

# Polar alicyclic rings: Synthesis and structure of all *cis*-1,2,3,4-tetrafluorocyclopentane

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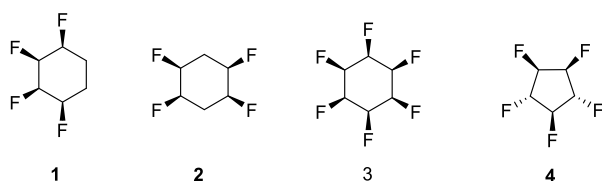
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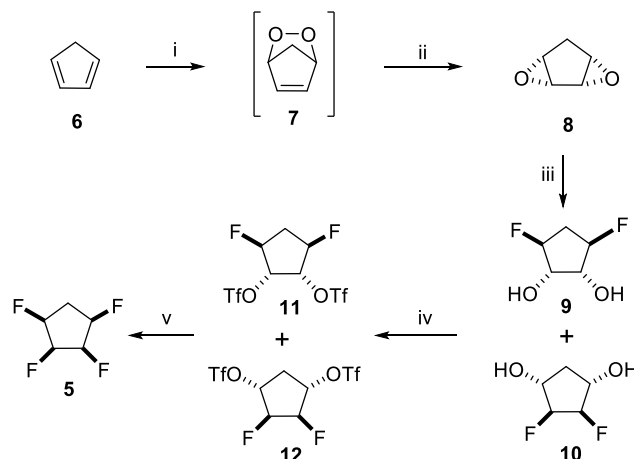
The all-*cis* isomer of 1,2,3,4-tetrafluorocyclopentane is prepared and characterised by NMR and X-ray crystallography and the experimental structure compared with theory. The structure has a similarly high polarity to all-*cis* tetrafluorocyclohexanes despite the increased conformational flexibility of a cyclopentane.

Recently we reported the synthesis and analysis of cyclohexanes containing four<sup>1,2</sup> or six fluorine<sup>3</sup> atoms each with only one fluorine on each carbon, and with the fluorines configured stereochemically such that all of the fluorine atoms are 'up' or *cis* to each other. The structures 1-3 are illustrated in Figure 1. These all-*cis* fluorinated cyclohexanes are perhaps unexpectedly solid materials at room temperature. Eg all *cis*-1,2,3,4-tetrafluorocyclohexane 1 has a melting point of 83 °C and a calculated dipole moment of  $\mu = 4.91$  D and the all *cis*-1,2,4,5-isomer 2 has a melting point of 106 °C and a dipole moment of  $\mu = 5.24$  D. The high melting points and polarity arise because of the polarity induced by having 1,3 diaxial C-F bonds in the chair conformation of the cyclohexane rings, the C-F bond being the most polar covalent bond to carbon.<sup>4</sup> In the case of all *cis*-1,2,3,4,5,6-hexafluorocyclohexane 3,<sup>3</sup> there are three axial C-F bonds in the chair conformation, and this molecule has a melting point of 206 °C and a calculated dipole moment of  $\mu = 6.2$  D, the highest recorded for an aliphatic compound.<sup>3</sup>



There is a general interest in polar organofluorine aliphatics in performance materials such as liquid crystals<sup>5</sup> for displays or piezoelectric materials for electrical devices such as actuators.<sup>6</sup> New motifs that might enhance exploration into these areas are desirable. As an extension of our investigation into the small polar cyclohexane rings 1-3 containing *cis*-vicinally arranged fluorines, we have begun to explore cyclopentanes with appropriately configured C-F bonds. Cyclopentanes are conformationally more flexible than cyclohexanes,<sup>7</sup> and it was of interest to determine if we could prepare an all-*cis*, vicinally substituted cyclopentane and how ordered such a system would be in both the solution and solid state.

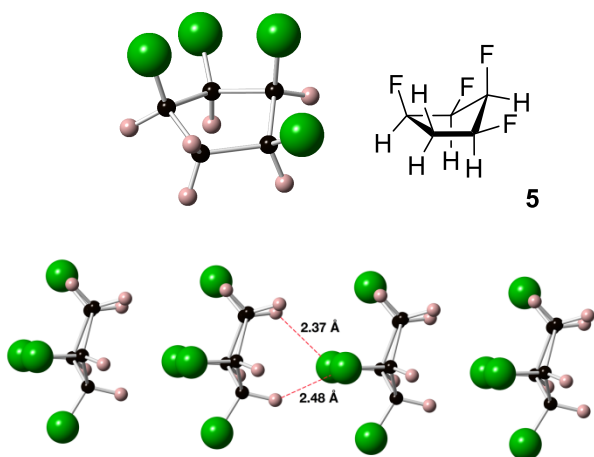
Monofluorocyclopentane is well known<sup>8</sup> and *cis*- and *trans*- 1,2-difluorocyclopentanes have been prepared.<sup>9</sup> There are no examples of vicinal fluorinated tri- or tetra- cyclopentanes in the literature. Intriguingly there is a report<sup>10</sup> from 1966 of the preparation and characterisation of a single stereoisomer 4 of 1,2,3,4,5-pentafluorocyclopentane. This compound was isolated as a low level component (0.5%) from the CoF<sub>3</sub> fluorination of cyclopentane. However isomer 4 is of a stereochemistry where polarity is compromised, because there are fluorines on both sides of the ring. Cyclopentane 4 is a liquid (bp 109-110°C) at room temperature and pressure rather than a solid material expected of a more polar ring system. In this *Communication* we report the synthesis of all-*cis* 1,2,3,4-tetrafluorocyclopentane 5, with the four fluorines arranged on one face of the cyclopentane. The synthesis of 5 exploited a protocol of Suzuki *et al.*,<sup>11</sup> for the conversion of freshly cracked cyclopentadiene 6 to *cis*-diepoxide 8, via endoperoxide 7 as illustrated in Scheme 1.



**Scheme 1.** Synthesis of tetrafluorocyclopentane 5 (i) O<sub>3</sub>, P(OPh)<sub>3</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 38%; (ii) Ru(PPh<sub>3</sub>)<sub>3</sub>Cl<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, -78 °C, 1h; -40 °C, 0.5 h; -25 °C, 1h; (iii) Et<sub>3</sub>N·3HF, 120 °C, 24h; (iv) Tf<sub>2</sub>O, pyridine, RT, 24h; (v) Et<sub>3</sub>N·3HF, 100 °C, 48h, 9% over steps (iii)–(v).

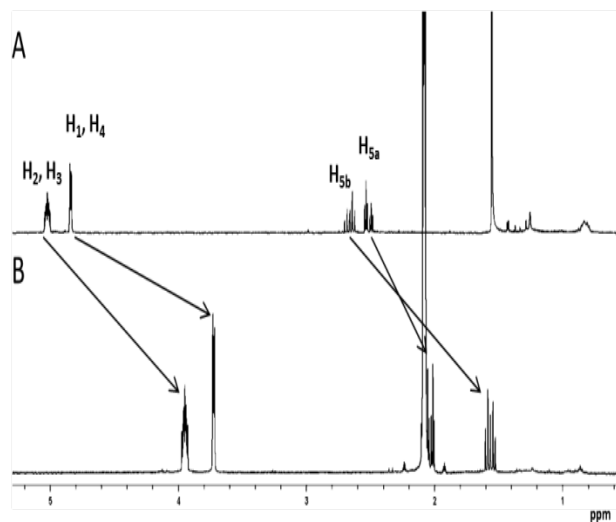
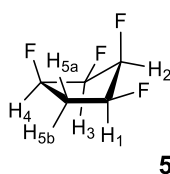
Ring opening of the epoxides was accomplished using Et<sub>3</sub>N·3HF<sup>12</sup> to generate a mixture of regioisomers 9/10. Triflation of the free alcohols (mix of isomers) generated 11/12 and then treatment of the triflates with Et<sub>3</sub>N·3HF<sup>13</sup> gave a sample of 5. Cyclopentane 5 was indeed isolated as a solid although with a melting point of 39 °C and it was noticeably volatile and sublimed on standing over a period of a few days at ambient temperature. As a consequence it proved challenging to isolate 5 in significant quantities by chromatography. None-the less analytical samples were secured in sealed flasks and a suitable crystal was used for single crystal analysis. The resultant structure of 5 is shown in Figure 1.

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See <http://dx.doi.org/10.1039/b000000x>



80 **Figure 1.** X-Ray structure of **5**. Upper image shows an isolated structure. The lower image shows four molecules linearly stacked with fluorine faces pointing to adjacent hydrogen faces consistent with electrostatic ordering. The distances highlighted are the shortest intermolecular CF...HC contacts.

85 The molecular ordering in the solid state (bottom of Figure 1) clearly illustrates the facial polarity of cyclopentane **5**, a characteristic which was observed for the all-*cis* fluorinated cyclohexanes **1-3**.<sup>1-3</sup> The molecules of **4** stack one on top of each other perpendicular to the ring plane (four molecules are shown



Proton signal	$\delta$ CDCl <sub>3</sub> (ppm)	$\delta$ [ <sup>2</sup> H <sub>8</sub> ]-Toluene (ppm)	$\Delta\delta$ (ppm)
H <sub>5a</sub>	2.51	2.03	+0.48
H <sub>5b</sub>	2.66	1.56	+1.10
H <sub>2</sub> , H <sub>3</sub>	4.84	3.77	+1.12
H <sub>1</sub> , H <sub>4</sub>	5.02	3.95	+1.10

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**Figure 2.** A) shows the <sup>1</sup>H{<sup>19</sup>F} NMR spectrum of **7** in CDCl<sub>3</sub>, and B) shows the <sup>1</sup>H{<sup>19</sup>F} NMR spectrum of **5** in [D<sub>8</sub>]toluene. There are significant upfield-shifted signals in toluene, of which the signal at 2.03 ppm(H<sub>5a</sub>) corresponds to the lower face hydrogen which is shielded by C-H/ $\pi$  electrostatic interaction with toluene, and indicative of facial polarity of the tetrafluorocyclopentane **5**.

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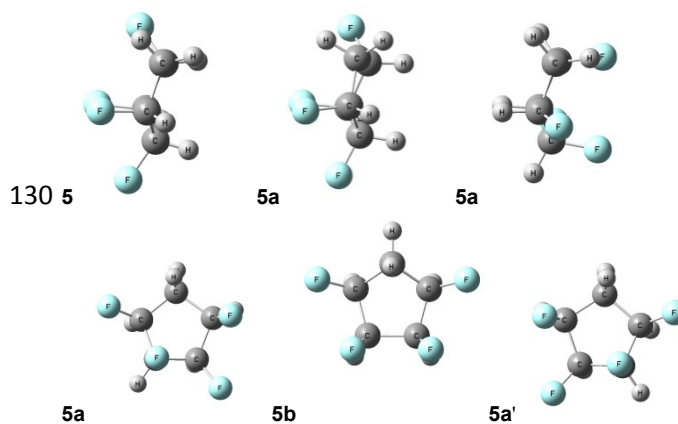
in Figure 1) and there are short CF...HC contacts between adjacent molecules indicative of a strong electrostatic attraction between the non equivalent faces of the rings. For cyclohexanes **1-3**, their polar aspect was revealed in comparative solution state NMR experiments, recorded in [<sup>2</sup>H<sub>2</sub>]-dichloromethane and then an aromatic solvent such as [<sup>2</sup>H<sub>6</sub>]-benzene or [<sup>2</sup>H<sub>8</sub>]-toluene. In those cases the axial hydrogens on the lower face of the ring experienced an anisotropic upfield shift due to the aromatic solvent associating with the electropositive (hydrogens) face of the ring. The same comparative experiment was conducted for cyclopentane **5** and the results are shown in Figure 2. A similar effect to that observed for **1-3** occurs. It is clear that all of the protons of **5** experience a significant upfield shift in [<sup>2</sup>H<sub>8</sub>]-toluene relative to CDCl<sub>3</sub>. However the least shifted proton ( $\Delta$  +0.48 ppm) is assigned to the upper face H<sub>5a</sub> proton of the only CH<sub>2</sub> methylene group in the ring. This smaller shift is consistent with its location in the more electronegative face of the cyclopentane ring and thus it is repelled from as close an association as the lower hydrogens with the aromatic solvent.

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As stated above, cyclopentane and its derivatives are conformationally flexible.<sup>7</sup> To explore the energies of the various conformations of **5** we performed density functional theory (DFT) optimisations at the B3LYP-D3/6-311+G(d,p) level, a level which has performed well in the conformational analysis of floppy fluorinated macrocycles.<sup>15</sup>

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**Figure 3.** Calculated structures of **5** (B3LYP-D3/6-311+G(d,p) level of theory); at the top left the X-ray structure, **5a** is the sole minimum in different orientations (**5a'** its mirror image).

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Optimisations starting from all possible unique permutations of the F and H atoms in an envelope form of **5** converged to one and the same minimum, **5a** (Figure 3). This minimum is slightly twisted from the structure in the solid state (compare **5** and **5a** in the top left of Figure 3). Although relatively small, this twist affords another envelope conformer, but now with the F atom at the tip of the envelope in an axial, rather than an equatorial position (compare the two structures **5a** in the top right of Figure 3; these are identical, but shown in different orientations). This small distortion occurs irrespective of the level of theory (other

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DFT functionals, MP2 level) or the environment (gas phase, a second molecule stacked on top or a polarisable continuum model). For an estimate of the energetic effect of this conformational twist, we performed a partial optimisation freezing the conformation of the C<sub>5</sub> ring to that observed in the solid (by fixing the C-C-C-C dihedral angles) and relaxing all other structural parameters. The resulting structure of **5**, denoted **5(fix)**, is 2.2 kcal/mol higher in energy than the fully optimised minimum **5a**. It may be that the structure in the crystal is affected by packing forces. A single molecule carved out of the crystal has a higher computed dipole moment (5.8 D) than the minimum **5a** (4.9 D, B3LYP-D3 level, see Figure S1 in the ESI for a plot of the electrostatic potential), which would serve to reinforce the stacking shown in Figure 1.

Two of the alternative envelope forms (with a CH<sub>2</sub> group at the envelope tip) can be optimised imposing C<sub>s</sub> symmetry. Essentially isoenergetic, they are not minima but transition states with a single imaginary frequency each, involved in the rearrangement of **5a** with its mirror image, **5a'**. One of these transition states, **5b**, is depicted at the bottom of Figure 3. The computed barrier for this pseudorotation-type rearrangement is  $\Delta H^\ddagger = 2.5$  kcal/mol at room temperature. This very low value is consistent with the apparent C<sub>s</sub> symmetry on the NMR time scale and the failure to detect any line broadening even at temperatures as low as -80 °C.

**Table 1:** Selected computed *J*(H,H) coupling constants (in Hz), BHandH/6-311+G(2d,p)/B3LYP-D3/6-311+G(d,p) level.

	H <sub>5a</sub> -H <sub>5b</sub>	H <sub>5a</sub> -H <sub>1,4</sub> <sup>a</sup>	H <sub>5b</sub> -H <sub>1,4</sub> <sup>a</sup>	MAD <sup>b</sup>
Expt <sup>c</sup> <b>5</b>	16.3	4.3	7.4	<i>n.a.</i>
Calc. <b>5a</b>	-15.1	4.5	7.6	<b>0.5</b>
Calc. <b>5(fix)</b> <sup>d</sup>	-15.8	1.8	7.6	<b>1.1</b>
Calc. <b>5b</b>	-10.9	10.8	5.6	<b>5.5</b>

<sup>a</sup>Mean value of couplings to H<sub>1</sub> and H<sub>4</sub> (See Table S1 in the Supporting Information for individual values). <sup>b</sup>Mean absolute deviation from experiment [absolute values used for *J*(H<sub>5a</sub>,H<sub>5b</sub>)]. <sup>c</sup> Experimental data (this work, CDCl<sub>3</sub>). <sup>d</sup>Partially optimised structure with C<sub>s</sub> conformation as observed in the solid.

Indirect spin-spin coupling constants involving the CH<sub>2</sub> group have been computed at the BHandH/6-311+G(2d,p) level.<sup>16</sup> The results collected in Table 1 clearly show that the apparent C<sub>s</sub> symmetry on the NMR time scale cannot arise from a static symmetric structure such as **5b**, because this shows large deviations between observed and computed *J*(H,H) values. Good agreement is obtained for the averaged couplings in both fully and partially optimised structures (assuming fluxional motion as discussed above); incidentally the values computed for the fully optimised minimum **5a** fit slightly better to experiment than those for **5(fix)**, with mean absolute deviations of 0.5 Hz and 1.1 Hz, respectively (see rightmost column in Table 1). These data thus support the interpretation that the dominant conformation in solution may be closer to the pristine minimum **5a** than the structure found in the solid state.

In conclusion we have prepared cyclopentane **5** and demonstrated experimentally by X-ray structure analysis in the solid state and by NMR analysis in solution, that it has highly polarised faces. Theory studies indicate fluxionality with a low barrier for pseudorotation, to the extent that the precise conformation observed in the solid may be different from that of the pristine molecule in the gas phase or in solution. The calculated

molecular dipole moment of minimised conformations is large ~5.0 D placing this cyclopentane in a similar and very polar category to that of the more conformationally defined cyclohexanes **1-2**. It follows that functionalised all-*cis* tetrafluorocyclopentanes would offer an interesting new motif for the design of performance molecules extending from organic materials to medicinal or agrochemicals research.

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## References

- A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan, *Chem. Commun.*, 2011, **47**, 8265 - 8267.
- A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch, D. O'Hagan, *Chem Commun*, 2012, **48**, 9643-9645.
- N. S. Keddie, A. M. Z. Slawin, T. Lebl, D. Philp, D. O'Hagan *Nature Chemistry*, 2015, **7**, 483-488.
- D. O'Hagan, *Chem. Soc. Rev.*, 2008, **37**, 308 - 319.
- (a) M. Bremer, P. Kirsch, M. Klasen-Memmer, K. Tarumi, *Angewandte, Chemie, Int. Ed.*, 2013, **52**, 8880-8896; (b) P. Kirsch, M. Bremer, *ChemPhysChem.*, 2010, **11**, 357-360.
- (a) T. Zeng, R. Claus, Y. Liu, W. Du, K. L. Cooper, *Smart Mater. Struct.*, 2000, **9**, 801 - 804; (b) G. M. Sessler, *J. Acoust. Soc. Am.*, 1981, **70**, 1596 - 1608; S. Horiuchi, Y. Tokura, *Nature Materials.*, 2008, **7**, 357 - 366.
- E.L. Eliel, S.H. Wilen and L.N. Mander, 'Stereochemistry of Organic Compounds', Wiley, New York, 1994.
- (a) N. P. Mankad, F. D. Toste, *Chem. Sci.*, 2012, **3**, 72-76; (b) V. A. Petrov, S. Swearingen, W. Hong, W. C. Petersen, *J. Fluorine Chem.*, 2001, **109**, 25-31.
- (a) D. F. Shellhamer, A. A. Briggs, B. M. Miller, J. M. Prince, D. H. Scott, V. L. Heasley, *J. Chem. Soc., Perkin Trans. 2*, 1996, 973 - 977; (b) M. Hudlicky, *J. Fluorine Chem.*, 1987, **36**, 373 - 384; (c) A. Baklouti, R. El Gharbi, *J. Fluorine Chem.*, 1979, **13**, 297 - 314;
- A. Bergomi, J. Burdon, T. M. Hodgins, R. Stephens, J. C. Tatlow, *Tetrahedron*, 1966, **22**, 43-51.
- M. Suzuki, H. Ohtake, Y. Kameya, N. Hamanaka, R. Noyori, *J. Org. Chem.*, 1989, **54**, 5292 - 5302.
- D. Wölker, G. Haufe, *J. Org. Chem.* 2002, **67**, 3015 - 3021.
- A. J. Durie, T. Fujiwara, R. Cormanich, M. Bühl, A. M. Z. Slawin, D. O'Hagan, *Chem. Eur. J.*, 2014, **20**, 6259-6263.
- (a) J. D. Dunitz, R. Taylor, *Chem. Eur. J.*, 1997, **3**, 89 - 98; (b) J.A.K. Howard, V. J. Hoy, D. O'Hagan, G. T. Smith, *Tetrahedron*, 1996, **52**, 12613-12622.
- M. J. Corr, R. A. Cormanich, C. N. von Hahmann, M. Bühl, D. B. Cordes, A. M. Z. Slawin, D. O'Hagan, *Org. Biomol. Chem.* **2016**, *14*, 211-219.
- Similar levels have been found to perform well for this property, see a.g.: (a) T. Kupka, *Magn. Reson. Chem.*, 2009, **47**, 674. (b) R. Suardiaz, C. Pérez, R. Crespo-Otero, J. M. García de la Vega, J. San Fabián, *J. Chem. Theor. Comput.*, 2008, **4**, 448

