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in,in-Cyclophanes with Bridgehead Methyl Groups

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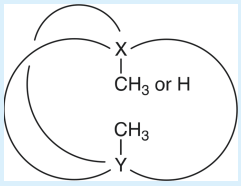
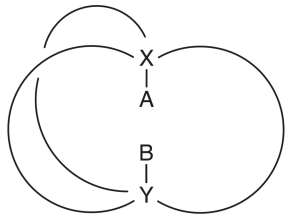
Supporting Information

ABSTRACT: Two *in,in*-cyclophanes that contain methyl groups in their central cavities have been synthesized, and their X-ray structures have been determined. One of these molecules contains a very short nonbonded contact between a hydrogen atom and a methyl group, and the other is the first example of a macrobicyclic compound that contains two inwardly directed methyl groups.



During the last five years, we have synthesized numerous *in,in*-cyclophanes (**1**) with a wide variety of inwardly directed functional groups at their bridgeheads. These include C−H, N-lp (lp = lone pair), Si−H, Si−OH, Si−F, P-lp, and P−H, as well as one example of metal encapsulation by inwardly directed lone pairs (P−Ag−P).[1−6] Some of these compounds display extraordinarily short hydrogen−hydrogen nonbonded contact distances,[2,6] and others display unusual through-space spin−spin coupling in their NMR spectra.[1,3−6]



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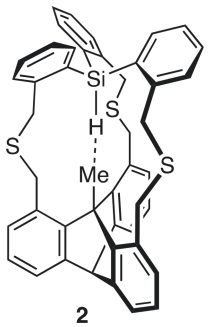

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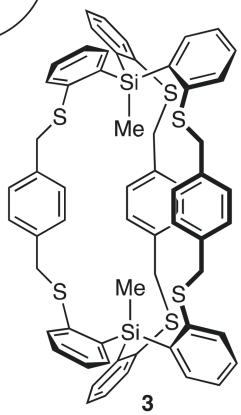

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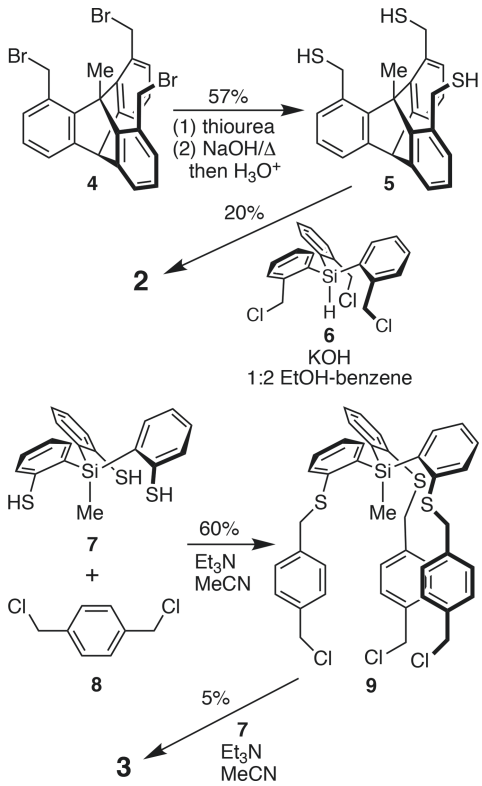
Notably absent is any example of an *in*-methyl group, and our prior attempts to incorporate methyl groups into *in,in*-cyclophanes have led only to *in,out*-isomers.[3,5] Further, Alder and East's review of *in/out* isomerism[7] contains no examples of *in*-methyl groups in such molecules. We now report the syntheses, spectroscopic characterization, and X-ray structures of two *in,in*-cyclophanes bearing methyl groups on one or both bridgehead atoms: compound **2**, which contains a very close C−CH_3···H−Si nonbonded contact, and **3**, which contains two inwardly directed methyl groups.

The preparation of compounds **2** and **3** is relatively simple in concept (Scheme 1), and benefits greatly from precursors made

Scheme 1. Syntheses of *in*-Methyl Cyclophanes



during our past syntheses of *in*- and *in,in*-cyclophanes. For the preparation of cyclophane **2**, 1,8,13-tris(bromomethyl)-9-methyltriptycene[8] (**4**), containing a mixture of 1,8,13- and 1,8,16-isomers, was converted to the corresponding trithiol **5** in 57% yield by treatment with thiourea, followed by hydrolysis. The presence of the "trans" isomer of the trithiol is not a serious problem because any macrocycles formed from this material are oligomers that are more polar than the desired cyclophane. In this reaction, the trithiol mixture was condensed

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with tris[2-(chloromethyl)phenyl]silane[2] (**6**) to give cyclophane **2** in a respectable 20% yield, based on the amount of the 1,8,13-isomer in the starting trithiol.

Cyclophane **3** is formed in very low yield by the reaction of tris(2-mercaptophenyl)methylsilane[3] (**7**) and commercial 1,4-bis(chloromethyl)benzene (**8**), but the two-step procedure illustrated in Scheme 1 is far superior, if not high-yielding. Compound **7** was first treated with an excess of **8** to give the triple adduct **9** in 60% yield after purification, and then condensation of **9** with another molecule of **7** at high dilution gave the dimethyl cyclophane **3** in 5% yield.

The ^{1}H NMR spectrum of cyclophane **2** shows it to be more conformationally restricted than **3**. In the former, the protons on the bridging methylene groups are diastereotopic, indicating that the enantiomerization of the molecule is slow on the NMR time scale. In contrast, the methylene resonances for **3** are singlets, indicating greater conformational mobility.

Most of the C_3-symmetric cyclophanes that we have prepared in the past yielded single crystals large enough for X-ray analysis quite easily, but compounds **2** and **3** proved more difficult. A wide variety of solvents was examined for both molecules.

In the case of cyclophane **2**, the usual result was crystals that were twinned. The structures could be solved, and the *in,in*-geometry could be confirmed, but the refinement was poor. Eventually, the slow crystallization of **2** from THF gave a very good crystal of its bis(THF) solvate. The structure was solved in the common space group $P2_1/c$, and it refined to an excellent $R(F)$ = 3.96%. The molecular structure of compound **2** is illustrated in Figure 1.

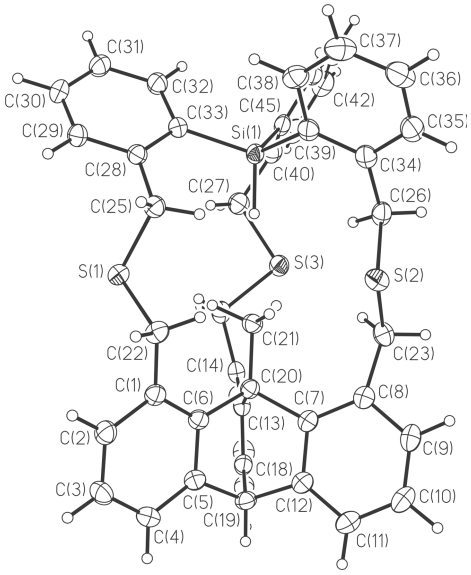

Figure 1. Molecular structure of cyclophane **2**. Ellipsoids are set at 50% probability.

In the case of cyclophane **3**, which is highly soluble only in chlorinated solvents, it was even more difficult to obtain good crystals. Finally, the evaporation of a relatively dilute solution in nitrobenzene over a period of four months gave single crystals of **3** as its bis(nitrobenzene) solvate. This structure was solved in the space group $P\bar{1}$, and it refined to $R(F)$ = 5.69%. There are two similar but crystallographically independent molecules of compound **3** in the structure, and the molecular structure of one of them is illustrated in Figure 2.

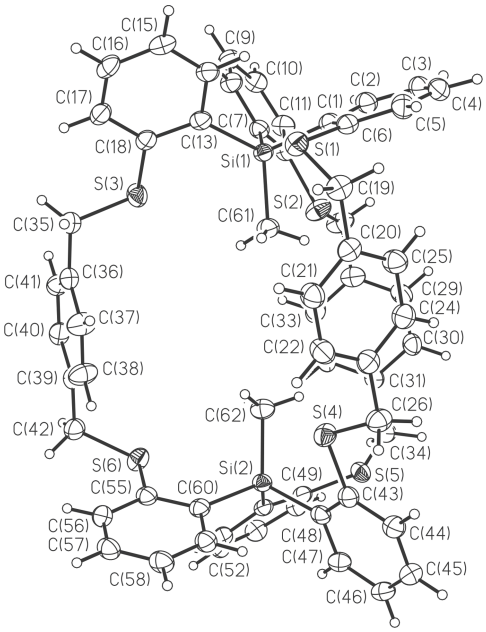

Figure 2. Molecular structure of cyclophane **3**. Ellipsoids are set at 50% probability.

The structure of cyclophane **2** is extremely unusual: it is a rare case of a hydrogen atom pressed close to the "top" of a methyl group. The observed contact distance (d_{H1-C21} using the crystallographic numbering scheme) is 2.55(2) Å, but of course, the actual distance must be shorter due to foreshortening of the Si−H bond[9] in the X-ray structure. If a standard Si−H bond distance of 1.48 Å is assumed,[10] then the true contact distance is 2.44 Å.[11] Evidence of steric compression is found in the IR spectrum of **2**, where the Si−H stretching frequency of 2269 cm^{-1} is 92 cm^{-1} higher than the same band in an acyclic model[14] (2177 cm^{-1}). This is, however, 188 cm^{-1} less than the Si−H stretch (2457 cm^{-1}) in another of our very congested *in*-silaphanes.[14]

Manifestations of the close contact are less obvious in the NMR spectra. There is no evidence of through-space spin−spin coupling of the silane and methyl protons in the ordinary ^{1}H NMR and COSY spectra of compound **2** nor is there evidence of coupling of the silane proton and methyl carbon in the fully proton-coupled ^{13}C NMR spectrum of **2**. The methyl resonance for **5** is observed at δ 3.74, while that of **2** is found at δ 5.09, an apparent example of steric deshielding,[15] but this conclusion is undermined by the absence of such deshielding for the silane proton, which is observed at δ 6.16 in precursor **6**, but only δ 5.21 in cyclophane **2**.

The C−CH$_3$ bond distance ($d_{C20-C21}$) in cyclophane **2** is also compressed. The average C−CH$_3$ bond distance for unconstrained, well-determined structures ($R \leq 0.05$) of 9-methyltriptycenes in the Cambridge Structural Database[12] is 1.519 ± 0.004 Å (n = 23), which is slightly longer than the experimental bond distance of 1.510(2) Å in **2**. Computational studies of cyclophane **2** using a variety of methods[16] invariably yield even shorter C−CH$_3$ bond distances, ranging from 1.497 to 1.508 Å (Table 1).

Overall, the conventional B3PW91 functional[17] gives structures in the best agreement with the experiment, with both the smaller 6-31G(d) basis set[18] and the much larger cc-pVTZ basis set[19] giving very similar results. When dispersion corrections[20] are included, either with variations of Grimme's

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Table 1. Experimental and Calculated Interatomic Distances for the Axial Atoms of Cyclophane 2

method	d_{H1-C21} (Å)	$d_{Si1-C21}$ (Å)	$d_{C20-C21}$ (Å)
experimental (X-ray)	2.55(2)	3.902(2)	1.510(2)
B3PW91/6-31G(d)	2.420	3.895	1.508
B3PW91/cc-pVTZ	2.418	3.894	1.503
B3PW91-D3/6-31G(d)	2.311	3.780	1.503
B3PW91-D3/cc-pVTZ	2.320	3.789	1.498
B3PW91-D3(BJ)/6-31G(d)	2.280	3.748	1.502
B3PW91-D3(BJ)/cc-pVTZ	2.287	3.756	1.497
M062X/6-31G(d)	2.337	3.808	1.506
M062X/cc-pVTZ	2.350	3.818	1.502
M062X-D3/6-31G(d)	2.331	3.801	1.506
M062X-D3/cc-pVTZ	2.345	3.812	1.502
MP2/6-31G(d)	2.309	3.777	1.501

D3 correction[21,22] or by employing the M062X functional,[23] the agreement is poorer. This is most apparent in the silicon-methyl carbon distance ($d_{Si1-C21}$), which is well determined in the X-ray structure at 3.902(2) Å. The B3PW91 functional gives values within 0.01 Å of the experiment, but the dispersion-corrected structures yield values that are too short by 0.08−0.15 Å.

Cyclophane **3** does not possess especially close nonbonded contacts (the methyl groups are approximately 5 Å apart), but the presence of two *in*-methyl groups is, as far as we can tell, unique. Whether a more highly congested *in,in*-dimethyl cyclophane can be prepared is an open question, but if the two methyls could be brought close enough to enmesh the hydrogen atoms, then it might be possible to observe correlated rotation of suitably labeled methyl groups.

In summary, the two macrobicyclic compounds described herein are the first *in,in*-cyclophanes to contain methyl groups in their interior cavities.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00773.

Synthetic procedures; ^{1}H and ^{13}C NMR spectra of **2**, **3**, **5**, and **9**; IR spectrum of **2**; atomic coordinates and energies of the calculated structures of **2** (PDF)

Accession Codes

CCDC 1826993−1826994 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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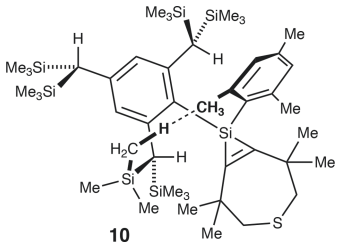
(11) A careful search of the Cambridge Structural Database[12] found several examples of H···Me contact distances shorter than that observed in compound **2**, but nearly all of these are observed in structures that exhibit significant disorder or poor refinement parameters. A notable exception is the X-ray structure of silacyclopropene **10**.[13]



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This is a well-determined structure with no apparent disorder, which contains a H···Me contact very similar in orientation to that in **2**, but with an even shorter contact distance: 2.404 Å. The hydrogen positions were not refined, but if a standard C−H bond distance of 1.09 Å is assumed, then the true contact distance is a very short, 2.26 Å. We suspect, however, that this close contact is at least partly due to packing forces and that, in solution, the contact distance is not nearly so short. The authors of the paper did not note any unusual contacts, and their spectral data shed no light on this aspect of the molecular structure.

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