Synthesis and Structures of [2_n](2,7)Naphthalenophanes (n=2–4)

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Abstract

Reductive coupling of 2,7-bis(bromomethyl)naphthalene using phenyllithium gave *anti*-[2_2](2,7)naphthalenophane, [2_3]- and [2_4](2,7)naphthalenophanes, the distribution of which was dependent on the reaction conditions. The structures of the first compound was established by X-ray crystallographic analysis. On the basis of the similarity between the NMR and UV spectra of [2_3](2,7)naphthalenophane with those reported for *syn*-[2_2](2,7)naphthalenophane, we conclude that the compound originally assigned to be *syn*-**4** was in fact **6**.

Key words

cyclophanes, aromatic compounds, reductive coupling, X-ray crystal structure analysis

Introduction

[2_2]Metacyclophane (*anti*-**1** and *syn*-**1**) among others is one of representative [2_2]cyclophane isomers in view of its structural characteristics including conformational isomerism between *anti* and *syn* isomers and chemical shift perturbation due to anisotropic shielding in ^{1}H NMR and steric compression in ^{13}C NMR spectra, both which are caused by proximate benzene ring in the molecule.[1] Although *anti*-**1** was synthesized easily, *syn*-**1** turned out to be elusive due to facile ring inversion to *anti*-**1**. The first derivative of *syn*-**1** was synthesized by Boekelheide by introducing an electron-withdrawing group to one of the benzene rings of **1**, thereby stabilizing the *syn* isomer by intramolecular charge-transfer interaction.[2] Parent hydrocarbon *syn*-**1** was synthesized for the first time by Mitchell in an elegant fashion by taking advantage of the electron-withdrawing effect of $Cr(CO)_3$ group coordinated to one of the benzene rings and it was oxidatively removed at the final stage of the synthesis.[3] *Syn*-**1** thus obtained was proven to isomerize to *anti*-**1** quickly with an activation energy of 18.4 kcal/mol. Because derivatives of [2_2]metacyclophanediene (**2**), undergo ring closure isomerization upon heating or photo-irradiation to form the corresponding bridged [14]annulene framework (i.e. dihydropyrene (**3**)) and they revert to **2** by photochemical ring opening, these compounds constitute as a photochromic system that can also be applied to multi-stage systems.[4] Moreover, the bridged [14]annulenes **3** bearing internal alkyl groups serve as a tool to evaluate tropicity of a cyclic conjugated system fused

to the annulene ring by monitoring the chemical shift of the internal methyl groups as a probe.[5] Reg Mitchell has made significant contributions to the rich chemistry of [2_2]metacyclophane and its congeners mentioned above.

Insert Chart 1 here.

Cyclophanes bearing condensed aromatic rings are of interest not only in terms of the conformational and physical properties due to proximate aromatic rings but also as host molecules with large cavities and precursors of topologically interesting polycyclic aromatic compounds.[6] However, in contrast to extensively investigated [2_2]metacyclophanes, little has been studied for the close cousin, [2_2](2,7)naphthalenophane (**4**). The first synthesis was reported as early as 1951 as a precursor of coronene based on the Wurtz coupling of 2,7-bis(bromomethyl)naphthalene (**5**) with sodium metal.[7] This was followed by an improved synthesis using phenyllithium in the next year.[8] In addition to **4**, isolation of a small amount of [2_3](2,7)naphthalenophane (**6**) was reported yet with limited spectral information.[9] Further improvement was achieved by using Stevens rearrangement of dithia[3.3](2,7)naphthalenophane (**8**), yielding bis(thiomethyl)naphthalenophane **9** as a mixture of regio- and stereoisomers (Scheme 1).[10] Desulphurization of **9** gave **4** whose structure was assigned *anti* on the basis of ^{1}H NMR spectrum. Methylation or oxidation followed by elimination of **8** gave diene **10**, which upon photo-irradiation in the presence of iodine afforded coronene quantitatively.[10] It is worth mentioning that dianion and dication of

tetramethyl-substituted derivative of **10** are predicted theoretically to exhibit two-electron-four-center bonding between the naphthalene cores.[11] On the other hand, Sato and co-workers separated three products of the reductive coupling of **5** from which two were assigned to *anti*-**4** and *syn*-**4** on the basis of mass and NMR spectra.[12] In view of the facile ring inversion of *syn*-**1** to *anti*-**1** in the [2.2]metacyclophane system, isolation of *syn*-**4** is worthy of note. Hence, not only because of the inherent interest in *anti*-**4** and *syn*-**4** but also as potential precursors to coronene-related aromatic compounds, we reexamined preparation of *anti*-**4** and *syn*-**4** by reaction of **5** with phenyllithium. As a result, we obtained *anti*-**4**, [2_3](2,7)naphthalenophane (**6**), and [2_4](2,7)naphthalenophane (**7**), while *syn*-**4** was not detected. The structures of *anti*-**4** was established by X-ray crystallographic analysis and those of **6** and **7** were elucidated on the basis of the spectral data. Because of the similarity between the NMR and UV spectra of **6** with those reported for *syn*-**4**, we conclude that the compound originally assigned to be *syn*-**4** was in fact **6**.

Insert Chart 2 and Scheme 1 here.

Experimental

Bis(bromomethyl)naphthalene (**5**) was prepared according to the reported procedures.[13] Phenyllithiun solution in hexane was purchased from Aldrich. NMR spectra were measured at 400 MHz for ^{1}H and 100 MHz for ^{13}C in $CDCl_3$ at 30 °C with its residual chloroform peaks at

7.25 and 77.0 ppm as the references, respectively. More details are described in Supporting Information.

Reaction of 5 with PhLi (procedure 1): In a 500 mL flame-dried three-necked round-bottom flask equipped with a stirrer bar, compound **5** (4.00 g, 12.8 mmol) in benzene (260 mL) was added dropwise over 30 h to a 1.08 M PhLi solution in hexane (30 mL) under argon. The reaction mixture was heated at 60 °C and stirred for ca. 3 h before the reaction was quenched by addition of water. The mixture was extracted with $CHCl_3$, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Separation of the products was done by column chromatography (SiO_2, hexane/$CHCl_3$ 5:1) followed by GPC to afford *anti*-**4** (428 mg, 1.39 mmol, 22%), **6** (49.6 mg, 0.107 mmol, 2%), and **7** (7.90 mg, 0.0128 mmol, 0.4%).

***anti*-4**: colorless solid, mp 221.0-221.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ 7.79 (d, J = 8.8 Hz, 4H), 7.27 (dd, J = 8.2, 1.4 Hz, 4H), 5.04 (d, J = 1.6 Hz, 4H), 3.21 (m, 4H), 2.26 (m, 4H); ^{13}C NMR (100MHz, $CDCl_3$, 30 °C) δ 136.1, 133.2, 131.8, 130.9, 127.7, 126.7, 38.9; IR (KBr, cm^{-1}) 3056, 3036, 3014, 2941, 2921, 2852, 1920, 1907, 1898, 1825, 1781, 1623, 1600, 1509, 1458, 1439, 1353, 1283, 1256, 1180, 1168, 1146, 1119, 989, 962, 947, 921, 863, 832, 686, 658, 636, 491, 461; HRMS (FAB) *m/z* calcd for $C_{24}H_{20}$: 308.1565, found 308.1566 (M^+).

6: colorless solid, mp 241.5-242.5 °C.; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ 7.65 (d, J = 8.4 Hz, 6H), 7.27 (dd, J = 8.6 , 1.8 Hz, 6H), 6.96 (s, 6H), 3.17 (s, 12 H); ^{13}C NMR (100MHz,

$CDCl_3$, 30 °C) δ 138.4, 133.7, 130.8, 127.9, 127.13, 127.06, 36.3; IR (KBr, cm^{-1}) 3044, 3012, 2920, 2897, 2854, 1733, 1717, 1685, 1636, 1607, 1509, 1457, 1439, 1354, 1273, 1213, 1183, 1134, 1092, 1038, 920, 909, 832, 764, 658, 607, 477; MS (FAB) *m/z* 462.2 (M^+), HRMS (FAB) *m/z* calcd for $C_{36}H_{30}$: 462.2348, found 462.2346 (M^+).

7: colorless solid, mp 195.0-196.0 °C.; ^{1}H NMR (400 MHz, $CDCl_3$, 30 °C) δ 7.72 (d, *J* = 8.4 Hz, 8H), 7.24 (dd, *J* = 8.4 , 1.6 Hz, 8H), 6.70 (s, 8H), 3.02 (s, 16 H); ^{13}C NMR (100MHz, $CDCl_3$, 30 °C) δ 138.7, 133.4, 130.8, 127.6, 127.2, 126.8, 37.6; MS (FAB) *m/z* 616.3 (M^+), HRMS (FAB) *m/z* calcd for $C_{48}H_{40}$: 616.3130, found 616.3132 (M^+).

Reaction of 5 with PhLi (procedure 2): In a 30 mL flame-dried three-necked round-bottom flask equipped with a stirrer bar, a 1.09 M PhLi solution in hexane (1.49 mL) was added dropwise over 8 min to a solution of **5** (200 mg, 0.642 mmol) in benzene (260 mL) under nitrogen. The reaction mixture was heated at 60 °C and stirred for 3.5 h before the reaction was quenched by the addition of purified water. The crude reaction mixture was extracted with $CHCl_3$, the combined extracts were washed with brine and dried ($MgSO_4$), and the solvent was removed under reduced pressure. Separation of the products by column chromatography (SiO_2, hexane/$CHCl_3$ 2:1) afforded *anti*-**4** (10.1 mg, 0.0328 mmol, 10%) and **6** (15.3 mg, 0.0331 mmol, 16%).

Results and discussion

The distribution of products *anti*-**4**, **6**, and **7** was dependent on the reaction conditions. Typically addition of a benzene solution of **5** to PhLi gave *anti*-**4** as the major product (22%) together with small amounts of [2_3]naphthalenophane **6** and [2_4]naphthalenophane **7**. On the other hand, the reverse addition gave **6** as the major component (16%) together with *anti*-**4** (10%). The products were separated by chromatography on silica gel and GPC.

The last eluted (the smallest sized) product in GPC was *anti*-**4**, which showed identical spectroscopic data as those reported previously in ref. 12 (given in parentheses for comparison), including diagnostic up-field shifted signal at 5.04 (5.01) ppm due to the inner naphthalene proton in ^{1}H NMR spectrum and the down-field shifted signal at 130.9 (130.8) ppm in ^{13}C NMR spectrum.[12] These are attributed to the anisotropic shielding and steric compression effects due to another naphthalene ring, respectively. The methylene protons appeared as an AA'BB' pattern at 2.26 (2.21) ppm as reported. In addition, in UV spectrum the product exhibit absorption maxima at 226 and 296 nm, which are virtually identical with those reported as shown in the overlaid spectra (Figure S1). The structure was confirmed by X-ray crystallographic analysis as described below.

The second last eluted product in GPC showed a peak at *m*/*z* 462.2 in FAB mass spectrum, indicating that this is a product of reductive trimerization, i.e. [2_3](2,7)naphthalenophane (**6**). However, the NMR and UV spectral data of this product are very reminiscent with those reported for *syn*-**4**, which are shown below in parentheses for comparison.[12] In ^{1}H NMR

spectrum, the aromatic proton signals were observed at 7.65 (7.63), 7.27 (7.22), 6.96 (6.95) and 3.17 (3.14) ppm. Lowering the temperature down to −70 ºC did not change the spectrum, indicating the conformational flexibility of the macrocyclic ring. ^{13}C NMR signals were observed at 138.4 (137.8), 133.7 (133.1), 130.8 (130.3), 127.9 (127.2), 127.13 (126.5), 127.06 (126.5), and 36.3 (35.8) ppm. With the constant shift of 0.5 ppm, the chemical shifts are virtually identical. In UV spectrum, absorption maxima were observed at 228 and 279 nm, which resemble well the reported spectrum for ***syn*-4** as shown in the overlaid spectra (Figure S2). These results indicate that the product assigned as *syn*-**4** is not likely a [2_2](2,7)naphthalenophane but a [2_3](2,7)naphthalenophane, i.e. **6**. All these spectral properties are not much different from those of simple naphthalene model such as 2,7-dimethylnaphthalene,[12] and do not show any specific feature arising from constraint due to the [2_2]cyclophane framework. However, in the literature, the absence of up-field shifted aromatic proton was ascribed to the geometry of *syn*-**4**, in which the inner naphthalene proton is not located in the shielding region of another naphthalene ring. The appearance of the methylene proton signal as a singlet, in spite of the significant difference in the steric environment of the germinal hydrogen atoms, was attributed to the conformational mobility of the ring system. Moreover, the absence of down-field shift of the inner naphthalene carbon in ^{13}C NMR spectrum was explained in terms of the relative orientation (almost perpendicular) of the compressed p orbitals in the two naphthalene rings.[12] These NMR

characteristics which puzzled Reg Mitchell[1,3b] are readily accounted for by **6** with a flexible macrocyclic ring and little constraint.

The first eluted product was assigned to [2_4](2,7)naphthalenophane (**7**) on the basis of the spectroscopic data. The parent peak in FAB mass spectrum was observed at *m*/*z* 616.3. NMR spectra are indicative of a structure of high symmetry in consistent with the expected conformational mobility of the macrocyclic ring.

Crystals suitable for X-ray analyses of *anti*-**4** was obtained by recrystallization from a mixture of chloroform/hexane As shown in Figure 1a, *anti*-**4** adopts a conformation in which the two naphthalene rings orient parallel to each other with a dihedral angle between the two mean naphthalene planes of 0º. The bridging C(sp^3)-C(sp^3) bond orients nearly perpendicular to the mean naphthalene plane with an angle of 82.6º. The naphthalene rings are slightly deformed from planarity with a dihedral angle between the mean planes of the six-membered rings of 13.6º. The inner aromatic hydrogen atom is located at 2.92 Å away from the mean plane of the facing six-membered ring, thereby susceptible to anisotropic shielding effect in ^{1}H NMR spectrum as observed.

Insert Figure 1 here.

Theoretically optimized structures of *anti*-**4**, *syn*-**4**, *anti*,*syn*-**6** and *syn*,*syn*-**6** by DFT calculations at the B3LYP/631G(d) level of theory are shown in Figure 2. Selected structural parameters are listed in Table 1. The theoretical structure of anti-4 listed agrees reasonably

with the experimentally observed one. For [2_2](2,7)naphthalenophane conformers, *anti*-**4** is estimated to be more stable than *syn*-**4** by 46.1 kJ/mol, indicating unlikeliness of the formation of the syn isomer. In *syn*-**4**, the naphthalene rings are tilted to each other with a dihedral angle between the mean naphthalene rings of 36.0º. In this conformation significant perturbation of the NMR spectra from that of 2,7-dimethylnaphthalene is expected. For [2_3]naphthalenophane conformers, *anti*,*syn*-**6** is estimated to be more stable than *syn*,*syn*-**6** by 10.6 kJ/mol. In *anti*,*syn*-**6**, one of the naphthalene rings is tilted with respect to the mean plane of the macrocyclic ring, which contain all the methylene carbons and the naphthalene ring carbons to which the methylene carbons are attached, by 50.3º, whereas the other two rings are nearly perpendicularly oriented (dihedral angles: 75.0º and 85.3º), thus avoiding steric congestion. On the other hand, in *syn*,*syn*-**6** two of the naphthalene rings are tilted by 40.8º and 49.9º with respect to the macrocyclic ring and only one ring orients nearly perpendicular to it (dihedral angle: 77.4º), causing steric crowding around one of the faces of the macrocyclic ring.

Insert Figure 2 and Table 1 here.

Conclusion

We reexamined reductive coupling of 2,7-bis(bromomethyl)naphthalene (**5**) by with phenyllithium to obtain *anti*-[2_2](2,7)naphthalenophane (*anti*-**4**), [2_3](2,7)naphthalenophane

189 (**6**), and [2_4](2,7)naphthalenophane (**7**), but no product previously assigned to *syn*-**4** was
190 obtained. The structure of *anti*-**4** was established by X-ray crystallographic analysis and their
191 structural features were elucidated. On the basis of the similarity between the NMR and UV
192 spectra of **6** with those reported for *syn*-**4**, we conclude that the compound originally assigned
193 to be *syn*-**4** was in fact **6**.
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196 **Supplementary materials**
197 General experimental procedures, X-ray crystallographic structure analysis for ***anti*-4**, UV
198 spectra of *anti*-**4** and **6** overlaid to the reported spectra of *anti*-**4** and *syn*-**4**, respectively,
199 copies of ^{1}H NMR and ^{13}C NMR spectra of *anti*-**4**, **6**, and **7**, results of DFT calculations and
200 cif file for X-ray crystallographic analysis of *anti*-**4** are available with the article through the
201 journal Web site at:
202
203 **Acknowledgement**
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205 25620032).
206
207 **References**

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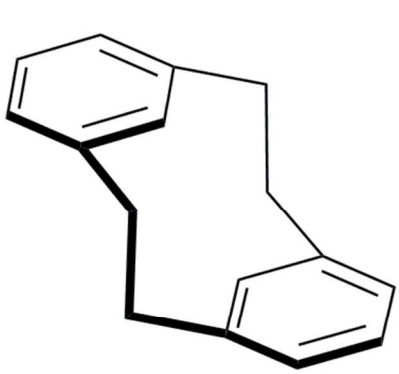
236 **Figure Captions**

237 **Figure 1.** ORTEP drawing of ***anti*-4** with thermal ellipsoids of a 50% probability level.

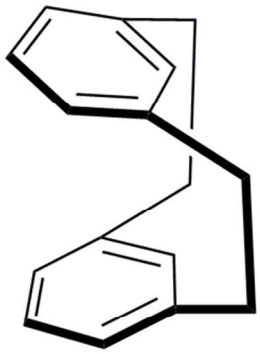
238 **Figure 2.** Theoretically optimized structures of ***anti*-4**, ***syn*-4**, ***anti,syn*-6** and ***syn,syn*-6**

239 **Table 1.** Selected geometrical parameters for X-ray and theoretical structures of ***anti*-4**.[a]

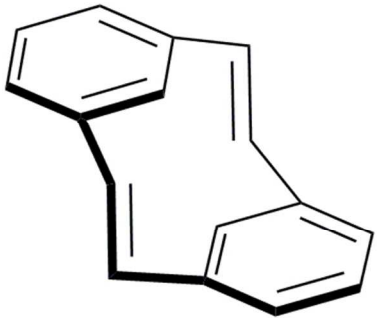
240 [a] For carbon numbering see Figure 2.



anti-**1**



syn-**1**



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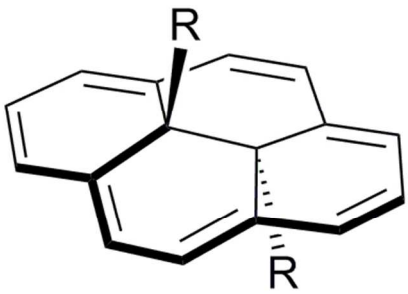

3 R=H, Me

Chart 1
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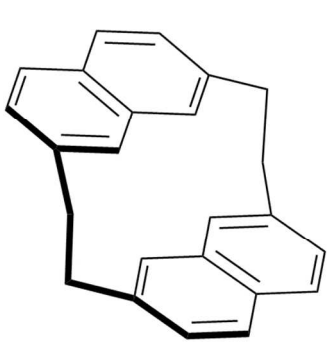
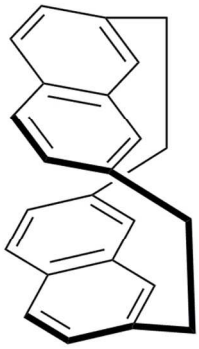
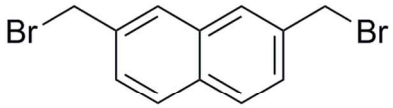


anti-**4**



syn-**4**



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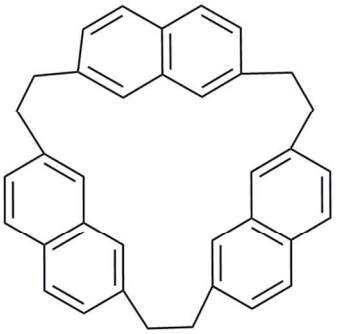

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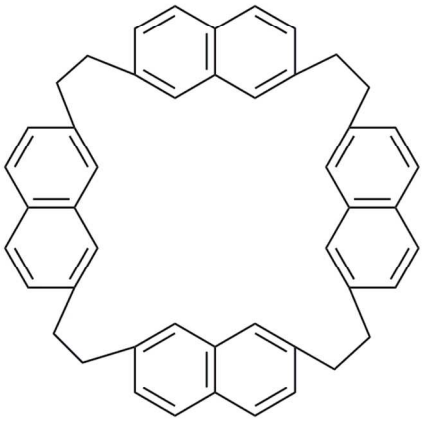

7

Chart 2
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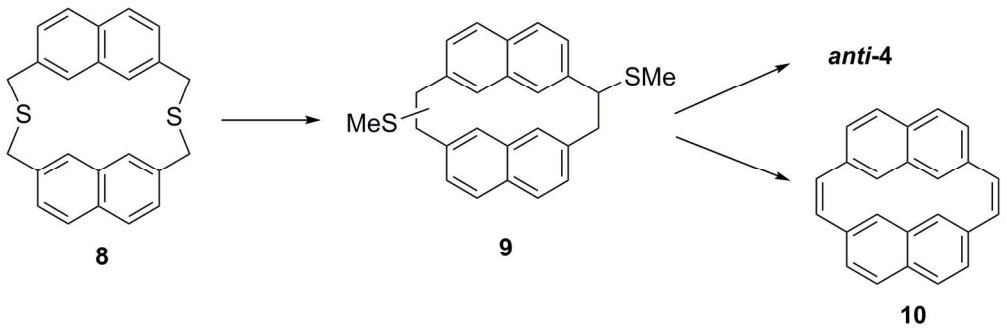

Scheme 1
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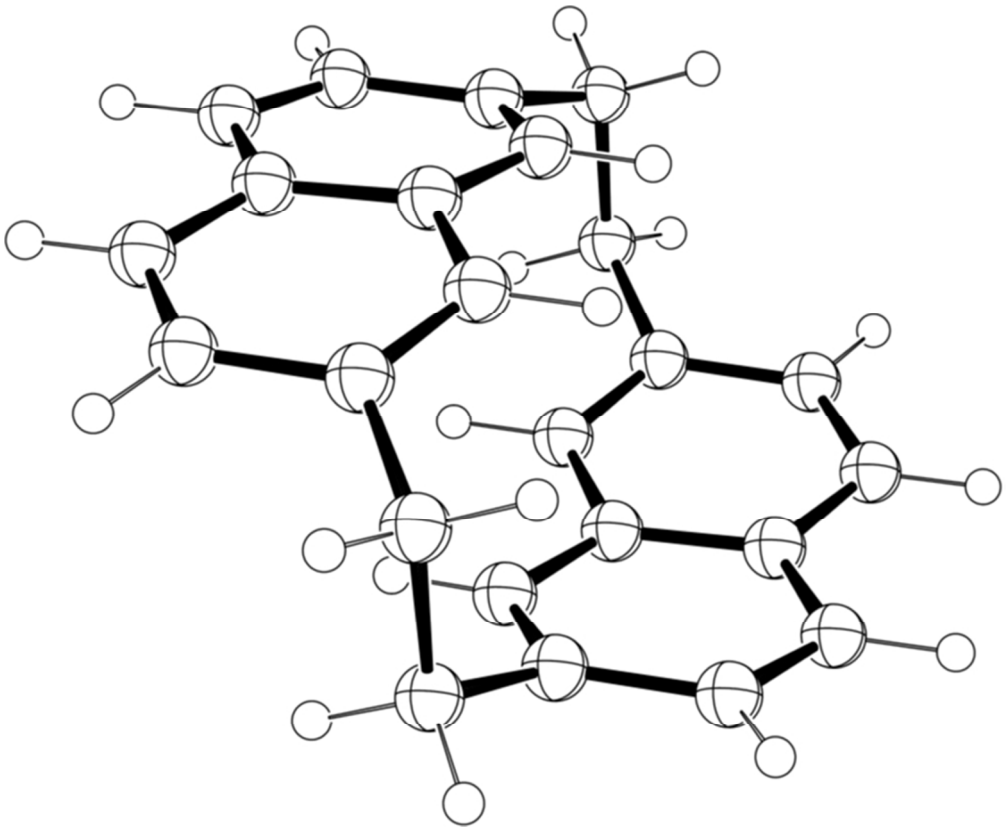

Figure 1. ORTEP drawing of anti-4 with thermal ellipsoids of a 50% probability level.
Figure 1
85x69mm (300 x 300 DPI)

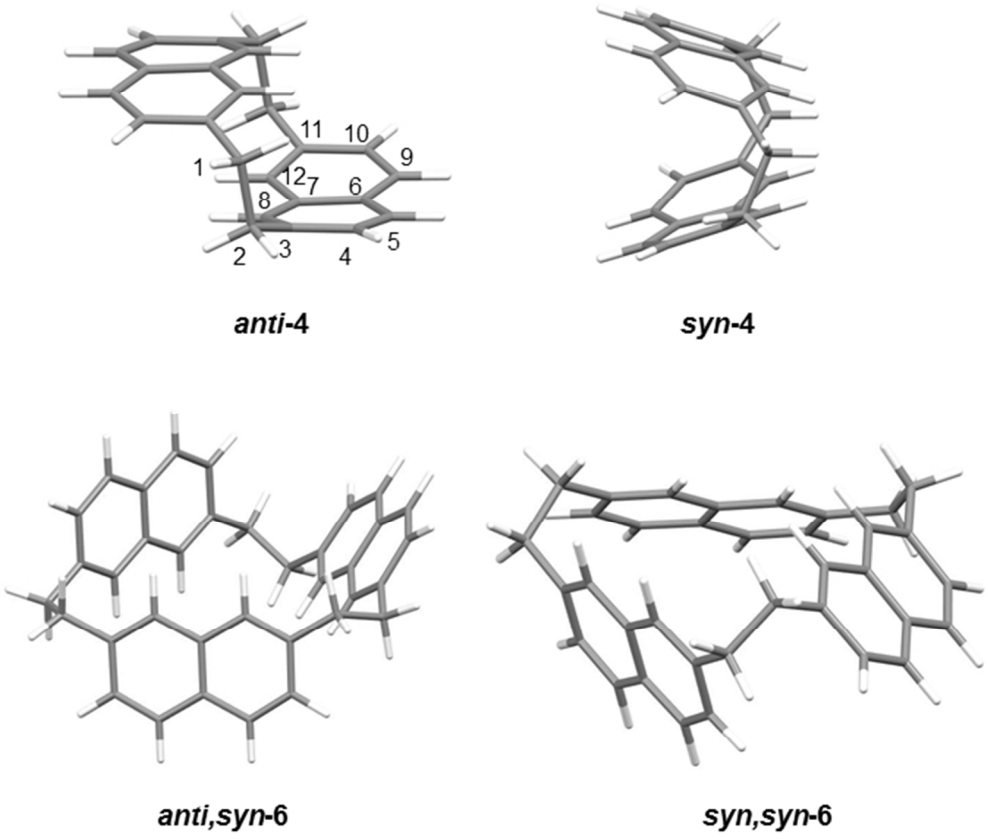

Figure 2. Theoretically optimized structures of anti-4, syn-4, anti,syn-6 and syn,syn-6.
Figure 2
144x124mm (120 x 120 DPI)

	X-ray analysis	DFT calculations
bond lengths / Å		
C(1)-C(2)	1.569	1.575
C(2)-C(3)	1.514	1.512
bond angle / º		
C(1)-C(2)-C(3)	110.32	112.48
C(2)-C(3)-C(4)	120.22	121.04
C(2)-C(3)-C(12)	120.27	120.18
dihedral angle / º		
between two mean six membered rings	11.62	13.55
bond vs. plane angle / º		
C(1)-C(2) vs. mean naphthalene ring (C(3)-C(12))	86.46	82.63
C(2)-C(3) vs. C(2)-C(4)-C(5)-C(6)-C(11)-C(12)	14.90	14.87