ChemComm

Cite this: *Chem. Commun.*, 2012, **48**, 9643–9645

www.rsc.org/chemcomm

COMMUNICATION

Fluorocyclohexanes: synthesis and structure of all-*syn*-1,2,4,5-tetrafluorocyclohexane†

Alastair J. Durie,[a] Alexandra M. Z. Slawin,[a] Tomas Lebl,[a] Peer Kirsch[b] and David O'Hagan*[a]

Received 29th June 2012, Accepted 3rd August 2012
DOI: 10.1039/c2cc34679f

The all-*syn* isomer of 1,2,4,5-tetrafluorocyclohexane is prepared and characterised by NMR and X-ray crystallography. It emerges to be a particularly polar cyclohexane analogue with differentially polarised faces.

Recently we reported the synthesis of the all-*syn* isomer of 1,2,3,4-tetrafluorocyclohexane **1**.[1] This was the first example of a tetrafluorocyclohexane to be prepared and unexpectedly it was a solid material at room temperature. X-ray crystallography revealed a chair conformation for cyclohexane **1** in the solid state with two C–F bonds orientated 1,3-diaxial (Fig. 1). Although formally non-chiral, cyclohexane **1** crystallised as a set of enantiomeric dimers. The two polar axial C–F bonds running parallel to each other contribute to a large molecular dipole (4.91 Dy).

As part of a general programme aimed at preparing aliphatic organic molecules containing vicinal C–F bonds of defined relative stereochemistry,[2] we now report a second example of an all-*syn*-tetrafluorocyclohexane, with the synthesis of isomer **2**. Diethylsulfur trifluoride (DAST) has been shown to react with epoxides at high temperature (50–70 °C) to yield *syn*-difluorides.[3] Therefore we decided to attempt this reaction with a diepoxide. Thus *syn*-1,2,4,5,-tetrafluorocyclohexane **2** was prepared directly by treatment of diepoxide **4** with DAST, at 70 °C as illustrated in Scheme 1.[4] The tetrafluorocyclohexane was isolated after repeated chromatography in 24% yield. Although a modest recovery the stereospecific incorporation of four C–F bonds makes this a useful reaction.

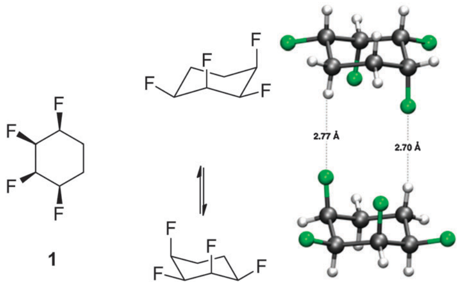
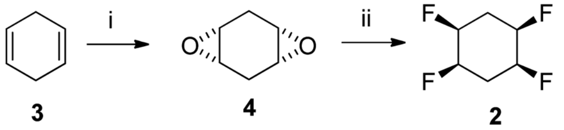


Fig. 1 Ring interconversion of **1** generates conformational enantiomers, with the fluorine atoms on one face of the molecule.



Scheme 1 Synthesis of **2**; (i) *m*CPBA, CH_2Cl_2, −15 → −10 °C, 52%. (ii) DAST, 70 °C, 24%.

The $^{19}F\{^1H\}$-NMR spectrum of **2** was recorded at ambient temperature, however this was featureless and broad (Fig. 2A). When the $^{19}F\{^1H\}$-NMR spectrum of **2** was recorded at a low temperature (193 K in $[^2H_8]$-toluene) two signals resolved corresponding to an equivalent set of axial and equatorial C–F bonds (Fig. 2B). The signals show an expected second order AA′XX′ pattern. The ^1H-NMR spectrum recorded at 193 K in both $[^2H_8]$-toluene (Fig. 3A) or $[^2H_2]$-dichloromethane (Fig. 3B) resolved into six individual proton signals due to relatively slow ring interconversion. On examination the signals for the three axial (red) protons $1H_a$ and $3H_a$ on the lower face of **2** are significantly shielded (Δ + 1.69 and Δ + 1.31 ppm), and the axial proton on the top face $4H_a$ is deshielded, (Δ − 0.15 ppm) in $[^2H_8]$-toluene relative to the

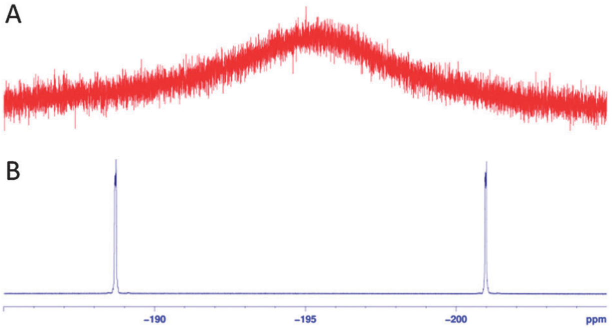
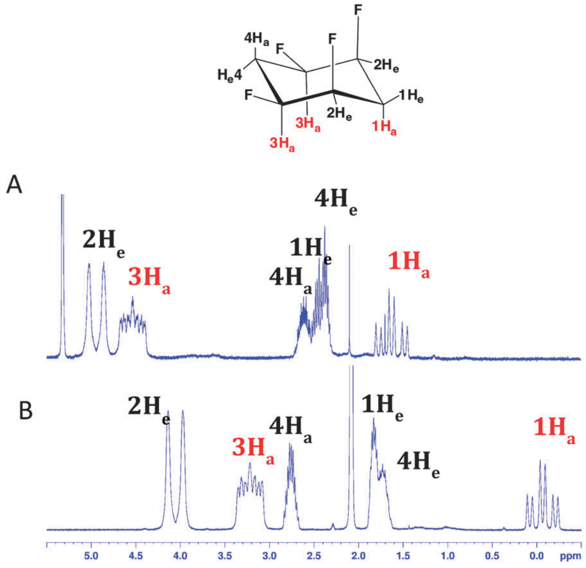


Fig. 2 (A) ^{19}F-NMR (282 MHz) of **2** at 298 K, in $[^2H_8]$-toluene. (B) ^{19}F-NMR (282 MHz) of **2** at 193 K, in $[^2H_8]$-toluene. The peak in the upper spectrum is over 3000 Hz wide, which resolves to an axial (−188.7 ppm) and an equatorial (−201.0 ppm) signal at low temperature.

---

[a] *University of St Andrews, School of Chemistry and Centre for Biomolecular Sciences, North Haugh, St Andrews, Fife, KY16 9ST, UK. E-mail: do1@st-andrews.ac.uk; Fax: +44 (0)1334 463800; Tel: +44 (0)1334 467171*
[b] *Merck KGaA, Frankfurter Str. 250, D 64293 Darmstadt, Germany*

† Electronic supplementary information (ESI) available. See http://dx.doi.org/10.1039/c2cc34679f



Proton Signal	δ CD_2Cl_2 (ppm)	δ [$^2H_8$]-Toluene (ppm)	Δδ (ppm)
$1H_a$	1.63	-0.06	+1.69
$1H_e$	2.46	1.74	+0.72
$2H_e$	4.94	4.06	+0.88
$3H_a$	4.53	3.22	+1.31
$4H_a$	2.61	2.76	-0.15
$4H_e$	2.37	1.84	+0.53

Fig. 3 (A) Low temp ^{1}H-NMR (300 MHz) of **2** at 193 K, in [$^2H_2$]-dichloromethane. (B) Low temp ^{1}H-NMR (300 MHz) of **2** at 193 K, in [$^2H_8$]-toluene. The upfield shifted peaks at 3.22 ppm ($3H_a$) and −0.06 ppm ($1H_a$) correspond to the lower face axial hydrogens which are shielded by C–H/π electrostatic interactions with toluene at low temperature.

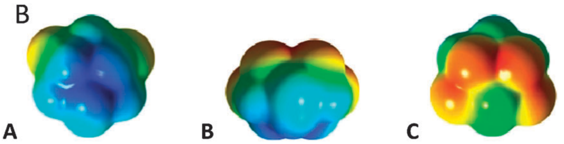


Fig. 4 Calculated electrostatic surface potential maps of **2** (geometry optimization: B3LYP/6-311+G(2d,p) level of theory; red corresponds to a partial charge of −0.043 *e*, blue to +0.097 *e*).[6] (A) A view of the lower 'hydrogen' face of **2** showing three axial and two equatorial (blue) hydrogens. (B) A side view of **2** showing the upper −ve (red) face and a lower +ve (blue) face. (C) A view of the upper 'fluorine' face of **2** with two axial (central) and two equatorial fluorine (red) atoms. The axial hydrogen is neutral (green).

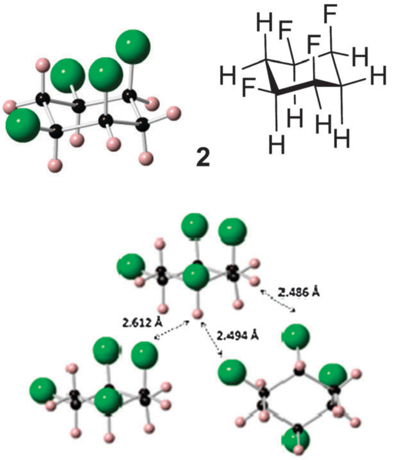


Fig. 5 Top: X-Ray structure and drawing of **2** showing a pair of 1,3-diaxial and 1,3-diequatorial C–F bonds. Bottom: Packing of three molecules of **2** in the X-ray structure showing intermolecular contacts between the positive and negative faces of the molecules. The distances are the shorter intermolecular CF···HC contacts.

spectrum recorded in [$^2H_2$]-dichloromethane (Fig. 3A). Most striking is the unusually high field signal at −0.06 ppm (dt), assigned to the axial $1H_a$ proton, on the lower face of **2** lying antiperiplanar to the two axial C–F bonds. The observed shifts in toluene are indicative of a C–H/π electrostatic interaction between the lower face axial protons and the π system of the aromatic ring.[5] This suggests that the two faces of the molecule are differently polarised. To explore this further an electrostatic surface potential map of **2** was calculated. This confirms that the two faces of the molecule are differentially polarised as illustrated in Fig. 4 with the upper 'fluorine' face electronegative and the lower 'hydrogen' face electropositive.

A suitable crystal (mp = 107–109 °C) of **2** was submitted for X-ray structure analysis and the resultant structure is shown in Fig. 5.

The structure of **2** posesses a set of axial and a set of equatorial C–F bonds each located 1,3 to each other. Ring interconversion generates an identical structure, unlike **1** which is enantiomeric. The intramolecular F···F distance between the two diaxial fluorines in **2** is 2.80 Å, and the C–F bonds are splayed 5.6° from perpendicular, presumably to minimise dipolar repulsion. The crystal packing arrangements between molecules of **2** reinforces the electrostatic analysis illustrated in Fig. 4 where the upper 'fluorine' faces contact the lower 'hydrogen' faces in the solid state (Fig. 5). Consistent with this are some relatively short CF···HC contacts (∼2.49 Å) indicating weak electrostatic hydrogen to fluorine contacts.[7] In order to explore how close the experimental structure was to a theory determined (MP2/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) + ZPE level of theory)[6] minimum gas phase structure, the X-ray coordinates were used as the starting point and the F···F distance was varied around 2.80 Å. The changes in energy (blue) and dipole moment (red) relative to the F···F distance are presented in a graphical form in Fig. 6. The lowest energy structure which emerged from this study had the intramolecular F···F distance at 2.81 Å similar to the experimental observation (2.80 Å). The calculated molecular dipole moment for **2** is 5.24 Dy, a higher value than that determined for isomer **1** (4.91 Dy).

The high polarity is consistent with the electrostatic surface potential map illustrated in Fig. 4. Increased splaying of the diaxial C–F bonds reduces the overall molecular dipole moment (Fig. 6), however the relative energy begins to increase due to emerging eclipsing interactions including those between vicinal C–F bonds. Thus the equilibrium structure is

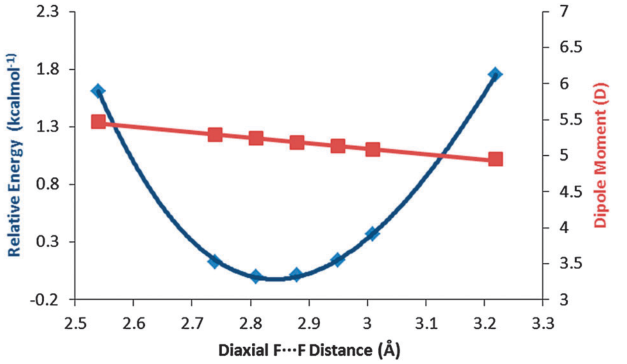


Fig. 6 Calculated structures of **2** (MP2/6-311+G(2d,p)//B3LYP/6-311+G(2d,p) + ZPE level of theory) varying the F···F distance.[6] The relative energy change (blue) in kcal mol^{-1}, generates a minimum structure at 2.81 Å and a dipole moment of 5.24 Dy.

tensioned between C–F/C–F eclipsing and C–F/C–F diaxial interactions.

In summary all-*syn* 1,2,4,5-tetrafluorocyclohexane **2** has been prepared and analysed both by solution and X-ray structure analysis. It is calculated to have a large dipole moment (5.18 Dy) for an aliphatic organic compound arising largely due to the 1,3-diaxial C–F bonds in the equilibrium structure. This leads to a polarisation with an electropositive and an electronegative face of the molecule. The structural motifs of **1** and **2** suggest design features for the incorporation of these moieties into liquid crystalline materials which demand molecular species with low viscosity but high polarity.

We are grateful to an Advanced Investigator Grant from the European Research Council (GO802567) and EPSRC (BB/F007426/1) for financial support. We are also grateful for EPSRC National Mass Spectrometry Swansea for Mass Spectrometry Analysis.

References

1 A. J. Durie, A. M. Z. Slawin, T. Lebl, P. Kirsch and D. O'Hagan, *Chem. Commun.*, 2011, **47**, 8265–8267.

2 (*a*) D. O'Hagan, *J. Org. Chem.*, 2012, **77**, 3689–3677; (*b*) D. Farran, A. M. Z. Slawin, P. Kirsch and D. O'Hagan, *J. Org. Chem.*, 2009, **74**, 7168–7171; (*c*) L. Hunter, P. Kirsch, A. M. Z. Slawin and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2009, **48**, 5457–5460; (*d*) M. Nicoletti, M. Bremer, P. Kirsch and D. O'Hagan, *Chem. Commun.*, 2007, 5075–5076; (*e*) L. Hunter, A. M. Z. Slawin, P. Kirsch and D. O'Hagan, *Angew. Chem., Int. Ed.*, 2007, **46**, 7887; (*f*) L. Hunter, D. O'Hagan and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2006, **128**, 16422–16423; (*g*) M. Nicoletti, D. O'Hagan and A. M. Z. Slawin, *J. Am. Chem. Soc.*, 2005, **127**, 482–483.

3 M. Hudlicky, *J. Fluorine Chem.*, 1987, **36**, 373–384.

4 DAST is unstable at 70 °C and is potentially explosive.

5 G. Dombi, J. Mattinen, K. Pihaja and J. Czombos, *Tetrahedron*, 1986, **42**, 2359–2367.

6 M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery Jr, T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez and J. A. Pople, *Gaussian 03, Revision D.01*, Gaussian, Inc., Wallingford CT, 2004.

7 (*a*) J. A. K. Howard, V. J. Hoy, D. O'Hagan and G. T. Smith, *Tetrahedron*, 1996, **52**, 12613–12622; (*b*) J. D. Dunitz and R. Taylor, *Chem.–Eur. J.*, 1997, **3**, 89–98.