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Synthesis and structure of all-syn-1,2,3,4-tetrafluorocyclohexane[†]

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Preparation of the all-*syn* isomer of 1,2,3,4-tetrafluorocyclohexane is reported; X-ray structural studies shows a conformation with two of the C–F bonds oriented 1,3-diaxial to each other and ¹⁹F-NMR reveals a through space diaxial ⁴ $J_{\rm FF}$ coupling constant of 29 Hz.

The C-F bond is the most polar in organic chemistry and as a consequence fluorine can influence the conformation and reactivity of molecules based largely on stereoelectronic effects and dipole-dipole interactions, rather than through steric repulsion.^{1,2} We have had a programme preparing single stereoisomers of alkanes carrying multiple vicinal fluoromethylene groups (\sim [CHF]_n \sim) and have reported the synthesis and conformation of straight chain alkanes with three,³ four,⁴ five⁵ and six⁶ vicinal fluorines. In these acyclic studies it emerges that the all syn-vicinal fluorine stereoisomers adopt helical structures, as a mechanism to avoid aligned 1,3-C-F bonds. In this *Communication* we report the synthesis of **1**, a cyclohexane ring carrying four sequential vicinal fluorines in the ring, with the all-syn stereochemistry. In this case the ring conformation overrides repulsive 1,3-C-F bond interactions generating a highly polar molecule. In 1969 Barton and Hassel received the Nobel Prize for their studies on conformational analysis based on cyclohexane⁷ and the motif is among the most common in organic chemistry. None the less, selectively fluorinated cyclohexanes are rare and only the mono-8 and some difluororepresentatives have been prepared,9,10 with no syntheses described of cyclohexanes containing three or more vicinal fluorine atoms.¹¹ The all-syn-tetrafluorocyclohexane 1 became a synthetic target as it is anticipated to be a polar organic molecule because the ground state chair conformation is forced to have two 1,3-diaxial C-F bonds, a unique aspect of a fluorinated cyclohexane to date. This interaction is anticipated to raise the ground state energy by $\sim 3.0 \text{ kcal mol}^{-1}$ due to dipolar repulsion.¹² Indeed the calculated (MP2/6-311 + G(2d,p))/(B3LYP/6-311 + G(2d,p) minimised chair conformer had all of the fluorines on one face of the molecule and molecular dipole

moment with a value of 4.91 Dy. Ring inversion generates iso-energetic enantiomeric chair (eaea to aeae) conformers, (Scheme 1). The synthetic route developed to prepare 1,2,3,4tetrafluorocyclohexane 1 is illustrated in Scheme 2. A key intermediate is the endoperoxide 3, which was prepared by a singlet oxygen reaction on cyclohexadiene 2 as previously reported by Murray and Kaplan.¹³ Disproportionation to diepoxide 4 was catalysed by Ru(PPh₃)₃Cl₂.¹⁴ In order to introduce the first fluorine atoms, a double epoxide ring opening with HF·Et₃N was investigated. This gave the difluorodiol 5 as a single regio- and stereo-isomer. Diol 5 was converted to cyclic sulfate 6, as an activated precursor for the introduction of the third fluorine, which was accomplished by treatment with HF·Et₃N. This resulted in trifluoroalcohol 7. The final fluorine atom was introduced after triflation of alcohol 7 and then treatment of 8 with HF·Et₃N. This resulted in fluoride ion substitution with an inversion of configuration.

The ¹⁹F-NMR spectrum of 1,2,3,4-tetrafluorocyclohexane 1 at RT (298 K) displays two particularly broad signals corresponding to the two sets of non-equivalent fluorines (Fig. 1b). Such broad signals do not indicate a particularly slow ring interconversion, but rather arise as a consequence of the large chemical shift difference between the fluorine signals. Warming well above RT (353 K) sharpened these two signals, consistent with speeding up the rate of ring interconversion (Fig. 1a). When the ¹⁹F-NMR spectrum was recorded at low temperature (200 K in CD₂Cl₂) all four of the fluorine atoms gave resolved signals, as they are non equivalent in the chair conformation and the interconversion is slow on the NMR timescale (Fig. 1c). A 2D¹⁹F-EXSY-NMR experiment¹⁵ recorded at this low temperature (200 K) enabled the four distinct fluorine signals arising from the chair conformation, to be assigned (Fig. 1d).

Of particular interest was a large through space ${}^{4}J_{FF}$ coupling of 29 Hz, between the two 1,3-diaxial fluorine atoms, a value around twice the magnitude of each of the vicinal *gauche* F–F coupling constants (~14 Hz). Through space F–F



eaea

aeae

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

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Scheme 2 Synthesis of 1; (i) (PhO)₃P, O₃, CH₂Cl₂, $-78 \degree C$ then 2, CH₂Cl₂, $-78 \rightarrow -25 \degree C$; (ii) Ru(PPh₃)₃Cl₂, CH₂Cl₂, $0 \degree C \rightarrow RT$, 46% from 2 steps; (iii) Et₃N·3HF, 90 °C; (iv) Thionyl chloride, pyridine, CH₂Cl₂, $0 \degree C$; (v) NaIO₄, RuCl₃·*x*H₂O, MeCN, H₂O, 35% from 3 steps; (vi) Et₃N·3HF, 120 °C, 70%; (vii) Tf₂O, pyridine, RT; (viii) Et₃N·3HF, 120 °C, 35% over 2 steps.



Fig. 1 (a) ¹⁹F-NMR of **1** at 353 K. (b) ¹⁹F-NMR of **1** at 298 K. (c) ¹⁹F-NMR of **1** at 200 K. (d) 2D¹⁹F-EXSY-NMR (mixing time 100 ms) of **1** at 200 K. The cross-peaks indicate exchange between axial and equatorial fluorines and facilitate assignment of the resonances.

couplings have been observed in rigid molecular frameworks,¹⁶ however it is unusual to observe such a large coupling constant in a system which displays conformational freedom.¹⁷ The through space coupling indicates the anticipated close proximity of the axial fluorines. Rate constants for the ring interconversion were determined by complete line shape analysis of the ¹⁹F NMR spectra recorded across the temperature range 200–242 K. Fitting the experimental data to the Eyring equation¹⁸ was used to determine the activation parameters $\Delta G^{\#}_{298} = 10.9$ kcal mol⁻¹, $\Delta H^{\#} = 9.1$ kcal mol⁻¹ and $\Delta S^{\#} = -6.3$ cal K⁻¹ mol⁻¹ (See Supplementary material). This experimental data was compared

to a theory study (MP2/6-311 + G(2d,p))//B3LYP/6-311 + G(2d,p) + ZPE level of theory).¹⁹ Real transition structures could not be located, but the energies of the four possible boat structures which could be involved in the ring inversion were calculated. These had energies between 7.90 and 9.47 kcal mol⁻¹ above the ground state *aeae* chair conformation (See Supplementary Material) and below the experimentally determined transition energy of 10.9 kcal mol⁻¹. The experimental NMR value indicates a ring inversion barrier very close to that of cyclohexane itself (~10.8 kcal mol⁻¹). However in the case of 1 it can be assumed that both the ground state and transition state energies are raised relative to cyclohexane due to diaxial and eclipsing C–F bond interactions in the ground and transition state structures.

Compound 1 was a relatively high melting solid (mp = $83 \degree$ C), perhaps surprisingly so given that carbon bound fluorine forms only weak hydrogen bonds.²⁰ A suitable crystal was selected for X-ray structure analysis and the resultant structure is shown in Fig. 2. Cyclohexane 1 adopts the classical chair conformation, and all three of the vicinal C-F relationships are gauche. The chair structure demands that two of the C-F bonds adopt 1.3-diaxial orientations, consistent with the ¹⁹F-NMR, through space ${}^{4}J_{\rm FF}$ -coupling. Repulsion between these axial C-F bonds is evinced in the X-ray structure by the fact that they splay from each other each by $\sim 5^{\circ}$ from the perpendicular. The molecules of achiral 1 form pairs of enantiomeric chair conformers within the unit cell, with an axial fluorine and hydrogen pairing with a mirror image hydrogen and fluorine respectively. The H.F contact distances are 2.77 Å and 2.70 Å, too long to represent stabilising hydrogen bonds,²⁰ but the orientation allows the enantiomer pair to maintain a spatial symmetry. Stability from this pairing may arise by attenuation of polarity in the solid state, as both of the fluorinated faces of each enantiomer



Fig. 2 X-Ray structure of 1 showing the pairing of enantiomer dimers. The antiparallel nature of the highlighted C–F···H–C contacts enables the enantiomeric conformers to maintain spatial symmetry within the unit cell. See Supplementary Information for full crystallographic details.

approach each other, and thus their molecular dipoles are opposed.

In summary 1,2,3,4-tetrafluorocyclohexane **1** has been prepared, the first example of a cyclohexane with more than two vicinal fluorine atoms. The all-*syn* stereochemistry forces a ground state 1,3 diaxial fluorine-fluorine interaction, which is clearly observed both *via* a through space coupling by low temperature ¹⁹F-NMR and in the solid state by X-ray crystallography. The polar nature of **1**, due to this 1,3 diaxial interaction is a unique aspect, which suggests prospects as a novel polar structural motif for organic materials.

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