmetrical **2e** were constructed (Scheme 2).[8] To our astonishment, the NMR spectra of **2d** and **2e** did not exhibit any changes in the appearance of the methylene singlet at temperatures as low as −70 °C (400 MHz, [D$_8$]toluene). An explanation for this behavior may be that in the flexible heliphenes methyl repulsion raises the ground state energy more than that of the transition state along the pathway to enantiomerization by effectively enlarging the helical climb.[21] This consideration and the fact that **1** and **2** constitute only the first two members of the helical series provided the impetus for tackling the synthetic challenge of assembling higher heliphene systems.[22]

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[10] At the B3LYP/6-31G* level; the maximum and (in parentheses) average deviations of the calculated from the experimental bond lengths are for **11**: 0.036 (0.012) Å; **1a**: 0.022 (0.0098) Å; **2a**: 0.022 (0.0081) Å.

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[14] X-ray structure analyses: **1a** (synchrotron radiation, Station 9.8, SRS Daresbury): crystal size $0.28 \times 0.01 \times 0.01$ mm^3, space group *Pbcn* (no. 60), scan range $4.70 < 2\theta < 44.5°$, $a = 3.8058(8)$, $b = 24.905(5)$, $c = 22.774(5)$ Å, $V = 2158.6(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.380$ g cm^{-3}, $\mu(\lambda = 0.6877$ Å$) = 0.79$ cm^{-1}, 4916 total reflections, 1562 unique reflections ($R_{int} = 0.0436$) at −53 °C, of which 1118 were taken as observed [$F^2 > 2.00\sigma(F^2)$], conventional $R_1 = 0.0514$, $R_w = 0.1197$ (on all 1562 F^2 data). **2a**: crystal size $0.39 \times 0.40 \times 0.03$ mm^3, space group *P*2/*c* (no. 13), scan range $3.00 < 2\theta < 51.3°$, $a = 9.061(1)$, $b = 14.632(1)$, $c = 9.8957(1)$, $\beta = 94.392(2)$ Å, $V = 1308.2(8)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.327$ g cm^{-3}, $\mu(\mathrm{Mo_{K\alpha}}) = 0.75$ cm^{-1}, 2300 unique reflections at −126 °C, of which 1110 were taken as observed [$F_o > 3.00\sigma(F_o)$], $R = 0.033$, $R_w = 0.034$. **11**: crystal size $0.17 \times 0.07 \times 0.02$ mm^3, space group $P2_1/c$ (no. 14), scan range $3 < 2\theta < 51.30°$, $a = 11.487(3)$, $b = 5.173(1)$, $c = 30.914(8)$ Å, $\beta = 99.716(5)°$, $V = 1810.6(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.37$ g cm^{-3}, $\mu = 0.78$ cm^{-1}, 3376 unique reflections at −148 °C, of which 600 were taken as observed [$F_o > 2.50\sigma(F_o)$], $R = 0.044$, $R_w = 0.040$. CCDC-180982 (**11**), -180983 (**1a**), and -180984 (**2a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit @ccdc.cam.ac.uk).

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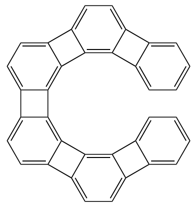
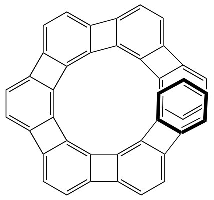
Total Syntheses of Angular [7]-, [8]-, and [9]Phenylene by Triple Cobalt-Catalyzed Cycloisomerization: Remarkably Flexible Heliphenes**

Sangdon Han, D. Ryan Anderson, Andrew D. Bond, Hiufung V. Chu, Raymond L. Disch, Daniel Holmes, Jerome M. Schulman, Simon J. Teat, K. Peter C. Vollhardt,* and Glenn D. Whitener

We have reported on the total syntheses of the first helical phenylenes (heliphenes), angular [6]- (**1**) and [7]phenylene (**2**), by a double cobalt-catalyzed cyclotrimerization strategy.[1] These hydrocarbons are the highest members of the, so far, five angular phenylene systems and, with **2**, match the current size limit of all phenylenes.[2] Their properties are intriguing, including unusual mass spectrometric fragmentations for **1**, a strongly attenuated bathochromic increment in the UV spectrum of **2**, shielding of the terminal rings in **2** as a result of spatial overlap, alternating ring current intensities along the angular frame, X-ray crystallographic data that detail the helical and σ-π distortive features, and, most surprisingly, an unusually low barrier for the enantiomerization of **2**, which decreases on introduction of terminal substituents. To better understand these results, the construction of even higher members of the series was deemed imperative.

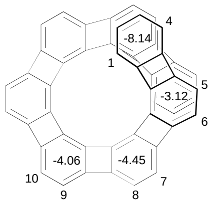


1

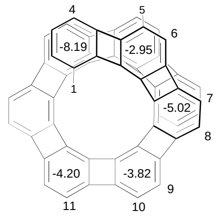


2

Here, we describe the total synthesis of angular [8]- (**3a**) and [9]phenylene (**4a**) [nucleus-independent chemical shift (NICS)(0) values are given inside the rings], together with another assembly of [7]phenylene (**2**), by an unprecedented triple cobalt-catalyzed cycloisomerization protocol, the X-ray structure of **3a**, and experiments addressing the conformational flexibility of the targets.



3a



4a

Retrosynthetic analysis of **3** and **4** along the lines used in the formation of the lower benzocyclobutadienologues **1** and **2**[1] proved problematic because of the absence of suitably functionalized angular [3]phenylene building blocks. As a result, a challenging disconnection of three inner benzene rings was contemplated. This approach would require the stitching together of the corresponding nonayne precursors and was first tested on a known final product, **2** (Scheme 1). For this purpose, the scaffold of the crucial intermediate **7** was put together by linking two units of **5**[1] with a C_2 bridge in a stepwise manner via **6**.[3] Gratifyingly, cobalt-catalyzed cyclization of **7** gave **2**. While the yield of this transformation is modest, it should be viewed within the context of what it accomplishes, namely the generation of the desired helical topology by forming nine rings in one step, including all six of the component cyclobutadienes with an associated estimated strain of about 300 kcal mol^{-1}![4]

Encouraged by these results, we employed the same strategy en route to **3** (Scheme 2) and **4** (Scheme 3). Triyne **8**[5] and the requisite biphenylene reagents **11**,[6] **12**,[1] and **16**[6] were known, allowing for the iterative Pd-catalyzed build-up of the target nonaynes **10** and **15**. Attempts to shorten the sequences depicted (in particular, exploiting the symmetry inherent in **7** and **15**) were less effective.

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