

All-*cis* 1,2,3,4,5,6-hexafluorocyclohexane is a facially polarized cyclohexaneKeddie, N. S.; Slawin, A. M. Z.; Lebl, T.; Philp, D.; O'Hagan, D.* *Nat. Chem.* **2015**, 7, 483–488.**1. Introduction**

1.1. Fluorinated compounds

- Fluorine is often used to modulate the properties of organic materials.
 - Medicine, pesticide, polymer (PTFE etc.), electric materials (PVDF etc.) and so on...
- C-F bond is the strongest and most polarized.
 - Fluorinated compounds has polar hydrophobic properties.
- Polar molecules are important for organic electronics application.

1.2. Cyclohexane

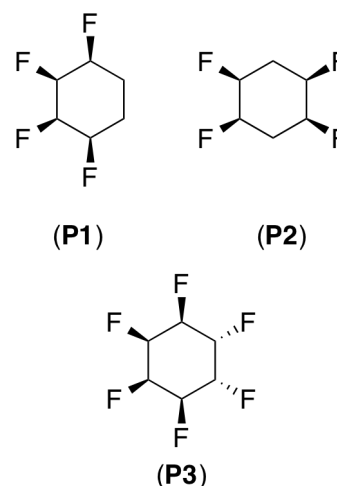
- In linear alkane C-F bonds tend to orientate away from each other due to dipolar repulsion.
 - If the conformation was fixed as aligned, highly polar organic molecules would result.
- Good core structural motif defined by its clear conformational preference.
 - It is suitable core structure to align C-F bonds for polar molecules.

1.3. Previous work

◦ Several kind of fluorinated cyclohexane were synthesized.

- All-*syn* tetrafluorocyclohexane^{1,2}
 - dipole moment $\mu = 4.9$ (**P1**) - 5.2 (**P2**)
- “4 up 2 down” hexafluorocyclohexane (**P3**) was synthesized from benzene³

⇒ “all up” hexafluorocyclohexane could have largest dipole moment.

**Figure 1.** Previously synthesized compounds

1.4. This work

- All-*cis* 1,2,3,4,5,6-hexafluorocyclohexane was synthesized.
- Molecular structure and crystal packing was analyzed from X-ray crystallography.
- Dipole moment and energy barrier of flipping was calculated from computational analysis and NMR study.

1.5. Isomers of hexafluorocyclohexane

- 8 configurations and a total 15 possible conformational isomers.

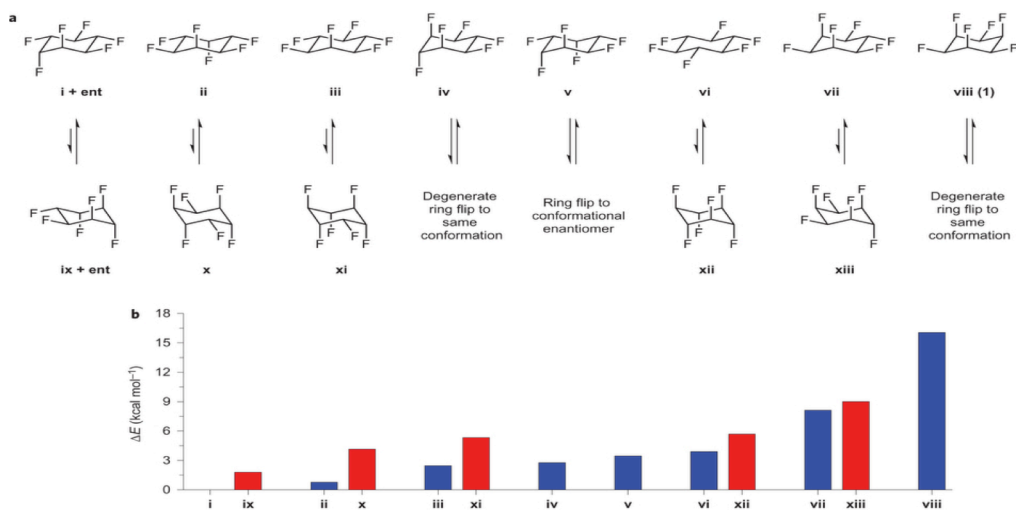


Figure 2. Isomers of hexafluorocyclohexane and its ground energies

→ All-cis (“all-up”) hexafluorocyclohexane has highest ground energy (> 15 kcal mol⁻¹ larger than most stable isomer.)

2. Results and Discussion

2.1. Synthesis

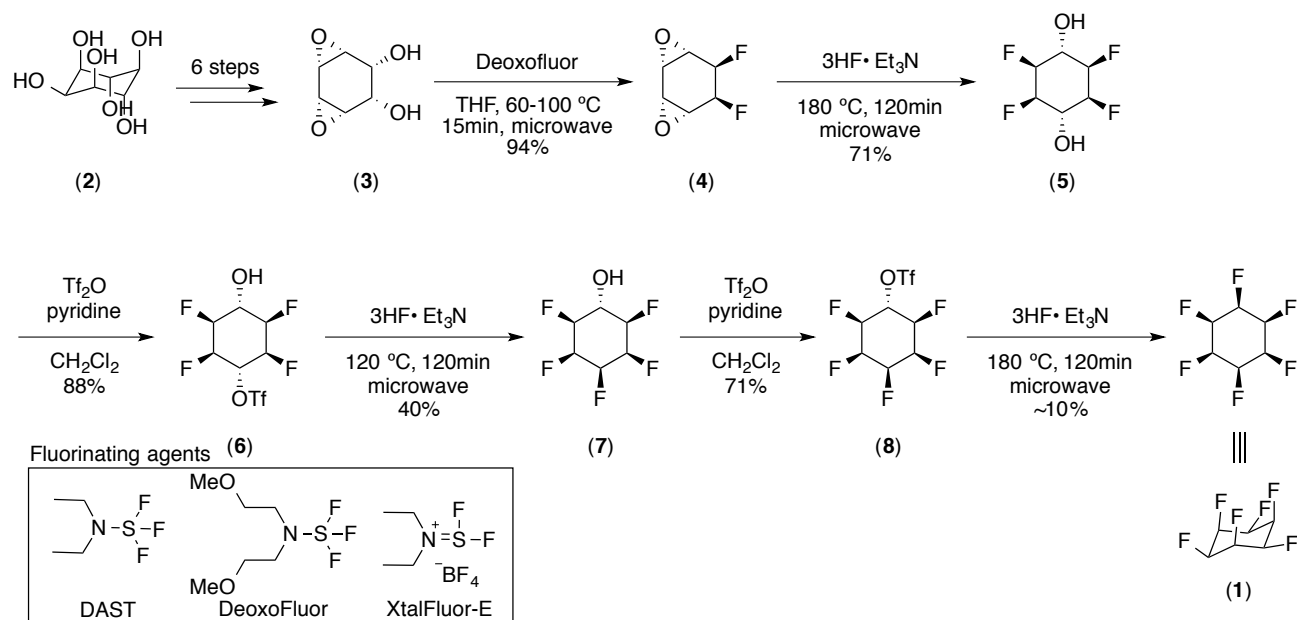


Figure 3. Synthetic route

- Synthesis was started from *myo*-inositol (2) via key intermediate (3)
- The strategy is stereospecific conversion of C-O to C-F bonds via S_N2 reactions occurring with

inversions of configuration.

- Direct deoxofluorination of compound **5** was failed to obtain compound **1** with DAST, Deoxofluor, XtalFluor-E.
- Due to large steric and electronic repulsion, elimination reaction might proceeded during last step.

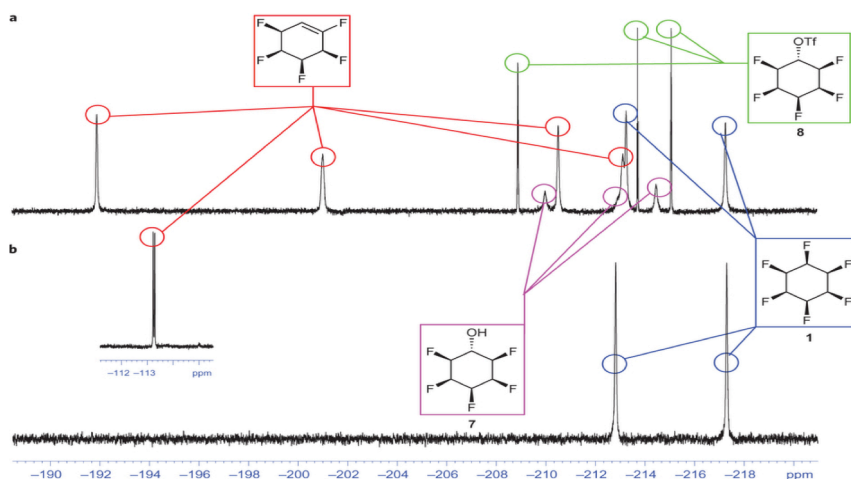


Figure 4. NMR spectra of reaction mixture of last step and product

- From NMR spectra of reaction mixture of last step, there are unreacted compound **8**, pentafluoroalcohol **7**, pentafluoro alkene and desired compound **1**.
- Pentafluoroalcohol **7** was generated via fluorolysis of triflyl group rather than fluoride ion displacement.

→Unusual reaction course for triflyl group, which indicates the difficulty in achieving the final substitution reaction.

- Total yield of compound **1** from **2** was ca. 2% (0.8 mg).

2.2. Structural analysis

- Compound **1** remained classic chair conformation for cyclohexane ring.
- Six C-F bonds locate alternating axial and equatorial position.
- The intermolecular axial/equatorial vicinal F...F distances ($F_{ax} - F_{eq}$) are shorter than the triaxial F...F distances ($F_{ax} - F_{ax}$)

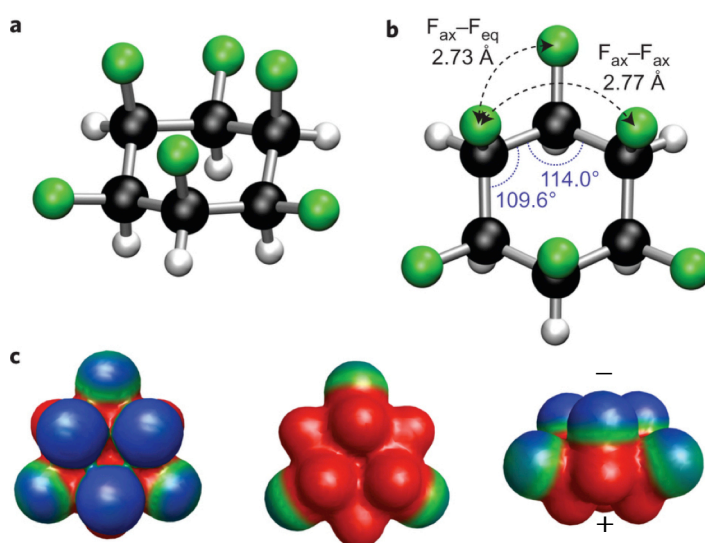


Figure 5. Molecular structure and electrostatic potential

→ Larger tension between the axial/equatorial fluorines.

→ These fluorines are forced back as the three axial fluorines become aligned to make overall dipole increased.

• The axial fluorines present a negative face of electrostatic potential and the axial hydrogen present a positive face of it.

→ The compound is facially polarized and has bipolar aspect.

• The value of dipole moment $\mu = 6.2 \text{ D}$ (calc. M11/611G(2d,p)), which is highest value of dipole among non-ionic, aliphatic or aromatic organic compound.

2.3. Crystal structure

• The individual molecules stack on top of one another in a manner consistent with electrostatic attraction between the non-equivalent faces of the cyclohexane.

2.4. Energy barrier of flipping

• From NMR study, the energy barrier to degenerate ring-flipping is $\Delta H^\ddagger = 13.3 \pm 0.43 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = -3.8 \pm 1.6 \text{ cal mol}^{-1}\text{K}^{-1}$. (cyclohexane $\Delta H^\ddagger = 10.8 \text{ kcal mol}^{-1}$, $\Delta S^\ddagger = 2.8 \text{ cal mol}^{-1}\text{K}^{-1}$)

→ The energy barrier is only a little higher than cyclohexane and suggested that the energy of ground state chair and transition structure are both raised.

3. Conclusion

- All-cis 1,2,3,4,5,6-hexafluorocyclohexane was synthesized.
- The compound has quite larger dipole moment and bipolar aspect.

4. Reference

- [1] Hagan, D. et al. *Chem. Commun.*, **2011**, 47, 8265 - 8267
- [2] Hagan, D. et al. *Chem. Commun.*, **2012**, 48, 9643 - 9645
- [3] Hagan, D. et al. *Angew. Chem. Int. Ed.*, **2012**, 51, 10086 - 10088

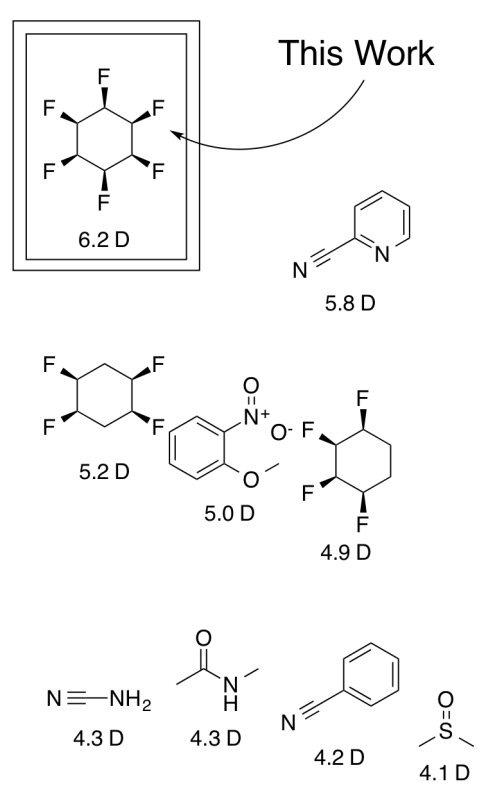


Figure 6. Dipole moment of organics

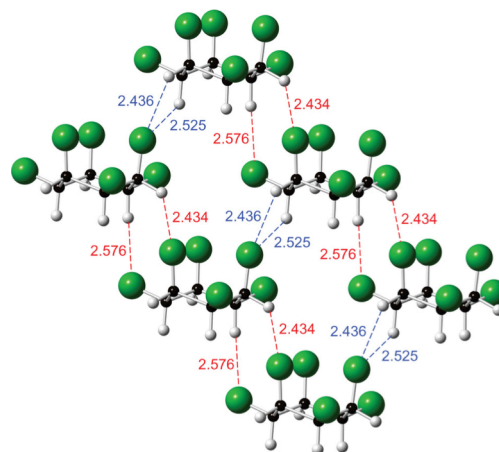


Figure 7. Crystal structure