The multi-vicinal fluoroalkane motif: an examination of 2,3,4,5-tetrafluorohexane stereoisomers†

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Three unique diastereoisomers of 2,3,4,5-tetrafluorohexane have been prepared, compounds intermediate between hexane and perfluorohexane in their degree of fluorination, and they show very different conformational behaviour and physical properties.

Introduction

Multi-vicinal fluoroalkanes (Fig. 1) are a new class of compounds which are conceptually intermediate between alkanes and perfluoroalkanes in terms of their degree of fluorination. As a class, these fluoroalkanes are expected to possess novel physical and chemical properties relative to hydrocarbons and perfluorocarbons, and within the class, it is anticipated that different diastereoisomers will possess unique characteristics due to dipole orientations and stereoelectronic effects associated with differently aligned C–F bonds. Such compounds have the potential to contribute properties to polar organic materials in which conformational control plays an important role (*e.g.* self-assembling monolayers and liquid crystals).

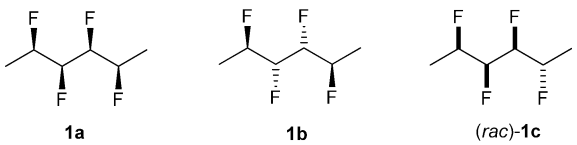


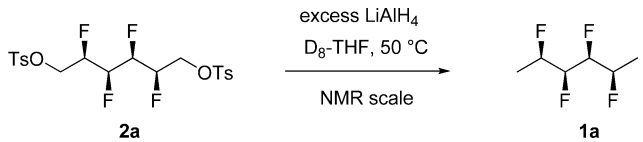
Fig. 1 Multi-vicinal fluoroalkanes **1a–c**.

We have described the diastereoselective syntheses of compounds containing three[1] and four[2,3] vicinal fluorines within larger molecular architectures, with the aim of establishing the conformational preferences of such multi-vicinal fluoroalkane motifs. In this article we report the synthesis of three 2,3,4,5-tetrafluorohexane diastereoisomers (Fig. 1). The preparation of these compounds has provided the first opportunity to investigate the physical and conformational properties of a multi-vicinal fluoroalkane motif in the absence of other functional groups.

Results and discussion

Synthesis

We have recently reported the synthesis of the ditosylates **2** (Scheme 1), examining their solid state X-ray structures and ^{1}H- and ^{19}F- NMR derived solution conformations.[3] These compounds gave an insight into the different conformational behaviour of the main chain for each of the tetra-vicinal fluoroalkane diastereoisomers **1a–c**, although the influence of the tosyl group could not be delineated. Accordingly, analyses of the parent tetrafluorohexane series **1a–c** became an objective.



Scheme 1 Synthesis of **1a**.

Compounds **1a–c** were prepared by treating the 1,6-ditosylate precursors **2a–c** with an excess of lithium aluminium hydride (Scheme 1). These reactions required quite forcing conditions, perhaps due to the deactivating α-fluorine substituents, but the absence of any obvious elimination products revealed an unexpected robustness of the vicinal fluoroalkane motif. Only milligram quantities of the 1,6-ditosylate precursors could be prepared through an 11-step sequence,[3] and the lower molecular weight and volatile nature of products **1a–c** meant that these compounds could not be isolated, but they were characterised by GC–MS and by NMR in solution. The reactions with $LiAlH_4$ were carried out in deuterated solvent ($^{2}H_8$-THF) to facilitate direct acquisition of ^{1}H-NMR spectra. Compounds **1a** and **1b** are enantiopure, while compound **1c** is racemic.

Conformational analysis

The ^{1}H- and ^{19}F-NMR spectra of **1a–c** provide complete sets of $^{3}J_{HH}$ and $^{3}J_{HF}$ values for each isomer[4] (Fig. 2). This shows that in solution, each of the three tetrafluoroalkanes adopts a unique carbon chain conformation.[5,6] For compounds **1a** and **1c**, the *J* values are generally consistent with the computed minimum-energy conformations[3] but are somewhat intermediate in magnitude, suggesting some averaging due to contributions from

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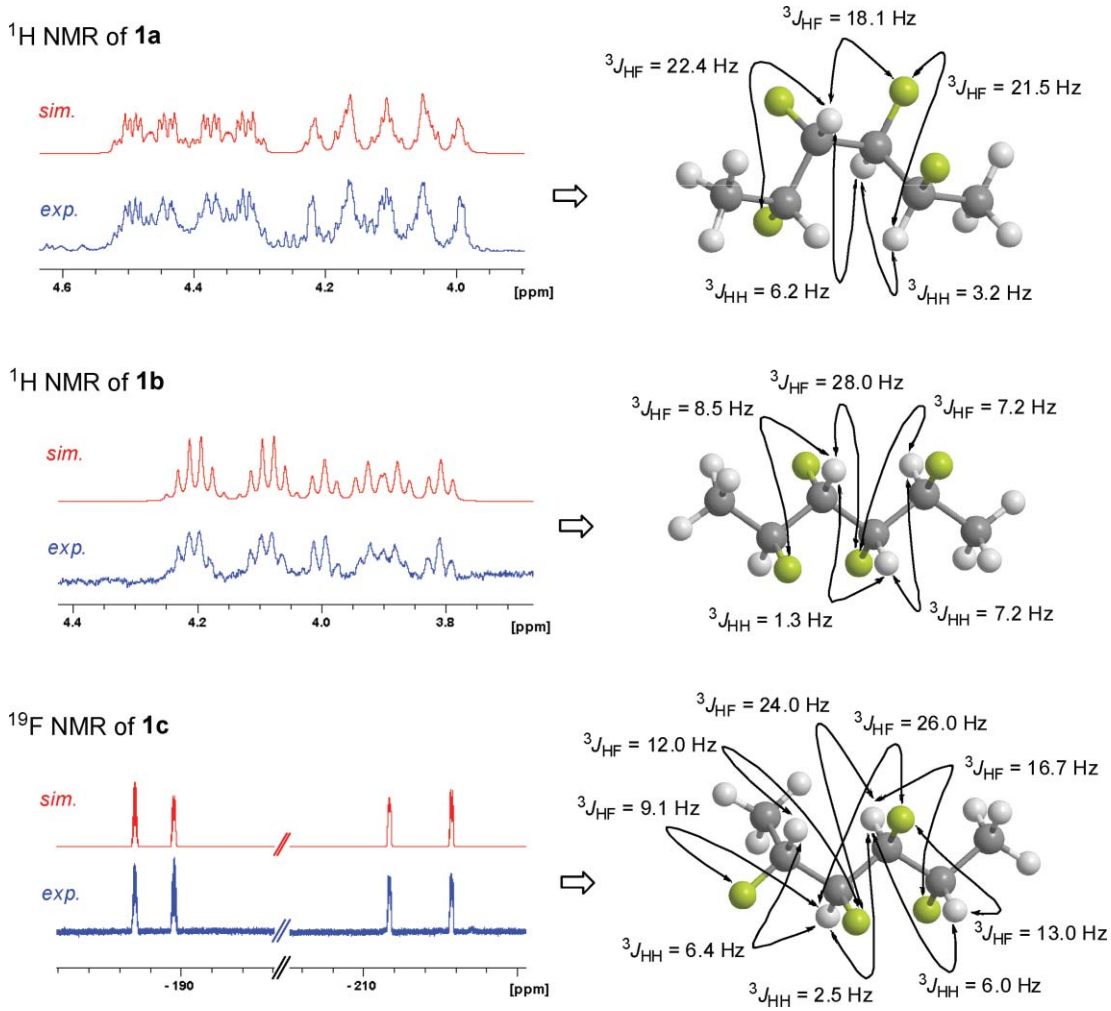

Fig. 2 NMR data and solution conformations for **1a** (top), **1b** (middle) and **1c** (bottom). The ^{1}H- and ^{19}F-NMR spectra of **1a–c** exhibited non-first-order character, so they were simulated using Bruker TopSpin software. In each case, the resulting $^3J_{HF}$ and $^3J_{HH}$ values indicate *gauche* and *anti* dihedral angles[5] that are consistent with the minimum-energy gas-phase conformers[3] of **1a–c** (illustrated here as ball-and-stick models; C grey, H white, F yellow).

other conformers. In contrast, the J values for **1b** clearly indicate *gauche* or *anti* dihedral angles consistent with the minimum-energy linear conformation, indicating that this conformation is strongly preferred in solution.

Variable-temperature NMR experiments were performed in order to investigate whether the minimum-energy conformers of **1a–c** would dominate more at low temperature. The available temperature range for NMR experiments was quite narrow due to the mixed solvent system used, but no clear differences in the J values were observed between room temperature and −20 °C for all isomers.[4]

Overall, for each of **1a–c**, a close conformational analogy with the corresponding 1,6-ditosylate diastereoisomers **2**[3] is observed. These results reinforce our earlier conclusion[3] that the dominant conformational driving force in these multi-vicinal fluoroalkane motifs is avoidance of 1,3-F···F and 1,3-F···CH_3 repulsive interactions.[7] The vicinal fluorine *gauche* effect,[8] which recognises that 1,2-vicinal fluorines have a *gauche* preference, is a weaker effect, and only influences the alkane conformation in the absence of 1,3-repulsive interactions.

Table 1 GC–MS data for hexane, perfluorohexane and **1a–c**[4]

Compound	Dipole/D[a]	Retention time/min
Perfluorohexane	0.09	10.2
Hexane	0.00	14.8
1b	0.25	17.6
1c	3.54	18.9
1a	2.19	19.4

[a] Dipole moment calculated for the minimum-energy conformer.

Physical properties

With the conformational preferences of **1a–c** established, some assessment of their physical properties was explored. The individual diastereoisomers were analysed by GC–MS and compared to hexane and perfluorohexane (Table 1).[4] The very non-polar perfluorohexane had the shortest retention time on GC, followed by hexane. The tetrafluorohexanes **1a–c** all have significantly longer retention times consistent with the polarised nature ($H^{\delta+}$–C–$F^{\delta-}$) of the individual fluoromethylene units.

Furthermore, and perhaps unexpectedly, the retention times vary significantly within the series **1a–c**. Molecular dipole moments were calculated at the B3LYP/6-311+G(2d,p) and MP2/6-311+G(2d,p) levels of theory[9] for the minimum-energy conformers for each isomer, and these values are shown in Table 1. Diastereoisomer **1b** has a significantly lower molecular dipole than **1a** and **1c**, and consistent with that, it has the shortest retention time. Diastereoisomers **1a** and **1c** eluted later than **1b**, but not in the expected order as predicted by the molecular dipole moment of the lowest energy conformers. However, compounds **1a** and **1c** elute quite close together with substantially longer retention times than **1b**, consistent with dipole moments that are much larger than **1b** but similar in magnitude to each other. Also, some degree of conformational mobility could cause the dipole moments of **1a–c** to fluctuate, contributing to the difficulty in predicting accurately their relative order of elution.[10] Another possible complicating factor is the enantiopurity of **1a** compared with the racemic **1c**.

Conclusions

In summary, we have described the synthesis and evaluation of three diastereoisomeric 2,3,4,5-tetrafluorohexanes. NMR analysis of **1a–c** confirms a different conformational preference for all three hydrocarbon chains, which arises as a consequence of competing 1,3-difluoro repulsion, the dominating effect, and a preference for vicinal 1,2-difluoro *gauche* alignments. This leads to **1a** having a helical solution conformation, **1b** having an extended solution conformation and **1c** having a conformation in which five of the six carbon atoms are arranged in the zig-zag conformation. GC–MS data reveal that this class of compounds is more polar than perfluorocarbons and hydrocarbons, and that the polarity of the individual diastereoisomers can vary significantly.

Experimental

General methods

D_8-Tetrahydrofuran was dried and stored over $LiAlH_4$. Perfluorohexane was purchased from Aldrich in 95% purity as a mixture of straight-chain and branched isomers, also containing perfluorocyclohexane and perfluoropentane (5%). All other commercial reagents and solvents were purchased in the highest available quality and were used as supplied. Reactions were conducted in oven-dried glassware under nitrogen atmosphere with magnetic stirring. Reactions were monitored by thin-layer chromatography using Merck Kieselgel 60 plates; visualisation was achieved by inspection under short-wave UV light followed by staining with phosphomolybdic acid dip. Nuclear magnetic resonance spectra were recorded using a Bruker AV-500, a Bruker AV-400 or a Bruker AV-300 instrument. Samples were dissolved in a mixture of $CDCl_3$ and D_8-THF, and the relative amounts of these two solvents were calculated by integrating the residual protio-solvent signals and comparing with a reference solvent mixture. Where necessary, molecular connectivities were assigned using two-dimensional (COSY, HSQC, homonuclear *J*-resolved) experiments, and coupling constants for complex or non-first-order spectra were determined by simulation/iteration sequences using the Daisy module of the Bruker TopSpin software. The GC–MS system was an Agilent 6890 GC directly linked to an Agilent 5973A MSD. A portion of the sample (1 μl) was automatically injected into the GC, which was equipped with a Poraplot Q capillary column (10 m × 0.32 mm with a 10 μm film thickness). Helium was used as carrier gas at a constant flow of 1.8 ml min^{-1}. The GC injector port temperature was maintained at 250 °C and the oven was programmed to hold at 50 °C for 1 min, then ramp at 10 °C min^{-1} to 200 °C and hold this temperature for 5 min. The transfer line and MSD source temperatures were set at 200 °C and 230 °C respectively. The MSD was programmed to measure ion currents between m/z 30 and 500 for both EI and CI ionisation modes. Methane was used as the reagent gas for CI. Fragment intensities are quoted as a percentage of the base peak.

Synthesis of 1a–c: general procedure

A solution of ditosylate **2** (5.8 mg, 0.012 mmol) in dry D_8-THF (1 mL) was added *via* cannula to a suspension of $LiAlH_4$ (5 mg, 0.14 mmol) in dry D_8-THF (0.5 mL) under nitrogen. The resulting mixture was stirred at 50 °C until TLC analysis indicated complete consumption of the starting material (4–7 h). The mixture was cooled to room temperature and filtered through a cotton wool plug, washing with $CDCl_3$ (0.5 mL). The filtrate was cooled to 0 °C, and excess $LiAlH_4$ was quenched by careful addition of a few drops of aqueous sodium tartrate. The organic phase was withdrawn and dried ($MgSO_4$) to provide a clear colourless solution of tetrafluorohexane **1**, which was characterised without further purification.

Data for 1a

^{1}H NMR (400 MHz, 80 : 20 v/v $CDCl_3$–D_8-THF) δ 4.52–4.30 (m, 2H), 4.24–3.99 (m, 2H), 0.92 (dddd, $J = 24.1, 6.5, 0.9, 0.9$ Hz, 6H); **^{19}F NMR** (376 MHz, 80 : 20 v/v $CDCl_3$–D_8-THF) δ −191.3 (m, 2F), −211.7 (m, 2F); **^{19}F {^{1}H dec} NMR** (376 MHz, 80 : 20 v/v $CDCl_3$–D_8-THF) δ −191.3 (m, 2F), −211.7 (m, 2F); **^{13}C NMR** (125 MHz, 80 : 20 v/v $CDCl_3$–D_8-THF) δ 91.3 (dm, $J = 184$ Hz), 86.8 (dm, $J = 172$ Hz), 14.6 (d, $J = 22$ Hz); **MS** (CI, +ve) m/z 139 ($MH^+ - HF$, 30%), 119 ($MH^+ - 2 \times HF$, 100%), 99 ($MH^+ - 3 \times HF$, 42%), 79 ($MH^+ - 4 \times HF$, 33%).

Data for 1b

^{1}H NMR (400 MHz, 76 : 24 v/v $CDCl_3$–D_8-THF) δ 4.46–4.28 (m, 2H), 4.25–4.01 (m, 2H), 0.98 (dddd, $J = 25.2, 6.2, 1.5, 1.5$ Hz, 6H); **^{19}F NMR** (376 MHz, 76 : 24 v/v $CDCl_3$–D_8-THF) δ −185.8 (m, 2F), −216.2 (m, 2F); **^{19}F {^{1}H dec} NMR** (376 MHz, 76 : 24 v/v $CDCl_3$–D_8-THF) δ −185.8 (AA′XX′, $^3J_{AX} = 14.7$ Hz, $^4J_{AX'} = 2.7$ Hz, $^5J_{AA'} = 0.4$ Hz, 2F), −216.2 (AA′XX′, $^3J_{AX} = 14.7$ Hz, $^3J_{XX'} = 8.2$ Hz, $^4J_{A'X} = 2.7$ Hz, 2F); **^{13}C NMR** (125 MHz, 76 : 24 v/v $CDCl_3$–D_8-THF) δ 89.9 (dm, $J = 174$ Hz), 85.8 (dm, $J = 169$ Hz), 16.6 (d, $J = 26$ Hz); **MS** (CI, +ve) m/z 139 ($MH^+ - HF$, 25%), 119 ($MH^+ - 2 \times HF$, 100%), 99 ($MH^+ - 3 \times HF$, 51%), 79 ($MH^+ - 4 \times HF$, 58%).

Data for 1c

^{1}H NMR (400 MHz, 81 : 19 v/v $CDCl_3$–D_8-THF) δ 4.55–4.32 (m, 2H), 4.31–4.08 (m, 2H), 1.01 (dddd, $J = 24.5, 6.5, 2.3, 0.5$ Hz, 3H), 0.98 (dddd, $J = 24.5, 6.5, 0.7, 0.7$ Hz, 3H); **^{19}F NMR** (376 MHz, 81 : 19 v/v $CDCl_3$–D_8-THF) δ −187.0 (ddddddd,

J = 47.0, 24.5, 14.2, 9.1, 3.4, 2.0, 1.6 Hz, 1F), −189.5 (ddddddd, J = 47.0, 24.5, 16.7, 13.2, 1.6, 1.4, 0.6 Hz, 1F), −211.7 (ddddddd, J = 47.0, 26.0, 13.2, 13.0, 9.8, 3.4, 2.0, 0.5 Hz, 1F), − 215.7 (ddddddd, J = 47.0, 24.0, 14.2, 12.0, 9.8, 2.0. 1.4, 0.5 Hz, 1F); **^{19}F {^{1}H dec} NMR** (376 MHz, 81 : 19 v/v $CDCl_3$–D_8-THF) δ −187.0 (ddd, J = 14.2, 3.4, 1.6 Hz, 1F), −189.5 (ddd, J = 13.2, 1.6, 1.4 Hz, 1F), −211.7 (ddd, J = 13.2, 9.8, 3.4 Hz, 1F), −215.7 (ddd, J = 14.2, 9.8, 1.4 Hz, 1F); **^{13}C NMR** (125 MHz, 81 : 19 v/v $CDCl_3$–D_8-THF) δ 91.3 (dm, J = 178 Hz), 90.9 (dm, J = 183 Hz), 87.9 (dm, J = 173 Hz), 86.0 (dm, J = 173 Hz), 16.3 (m), 15.9 (m); **MS** (CI, +ve) m/z 139 (MH^+ − HF, 29%), 119 (MH^+ − 2 × HF, 100%), 99 (MH^+ − 3 × HF, 43%), 79 (MH^+ − 4 × HF, 29%).

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References and notes

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10 Compound **2c**,[3] the 1,6-ditosylate precursor of **1c**, undergoes a conformational change between the average solution and the solid state structure involving one C–C bond rotation of *ca.* 120°; if **1c** adopts this altered conformation, the molecular dipole moment is considerably reduced (1.42 D).[4] This confirms that a small conformational change can have a large effect on the molecular dipole moment, thereby complicating the analysis of GC retention times. We also determined the molecular volumes and surface areas of **1a–c** in a further attempt to rationalise the GC retention times, but these analyses did not produce convincing correlations with the GC elution order[4].

