C–F Compounds

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Synthesis and Conformation of Multi-Vicinal Fluoroalkane Diastereoisomers**

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The incorporation of fluorine atoms is a powerful method for modulating the properties of organic compounds.[1] The selective introduction of one fluorine atom as a replacement for hydrogen or a hydroxy group can confer important properties in medicinal chemistry[2] because of the particular properties of the C–F bond, and perfluorination of alkanes has led to a wealth of industrially useful compounds.[3] Intermediate between these compound classes are partially fluorinated molecules, and they have been studied far less owing to the lack of good synthesis methods and control in multiple fluorine introduction. In this area we have been interested in exploring alkanes bearing multiple vicinal fluorine substituents (such as shown in Figure 1), a new

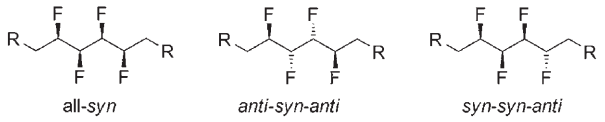

Figure 1. Three α,β,γ,δ-tetrafluoroalkane diastereoisomers.

class of compounds with potential applications as performance molecules in organic materials, for example as novel liquid crystals. Placing single fluorines vicinal to each other generates stereogenic centers, and careful evaluation of the properties of such molecules requires control in their synthesis. This stereochemical complexity is a key feature which sets multi-vicinal fluoroalkanes apart from both their hydrocarbon and perfluorocarbon analogues.

Our initial investigations developed synthetic routes to three-[4] and four-[5]vicinal-fluorine systems. Herein we report the preparation of three different diastereoisomers of a four-vicinal-fluorine motif (Figure 1, R = OTs, Ts = 4-methylphenylsulfonyl) and the evaluation of their relative conformations in the solid and solution states. This study is the first for this class of molecules and forms a basis for predicting more generally how multi-vicinal fluoroalkanes behave.

The first isomer of this series, the all-*syn* tetrafluoro compound **5a** (Scheme 1), was synthesized in nine steps from fluoro alkene **1**.[5] The synthetic sequence was then adapted for the preparation of the *anti-syn-anti* isomer **5b** and the racemic *syn-syn-anti* isomer **5c**.[6]

Tetrafluoroalkanes **5a**, **5b**, and *rac*-**5c** were crystalline, and their structures were confirmed by single-crystal X-ray analyses. In the structure of the all-*syn* isomer **5a**[5] (Figure 2),

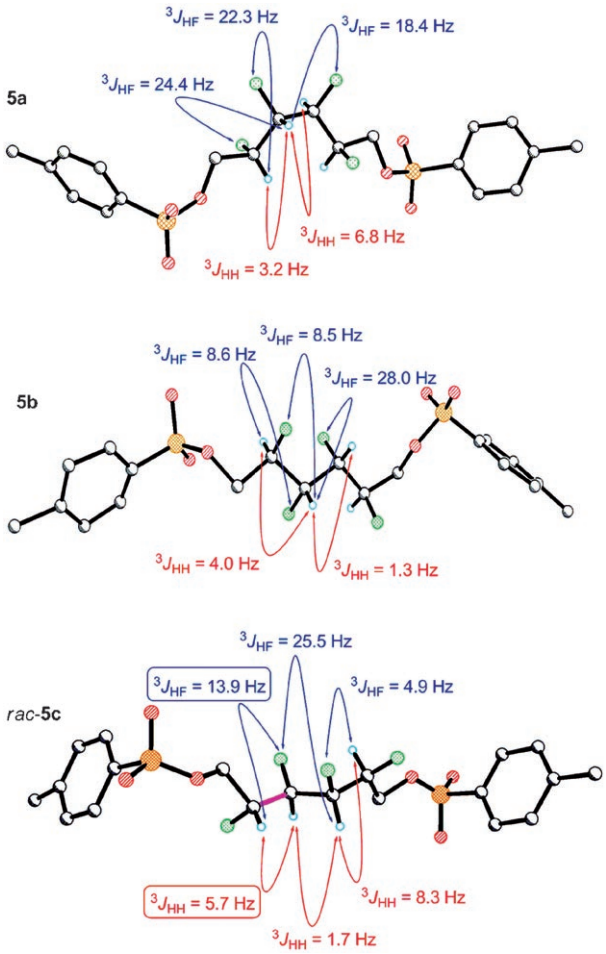

Figure 2. Crystal structures of **5a–c**. C white, F green, H blue, O red, S yellow. Dihedral angles (left to right) between vicinal fluorines: **5a**,[5]66.7, 59.7, and 66.7°; **5b**, 176.8, 66.9, and 176.8°; **5c** (only one enantiomer shown), 74.7, 77.7, and 32.9°. Selected coupling constants from the ^{1}H NMR spectra of **5a–c** are given; values which suggest differences between the solid- and solution-state conformations are highlighted in boxes. The solution conformation of **5c** is obtained by rotation of one C–C bond (shown in pink) to give a longer zigzag carbon chain.

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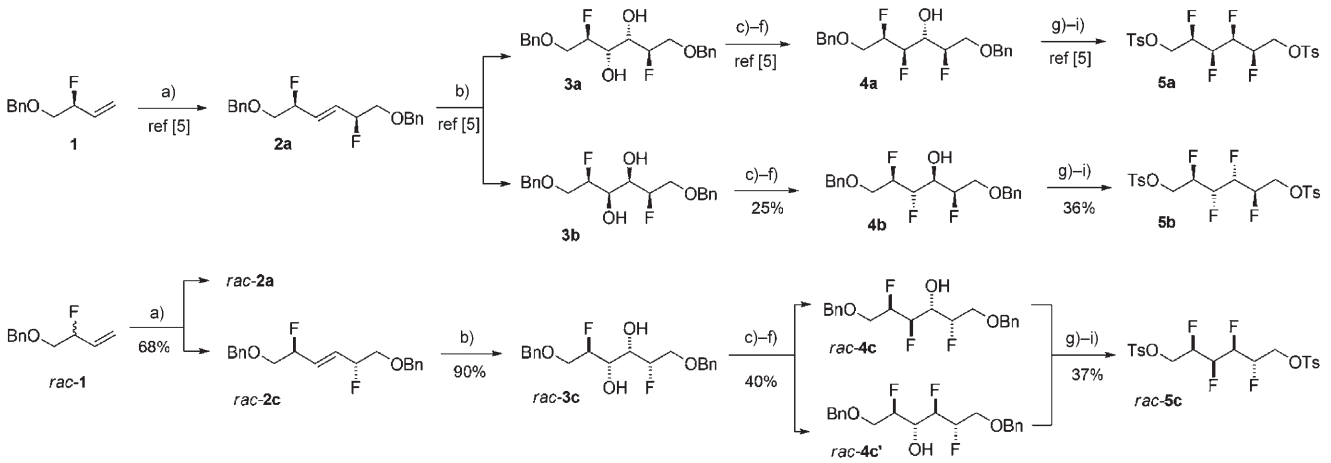

Scheme 1. Synthesis of **5a**,[5] **5b** and *rac*-**5c**. Reagents and conditions:[6] a) Grubbs 2nd-generation catalyst, CH_2Cl_2, Δ; b) $KMnO_4$, $MgSO_4$, EtOH, CH_2Cl_2, H_2O, 0°C; c) $SOCl_2$, pyridine, CH_2Cl_2, room temperature; d) $NaIO_4$, $RuCl_3$, MeCN, H_2O, room temperature; e) Bu_4NF, MeCN, room temperature; f) H_2SO_4, H_2O, tetrahydrofuran, RT; g) H_2, Pd/C, MeOH, room temperature; h) TsCl, collidine, 50°C; i) $(MeOCH_2CH_2)_2NSF_3$ (Deoxo-Fluor), CH_2Cl_2, Δ.

the fluoroalkyl portion of the molecule did not adopt an extended zigzag conformation: instead, the molecule preferred a C_2-symmetric "bent" conformation which nevertheless preserved *gauche* alignments[7] between each pair of vicinal fluorines, and also between the outer fluorines and the tosyl ester oxygen atoms.

As seen in the crystal structure[8] of isomer **5b** (Figure 2), the fluoroalkyl moiety also has C_2 symmetry, but in contrast with **5a** the chain of **5b** adopts an extended zigzag conformation in the solid state. This result is perhaps surprising since this extended conformation precludes two of the possible three fluorine *gauche* relationships.[7]

The solid-state conformation of *syn-syn-anti* isomer *rac*-**5c** was also investigated. Although *rac*-**5c** is crystalline, X-ray analysis was not straightforward because of poor crystal quality, substantial disorder, and the presence of two crystallographically independent, nonsymmetrical enantiomeric contributors which alternate throughout the solid-state structure. However, a diffraction data set with acceptably low disorder was obtained. In the resulting solid-state structure of *rac*-**5c**[8] (Figure 2), all three pairs of vicinal fluorines are approximately *gauche* but the dihedral angles deviate considerably from 60°. It thus appears that the aromatic tosyl groups dominate the crystal-packing interactions, with the fluoroalkyl chain apparently forced to adopt a somewhat strained conformation. This result highlights an important issue relating to the crystal structures of all three isomers **5a–c** (Figure 2): Since the tosyl groups are essential for the crystallinity of the materials, they must by definition dominate the crystal-packing interactions and may therefore obscure the intrinsic conformational preferences of the fluoroalkyl chains themselves. Thus, the NMR spectra of **5a–c** were examined to gain information about their solution conformations.

For compound **5a**, the $^3J_{HH}$ and $^3J_{HF}$ values obtained from the ^{1}H NMR spectrum were somewhat intermediate in magnitude[9] (Figure 2), suggesting that **5a** exhibits significant conformational flexibility in solution at 298 K. However, despite this flexibility, the X-ray conformation still seems to dominate, since the expected *gauche* alignments all give smaller ^3J values than the expected *anti* alignments. The ^{1}H NMR spectrum of **5a** was also recorded at 215 K, but only marginal differences in the $^3J_{HH}$ and $^3J_{HF}$ values were found at this lower temperature.[6]

In contrast with the somewhat ambiguous NMR spectroscopy results obtained for isomer **5a**, a clear picture emerged of the solution conformation of **5b** (Figure 2).[9] In this case, the conformation displayed in the X-ray structure was found to dominate in solution at 298 K, as evidenced by the more ideal $^3J_{HF}$ values which clearly reflect *gauche* and *anti* alignments consistent with the extended zigzag conformation. Thus, it seems that this conformation is intrinsically favored by the fluoroalkyl chain itself, and is not a product of competing crystal-packing forces in the solid state.

The hypothesis that crystal-packing forces are responsible for distortion of the fluoroalkyl chain of **5c** is supported by evidence of its solution conformation (Figure 2). In this case, the $^3J_{HH}$ and $^3J_{HF}$ values obtained from the ^{1}H NMR spectrum of **5c** all fell quite clearly into *gauche* or *anti* categories, suggesting that one conformation is strongly preferred in solution; however, this solution conformation does not match the X-ray conformation. It seems that in solution, the fluoroalkyl chain of **5c** foregoes one fluorine *gauche* interaction so that a longer section of the carbon chain can adopt the extended zigzag conformation.

To gain further insight into the behavior of multi-vicinal fluoroalkanes **5a–c**, computational analyses were performed. Model calculations[10] on fluorohexanes **6a–c** (Figure 3) indicate that of all three isomers in the linear zigzag conformation, **6b** has the lowest-energy. Within the series **6a–c**, **6b** is the only isomer where the linear conformation represents the global energy minimum, which is also reflected in the crystal structure of **5b** (Figure 2). For the all-*syn* isomer **6a**, the linear conformation is 6.50 kcal mol^{-1} higher in energy

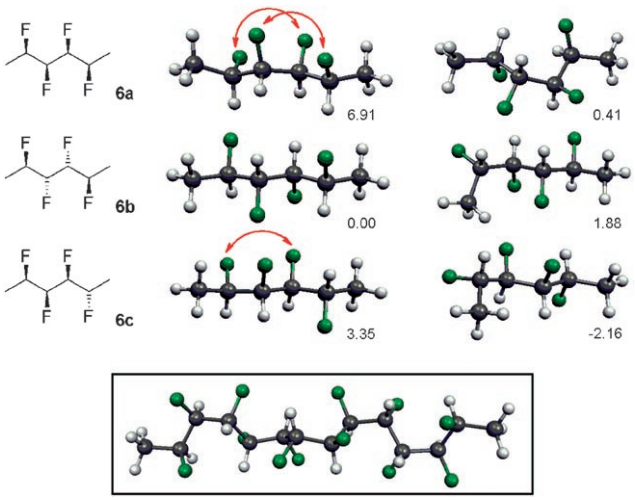

Figure 3. Left: The simplified model system **6**. Middle: Calculated linear conformations and right: either minimum (**6a**, **6c**) or next-higher energy conformation (**6b**). C gray, F green, H white; red arrows indicate g^+g^--F–F interactions.[11] Relative energies are in kcal mol^{-1}. Inset: the model system all-*syn*-$CH_3(CHF)_{12}CH_3$ with its helical minimum energy conformation.

than the lowest-energy conformer, which corresponds to the crystal structure of **5a** (Figure 2). The lowest-energy conformer calculated for isomer **6c** is similar to that for the solution structure determined by NMR spectroscopy of **5c**, providing further support that the crystal structure of **5c** (Figure 2) is dominated by packing of the tosyl groups.

The major conformational driving force for the structures in Figure 3 appears to be avoidance of 1,3-F···F and 1,3-F···CH_3 interactions. For the "linear" conformations, **6a** has two g^+g^- interactions,[11] whereas **6c** has only one, and **6b** none. From the sequence **6a**→**6c**→**6b** it is estimated that each g^+g^--F···F interaction costs about 3.4 kcal mol^{-1} in steric strain.[12] For the "bent" pair **6b** and **6c**, the main difference is a 1,3-F···CH_3 interaction, costing 4.04 kcal mol^{-1}. In this context, the vicinal fluorine *gauche* effect (ca. 0.8 kcal mol^{-1})[7] has only a secondary influence.

To gain insight into conformational effects in more extended sequences, the all-*syn*-$CH_3(CHF)_nCH_3$ series was studied by computational analysis. For each of the homologues from $n = 2$–12, the energies and structures of the linear and the lowest-energy conformation were calculated at the MP2/6-311 + G(2d,p)//B3LYP/6-31G(d) + ZPE level of theory.[10] Only for $n = 2$ does the linear conformer represent the energy minimum. There is a clear, first-order relationship between relative linearization energies and the number of g^+g^--F···F contacts,[6] with each such interaction incurring an energetic price of approximately 3.0 kcal mol^{-1}. In the lowest-energy conformation of the extended all-*syn* isomers (see Figure 3 with $n = 12$), a helical arrangement is adopted which places all the C–F bonds *gauche* with uniform handedness and thus avoids any g^+g^--F···F repulsions.

An additional stabilization of the linear-chain conformation of the shorter all-*syn*- and possibly also of fragments of the longer oligofluoroalkanes (all-*syn*-$CH_3(CHF)_nCH_3$) might arise from the formation of intermolecular H···F hydrogen bridges.[6] The dimerization energies are difficult to interpret in a quantitative manner because of the large variation in hydrogen-bond lengths and orientation, but typical energies seem to be in the range of 1.0–1.6 kcal mol^{-1} per H···F contact. However, because of steric restrictions,[6] the maximum dimerization energy is probably limited to about 6–7 kcal mol^{-1} for linear all-*syn* fluoroalkanes.

In summary, we have used our recently described synthetic methodology[5] to prepare three unique diastereoisomeric α,β,γ,δ-tetrafluoroalkanes, and the conformational preferences of each isomer in the solid and solution states has been examined. It emerges that the avoidance of 1,3-repulsive interactions is the dominant conformational consideration in these multi-vicinal fluorine compounds, with the fluorine *gauche* effect contributing a more subtle conformational influence, and we have extrapolated our findings to extended multi-vicinal fluorine systems. This work provides the first conformation study on this class of molecules and provides information on the behavior and properties of future performance molecules containing vicinal fluorine motifs.

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[9] Three-bond H–H and H–F coupling constants obey Karplus relationships with the corresponding H–C–C–H and H–C–C–F dihedral angles: "typical" $^3J_{HH}$ values are 1–3 Hz for *gauche* alignments and 6–8 Hz for *anti* alignments (see ref. [13]), while "typical" $^3J_{HF}$ values are 5–15 Hz for *gauche* alignments and 25–35 Hz for *anti* alignments (see ref. [14]).
[10] Gaussian 03 (Revision D.01): M. J. Frisch et al., see Supporting Information. The minimum geometries were optimized on the B3LYP/6-31G(d) level of theory, and were verified to have only positive eigenfrequencies. The energies of the conformers were calculated on the MP2/6-311 + G(2d,p) level of theory, using the B3LYP/6-31G(d) geometries and zero-point energies. The energies of the dimers were calculated at the same level of

theory and basis-set superposition error (BSSE)-corrected using the counterpoise method.
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