▌ **Organofluorine Chemistry**

A Computational Study of Vicinal Fluorination in 2,3-Difluorobutane: Implications for Conformational Control in Alkane Chains

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Abstract: A comprehensive conformational analysis of both 2,3-difluorobutane diastereomers is presented based on density functional theory calculations in vacuum and in solution, as well as NMR experiments in solution. While for 1,2-difluoroethane the fluorine *gauche* effect is clearly the dominant effect determining its conformation, it was found that for 2,3-difluorobutane there is a complex interplay of several effects, which are of similar magnitude but often of opposite sign. As a result, unexpected deviations in dihedral angles, relative conformational energies and populations are observed which cannot be rationalised only by chemical intu-

ition. Furthermore, it was found that it is important to consider the free energies of the various conformers, as these lead to qualitatively different results both in vacuum and in solvent, when compared to calculations based only on the electronic energies. In contrast to expectations, it was found that vicinal *syn*-difluoride introduction in the butane and by extension, longer hydrocarbon chains, is not expected to lead to an effective stabilisation of the linear conformation. Our findings have implications for the use of the vicinal difluoride motif for conformational control.

Introduction

Hyperconjugative interactions play an important role in stabilizing alkane conformations. The most stable conformation of ethane was shown to result from stabilizing $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ hyperconjugation interactions,[1] which require an antiperiplanar orientation of the two bonds involved. However, steric effects are responsible for determining the magnitude of the rotational energy barrier.[2] The contribution of hyperconjugative interactions is very pronounced in compounds containing two vicinal electronegative substituents.[3,4] Extensive computational studies have shown that the two fluorine atoms in 1,2-difluoroethane adopt a *gauche* orientation due to the stabilization from $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation (for both fluorine atoms), which is referred to as "the fluorine *gauche* effect".[5-11] This stabilization outcompetes the stabilization that would be gained from $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$ hyperconjugation (a situation which is reversed for the other halogens).[12] The fluorine *gauche* stabilisation also overrides destabilizing effects, mainly heteroatom steric/electrostatic repulsion (including C—F dipole–dipole repulsion in vacuum/nonpolar solvents). In polar solvents, this

gauche conformation is even more pronounced, due to additional stabilisation of the molecular dipole.

The conformational behaviour of longer chain alkanes is further determined by steric effects in which alkyl groups prefer to be located as far away as possible from each other. For example, the butane *gauche* (G) conformation is 0.89–0.97 kcal mol^{-1} (gas phase) less stable than the *anti* (A) conformation as determined by vibrational spectroscopy and electron diffraction.[12] When a vicinal difluoro motif is introduced in an alkyl chain, the resulting rebalancing of steric, electrostatic and hyperconjugation effects will lead to a modified conformational profile. For the simplest case, 2,3-difluorobutane, of which there are two possible diastereomers, comparison of the staggered conformations has been used to make qualitative first order predictions about their relative stability (Figure 1).

Of all the conformations shown, only AG(T) combines both stabilising features (methyl substituents in antiperiplanar position, and the fluorine atoms in the *gauche* position). For **2**, the destabilising methyl *gauche* feature in the two—enantiomeric—GG(E) rotamers is offset by a fluorine *gauche* arrangement. Hence, this has led to a general expectation that the linear butane conformation in **1** is even more stabilised compared to that in (nonfluorinated) butane, while **2** shows increased conformational disorder.[13-15]

Some physical data measurements are consistent with this expectation. The melting points (Figure 2) of the *threo* (T) isomers of 6,7-difluorododecane (**5**)[14,16] and 9,10-difluorostearic acid (**10a**)[13] are significantly higher than that of the corresponding *erythro* (E) isomers **7** and **11a**, which has been ex-

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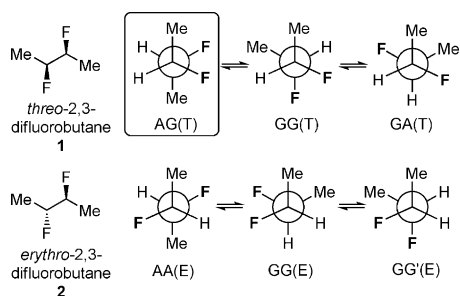E-mail: bruno.linclau@soton.ac.uk

Figure 1. Staggered conformations of the 2,3-difluorobutane *erythro* (E) and *threo* (T) diastereomers **1** and **2**. The letters refer to the respective dihedral angle of the substituents. The first letter refers to the methyl groups and the second letter to the fluorine atoms. A = *anti* (180°); G = *gauche* (60°).

plained by the more conformationally rigid nature of the former. Also, the polarity of the *threo* isomer **6**, as measured by retention time on silica gel, was slightly higher than that of the *erythro*-isomer **8**,[16] which appears also consistent with the above. This was also the case for **10b** and **11b**.[17] Furthermore, analysis of Langmuir isotherms of **10a** and **11a** clearly revealed a significant level of conformational disorder for **11a**, while the isotherm of **10a** was similar to that of stearic acid **9**.[13]
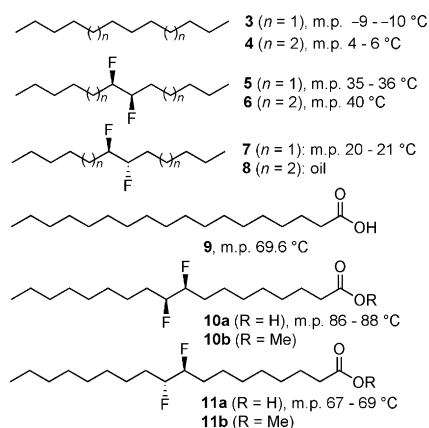

Figure 2. Melting point data of vicinal difluoride containing hydrocarbons that do not have additional functional groups in the vicinity of the fluorine atoms.

Schlosser reported $^3J_{HF}$ values of 22 and 14 Hz for **5** and **7**, respectively (C*H*F proton, in CDCl$_3$),[14] which was considered consistent with the preference of an extended zigzag conformation for the *threo* isomer **5**, and with the presence of all three rotamers for **7**. Rozen reported similar $^3J_{HF}$ values for **6** and **8**.[16] However, conformational studies of **1** and **2** by NMR spectroscopy (CDCl$_3$/[D$_6$]acetone) by Angelini et al.,[18] based on $^3J_{H-H}$ analysis, suggested that for the *threo* isomer **1**, either all possible staggered isomers are present in solution, or that only the AG(T) and the GG(T) isomers were present, and that for the *erythro* isomer, the GG(E) isomers were predominantly present.

Only few computational studies on alkanes featuring an isolated vicinal difluoride group have been reported. Only cases involving an isolated vicinal difluoride motif on an acyclic chain are discussed here, not cyclic[19–21] or multivicinal fluoride[15] derivatives.

Bitencourt et al. have studied 1,2-difluoropropane **12** (Figure 3) using MP2/aug-cc-pVTZ geometry optimised structures and NBO analysis at the B3LYP/aug-cc-pVTZ level in vacuum.[22] They determined that conformation **12(I)**, where both the C2-methyl and fluorine are *gauche* to the C1-fluorine, is optimal due to the two $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation interactions available, as opposed to the methyl group being positioned away from C1—F that would be preferable on the basis of only steric effects. However, the energy difference between the three conformers is very small (0.13 kcal mol^{-1}).
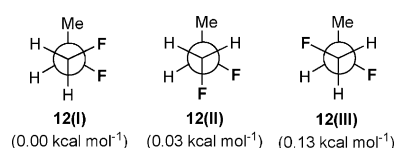

Figure 3. Conformations of 1,2-difluoropropane (**12**) with relative energies.

A computational study on the 2,3-difluorobutane isomers by Angelini et al.,[18] at the HF/STO-3G level, found that, for the *threo* isomer **1**, the AG(T) conformation was the more stable, as expected (Figure 4). The next stable conformer was shown to be GA(T), which is surprising as the two fluorine atoms are in antiperiplanar position, in contrast to the least stable conformer, GG(T). However, even more surprising is that for the *erythro*-diastereomer **2**, the different conformations were found not to be similar in energy, with the AA(E) conformation being the more stable, indicating that the steric destabilisation appears to outweigh hyperconjugation effects. However, these results are suspect due to the low level of theory used for these calculations; the Hartree–Fock method does not include any electronic correlation and the STO-3G (minimal) basis set is manifestly inadequate even for qualitative conclusions, especially in molecules such as these where the energy differences are often less than 1 kcal mol^{-1}.
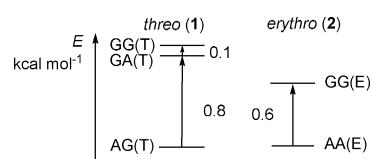

Figure 4. Energy differences between the respective conformations of *threo* and *erythro* 2,3-difluorobutane (HF/STO-3G level; zero level set independently for each diastereomer). Data from Angelini et al.[18]

In the same paper, Angelini et al. performed NMR studies, the results of which did not agree with their calculation data. In addition to the low level of their calculations, they appear to have neglected entropic contributions in their calculation of Boltzmann populations of the respective conformers by using their Hartree–Fock electronic energies instead of free energies. They also argued that the discrepancy could be due to solva-

tion effects on the relative stability of the rotamers. This was rationalised by the stabilisation of the larger dipole moments of the fluorine *gauche* conformations by solvents of increasing polarity.

Finally, O'Hagan et al. conducted a high-level computational (using B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d)+ZPE calculations) conformational analysis of *threo*-(1,2-difluoropropyl)cyclohexane **13** (Figure 5), and reported that the three most stable conformers possess a fluorine *gauche* motif.[23] Interestingly, one conformation with a linear alkyl chain, **13** (AG-2), is thought to be destabilised due to a repulsive interaction between the side chain fluorine and a cyclohexane equatorial hydrogen atom.
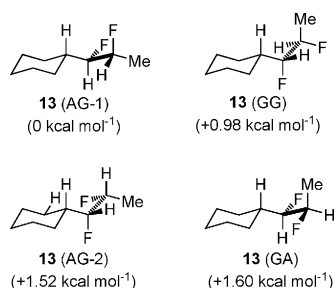

Figure 5. The four most stable minimum energy conformers of *threo*-(1,2-difluoropropyl)cyclohexane (**13**), with relative energies (B3LYP/6-311+G(2d,p)//B3LYP/6-31G(d)+ZPE level of theory).[23]

Conformational control by fluorination has emerged as a promising tool to promote and stabilise desired conformations, with reported applications in biological chemistry, organocatalysis and materials (e.g., liquid crystals).[24–26] While most of these applications involve fluoroamine-type motifs, or α-fluorination of carbonyl containing functional groups, the unperturbed alkane vicinal difluorination motif is another possible tool for achieving conformational control without the restriction of complete rotational rigidity (as in alkenes), as shown by O'Hagan for vicinal difluorides and multivicinal fluoride containing systems.[15, 20, 23] Hence, a thorough understanding of the factors governing the conformational effects is of great importance. The apparent discrepancy between the Angelini NMR spectroscopy and computational results merits a reinvestigation on the 2,3-difluorobutane system, particularly given the low level of theory used in their work. In addition, the relative energies of the conformations as calculated by Angelini do not conform with the conventional view of fluorine induced stereocontrol by the *gauche* effect as explained in Figure 1.

In this work, we use density functional theory (DFT) calculations with large basis sets to explore the stable conformations of the *erythro* and *threo* 2,3-difluorobutane diastereomers. Our analysis also required comparison with 1,2-difluoroethane, which is thus included in our study. Our calculations are complemented by natural bond orbital (NBO) analysis which allows us to dissect the intramolecular energy into electrostatic and steric energy (Lewis energy), and hyperconjugation components (non-Lewis energy) as well as to evaluate the strength of individual σ→σ* hyperconjugation interactions. We also exam-

ine the effect of solvation by performing calculations in a continuum solvation model studying solvents of increasing polarity (dielectric constant).[27] We discuss the actual conformational populations of the diastereomers involved by considering their respective free energies (as opposed by merely considering internal energy differences). In this respect our work departs completely from that previously published in that now entropy effects are explicitly incorporated. Finally, the obtained conformational populations were used as basis to obtain calculated coupling constants, which were compared to experimentally obtained *J* values from synthetic samples of **1** and **2**.

Computational details

We have performed DFT calculations with the M05-2X exchange-correlation functional[28,29] and the 6-311+G(d,p) basis set. We have selected the M05-2X hybrid exchange correlation functional instead of more widely used functionals, such as B3LYP, as it is recommended for the SMD implicit solvation model,[30] that we used for our calculations in solvent. All our calculations were performed with the Gaussian 09 program.[31]

A conformational sweep of the FC-CF torsion angle was performed on the *erythro* and *threo* 2,3-difluorobutane, sampling every 10 degrees. Only the FC-CF torsion angle was constrained and the rest of the molecule was allowed to relax (to an atomic force threshold of 3×10^{-4} E_h/a_0). Each low energy conformer (shown in Figure 1) was then separately geometry optimised to a tighter threshold (2×10^{-6} E_h/a_0) with no structural constraints. The calculations were performed in vacuum and in three different solvents: chloroform ($\varepsilon_r = 4.71$), acetone ($\varepsilon_r = 20.49$), and water ($\varepsilon_r = 78.35$). Given the deviation from an idealised tetrahedral shape of the fluorine-containing carbons,[20, 24] the corresponding CC-CC and HC-CF dihedrals were measured individually from the relaxed structures.

A normal mode vibrational frequency calculation was performed on each tightly optimized structure. In the context of the harmonic oscillator approximation, Gibbs free energies of each conformer were evaluated using standard statistical mechanics relationships. Relative populations of the conformers were computed using the Boltzmann distribution, assuming that the relative populations of each conformation are determined entirely by its Gibbs free energy that is, that the shape of the energy surface in the vicinity of each minimum is harmonic.

An energy decomposition approach using natural bond orbitals[32] was used to separate the total energy into the Lewis and non-Lewis (hyperconjugation) energy, as implemented in the NBO3.1 program which is integrated within Gaussian 09. Additionally, the strengths of individual hyperconjugation interactions $\sigma_{CX} \rightarrow \sigma^*_{CF}$ were computed for all molecules using the second-order perturbation theory approach[32] in NBO theory.

Computational *J* couplings were obtained and compared to experimental values. The strong dependence of NMR *J* couplings on dihedral angles[33] necessitated a careful scan of the FCCF dihedral angle followed by a Boltzmann average over the resulting set of conformations. A 72-point relaxed potential energy scan was performed with respect to the dihedral angle in question using the M05-2X/cc-pVTZ method[34] in SMD chloroform using the Gaussian 09 package. Vibrational analysis, corrected for the presence of internal rotations[35] and the presence of an imaginary frequency, was performed at each point, followed by the calculation of the Gibbs free energy including translational, rotational and vibrational contributions. *J* couplings were calculated for each of the 72 geo-

metries using the GIAO[36] M05-2X/cc-pVTZ method in SMD chloroform with the basis set decontracted and augmented with tight functions for the calculation of the Fermi contact contribution.[37] The resulting sets of J couplings and Gibbs free energies were combined, using the Boltzmann distribution, to obtain the conformationally averaged J coupling that may be compared with the NMR experiment at room temperature.

Results and Discussion

Validation on 1,2-difluoroethane

To validate our choice of functional and basis set, we have applied the M05-2X exchange-correlation functional and the 6-311+G(d,p) basis set to the *gauche* (G) and *anti* (A) conformations of 1,2-difluoroethane. These conformations were geometry optimised to a force threshold of 2×10^{-6} E_h/a_0. The A–G energy differences thus obtained corresponded well with values reported in the literature (our value: 0.68 kcal mol^{-1}; O'Hagan et al.:[10] 0.66 kcal mol^{-1}). We then examined the individual $\sigma \rightarrow \sigma^*$ hyperconjugations responsible for the *gauche* conformation, and a comparison of our results with literature values is shown in the Supporting Information (Table S1). Our calculations using the M05-2X functional estimate slightly stronger interactions than the B3LYP results; however, all follow the same trend, with the $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ interaction being around 5 kcal mol^{-1}, $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$ around 1.6 kcal mol^{-1}, and $\sigma_{C-H} \rightarrow \sigma^*_{C-H}$ around 2.3 kcal mol^{-1}, and agree to within the level of accuracy expected between different state-of-the-art functionals and basis sets.

The difluoroethane energy profile as a function of the FC-CF dihedral angle is well-reproduced, with the energy minimum at 72°.[5, 10, 12] This total energy minimum coincides with the minimum non-Lewis energy, and with the maximum Lewis energy, confirming that hyperconjugation dominates the 1,2-difluoroethane conformational profile as has been extensively investigated and confirmed in the study by Goodman et al.[5] The inspection of the energy profile as a function of the HC-CF angle (Figure 6 shows the region −150 to 150°) demonstrates that the minimum total energy is at a HC-CF dihedral angle of 170° which is not at the expected ideal antiperiplanar HC-CF dihedral angle of 180°. A similar value (169.29°) was reported by Souza et al.[12] As a further consequence of the stabilisation by hyperconjugation, this minimum energy structure also has the shortest C—C bond length.

This intriguing deviation from antiperiplanarity for optimum hyperconjugation can be understood by visualising the natural bond orbitals involved in the hyperconjugation (Figure 7) where it can be seen that the σ_{C-H} electron donor is polarised away from the second fluorine atom. Hence, it is not fully aligned with the electron acceptor σ^*_{C-F} NBO at the 180° HC-CF dihedral angle (top drawings). In contrast, at a 170° HC-CF dihedral angle (bottom drawings), maximum $\sigma_{CH} \rightarrow \sigma^*_{CF}$ orbital overlap and hyperconjugation stabilisation occurs.

Hence, the polarisation of the σ_{C-H} orbital caused by the *gauche* fluorine atom leads to the FC-CF angle widening. This is also observed for 2,3-difluorobutane (see below).
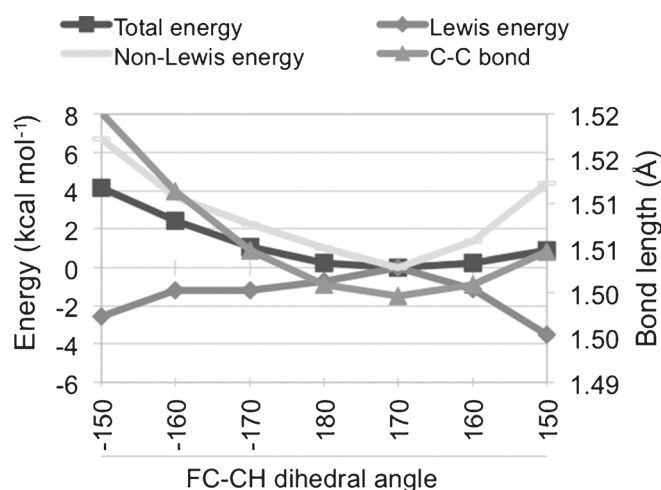

Figure 6. Energy profile of 1,2-difluoroethane as a function of the HC-CF torsion angle, showing the total energy, Lewis energy, non-Lewis energy as well as the C—C bond length (M05-2X/6-311+G(d,p)).
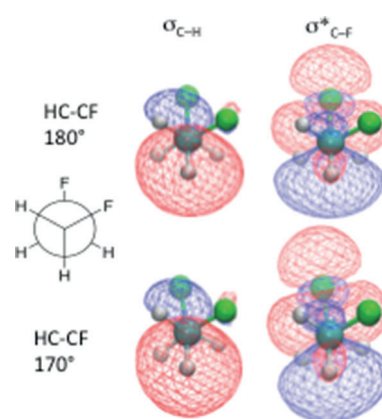

Figure 7. Top: structure of 1,2-difluoroethane shown as Newman projection at a HC-CF dihedral angle of 180°. Bottom: at a HC-CF dihedral angle of 170°. Superimposed are the wireframe isosurfaces of the electron donor σ_{CH} (left) on the front carbon and electron acceptor σ^*_{CF} (right) on the rear carbon, natural bond orbitals of 1,2-difluoroethane, corresponding with the respective torsional angles. In both cases, the top lobe of σ_{CH} is distorted away from the geminal fluorine. Hence, comparison of the top figures with the bottom figures clearly shows that at 170° there is a better overlap (alignment) between the donor and acceptor orbitals leading to a stronger hyperconjugation interaction.

Calculations on 2,3-difluorobutane

Rotational energy profiles

The rotational energy profiles from our M05-2X/6-311+G(d,p) DFT calculations for both the *threo* 1 and the *erythro* 2 diastereoisomers of difluorobutane are shown in Figure 8a, with a representation of the respective conformational energy minima in Figure 8b. Both the profiles in vacuum (top) and water (bottom) are shown.

Close inspection reveals a number of unexpected outcomes. In vacuum, while for both diastereoisomers the conformers featuring the antiperiplanar position of the methyl groups are the global minimum structures, it is not the AG(T) conformer
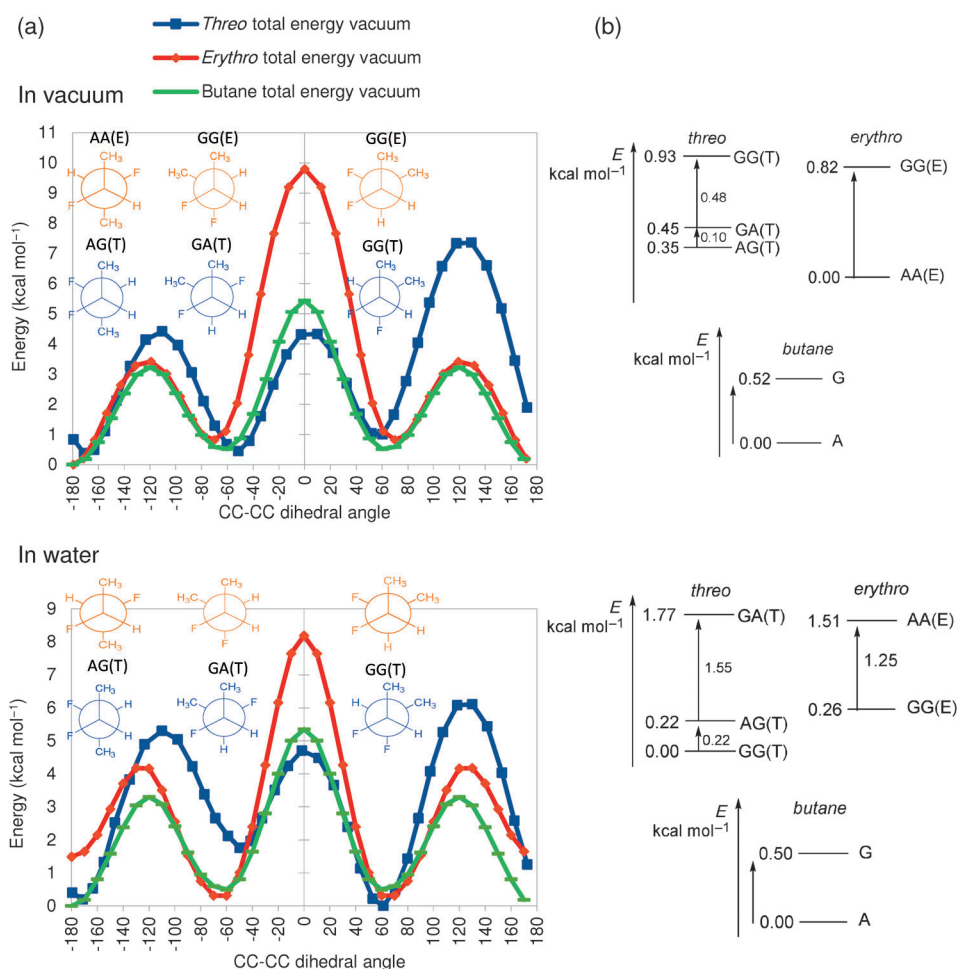
Figure 8. a) Relative energy of *threo*-2,3-difluorobutane (squares), *erythro*-2,3-difluorobutane (diamonds), and butane (line) as a function of the C-C-C-C torsion angle, in vacuum (top) and in water (bottom). T and E energies are relative the lowest energy of E (top) and T (bottom), whereas butane is relative to its lowest energy. b) Calculated energy differences between the 2,3-difluorobutane T and E conformers (M05-2X/6-311+G(d,p) level) in vacuum (top) and in water (bottom). T and E energies are relative the lowest energy of E (top) and T (bottom), whereas butane is relative to its lowest energy.

still the minimum energy conformation (Figure 8, green line). Nevertheless, the AG(T) conformer is only 0.22 kcal mol^{-1} less stable than the GG(T) conformer. Interestingly, in both cases the energy differences with the least stable conformer have considerably increased. These calculations emphasise the crucial role solvation can play in affecting conformer stability.

The local maximum energy structures correspond to the eclipsed conformations (see full discussion in the Supporting Information, Figure S2). It is interesting to observe that the destabilization due to eclipsed C—F/C—F bonds is higher than the destabilization from eclipsed C—Me/C—Me bonds.

Dihedral angles

The rotational energy profiles in Figure 8 clearly indicate that the staggered conformations do not possess "ideal" 60° dihedral angles. This aspect was further investigated. The rotational energy profiles for **1** and **2** were plotted as a function of the CC-CC, FC-CF, and HC-CF dihedral angles (Figure 9, blue line). The vertical black line accentuates the position of the local minimum, while the green line shows the "ideal" dihedral angle position.

The dihedral angle deviations are visualized by the Newman projection of the minimum structures (Table 1), with the calculated dihedral angles and their deviation from the "ideal" angle.

Clearly some significant deviations are observed. For example, the AG(T) conformation shows an 11° deviation from perfect butane antiperiplanarity, while the FC-CF dihedral angle is 72.7°, which resembles the 1,2-difluoroethane situation. Despite the widening of the FC-CF dihedral angle, the methyl groups are skewed *towards* the fluorine atoms, which is unexpected on steric grounds. The opposite situation appears to occur for the GA(T) conformation, where there is a reduced (7.2°) dihedral angle between the *gauche* methyl groups, with the fluorine atoms 8° from antiperiplanarity in the opposite direction, resulting in a *wider* CC-CF dihedral angle. The reduced dihedral angle between the methyl groups (−7.2°) contrasts with the +3° angle in nonfluorinated butane (Table S2 in the Supporting Information).

which is the most stable overall, but the AA(E) conformer.[38] This is surprising, given the fluorine atoms in the AA(E) conformer are *not* in a *gauche* position, in contrast to the AG(T) conformation. Our calculations also show much larger energy differences between the different conformations of the *erythro* isomer (0.82 kcal mol^{-1}, Figure 8b) compared to those of the *threo* isomer (0.58 kcal mol^{-1}), which contrasts with the Angelini results. The two most stable conformers of the *threo* isomer are found to be very close in energy, which also differs from Angelini's results (0.1 vs. 0.8 kcal mol^{-1}, see Figure 4, above). Both findings appear at odds with the contention that only the *threo* isomer exists mainly as one main conformer.

The minimum energy structure profile in water is considerably different. Now for both **1** (*threo*, blue line) and **2** (*erythro*, red line), the respective minimum energy conformation has both the methyl groups and fluorine atoms in *gauche* positions, and the overall minimum structure corresponds to that of the *threo* isomer (GG(T)). Hence, this means that the linear butane chain for both **1** and **2** is not the most stable structure in water, in contrast to butane, where the *anti* conformation is
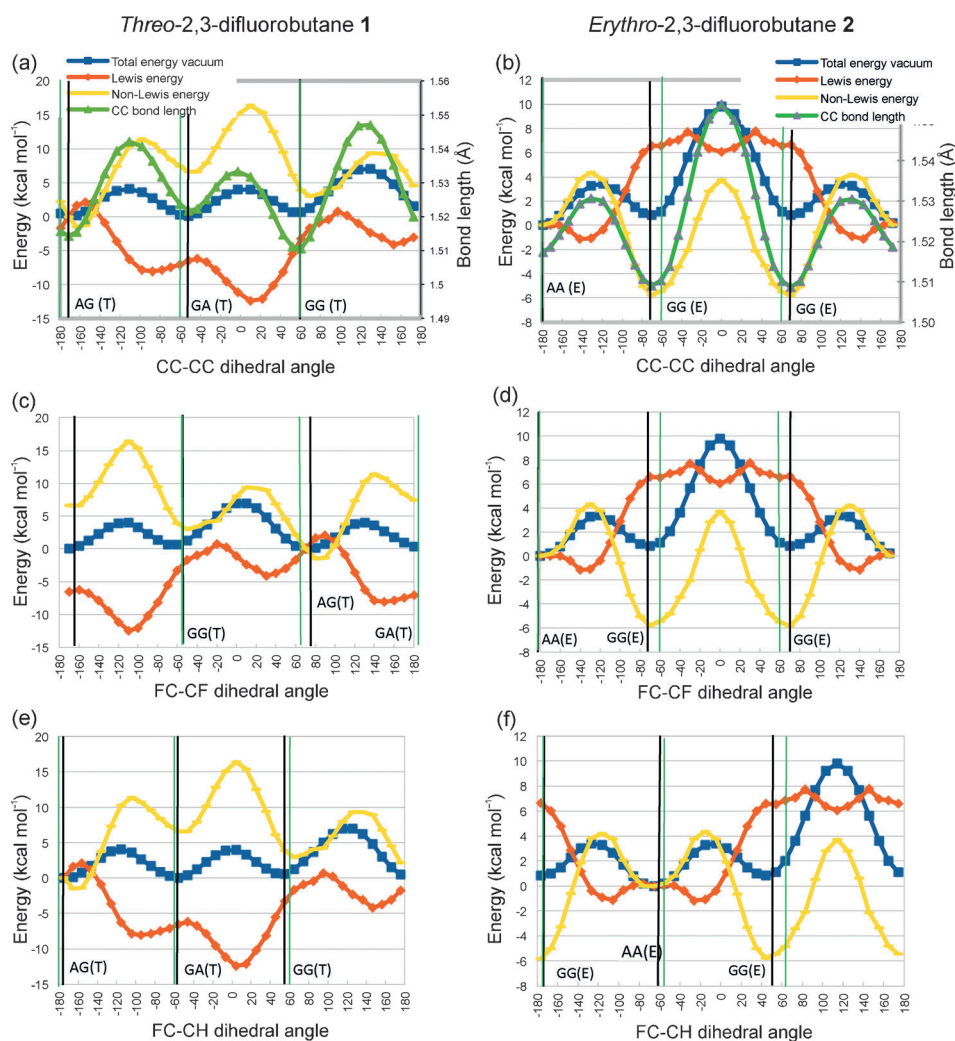
Figure 9. Energy breakdown of 2,3-difluorobutane for the conformational sweep of the indicated dihedral angles. The black vertical line shows the actual local minima, and the green line notes the "perfect" dihedral angle. a, b) The CC-CC dihedral angle versus the energy, as well as the C—C bond length. c, d) The FC-CF dihedral versus the energy. e, f) The HC-CF dihedral versus the energy.

files as a function of the CC-CC, FC-CH, and FC-CF dihedral angles.[39]

For the *threo* isomer, we can observe that the total energy minimum (AG(T) conformer) almost coincides with the lowest minimum of the non-Lewis energy. However, the Lewis energy is almost at its maximum. This indicates that the stabilization from hyperconjugation overrides the destabilization by steric and electrostatic effects, a situation analogous to 1,2-difluoroethane. In contrast, for the *erythro* isomer, the total energy minimum, which occurs for the AA(E) conformer, almost coincides with the lowest minimum of the Lewis energy, while the non-Lewis energy is at its highest local minimum. Hence, this indicates that this conformer is mainly stabilized by steric and electrostatic effects, and less so by hyperconjugation.

Specific values for the energy components including Lewis and non-Lewis energies for the minimum conformations as obtained by NBO analysis are provided in Table 2. The Table also provides estimates for the dominant hyperconjugation interactions which were computed via the second order perturbation theory approach to NBO.[32] As can be seen the stronger interactions are $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ which produce stabilisations between −6 and −5 kcal mol^{-1}, then followed by $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ which are about −3 kcal mol^{-1} and then by the weakest, $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$, which are about −2 kcal mol^{-1}. While the stabilization values of hyperconjugations involving the terminal methyl groups do somewhat depend on the conformation, the key differences concern the hyperconjugations involving the substituents at the internal carbons: these involve two C—H bonds for the AG(T), but two C—C bonds for GG(T) conformer. The GA(T) conformer only has a $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$ hyperconjugation, as does the AA(E) conformer, and one C—H/ one C—C bond is involved for GG(E). Given that the hyperconjugation due to a $\sigma_{C-C} \rightarrow \sigma^*_{C-F}$ delocalization is approximately 3 kcal mol^{-1} less stabilizing than a $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation,[10,40] it is important to realize that the fluorine *gauche* effect has a reduced importance if the group antiperiplanar to the C—F bond is not a C—H bond. Thus, the order in which the total non-Lewis energy varies can be explained by these components and indeed we can observe that the sum of all hyper-

The *gauche* methyl dihedral angle for the GG(T) conformer is also reduced, albeit less so, while the *gauche* fluorine atoms have a larger dihedral angle, but with a smaller increase compared to the angle in the AG(T) conformer. In the GG(E) conformation, both dihedral angles between *gauche* methyl and fluorine atoms are much larger, with a greater than 10° deviation in each case. One of the HC-CF dihedrals is significantly reduced (−15.4°). The exact 180° for the CCCC and FCCF angles for the AA(E) conformer is due to the symmetry of the system.

NBO analysis

Local minimum and maximum energy levels

A breakdown of the total energy, split into the total Lewis energy, which is the energy of all intramolecular steric and electrostatic effects, and the non-Lewis energy, which is the stabilization energy by hyperconjugation, is shown for the *threo* and *erythro* isomers in Figure 9, as rotational energy pro-

Table 1. Newman projections of the calculated local minima of **1** and **2**, with corresponding dihedral angles of the geometry optimised conformers (with their deviation from "ideal" angles in brackets).

	AG(T)	GA(T)	GG(T)	GG(E)	AA(E)
CC-CC	−169.0 (−11.0)	−52.8 (−7.2)	56.5 (−3.5)	70.8 (+10.8)	180.0
FC-CF	72.7 (+12.7)	−171.6 (−8.4)	−64.5 (+4.5)	70.5 (+10.5)	180.0
HC-CF	−172.3 (−7.7)	−57.2 (−2.8)	50.5 (−9.5)	−44.6 (−15.4); −175.0 (−5.0)	65.0 (+5.0)
CC-CF	−48.1 (−11.9)	67.8 (+7.8)	176.0 (−4.0)	−168.9 (−11.1); −49.8 (−10.2)	−60.4 (+0.4)
HC-CH	−57.3 (−2.7)	57.3 (−2.7)	165.5 (−14.5)	69.9 (+9.9)	180 (0)

Hence, this is fundamentally different compared to 1,2-difluoroethane, where the fluorine *gauche* conformation is the most stable. This difference emphasises the importance of considering the overall molecular environment surrounding the vicinal difluorination: context matters.

Dihedral angles

From first order considerations, the higher Lewis energy of AG(T) compared to that of GG(T) is not expected as both conformers possess a fluorine *gauche* arrangement (hence similar electrostatic destabilization). In addition, GG(T) also has the methyl groups in *gauche* position, which should result in an additional steric destabilizing component in the Lewis energy. To gain further insight, the Lewis energy was decomposed into steric and electrostatic components using NWChem 6.1, coupled with the NBO5.9.[41,42] To our surprise, the total steric energy of AG(T) was computed to be 2.7 kcal mol^{-1} *larger* than for GG(T) suggesting that electrostatics indeed are not responsible for the difference in Lewis-energy (as both feature a fluorine *gauche*). Hence, there is an extra unfavourable steric energy term contributing to the relative energy of the AG(T) conformer, explaining its unexpected relative energy compared to both the AA(E) and the GG(T) conformers.

Analysis of the deviations in dihedral angles indicates a possible explanation for this steric energy term. Visualization of the NBO orbitals involved in the hyperconjugation show, as for 1,2-difluoroethane in Figure 7, that the polarisation of the σ_{C-H} orbital caused by the *gauche* fluorine atom (Figure 10) is responsible for the FC-CF angle widening. For AG(T), this amounts to a 7.7° reduction in HC-CF dihedral angle (Table 1), compared to 10° for difluoroethane, causing the methyl groups to lean towards the corresponding β-fluorine atoms, leading to the significant 11.9° decrease from the "ideal" CC-CF

conjugation interactions agrees very well with the relative non-Lewis energies.

On balance, we can observe that the higher energy minimum *threo* conformers (GA(T) and GG(T)) are stabilized by the Lewis energy in contrast to the global minimum AG(T) which is stabilized by the non-Lewis energy. This situation is reversed in the *erythro* systems where the global minimum AA(E) is stabilized by the Lewis energy while the two (degenerate) higher energy GG(E) conformers are stabilized by the non-Lewis energy. Comparing the *threo* with the *erythro* isomer, the unexpectedly lower absolute energy of AA(E) compared to AG(T) in vacuum, (Figure 8) shows that the very favourable hyperconjugation energies of the latter are not able to sufficiently compensate for a number of destabilisations, which, as for 1,2-difluoroethane, include electrostatic destabilization caused by the aligned C−F dipole moments. For the AA(E) conformation, the stabilising $\sigma_{C-F} \rightarrow \sigma^*_{C-F}$ hyperconjugation is much smaller, but so is the electrostatic and steric repulsion. In fact the balance shows that compared to AG(T), AA(E) has a lower energy.

Table 2. The relative energies of the T and E conformations and the key $\sigma \rightarrow \sigma^*_{CF}$ interactions [kcal mol^{-1}] in vacuum.[a]

Entry	Structure	Total energy	Lewis energy	Non-Lewis energy	$\sigma_{C1-H} \rightarrow \sigma^*_{C2-F}$	$\sigma_{C3-H} \rightarrow \sigma^*_{C2-F}$	$\sigma_{C2-F} \rightarrow \sigma^*_{C3-F}$	$\sigma_{C1-C2} \rightarrow \sigma^*_{C3-F}$	Sum of all $\sigma \rightarrow \sigma^*$ interactions
1	AG (T)	0.00	0.00	0.00	−5.90	−5.66			−30.64
2	GA (T)	0.10	−7.15	7.25	−6.03		−1.90		−23.60
3	GG (T)	0.58	−4.64	5.22	−5.23			−2.90	−24.56
4	AA (E)	0.00	0.00	0.00	−5.99		−1.96		−21.88
5	GG (E)	0.82	6.60	−5.78	−5.59	−5.41		−2.91	−28.01

[a] Carbon numbering refers to the butane chain.

dihedral angle of 60°. We suggest that these reduced CC-CF dihedral angles introduce substantial unfavourable steric interactions between the methyl groups and the adjacent fluorine atoms, and represents the extra unfavourable steric energy term found for AG(T). It is nevertheless surprising that the 3.5° lower dihedral angle between the two *gauche* methyl groups in the GG(T) conformation still results in a lower steric destabilization than that between the two *gauche* methyl and fluorine groups in the AG(T) conformation.
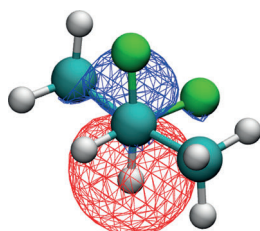
Table 3. Dipole moments (μ), relative energies (E: electronic energy, G: free energy) and, in brackets, populations of (E/T)-2,3-difluorobutane conformations, in vacuum and solvents of increasing polarity. Energies are shown in kcal mol^{-1}, with the most stable conformer at 0 kcal mol^{-1}.

| | μ [D] | Relative energy[a] (population)[b] |
| | | vacuum | | chloroform | | acetone | | water | |
		E	G	E	G	E	G	E	G
AG(T)	2.9	0.00	0.58 (20%)	0.07	0.67 (19%)	0.20	0.20 (39%)	0.22	0.30 (35%)
GA(T)	0.7	0.10	0.00 (55%)	0.95	0.63 (21%)	1.63	1.26 (7%)	1.77	1.37 (6%)
GG(T)	3.7	0.58	0.47 (25%)	0.00	0.00 (60%)	0.00	0.00 (54%)	0.00	0.00 (59%)
AA(E)	0.0	0.00	0.00 (68%)	0.37	0.30 (23%)	1.01	0.54 (16%)	1.25	0.58 (16%)
GG(E)[c]	3.3	0.82	0.86 (16%)	0.00	0.00 (39%)	0.00	0.00 (42%)	0.00	0.00 (42%)
GG(E)[c]	3.3	0.82	0.86 (16%)	0.00	0.00 (39%)	0.00	0.00 (42%)	0.00	0.00 (42%)

[a] M05-2X/6-311 + G(d,p). [b] Calculated using the Boltzmann distribution. [c] Degenerate structure.

Figure 10. Wireframe isosurface of the electron donor σ_{C-H} on the rear carbon of AG(T).

Interestingly, calculation of the hybridisation state of the individual bonds shows a significant rehybridisation, with the C—F bond gaining significantly more *p*-character (Table S3 in the Supporting Information). This is due to the strong electronegative character of the fluorine atoms.[24] This causes a distortion of perfect tetrahedral geometry, which naturally impacts on the dihedral angles as well.

Boltzmann populations

The discussion so far has focused on intramolecular electronic energy terms and we have sought to understand how the interplay between often opposing terms affects the potential energy profile of the different conformers. However, the relative populations of conformers (assuming equilibrium) are determined by the free energies rather than the internal energies. We have obtained free energies under the harmonic approximation by performing vibrational frequency calculations on the geometry optimized structures of the conformers we found. From these, the relative populations were obtained with the Boltzmann equation. We have performed these calculations not just in vacuum but also in chloroform (CHCl$_3$), acetone (CH$_3$COCH$_3$), and water, to study the influence of solvent polarity. These values are presented in Table 3 in which for each isomer, the corresponding conformer populations are given.

These data show that the free energies (namely the inclusion of vibrational thermal energy and entropy) are such that they radically change the order of relative stabilities of the conformers for each isomer. For example, the lowest energy *threo* conformer in vacuum, AG(T), is not the most populated, but it is the GA(T) instead. It is however even more noteworthy to observe what happens as solvents of increasing polarity are introduced. In this case, GA(T) becomes essentially unpopulated (6% in water) and a population ratio of approximately 1.5:1 of GG(T) over AG(T), which both have a fluorine *gauche* arrangement, is obtained. The larger population of the GG(T) conformer, which displays a methyl *gauche* destabilization, is explained by its higher dipole moment, which stabilization in a polar solvent becomes more important than the steric hindrance. For the *erythro* isomer, the GG(E) conformers become much more populated in aqueous medium than the AA(E) conformer, which was the most stable in vacuum.

Hence, in water, for both the *threo* and *erythro* 2,3-difluorobutane, the most populated conformations have the fluorine atoms in the *gauche* conformation. That the nonlinear GG(T) conformation is the major constituent for the *threo* isomer is unexpected given the discussion in the introduction regarding the importance of steric, electrostatic and hyperconjugation effects. In polar solvents, the most polar conformations will tend to dominate, and the GG(T) has the largest dipole moment of all *threo* conformers.

Validation of the computational data by NMR spectroscopy

The conformer distribution figures allowed calculation of theoretically expected coupling constants, which were then compared with the experimentally obtained values. In Figure 11, the change of the calculated $^3J_{H2-H3}$ values with the dihedral angle, obtained as explained in the methods section above, is shown (blue line). It is clear from the shape of the curve that the Karplus equation alone is not a good approximation in fluorine-containing systems and a full dihedral angle scan followed by a statistical average is necessary in all cases. The barrier heights (Figure 9) and the appearance of the NMR spectra indicate that the interconversion between the different conformations is fast on the time scale of the NMR experiment.
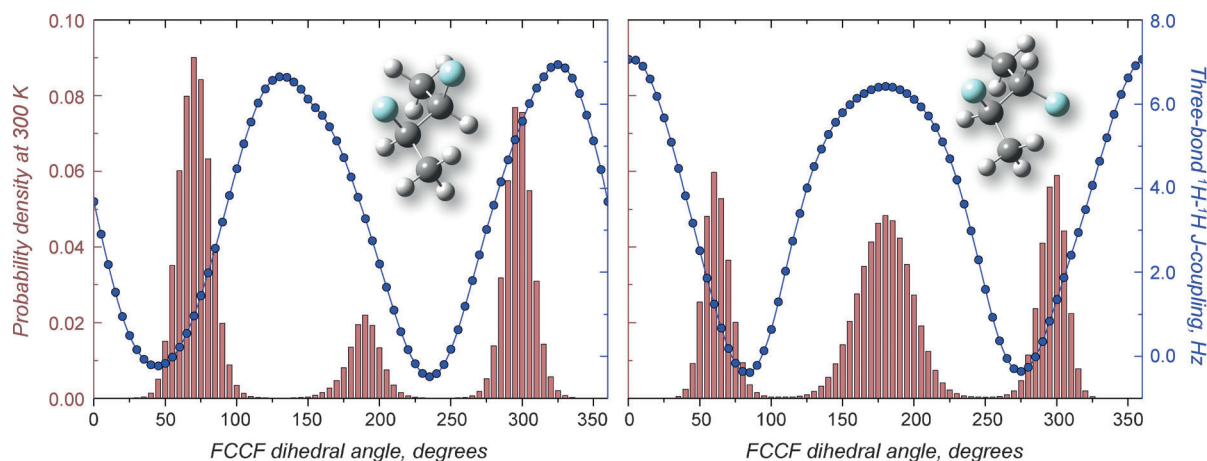
Figure 11. Boltzmann population distribution (histograms) and three-bond H-H *J* coupling (curve) for *threo* (left) and *erythro* (right) 2,3-difluorobutane.

In his 1991 paper, Angelini had reported a number of experimentally determined vicinal coupling constants for both *threo* and *erythro* 2,3-difluorobutane.[18] Given the strong second order ^{1}H and ^{19}F NMR spectra, and the considerable developments in correlating coupling constants with dihedral angles over the past 20 years, both **1** and **2** were resynthesized (see the Supporting Information for details), their spectra taken, and their coupling constants extracted by data fitting. These values are also given in Table 4. The comparison of the calculated coupling constants with the experimentally obtained values is shown in Table 4. Interestingly, there is a excellent agreement between the experimental *J* coupling values for the 2,3-difluorobutane diastereomers **1** and **2** reported by Angelini[18] and the data obtained by us. Furthermore, there is a good agreement between the experimental *J* values and the calculated values, certainly taking the trends into consideration, indicating the validity of the DFT calculations. The $^3J_{H2-F3}$ values do differ from the values reported by Schlosser and Rozen for the larger 6,7-difluorododecane isomers **5** and **7**, and the 7,8-difluorotetradecane diastereomers **6** and **8** (Figure 2).

Conclusion

In this study, the 2,3-difluorobutane conformational profile has been extensively studied using a combination of state-of-the-art theory and experiment. We find that the classical fluorine

gauche effect is not dominant in controlling the conformation of 2,3-difluorobutane, in contrast to that of 1,2-difluoroethane. Conventional considerations predict the AG(T) conformer to be much more stable than the other two *threo* conformers, and that the *erythro* conformers are similar in energy. We find that this is not the case.

In vacuum, an unexpected unfavourable steric contribution is responsible for a higher than expected internal energy of the AG(T) conformation. This results in the AG(T) being less stable than the most stable *erythro* conformer, AA(E), and being close in energy to the next most stable *threo* conformer, GA(T).

Calculation of the relative free energies and corresponding conformer populations alters further the predicted stability order. For the *threo* isomer in vacuum, AG(T) now becomes the least stable, hence the least populated conformer, while the GA(T) conformation is now the dominant conformer (55% population). For the *erythro* isomer there is no change in the relative order of conformer stability.

Finally, adding solvation again leads to a significant change. For the *threo* isomer, those conformations having a fluorine *gauche* arrangement, AG(T) and GG(T), become the most populated. Surprisingly, the nonlinear GG(T) conformation is more populated than AG(T), which is completely unexpected from first order considerations of local geometry, but consistent with its higher dipole moment. A similar change is seen for the *erythro* isomer, where the more polar GG(E) conformers are the most populated in water. Hence, in polar media, the stabilisation of polar conformations is the dominant effect on conformer stability.

The sizes of the calculated conformer energies are such that vicinal difluorination does not exert overwhelming conformational control. Indeed, the influence of the molecular environment surrounding the vicinal difluorination has a significant effect on the actual free energy landscape, and we suggest that careful computational studies are required to establish the actual free energy landscape for individual cases.

Table 4. 2,3-Difluorobutane *J* coupling constant values [Hz] from NMR in CDCl$_3$ by Angelini et al., in this work, and our DFT calculations at the M05-2X/aug-cc-pVTZ level using the SMD model with a dielectric constant representing chloroform. Our samples were contaminated with tetrahydrofuran.

	$^3J_{H2-H3}$		$^3J_{H2-F3}$		$^3J_{F2-F3}$		$^4J_{F2-Me4}$	
	threo	*erythro*	*threo*	*erythro*	*threo*	*erythro*	*threo*	*erythro*
Angelini[a]	4.5	3.6	18.2	15.6	−11.6	−13.8	–	–
our data[a]	4.36	3.59	18.15	15.73	−11.61	−13.58	0.90	1.44
DFT[b]	3.1	2.9	16.2	14.1	−12.4	−17.5	1.4	1.8

[a] Experimental ^{19}F NMR data obtained by data fitting. [b] Our data.

In relation to previously published data on the remarkable influence of a single C-F stereogenic centre as part of an internal vicinal fluorine motif of long chain alkane containing structures, as reported with melting point and Langmuir data, we suggest that intermolecular interactions might play a more significant role than previously thought. A recent report by O'Hagan involving a *threo*-difluoro motif embedded in a more complex liquid crystal structure indeed supports this view of the importance of intermolecular interactions in affecting melting points.[43] While it is possible that 2,3-difluorobutane is still not an adequate model for such longer alkane systems, our data do suggest that the importance of the fluorine *gauche* effect on the overall conformation of these large molecules is limited.

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