

NOTE

The most polar nonionic aliphatic and aromatic compounds*

All-*cis* 1,2,3,4,5,6-hexafluorocyclohexane

In April 2015, David O'Hagan, Neil S. Keddie, and coworkers (University of St. Andrews, UK) reported the synthesis of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane. This is a ring molecule with all six fluorines pointing "up" and all six hydrogens looking "down."¹ The molecule is remarkable for having a molecular dipole value of 6.2 D. The magnitude of molecular

dipole moment is the highest for a non-ionic, aliphatic, or aromatic organic compound. It is more polar than most polar organic molecules, such as 2-pyridinecarbonitrile (5.78 D), 2-methoxy-nitrobenzene (5.0 D), *N*-methylacetamide (4.3 D) and benzonitrile (4.18 D). The target molecule is synthesized in 12 steps (Figure 1). The product is isolated as a crystalline solid.

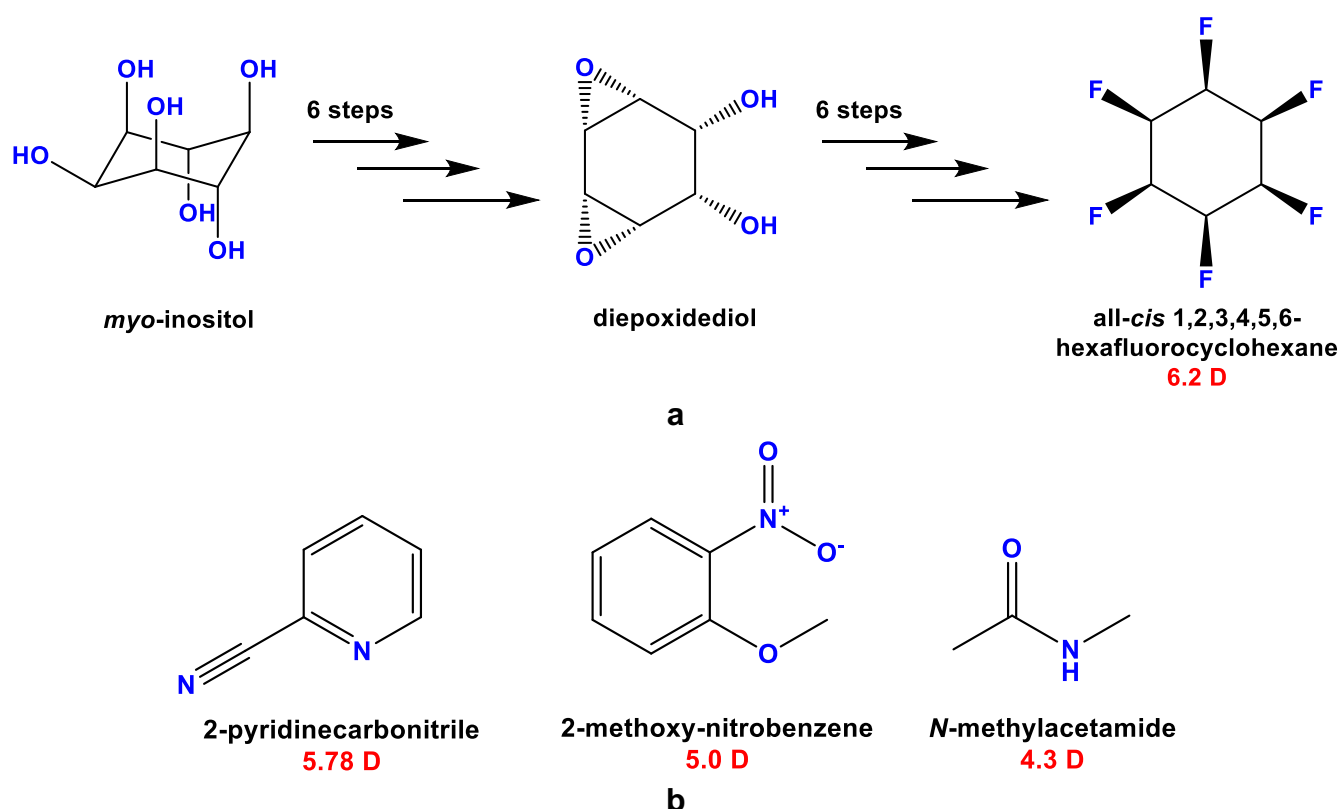


Figure 1. (a) Schematic presentation for the synthesis of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane of molecular dipole moment 6.2 D. This dipole moment is the highest for a non-ionic, aliphatic, or aromatic organic compound. (b) Examples of some highly polar organic molecules. Redrawn from Reference [1]. Keddie *et al.*, *Nat. Chem.* **2015**, *7*, 483–488. Copyright © 2015, Springer Nature.

* Contributed by S. Samal, Editor, CSR

The synthesis commenced from myo-inositol, which was converted to diepoxidediol (*cis*-dianhydroinositol). This is an appropriately functionalized cyclohexane with all of the C–O bonds on one face of the cyclohexane ring. The synthesis of all-*cis* 1,2,3,4,5,6-hexafluoro-cyclohexane was then achieved by progressing through a sequence of deoxyfluorination reactions occurring with an inversion of configuration at each carbon atom to accomplish the desired all-*cis* arrangement of the fluorine atoms.

X-ray analysis reveals a classic chair conformation for the cyclohexane with six alternating axial and equatorial C–F bonds (Figure 2). The intramolecular $F_{ax}\cdots F_{ax}$ (1,3-diaxial) distances (~ 2.77 Å) are longer than the vicinal $F_{ax}\cdots F_{eq}$ (1,2-axial equatorial) distances (~ 2.73 Å), suggesting a slightly higher tension between the axial/equatorial fluorines than between axial/axial fluorines. The tension is also manifested in the C–C–C angles, which alternate as wider ($\sim 114^\circ$) and narrower

($\sim 109^\circ$) angles around the ring. This suggests that these fluorines are forced back as the three axial fluorines become aligned, increasing the overall molecular dipole. Space-filling models of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane show that the molecule is highly polarized with a negative (green, fluorine) and a positive (grey, hydrogen) face. Clustering the highly electronegative fluorine atoms in close proximity generates cyclohexane derivative with a high molecular dipole ($\mu = 6.2$ D), making it the most polar nonionic aliphatic compound known to exist. The derivatives of such a fluorinated ring system should impart particular properties when incorporated into higher molecular architectures for applications ranging from organic materials to bioactive species or for exploration in supramolecular chemistry. In a supramolecular arrangement, if hydrogen atoms absorb to the lower face, the resulting material will become positively polarized, possessing a permanent transverse electric field.

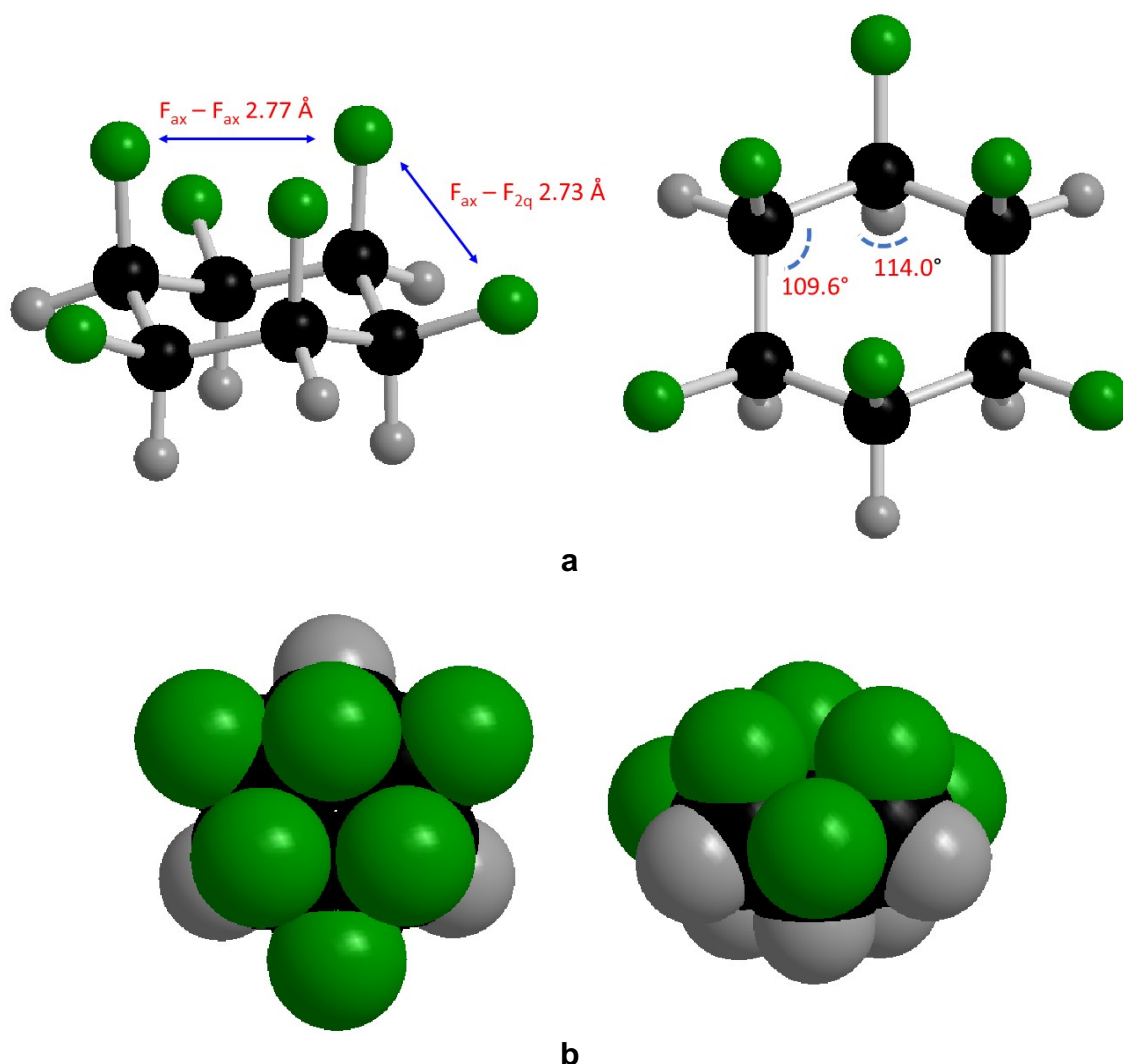


Figure 2. (a) Two structural orientations of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane with alternating axial and equatorial C–F bonds. 1,3-Diaxial F – F distance is slightly longer than the vicinal axial – equatorial F – F distance. The mean C–C–C angles vary around the ring alternating at 109.6° and 114.0° . (b) Space-filling models of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane. The top and side views show that the molecule is highly polarized with a negative (green, fluorine) and a positive (grey, hydrogen) face. Redrawn from Reference [1]. Keddie *et al.*, *Nat. Chem.* **2015**, *7*, 483–488. Copyright © 2015, Springer Nature.

Hexasubstituted benzene derivatives with ultrastrong dipole moments

In February 2016, Klaus Müllen and coworkers of the Max Planck Institute for Polymer Research made the world's most polar aromatic compounds.² They synthesized several hexa-substituted benzenes (Figure 3). Electron-withdrawing cyano groups and electron-donating amino groups align the molecule's electron density in the same direction. The dipole moments of the benzene derivatives are determined by dielectric spectroscopy and DFT methods. These derivatives have dipole moments above 10 debye. The authors did the functionalization of diaminophthalonitrile to its brominated and tetracyanated

derivatives. Furthermore, they demonstrated a new synthetic route towards dihydrobenzimidazoles through the use of acetals instead of ketones under mild conditions. The compounds are remarkable for being the most polar neutral molecules now known to exist. Such dipole moments are desirable in ferroelectrics, nonlinear optics, and in organic photovoltaics. Blending organic semiconductors with hexa-substituted benzene derivatives that have ultrastrong dipole moments will lead to enhanced efficiency of charge separation by decreasing the exciton binding energy.

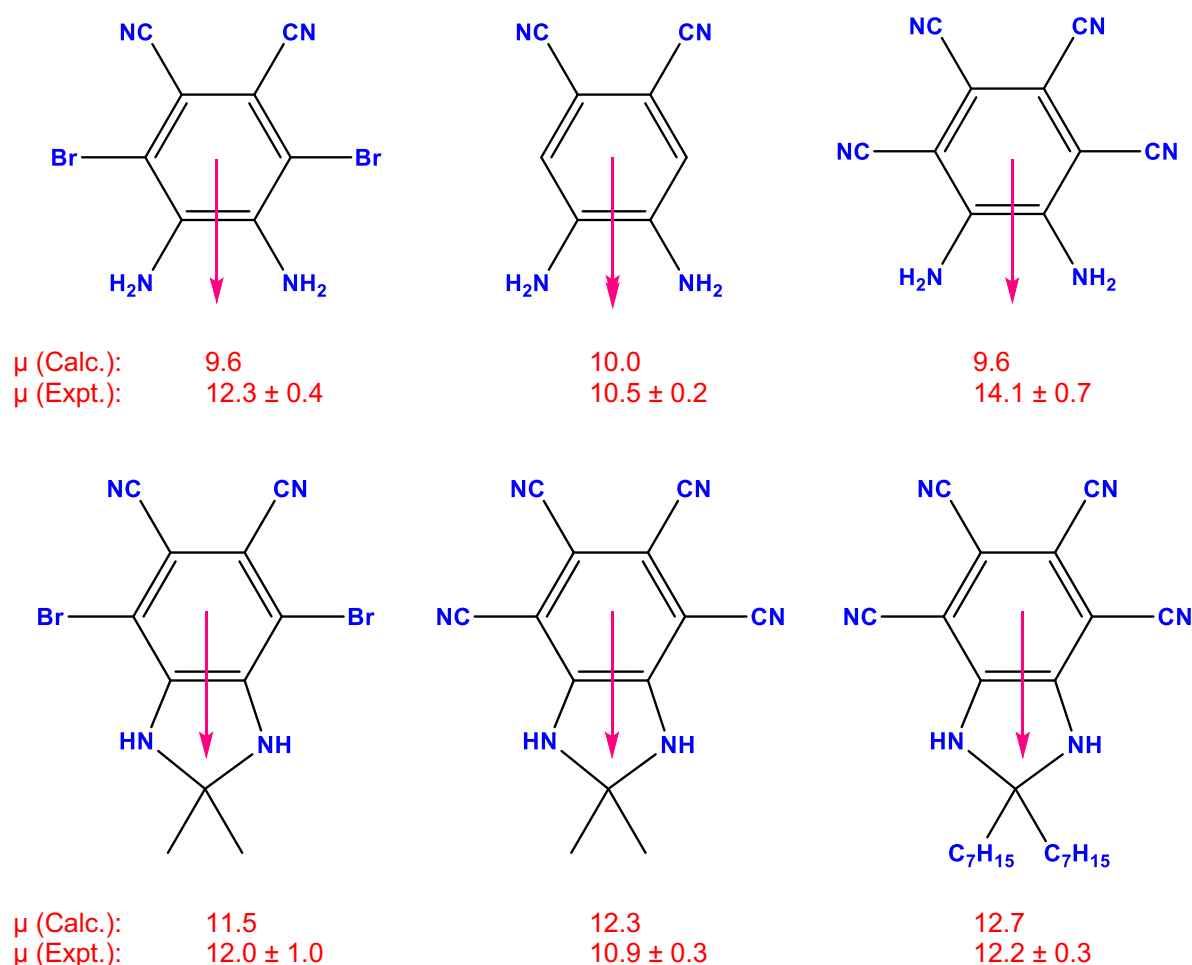


Figure 3. The hexa-substituted benzenes with their calculated and experimental dipole moments. Redrawn from Reference [2]. Wudarczyk *et al.* *Angew. Chem. Int. Ed.* **2016**, *55*, 3220-3223. Copyright © 2016 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

References

1. N. S. Keddie, A. M. Slawin, T. Lebl, D. Philp, D. O'hagan, All-cis 1, 2, 3, 4, 5, 6-hexafluorocyclohexane is a facially polarized cyclohexane. *Nature Chem.* **2015**, *7*, 483–488.
2. J. Wudarczyk, G. Papamokos, V. Margaritis, D. Schollmeyer, F. Hinkel, M. Baumgarten, G. Floudas, K. Müllen, Hexasubstituted benzenes with ultrastrong dipole moments. *Angew. Chem. Int. Ed.* **2016**, *55*, 3220-3223.

Flashback

Disubstituted cyclohexanes

The structure of *trans*-1,2-dimethylcyclohexane is shown in Figure 4. The diequatorial (*e,e*) and diaxial (*a,a*) forms are readily interconvertible. The difference in stability of the two forms, based on the number of butane gauche interactions, is 2.7 kcal./mole. At room temperature, the molecule is almost entirely (99%) in the diequatorial form. Both *e,e* and *a,a* forms are dissymmetric and possess a non-identical mirror image which represents the enantiomer. Therefore, *trans*-1,2-dimethylcyclohexane forms a *dl* pair. With *cis*-1,2-dimethylcyclohexane (Figure 4, bottom), each conformational isomer of this compound has one axial and one equatorial substituent. Since the two forms are equally stable, half of the molecules exist in one and a half in the other. The molecules

have no element of symmetry and, thus, should be optically active. However, the conformational isomers are also mirror images (seen by rotating the *a,e* isomer by an angle of 120° around a vertical axis). Since the two isomers are present in equal amounts, *cis*-1,2-dimethylcyclohexane exists as a *dl* pair. But since the potential barrier between the isomers is too low to allow separation, the *dl* pair is inseparable. For the all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane, the vicinal C – F bonds are axial-equatorial (*a,e*), or equatorial-axial (*e,a*). The molecule with *a,e,a,e,a,e* conformation of the C – F bonds when inverted will have the corresponding C – F bonds oriented as *e,a,e,a,e,a*. In either of the energetically similar forms, all the F atoms will be aligned on one side of the molecule.

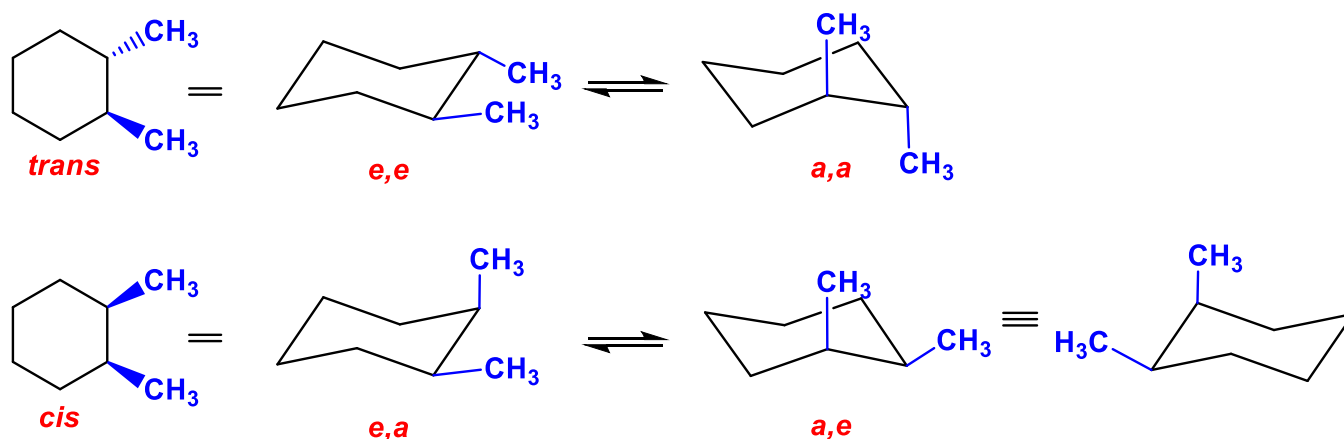


Figure 4. *trans*-1,2-Dimethylcyclohexane (one enantiomer) and *cis*-1,2-dimethylcyclohexane. Redrawn from *Stereochemistry of Carbon Compounds* by Ernest L. Eliel, Tata McGraw-Hill Publishing Company, New Delhi, 1975, Chapter 8, p-211-212.
