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An *in*-Fluorosilaphane: The Largest *in*-Functional Group Is a Uniquely Encapsulated Fluorine Atom

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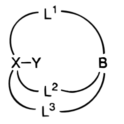
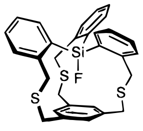
in/*out* stereoisomerism is a common phenomenon in medium- and large-ring bicyclic organic structures. For the *in*-isomers of such molecules, schematically represented by **1**, there must be sufficient space to accommodate the inwardly directed functionalities X−Y. In a recent, comprehensive review of *in*/*out* stereoisomerism,[1] Alder and East noted that the vast majority of inside functional groups are methines (X−Y = C−H), amines (N−lp), and ammonium ions (N^+−H), but the only compounds containing *in*-functionalities with Y larger than a hydrogen atom or lone pair are the *in,out*-isomers of Whitlock's enormous, macrocyclic bis(phosphine oxides),[2] where the linking arms (L) between the phosphine oxide bridgeheads are 14−16 atoms long and steric congestion is not an issue. We now report the synthesis and crystallographic characterization of *in*-cyclophane **2**, in which an *in*-fluorosilane (X−Y = Si−F) is pressed into the face of a benzene ring.



1



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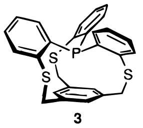

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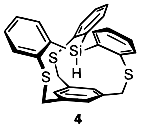
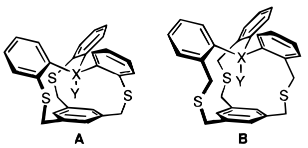


4

The syntheses of *in*-phosphine **3** and *in*-silane **4** have been reported previously,[3,4] but attempts to place larger apical functionality in that framework were unsuccessful. AM1 calculations[5,6] (Table 1, series **A**) indicate that *in*-geometries are favored for **3** and **4**, but the X-ray structure of **4** shows significant distortions of the basal ring due to pressure from the *in*-hydrogen,[4] so it is not surprising that the *in*-phosphine oxide **5** and *in*-fluorosilane **6** are calculated to be much more strained than the corresponding *out*-isomers. However, the addition of one methylene group to each of the linking bridges in these cyclophanes (Table 1, series **B**) would seem to permit the inclusion of a non-hydrogen *in*-atom.

Table 1. Computational Data for *in*-Cyclophanes and Their *out*-Isomers



central atoms	ΔH_f (AM1, kcal/mol)[a,b] *in*-isomer	*out*-isomer	difference[c] (*in* − *out*, kcal/mol)
Cyclophanes with Two-Atom Links (**A**)			
X = P, Y = lp[d] (**3**)	165.65	171.06	−5.41
X = Si, Y = H (**4**)	116.28	116.29	−0.01
X = P, Y = O (**5**)	104.64	87.86	16.78
X = Si, Y = F (**6**)	55.57	27.69	27.88
Cyclophanes with Three-Atom Links (**B**)			
X = P, Y = lp[d] (**7**)	140.56	146.88	−6.32
X = Si, Y = H (**8**)	86.07	93.40	−7.33
X = P, Y = O (**9**)	55.91	61.41	−5.50
X = Si, Y = F (**2**)	3.55	4.10	−0.55
X = Si, Y = Me (**10**)	91.32	83.12	8.20

[a] See ref 6 for computational details. [b] All structures possess C_3 symmetry. [c] Negative values favor the *in*-isomer. [d] lp = lone pair electrons.

We first attempted to prepare an *in*-oxide such as **9**. Condensation of tris[2-(chloromethyl)phenyl]phosphine[7] (**11**) with 1,3,5-tris(mercaptomethyl)benzene[8] gave the *in*-phosphaphane **7** in 59% yield,[9] but vigorous oxidation of **7** led only to the trisulfone **12**;[10] none of the phosphine oxide was formed (Scheme 1). X-ray analysis confirmed the *in*-geometry of **12** (not shown). All attempts to form **9** or a related phane by the direct cyclization of tris[2-(chloromethyl)phenyl]phosphine oxide[7] (**13**) with a variety of tripodal nucleophiles under many different conditions were unsuccessful.

Fluorosilanes are larger than phosphine oxides (typical bond distances: C_3Si−F, 1.64 Å; C_3P=O, 1.49 Å), but with the former there is no chance of neighboring group participation by the fluorine in the cyclization reactions (a possible complicating factor with phosphine oxides). For the synthesis of the fluorosilaphane **2**, tri(*o*-tolyl)silane[11] (**14**) was fluorinated at silicon with AgF, and then brominated to yield tris[2-(bromomethyl)phenyl]fluorosilane (**16**). Condensation of **16** with 1,3,5-tris(mercaptomethyl)benzene gave the desired **2**, but in an abysmal 0.4% yield.[12] Even so, the isolation of **2** was achieved only by its direct crystallization from an otherwise intractable chromatographic fraction! The X-ray structure of **2** (Figure 1) unambiguously establishes the inside location of the fluorine atom.[13] Cyclophane **2** has approximate C_3 symmetry, and the distance from the fluorine to the mean plane of the basal aromatic ring is 2.826(7) Å. Interestingly, the ^{1}H NMR and mass spectra of **2** suggest that a small amount (∼15%) of the *in*-hydroxo cyclophane is present,

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(1) Alder, R. W.; East, S. P. *Chem. Rev.* **1996**, *96*, 2097−2111.

(2) (a) Friedrichsen, B. P.; Whitlock, H. W. *J. Am. Chem. Soc.* **1989**, *111*, 9132−9134. (b) Friedrichsen, B. P.; Powell, D. R.; Whitlock, H. W. *J. Am. Chem. Soc.* **1990**, *112*, 8931−8941.

(3) Pascal, R. A., Jr.; West, A. P., Jr.; Van Engen, D. *J. Am. Chem. Soc.* **1990**, *112*, 6406−6407.

(4) L'Esperance, R. P.; West, A. P., Jr.; Van Engen, D.; Pascal, R. A., Jr. *J. Am. Chem. Soc.* **1991**, *113*, 2672−2676.

(5) Dewar, M. J. S.; Zoebisch, E. G.; Healy, E. F.; Stewart, J. J. P. *J. Am. Chem. Soc.* **1985**, *107*, 3902−3909.

(6) Semiempirical molecular orbital calculations were performed by using the SPARTAN program package (version 5.0; Wavefunction, Inc., Irvine, CA), and its built-in default thresholds for wave function and gradient convergence were employed.

(7) Letsinger, R. L.; Nazy, J. R.; Hussey, A. S. *J. Org. Chem.* **1958**, *23*, 1806−1807.

(8) Nakazaki, M.; Yamamoto, K.; Miura, Y. *J. Org. Chem.* **1978**, *43*, 1041−1044.

(9) For **7**: mp 288−291 °C; ^{1}H NMR ($CDCl_3$) δ 3.69 (s, 6 H), 3.75 (d, J = 4 Hz, 6 H), 6.57 (ddd, J = 8, 4, 1 Hz, 3 H), 7.07 (ddd, J = 8, 8, 1 Hz, 3 H), 7.26 (s, 3 H), 7.28 (ddd, J = 8, 8, 1 Hz, 3 H), 7.44 (ddd, J = 8, 5, 1 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 31.4 (d, J_{PC} = 32 Hz), 36.6, 127.5, 129.4, 129.6, 129.9 (d, J_{PC} = 4 Hz), 134.4, 134.6 (d, J_{PC} = 13 Hz), 139.2 (d, J_{PC} = 2 Hz), 142.8 (d, J_{PC} = 27 Hz); MS *m*/*z* 514 (M^+, 86), 481 (M − SH, 4), 71 (100); exact mass 514.1029, calcd for $C_{30}H_{27}PS_3$ 514.1015.

(10) For **12**: mp > 400 °C; ^{1}H NMR (DMSO-d_6) δ 4.69 (br s, 6 H), 4.82 (s, 6 H), 7.40 (m, 12 H), 7.77 (s, 3 H); MS *m*/*z* 610 (M^+, 27), 546 (M − SO_2, 12), 482 (M − 2SO_2, 6), 418 (M − 3SO_2, 100); exact mass 610.0705, calcd for $C_{30}H_{27}PS_3O_6$ 610.0709.

(11) Benkeser, R. A.; Riel, Frank J. *J. Am. Chem. Soc.* **1951**, *73*, 3472−3474.

(12) For **2**: ^{1}H NMR (CD_2Cl_2) δ 3.71 (s, 6 H), 3.77 (s, 6 H), 7.14 (m, 6 H), 7.16 (s, 3 H), 7.36 (m, 6 H); ^{19}F NMR (CD_2Cl_2) δ 5.3; MS *m*/*z* 530 (M^+, 19), 439 (M − C_7H_7, 5), 408 (M − C_7H_6S, 10), 178 (100); exact mass 530.1018, calcd for $C_{30}H_{27}FS_3Si$ 530.1030.

S0002-7863(98)01009-9 CCC: $15.00

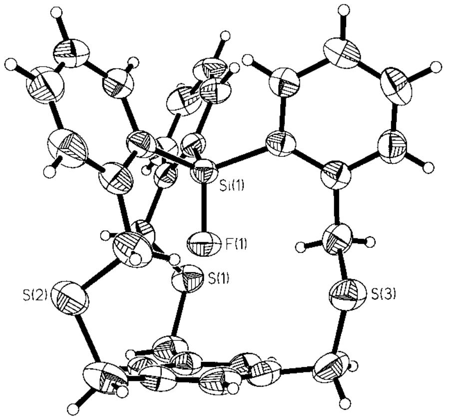
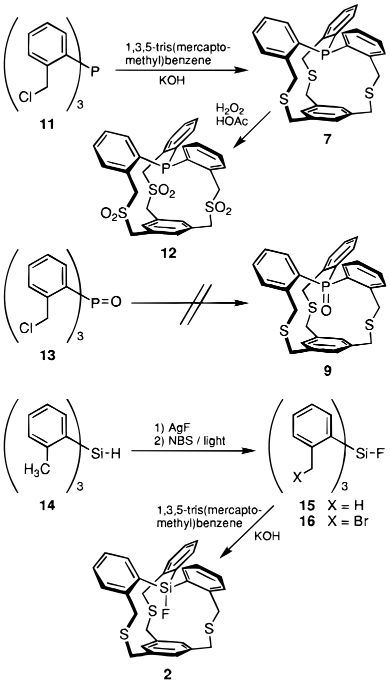


Figure 1. Molecular structure of *in*-cyclophane **2**. Thermal ellipsoids have been drawn at the 50% probability level.

but the X-ray structure shows no evidence of partial occupancy by oxygen in the fluorine site.

Scheme 1



The fluorosilane in **2** is quite unusual. First, the Si−F bond distance of 1.591(3) Å is very short for a tri(alkyl/aryl)fluorosilane (other fluorosilanes can have shorter bonds[16]). The only tetracoordinate triarylfluorosilane in the Cambridge Structural Database[17] is tris{2-[(dimethylamino)methyl]phenyl}fluorosilane,[18] where the Si−F distance is 1.627 Å, and the mean Si−F distance for all tetracoordinate tri(alkyl/aryl)fluorosilanes in the database is 1.64 Å, with none less than 1.604 Å. Second, the ^{19}F NMR resonance for **2** (δ 5.3) is 155 ppm upfield from that of tri(*o*-tolyl)fluorosilane (**15**, δ 160.6). Such enormous shielding must arise from the proximity of the fluorine to both the silicon atom and the center of the basal aromatic ring. Taken together, the observed bond distance and NMR shielding suggest that the Si−F bond has been shortened due to steric compression.[19] In such circumstances, one might also expect to observe compressional frequency enhancement of the Si−F stretching band in the IR spectrum of **2**, a common phenomenon in cyclophanes with *in*-C−H and *in*-Si−H bonds,[4,20] but the Si−F stretch falls in a complex region of the IR (800−1000 cm^{-1}), making a definite assignment of this band impossible. The reactivity of **2** has yet to be explored in detail, but an attempt to invert the configuration at silicon, by treatment with 0.1 M KF in refluxing methanol, returned only unchanged **2**.

It is clear from the 100-fold difference in the yields of the syntheses of **7** and **2** that the presence of the *in*-atom strongly inhibits macrocyclization. Not only is the *in*-atom a steric impediment to the approach of the sulfur nucleophile, but it may also bias the conformation of partly cyclized intermediates to give unfavorable geometries for cyclization. For this reason we suspect that the placement of still larger *in*-functionalities in small cyclophanes will require an entirely different synthetic approach.

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Supporting Information Available: Experimental procedures for the syntheses of cyclophanes **2**, **7**, and **12**, and crystal structure report for compound **2** (including full experimental details, tables of atomic coordinates, bond distances, bond angles, and thermal parameters, and selected figures). An X-ray crystallographic file, in CIF format, is available through the Internet only. See any current masthead page for ordering information and Web access instructions.

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(13) Crystal data for **2**: $C_{30}H_{27}FS_3Si$; monoclinic, space group $P2_1/c$; $a = 10.38(2)$ Å, $b = 17.27(4)$ Å, $c = 15.41(2)$ Å, $\beta = 108.97(11)°$, $V = 2612(8)$ Å^3, $Z = 4$, $D_{calcd} = 1.350$ g/cm^3. Intensity data were collected with $2\theta \le 93°$ by using Cu Kα radiation (1.541 78 Å) at 298 K on a Rigaku R-AXIS IIC image plate system. A total of 13 353 reflections were indexed, integrated, and corrected for Lorentz and polarization effects (using the program DENZO[14]), and the data were scaled and merged to give 2197 unique reflections ($R_{int} = 0.030$). The structure was solved by direct methods; non-hydrogen atoms were refined anisotropically, with hydrogens riding [C−H = 0.93 or 0.97 Å, $U(\mathrm{H}) = 1.2U(\mathrm{C})$] (SHELXTL[15]). The refinement converged to $R(F) = 0.0276$, $wR(F^2) = 0.0724$, and $S = 1.044$ for 2110 reflections with $I > 2\sigma(I)$, and $R(F) = 0.0311$, $wR(F^2) = 0.0948$, and $S = 1.032$ for 2196 unique reflections, 317 parameters, and 0 restraints (one reflection was suppressed). Full details are provided in the Supporting Information.

(14) Otwinowski, Z.; Minor, W. *Methods Enzymol.* **1997**, *276*, 307−326.

(15) Sheldrick, G. M. *SHELXTL*, Version 5; Siemens Analytical X-ray Instruments: Madison, WI, 1996.

(16) The presence of additional fluorine atoms (or other heteroatoms) significantly shortens the Si−F bond. For example, the average Si−F bond distance for $C_2XSi{-}F$, where X = O or F, is 1.60 Å, and, among these, Si−F distances of 1.57 Å are not uncommon.

(17) Allen, F. H.; Kennard, O.; Taylor, R. *Acc. Chem. Res.* **1983**, *16*, 146−153.

(18) Breliere, C.; Carre, F.; Corriu, R. J. P.; Royo, G.; Wong Chi Man, M. *Organometallics* **1994**, *13*, 307−314.

(19) However, the compression cannot be *too* great: the apical silicon is only slightly flattened, with average C−Si−F and C−Si−C bond angles of 108.6° and 110.4°, respectively.

(20) (a) Pascal, R. A., Jr.; Grossman, R. B.; Van Engen, D. *J. Am. Chem. Soc.* **1987**, *109*, 6878−6880. (b) Pascal, R. A., Jr.; Winans, C. G.; Van Engen, D. *J. Am. Chem. Soc.* **1989**, *111*, 3007−3010.