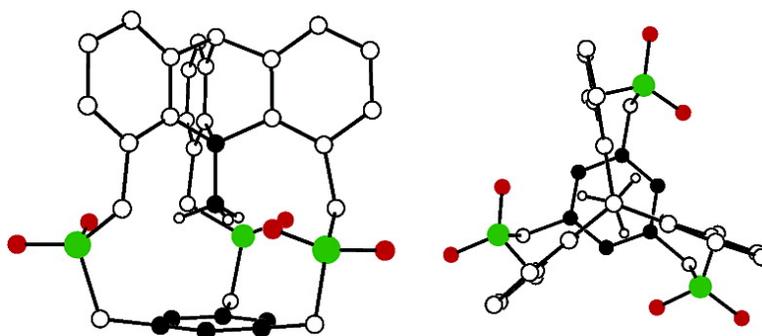


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J. Am. Chem. Soc., **2005**, 127 (32), 11246-11247 • DOI: 10.1021/ja0529384 • Publication Date (Web): 26 July 2005

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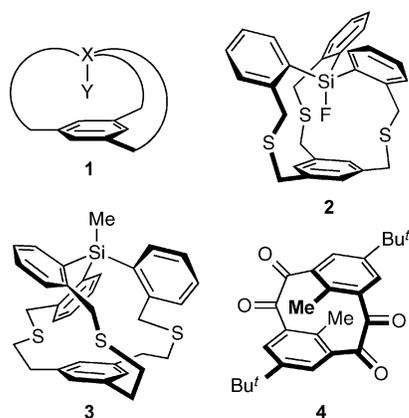
Sterically Congested *in*-Methylcyclophanes

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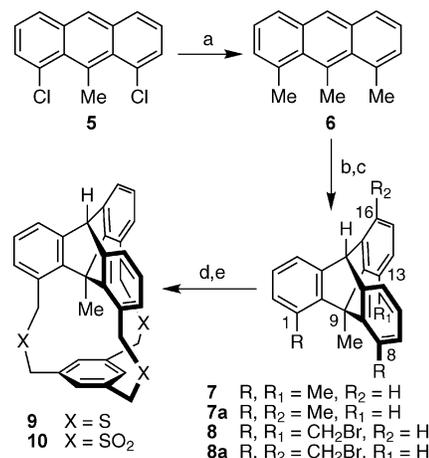
The synthesis of molecules containing very close nonbonded interactions is a persistent theme in cyclophane chemistry, and C_3 -symmetric *in*-cyclophanes (**1**) are superior frameworks for the projection of functional groups toward the centers of aromatic rings.¹ As with the vast majority of compounds capable of showing *in/out* isomerism,² the *in*-functional groups in molecules with topology **1** are limited mainly to hydrogen atoms and lone pair (lp) electrons. A variety of *in*-isomers exist, where X–Y is C–H,³ N–H,⁴ N–lp,⁵ Si–H,⁶ and P–lp,^{6,7} but heavy-atom Y's are very rare.² A few years ago, we prepared the *in*-fluorosilane **2** by the direct condensation of trithiol and tribromide precursors,^{7c} but a similar attempt to make an *in*-methylsilane gave only the *out*-isomer **3**.^{7c} Until now, metacyclophane **4** has possessed the closest approach of a methyl carbon to the center of an aromatic ring (3.00 Å),^{1,8} even though the C–Me bond vector does not even point toward the opposing ring! We now report the syntheses of *in*-methylcyclophanes **9** and **10** (Scheme 1), in which the methyl groups are forced into the centers of the basal aromatic rings with interesting spectroscopic and structural consequences.



Ab initio calculations clearly indicate that compound **3** is *less stable* than its *in*-isomer;^{7c} so the formation of the *out*-isomer must be kinetically preferred. To prepare a sterically congested *in*-methylcyclophane, *out*-isomer formation must be suppressed. This was accomplished by using a derivative of 1,8,9,13-tetramethyltripterycene (**7**) for the “top” of the cyclophane; the aryl rings are fixed in a conformation that permits only the *in*-isomer to exist.

The synthetic plan was relatively straightforward, hampered only by our inability to separate triptycene isomers at intermediate stages of the synthesis. Treatment of 1,8-dichloro-9-methylanthracene⁹ (**5**) with AlMe₃ and (DPPP)NiCl₂ under the conditions of Seiders et al.¹⁰ gave 1,8,9-trimethylanthracene (**6**) in >98% yield. Addition of 3-methylbenzylzinc to **6** produced triptycene **7** as a 1:2 mixture with its *anti* isomer, 1,8,9,16-tetramethyltripterycene (**7a**), in 80% yield. Subsequent NBS bromination gave a mixture of tris-(bromomethyl)-9-methyltripterycenes, and this was slightly enriched in the desired *syn* isomer **8** by a combination of crystallization and

Scheme 1. Synthesis of *in*-Methylcyclophanes^a



^a Reaction conditions: (a) AlMe₃, (DPPP)NiCl₂, DME, reflux; (b) 2-amino-6-methylbenzoic acid, isoamyl nitrite, 1,2-dichloroethane, reflux; (c) NBS, benzene, light, reflux; (d) 1,3,5-tris(mercaptomethyl)benzene, KOH, 2:1 benzene–EtOH, reflux; (e) H₂O₂, HOAc, reflux.

chromatography (2:3 **8:8a**, 49%). The base-promoted condensation of the tribromides in benzene–ethanol gave *in*-cyclophane **9**¹¹ in 17% yield based on the amount of **8** in the tribromide mixture, and this material was easily separated from the various oligomeric byproducts.

The ¹H NMR spectrum of **9** exhibits an *in*-methyl resonance at δ 2.52, about 1 ppm upfield from the 9-methyl resonances of **7** (δ 3.16) and **8** (δ 3.85). This modest degree of shielding is due to the fact that the methyl protons lie above the inside edge of the basal aromatic ring, not its center. The *in*-methyl ¹³C NMR resonance in **9** appears at δ 14.8, significantly upfield from any of the methyl resonances in **7**, **7a**, **8**, or **8a** (δ_C ≥ 18.4). As for many congested cyclophanes, the diastereotopic benzylic proton resonances for **9** are broadened due to exchange via the enantiomerization of the cyclophane at room temperature. At –50 °C (slow exchange limit), they are resolved into four doublets, and at 100 °C (fast exchange limit), they have coalesced into two sharp singlets. A variable temperature NMR analysis¹² yielded a ΔG[‡] of 14.3 kcal/mol for the enantiomerization.

Large crystals of **9** were difficult to obtain, so **9** was oxidized to the trisulfone **10**¹³ by boiling in H₂O₂ and acetic acid. The relatively insoluble **10** formed colorless prisms from DMSO–ethanol, and its X-ray structure was determined.¹⁴ Compound **10** crystallizes in the space group $R\bar{3}$ with $Z = 12$ (hexagonal setting); thus, there are two independent molecules in the structure, each possessing crystallographic C_3 symmetry.

The molecular structures of the two molecules of **10** are illustrated in Figure 1. It is clear that the *in*-methyl groups are pressed firmly against the basal rings of the cyclophanes. The C_{methyl}–ring centroid distances in molecules A and B are 2.896(5) and 2.869(5) Å, respectively: the new “world record” for such

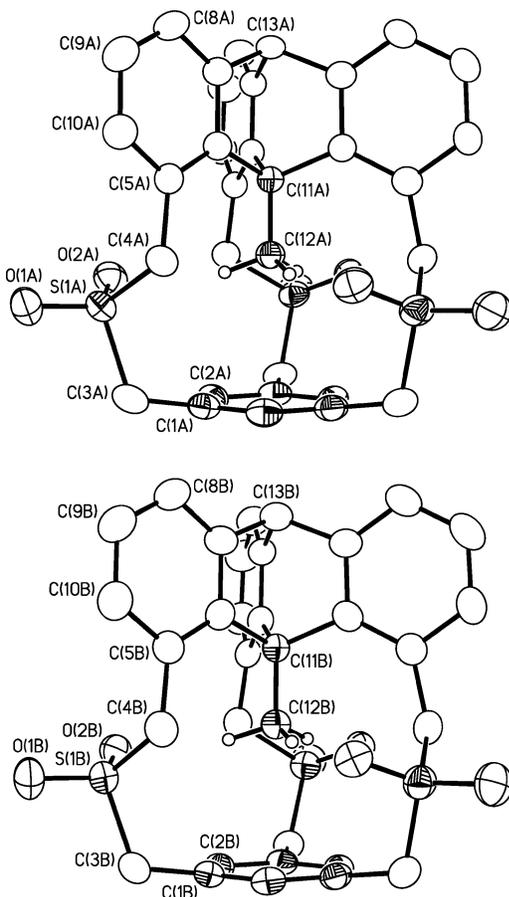


Figure 1. Molecular structure of compound **10**. The crystallographically independent molecules A (above) and B (below) are illustrated. Thermal ellipsoids have been drawn at the 50% level, and all but the methyl hydrogen atoms have been omitted for clarity.

contacts.¹ The experimental contacts are a bit tighter than those found by calculations¹⁶ at the HF/3-21G(*) (2.943 Å) and B3LYP/6-31G(d) (3.024 Å) levels of theory, but such methods frequently overestimate cyclophane nonbonded contact distances.¹⁷ Interestingly, the C–Me bond distances in the experimental structures appear to be compressed, at 1.475(6) and 1.495(6) Å, when compared with the C–Me distances observed in various structures of 9-methyltritycenes and other 1,1,1-triarylethanes in the Cambridge Structural Database¹⁸ (average distance 1.545 ± 0.012 Å, $n = 28$ ¹⁹). Computational studies agree; the C–Me bond length in **7** is calculated to be 1.529 Å [HF/3-21G(*)] and 1.528 Å [B3LYP/6-31G(d)], but the C–Me distance in **10** is found to be 1.499 and 1.502 Å, respectively, by the same two methods.

The successful syntheses of the congested *in*-methylcyclophanes **9** and **10** suggest that the use of 9-substituted triptycenes as building blocks will permit the preparation of a variety of cyclophanes with exceptionally close contacts between arenes and functional groups that have so far escaped such “high-pressure” situations.

Acknowledgment. This work was supported by National Science Foundation Grant CHE-0314873, which is gratefully acknowledged.

Supporting Information Available: Synthetic procedures for compounds **6–10**, ¹³C NMR spectra for compounds **6–9**, and a crystallographic information file (CIF) containing the X-ray structural information for compound **10**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (11) For **9**: mp > 300 °C; ¹H NMR (CDCl₃) δ 2.52 (s, 3 H, *in*-CH₃), 3.88 (broad, 12 H, CH₂’s), 5.14 (s, 1 H), 6.86 (m, 6 H), 7.19 (dd, *J* = 5, 3.5 Hz, 3 H), 7.32 (s, 3 H); ¹³C NMR (CDCl₃) δ 14.8, 34.0, 38.6, 56.2, 56.6, 123.4, 125.1, 129.8, 131.5, 132.2, 139.8, 146.8, 147.7; MS (EI) *m/z* 520 (M⁺, 100); exact mass 520.1353, calcd for C₃₃H₂₈S₃ 520.1353.
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- (13) For **10**: mp > 400 °C; ¹H NMR (DMSO-*d*₆) δ 1.56 (s, 3 H, *in*-CH₃), 4.25 (d, *J* = 14.5 Hz, 3 H), 4.67 (d, *J* = 14 Hz, 3 H), 4.89 (d, *J* = 14.5 Hz, 3 H), 5.10 (d, *J* = 14 Hz, 3 H), 5.58 (s, 1 H), 6.92 (d, *J* = 7.5 Hz, 3 H), 7.00 (t, *J* = 7.5 Hz, 3 H), 7.43 (d, *J* = 7.5 Hz, 3 H), 7.94 (s, 3 H); MS (EI) *m/z* 488 (M – 2SO₂, 9), 426 (97), 424 (M – 3SO₂, 96), 279 (100).
- (14) Crystal data for **10**: C₃₃H₂₈S₃O₆·2.5C₂H₆O, *M* = 731.90; trigonal, space group R3 (No. 148); *a* = 13.7443(2), *c* = 60.7777(2) Å, *V* = 9943.1(2) Å³, *Z* = 12, ρ_{calcd} = 1.467 g/cm³. Data were collected at 220 K with θ ≤ 27.5° and λ = 0.71073 Å; a total of 25 908 reflections were processed to give 5085 unique reflections (*R*_{int} = 0.088) by using the programs DENZO,^{15a} SHELXTL,^{15b} and PLATON.^{15c} Refinement converged to *R*(*F*) = 0.0550, *wR*(*F*²) = 0.1296, and *S* = 1.196 for 3247 reflections with *I* > 2σ(*I*), and *R*(*F*) = 0.0889, *wR*(*F*²) = 0.1408, and *S* = 1.026 for 5085 unique reflections and 260 parameters.
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- (19) Only nonionic, nonorganometallic structures are included in this average.

JA0529384