The Influence of Electronic Perturbations on the Sulfur-Fluorine *Gauche* Effect

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Dedicated to Prof. Dr. Antonio Togni on the occasion of his 60th birthday.

Keywords

Conformation analysis, Hyperconjugation, NMR spectroscopy, Physical organic chemistry, Sulfur-Fluorine *Gauche* Effect

Abstract

Herein, a solution phase NMR conformer population analysis is employed to probe the effect of remote electronic perturbations on the conformational equilibria of a series of *para*-substituted β -fluorosulfides (**1**), sulfoxides (**2**) and sulfone derivatives (**3**). Conformations that allow for stabilizing stereoelectronic ($\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$) and electrostatic ($\text{F}^{\delta-} \cdots \text{S}^{\delta+}$) interactions predominate: this is consistent with the *Sulfur-Fluorine Gauche Effect*. The molar fractions (χ) of the two possible *gauche* conformers correlate linearly with the electron-withdrawing aptitude of the *para*-substituent, rendering the system ideally suited for a Hammett-type analysis. Despite the clear influence that the remote *para*-substituents have on conformer population, this is superseded by the oxidation state on sulfur (II, IV, VI), where an increased preference for the *gauche* conformer follows the trend: sulfide < sulfone < sulfoxide. It is envisaged that this proof of concept in controlling conformer population, either by proximal (oxidation state) or remote tuning (*para*-substituent), will find application in molecular design.

1. Introduction

The fluorine-heteroatom *gauche* effect describes the preference of a generic 1,2-disubstituted β -fluoro-ethane fragment (F-C1-C2-X) to preferentially adopt *gauche* conformations over the *anti* arrangement (Figure 1).^[1] This intriguing behaviour is a consequence of fluorine's high electronegativity and negligible steric footprint: Together these features allow this counterintuitive *syn-clinal* arrangement to predominate by simultaneously facilitating stabilising hyperconjugative interactions, to engage the low-lying anti-bonding orbital of the C-F bond (e.g. $\sigma_{\text{C-H}} \rightarrow \sigma_{\text{C-F}}^*$), without generating un-favourable non-bonding interactions. Indeed this latter feature allows proximal groups with opposing (partial) charges to interact electrostatically, further augmenting the interaction. As a general rule, the electron-withdrawing capability of the heteroatom substituent (X), can be correlated with the *gauche* conformational bias. Whilst this notion is well studied and has found

2. Results and Discussion

To provide a fully experimental validation of this working hypothesis, and complement the existing theoretical treatment,^[3,4] three sets of electronically modulated compound classes were prepared and subjected to a solution phase conformer population analysis (Figure 2A). Specifically, the electronics of the parent sulfide, sulfoxide and sulfone scaffolds (**1e**, **2e**, **3e**) were perturbed through the introduction of electron-donating and electron-withdrawing substituents [R = NH₂ (**a**), OH (**b**), OMe (**c**), Me (**d**), H (**e**), F (**f**), Cl (**g**), CO₂H (**h**), CO₂Et (**i**) and NO₂ (**j**)]. Furthermore, the corresponding thioester **4** was explored on account of the importance of acetyl-CoA in biosynthetic transformations,^[6] and finally the thiocyanate **5** bearing an electron deficient S-atom. These systems serve as valuable scaffolds to comparatively evaluate how subtle electronic attenuations translate into conformer populations, as reflected by the respective molar fractions (χ_I , χ_{II} , χ_{III} ; Figure 2B).

Figure 2. A: The sulfides (**1a-j**), sulfoxides (**2a-g,i-j**) and sulfones (**3a-g,i-j**) as well as thioester **4** and thiocyanate **5** used in this study. **B:** The three staggered conformers partitioned by 120° that were considered and described as molar fractions (χ_I , χ_{II} , χ_{III}).

Preparation of the target sulfides (**1a-j**) proved facile and could be achieved by unifying commercially available, *para*-substituted thiophenols with 2-fluoroethane tosylate. The desired products were generated cleanly and in good yields (24 – 87%) (Figure 2A). Through sequential oxidation using *m*-CPBA it was possible to access the respective sulfoxides (**2a-g,i-j**; 40 – 89%) and ultimately the sulfones (**3a-g,i-j**; 40 – 89%) (Full experimental details are provided in the supporting information). Since compound **1h** was the synthetic precursor for **1i** it was also included in the ensuing analysis, however, the corresponding sulfoxide and sulfone to **1h** were not prepared. *S*-(2-fluoroethyl) thioacetate (**4**) and 1-fluoro-2-thiocyanatoethane (**5**) were prepared in 44 and 38% yield by treating 2-fluoroethane tosylate with sodium thioacetate and sodium thiocyanate, respectively, following a literature protocol.^[7]

Despite the structural diversity of the systems **1 – 3** prepared, very few samples proved to be crystalline thereby precluding the use of crystallographic techniques for the conformational analysis.

The solution phase NMR analysis was performed with the pre-condition that only the three conformers partitioned by 120° would be considered: these include the two *gauche* (g^+ / g^-) arrangements and the corresponding *anti* conformation (Figure 2B). Furthermore, in the case of the sulfide ($n = 0$) and sulfone ($n = 2$), substitutions g^+ and g^- are equivalent and thus the sum of both is reported. The required NMR samples were prepared in CDCl₃ at concentrations between 0.1 and 0.2 mM and standard experiments (¹H & ¹⁹F) were conducted at ambient temperature.

The following population analysis was based on the experimental $\langle {}^3J_{\text{HF}} \rangle$ coupling constants as summarized in Table 1 and theoretical values (J^{anti} and J^{gauche}), which were determined as previously described by Béguin and co-workers.^[8] Hence, J^{anti} and J^{gauche} were calculated according to $J^{\text{anti}} = 65.75 - 7.52 \times \Sigma(\Delta E)$ and $J^{\text{gauche}} = 15.35 \times \exp(-0.266 \times \Sigma(\Delta E))$ here $\Sigma(\Delta E)$ represents the sum of the Huggins electronegativity differences between a substituent (SO_nR, F) and hydrogen.

For fluorine, a value of 1.70 for ΔE was used and the sulfur component's group electronegativities relative to hydrogen (ΔE) are based on the internal proton shift differences $\delta(\text{CH}_3)$ - $\delta(\text{CH}_2)$ of the

corresponding ethyl derivatives, *e.g.* EtSPh for R = H and n = 0 (**1e**), correlated to group electronegativities previously reported (values tabulated in the supporting information).^[8] Thus, ΔE values were deduced averaging 0.70, 0.72 and 0.89 for sulfide, sulfoxide and sulfone systems, respectively; this is in agreement with group electronegativity values reported for SH (0.76) and SO₂Cl (0.69).^[9] It is interesting to note that the *para*-substituent R only had a small effect on J^{anti} and J^{gauche} ; this is exemplified by the values of 47.9 and 8.2 Hz, and 47.4 and 8.0 Hz, for the two electronic extremes of the sulfides studied (n = 0), *i.e.* **1a** (R = NH₂, σ_{para} = -0.66) and **1j** (R = NO₂, σ_{para} = 0.78), respectively. As a consequence, when populations were calculated using the J^{anti} and J^{gauche} values of the R = H derivatives (**1e**, **2e**, **3e**) the values obtained typically differed by less than 2% from those reported in Table 1.

Upon oxidation to the sulfoxide (n = 1; **2a-g,i-j**) no significant change was observed in J^{anti} and J^{gauche} with average values of 47.5 ± 0.2 and 8.1 ± 0.1 Hz having been calculated. Only in the case of sulfones (n = 2; **3a-g,i-j**), were smaller values generally observed with average values of 46.2 ± 0.5 and 7.7 ± 0.1 Hz for J^{anti} and J^{gauche} , respectively. Conversely, the experimental values $\langle {}^3J_{HF} \rangle$ displayed a slightly broader distribution as determined by comparison of the data sets of the electronic extremes (R = NH₂; R = NO₂) with (**1a** 17.0; **1j** 19.2), (**2a** [28.0, 21.8]; **2j** [30.3, 20.5]) and (**3a** 21.4; **3j** 22.7) Hz for n = 0, 1 and 2, respectively. Note that in the sulfoxide system the protons at carbon atom C2 are diastereotopic, thus resulting in two experimentally distinct coupling constants $\langle {}^3J_{HF} \rangle$. To translate these values into *gauche* conformer populations χ_I and χ_{III} the data was subjected to analysis using equation (1). The corresponding *anti* conformer population could be determined by simple extrapolation: $\chi_{II} = 1 - \chi_I - \chi_{III}$.

$$\chi_{I/III} = (\langle {}^3J_{HF} \rangle - J^{gauche}) / (J^{anti} - J^{gauche}) \quad (1)$$

The resulting values determined throughout the course of the study are summarized in Table 1. Additionally, to improve the comparison across the sulfur oxidation states, summed *gauche* conformer populations were considered ($\Sigma g = \chi_I + \chi_{III}$), which allowed graphical representations of the form $\Sigma g \sim \sigma_{para}$ to be constructed (Figure 3). For the sulfoxide systems ($n = 1$), the conformer populations were also calculated independently based on the sets of experimental $\langle {}^3J_{HH} \rangle$ coupling constants of each of the diastereotopic protons adjacent to sulfur: The values obtained correlate well with the initial data set derived from $\langle {}^3J_{HF} \rangle$ (see supporting information).^[8]

Table 1. Summary of experimental and calculated coupling constants, the conformer populations (χ_I – χ_{III}) derived, and the summed *gauche* populations (Σg).

Entry	$\sigma_{para}^{[a]}$	$\langle {}^3J_{HF}^1 \rangle /$ Hz ^[b]	$\langle {}^3J_{HF}^2 \rangle /$ Hz ^[b]	$J^{anti} /$ Hz ^[c]	$J^{gauche} /$ Hz ^[c]	$\chi_I (g^-)$	$\chi_{II} (anti)$	$\chi_{III} (g^+)$	Σg
1a	-0.66	17.0	-	47.9	8.2	0.22	0.56	0.22	0.44
1b	-0.37	17.3	-	47.8	8.1	0.23	0.54	0.23	0.46
1c	-0.27	17.2	-	47.8	8.1	0.23	0.54	0.23	0.46
1d	-0.17	17.0	-	47.6	8.1	0.23	0.55	0.23	0.45
1e	0	17.0	-	47.5	8.1	0.23	0.55	0.23	0.45
1f	0.03	17.8	-	47.7	8.1	0.24	0.51	0.24	0.49
1g	0.23	17.8	-	47.7	8.1	0.25	0.51	0.25	0.49
1h	0.45	18.0	-	47.4	8.0	0.25	0.49	0.25	0.51
1i	0.45	17.8	-	47.4	8.0	0.25	0.49	0.25	0.51
1j	0.78	19.2	-	47.4	8.0	0.28	0.43	0.28	0.57

2a	-0.66	28.0	21.8	47.5	8.1	0.51	0.17	0.32	0.83
2b	-0.37	29.6	20.2	47.1	8.1	0.55	0.13	0.31	0.87
2c	-0.27	28.7	21.3	47.5	7.1	0.52	0.14	0.34	0.86
2d	-0.17	29.8	19.4	47.6	8.1	0.55	0.16	0.29	0.84
2e	0	30.1	19.5	47.7	8.1	0.56	0.16	0.29	0.84
2f	0.03	30.0	19.9	47.6	8.1	0.55	0.15	0.30	0.85
2g	0.23	30.2	19.7	47.6	8.1	0.56	0.15	0.29	0.85
2i	0.45	30.3	19.3	47.6	8.1	0.56	0.15	0.28	0.85
2j	0.78	30.3	20.5	47.3	8.0	0.57	0.12	0.32	0.88
3a	-0.66	21.4	-	46.3	7.7	0.36	0.29	0.36	0.71
3b	-0.37	22.0	-	46.3	7.7	0.37	0.26	0.37	0.74
3c	-0.27	21.8	-	46.5	7.8	0.36	0.28	0.36	0.72
3d	-0.17	21.8	--	46.4	7.8	0.36	0.27	0.36	0.73
3e	0	22.0	-	46.7	7.8	0.37	0.27	0.37	0.73
3f	0.03	22.7	-	46.3	7.7	0.39	0.22	0.39	0.78
3g	0.23	22.8	-	46.4	7.7	0.39	0.22	0.39	0.78
3i	0.45	22.7	-	46.2	7.7	0.39	0.22	0.39	0.78
3j	0.78	23.8	-	44.9	7.4	0.44	0.12	0.44	0.88

[a] Preferred values taken from reference [10]; [b] determined by ^1H NMR spectroscopy; [c] calculated according to reference [8].

Figure 3. Hammett-type correlations between Σg and σ_{para} for sulfides **1**, sulfoxides **2** and sulfones **3**.

These data suggest that *gauche* conformation population increases the more electron-withdrawing the substituent R ($\sigma_{para} > 0$).

Inspection of entries **1a-j** in Table 1 indicates that the *para*-substituent R has a clear effect on the calculated populations which range from $\Sigma g:anti = 0.44:0.56$ to $0.57:0.43$. This is further supported by the Hammett-type analysis presented in Figure 3, suggesting a linear correlation between the electron-donating ($\sigma_{para} < 0$) or electron-withdrawing ($\sigma_{para} > 0$) properties of the *para*-substituent R and the population of the *gauche* conformers Σg . This logically supports intuition, that the more electron deficient the sulfur centre, the more pronounced the preference for the *gauche* conformers. This is in line with a stereoelectronic interpretation of the sulfur-fluorine *gauche* effect, that the key hyperconjugative interaction ($\sigma_{C2-S} \rightarrow \sigma^*_{C1-F}$) should diminish with increasing electron-deficiency of the C2-S bond. However, it should also be noted that since an average value Σg of 0.48 ± 0.04 is found, these data suggest that rotation around C1-C2 is relatively unhindered in the sulfide system the presence of a small energetic preference for the *anti* conformer (since for a statistical mixture a Σg value of 0.67 is expected); this is in keeping with our previous results for (2-fluoroethyl)(methyl)sulfide (*anti* preference) and the most recent calculations by Baranac- Stojanović and co-workers for the same sulfide (*anti* preference).^[4]

Figure 4. **A:** X-ray structure of sulfide **1h**. Only one molecule of two found in the asymmetric unit is shown. Thermal ellipsoids shown at the 30% probability level. **B:** Dimeric structure of **1h** between the two molecules found in the asymmetric unit involving O-H...H interactions.^[11]

In the case of compound **1h** (R = CO₂H) single crystals that were suitable for solid-state structure determination were obtained by evaporation of a solution in dichloromethane.^[11] From the analysis, a clear *gauche* arrangement was found between the fluorine and sulfur atom (F-C1-C2-SAr, torsion angle $\phi_{\text{SCCF}} \approx 67^\circ$, Figure 4) with geometries that allow for hyperconjugative interactions ($\phi_{\text{HCCF}} \approx -172^\circ$ and $\phi_{\text{HCCS}} \approx -172^\circ$). To the best of our knowledge, this constitutes the first X-ray analysis of this fragment sub-class displaying a “sulfide”-fluorine *gauche* effect. However, the results of the X-ray analysis are in contrast to the initial solution phase analysis, ~~where no profound preference of either conformer was found~~ where a small preference for the *anti* conformer was found ($\Sigma g\text{:anti}$ 0.51:0.49). Furthermore, in the fluoro-ethane motif, bond angles of 110.0° and 109.8° were determined for F-C1-C2 and C1-C2-H, respectively. Since these values were available, an angle-dependent determination of J^{anti} and J^{gauche} was possible.^[12] These values were calculated to be 45.7 Hz and 12.0 Hz, respectively, thus leading to a marginally altered population ratio of $\Sigma g\text{:anti}$ = 0.36:0.64, as determined by equation 1. This discrepancy between solid and solution phase preference may stem from crystal packing effects: the formation of homo-dimers involving the carboxylic acid moiety [O2A-H2A...O1B 1.829 Å, O2B-H2B...O1A 1.775 Å] was noted in addition to FCH₂...F [2.374 Å] and Ar-H...S [2.985 Å] contacts (see supporting information for details). Overall, these ~~three~~ complementary analyses are consistent and reveal ~~the absence of a pronounced~~ the small preference of either the *anti* conformer in the sulfide system (average Σg of 0.48 ± 0.04): This experimental finding is fully consistent with the theoretical treatment previously reported.^[3,4]

Upon oxidation to the sulfoxide (n = 1), a markedly flatter slope was calculated for the correlation $\Sigma g \sim \sigma_{\text{para}}$ (0.08 ± 0.01 with n = 0; 0.02 ± 0.02 with n = 1) and a low R² value was obtained (Figure 3). In addition, the data display a narrower distribution in comparison to the sulfide system with a difference of 13% and 5% for n = 0 and 1, respectively, between the minimal and maximal Σg values. Furthermore, the average Σg increased to 0.85 ± 0.02 . Clearly, the introduction of a second strong dipole moment (S=O) has an overriding effect.

Since the molecular structure of sulfoxide **2j** ($R = \text{NO}_2$) has previously been reported by this laboratory (CCDC 1048077)^[3] and displays a F-C-C-S dihedral angle of -55.87° , coupling constants $J^{anti} = 41.8 \text{ Hz}$ and $J^{gauche} = 11.0 \text{ Hz}$ could be derived for the angles F-C1-C2 and C1-C2-H of 113.0° and 108.8° , respectively. Assuming that the major diastereomer crystallized from solution, this conformation should lead to minimization of the overall molecular dipole. At the same time, stabilizing Coulombic interactions (dashed) reinforce the fluorine-sulfur *gauche* effect (Figure 5). The importance of this electrostatic interaction is further emphasised by the preference of the major diastereomer over the minor with average $\chi_I(g^-) = 0.55 \pm 0.02$ and $\chi_{III}(g^+) = 0.30 \pm 0.02$ population values (Table 1). This trend derived from a study of the linear scaffold corresponds well with a previous conformational analysis carried out on a cyclic system.^[3]

Figure 5. Putative intramolecular interactions (dipole minimization: arrow; Coulomb interaction: dashed) in the g^+ (minor) and g^- (major) sulfoxide conformers ($n = 1$).

Finally, oxidation to the sulfone ($n = 2$), which removes the stereogenic centre, reinstates the dependence of Σg on the electronics of the *para*-substituent with a slope of 0.11 ± 0.02 (Figure 3). In comparison to the sulfoxide, the average Σg value is slightly decreased to 0.76 ± 0.05 with the difference between the minimal and maximal Σg values being 17%. Based on a previously published molecular structure of sulfone **3j** (CCDC 1048078), $J^{anti} = 46.1 \text{ Hz}$ and $J^{gauche} = 11.8 \text{ Hz}$ were calculated (F-C1-C2: 109.5° , C1-C2-H: 108.6°) affording $\Sigma g = 0.70$ in good agreement with the *gauche* preference verified by the F-C-C-S dihedral angle of -68.12° . In keeping with the results delineated for the sulfide

system, the angle-dependent approach afforded a slightly smaller preference for the *gauche* conformers than an angle-independent treatment.

Finally, the solution phase conformation of S-(2-fluoroethyl) thioacetate (**4**) and 1-fluoro-2-thiocyanatoethane (**5**) were analysed, which were predicted to display almost no ~~a small *anti* (-0.15 kcal mol⁻¹)~~ and a ~~more pronounced small *gauche* (-0.73~~ 0.4 – 0.8 kcal mol⁻¹) preference in dichloromethane, respectively. These values were previously calculated using the polarizable continuum model.^[4] However, in the same report it was also suggested that explicit solute-solute and solute-solvent effects are likely to shift these conformational equilibria to favour the *gauche* conformer. Coupling constants of 21.5 Hz for **4** and values of $J^{anti} = 47.9$ Hz and $J^{gauche} = 8.2$ Hz were determined, indicating ~~a moderate preference for the *gauche*~~ the absence of a clear preference for either conformer ($\Sigma g:anti = 0.67:0.33$) in CDCl₃.

Compound **5** displays a similar conformational behaviour with respective values of $\langle^3J_{HF}\rangle = 21.4$ Hz, $J^{anti} = 48.5$ Hz and $J^{gauche} = 8.3$ Hz ($\Sigma g:anti = 0.65:0.35$). To improve the comparison with the computational approach, the respective coupling constants were also determined in CD₂Cl₂ ($\langle^3J_{HF}\rangle$ (**4**) = 21.7 Hz and $\langle^3J_{HF}\rangle$ (**5**) = 22.2 Hz): this did not result in significant changes for **4** ($\Sigma g:anti = 0.68:0.32$) or for **5** ($\Sigma g:anti = 0.69:0.31$). Overall, these data substantiate the initial prediction of almost no or a small *gauche* preference in these structurally related systems.

3. Conclusions

In summary, the effect of subtle electronic perturbations on the conformational equilibria of F-C1-C2-S(O)_nR systems has been investigated by solution phase NMR-based analysis. Generally, upon introduction of increasingly electron-deficient substituents, the *gauche* conformers become increasingly populated ~~favoured~~ leading to population differences of up to 17% between the most electron-donating (R = NH₂) and electron-withdrawing (R = NO₂) substituents investigated. Sequential oxidation of sulfur (n = 1, 2) has a more pronounced influence on conformational behaviour than the

para-substituent. The Σg populations of on average 48% for sulfides ($n = 0$) increase significantly to 85 and 76% for the sulfoxide ($n = 1$) and sulfone ($n = 2$) systems, respectively – this is in contrast to a recent computational study which suggested that sulfones preferentially adopt *gauche* arrangement over sulfoxide systems. This study demonstrates that the sulfur-fluorine *gauche* effect can be further tuned by the simple introduction of a *para*-substituted aryl sulfide, sulfoxide or sulfone unit into the model systems (i.e. F-C1-C2-S(O)_nAr). Efforts to exploit this phenomenon in molecular design are ongoing and will be reported in due course.

4. Experimental

Full experimental details are provided in the supporting information.

(2-Fluoroethyl)(phenyl)sulfane (1e)

To a solution of 2-fluoroethane tosylate (302 mg, 1.38 mmol, 1.0 eq.) in toluene (7 ml) were added sequentially thiophenol (170 μ l, 1.66 mmol, 1.2 eq.) and DBU (270 μ l, 1.80 mmol, 1.3 eq.) and the mixture was stirred at rt for 6 h under an atmosphere of argon. The reaction mixture was diluted with EtOAc (10 ml) and was then washed with aq. sat. NH₄Cl (10 ml), 1 M NaOH (2 x 8 ml) and brine. The separated organic layer was dried over Na₂SO₄ and concentrated under reduced pressure. Separation *via* column chromatography on silica gel (pentane) afforded the desired product as colourless oil (154 mg, 71%).

$R_f = 0.35$ (pentane); ¹H NMR (400 MHz, CDCl₃) δ = 7.42-7.38 (2H, m, H-C5), 7.34-7.28 (2H, m, H-C4), 7.26-7.21 (1H, m, H-C6), 4.54 (2H, dt, ²J_{HF} = 47.0, ³J_{HH} = 6.8, H-C1), 3.21 (2H, dt, ³J_{HF} = 17.0, ³J_{HH} = 6.9, H-C2) ppm; ¹³C NMR (101 MHz, CDCl₃) δ = 134.9 (C3), 130.4 (2C, C5), 129.3 (2C, C4), 127.0 (C6), 81.7 (d, ¹J_{CF} = 172.5, C1), 33.8 (d, ²J_{CF} = 21.6, C2) ppm; ¹⁹F NMR (282 MHz, CDCl₃) δ = -112.43 (1F, tt, ²J_{HF} = 47.0, ³J_{HF} = 17.0, F-C1) ppm; IR (ATR) $\tilde{\nu}$ = 3060w, 2963w, 2895w, 1583m, 1480m, 1439m, 1404w, 1385w, 1288w, 1231w, 1197w, 1088w, 1059m, 1024m, 1006m, 986m, 955m, 898w, 813w,

737s, 689s cm^{-1} ; **GC-MS** (EI): $t_R = 8.63$ min, m/z : 156.0 (M^+). Spectroscopic data are in agreement with previous literature.^[13]

((2-Fluoroethyl)sulfinyl)benzene (2e)

A solution of **1e** (76 mg, 0.49 mmol, 1.00 eq.) in CH_2Cl_2 (8 ml) was cooled to 0 °C and *m*CPBA ($\leq 77\%$, 118 mg, 0.51 mmol, 1.05 eq.) was added. After stirring for 16 h under an atmosphere of argon while warming to rt, the mixture was washed with aq. sat. NaHCO_3 (6 ml), brine, was dried over Na_2SO_4 and concentrated under reduced pressure. Separation by column chromatography on silica gel (CyH/EtOAc 1:1) afforded the desired product as colourless oil (49 mg, 58%).

$R_f = 0.25$ (CyH/EtOAc 1:1); **^1H NMR** (400 MHz, CDCl_3) $\delta = 7.67\text{--}7.63$ (2H, m, H-C5), 7.57–7.51 (3H, m, H-C4/C6), 4.92 (1H, dddd, $^2J_{\text{HF}} = 46.9$, $^2J_{\text{HH}} = 10.5$, $^3J_{\text{HH}} = 8.5$, 3.8, H-C1), 4.72 (1H, dddd, $^2J_{\text{HF}} = 46.3$, $^2J_{\text{HH}} = 10.5$, $^3J_{\text{HH}} = 4.8$, 4.6, H-C1), 3.11 (1H, dddd, $^3J_{\text{HF}} = 19.5$, $^2J_{\text{HH}} = 13.8$, $^3J_{\text{HH}} = 8.4$, 4.6, H-C2), 3.07 (1H, dddd, $^3J_{\text{HF}} = 30.1$, $^2J_{\text{HH}} = 13.9$, $^3J_{\text{HH}} = 4.8$, 3.8, H-C2) ppm; **^{13}C NMR** (101 MHz, CDCl_3) $\delta = 143.5$ (C3), 131.5 (C6), 129.6 (2C, C4), 124.0 (2C, C5), 76.8 (d, $^1J_{\text{CF}} = 170.4$, C1), 58.2 (d, $^2J_{\text{CF}} = 19.6$, C2) ppm; **^{19}F NMR** (282 MHz, CDCl_3) $\delta = -220.99$ (1F, tdd, $^2J_{\text{HF}} = 46.6$, $^3J_{\text{HF}} = 30.1$, 19.5, F-C1) ppm; **IR** (ATR) $\tilde{\nu} = 3055\text{w}$, 2967w, 2901w, 1474m, 1443m, 1389m, 1088m, 1038s, 991s, 957m, 829w, 745s, 691s, 633m cm^{-1} ; **HRMS** (ESI): m/z : 195.0253 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_8\text{H}_9\text{FOSNa}^+$: 195.0250).

((2-Fluoroethyl)sulfonyl)benzene (3e)

A solution of **1e** (20 mg, 0.13 mmol, 1.0 eq.) in CH_2Cl_2 (2.5 ml) was cooled to 0 °C and *m*CPBA ($\leq 77\%$, 74 mg, 0.32 mmol, 2.5 eq.) was added. After stirring for 7 h under an atmosphere of argon while warming to rt, the mixture was washed with aq. Na_2SO_3 (5%, 6 ml), aq. sat. NaHCO_3 (2 x 5 ml) and brine. The separated organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

Separation by column chromatography on silica gel (CyH/EtOAc 3:1) afforded the desired product as colourless oil (20 mg, 82%).

$R_f = 0.25$ (CyH/EtOAc 1:1); $^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 7.96\text{--}7.92$ (2H, m, H-C5), 7.70–7.65 (1H, m, H-C6), 7.61–7.55 (2H, m, H-C4), 4.80 (2H, dt, $^2J_{\text{HF}} = 46.5$, $^3J_{\text{HH}} = 5.6$, H-C1), 3.52 (2H, dt, $^3J_{\text{HF}} = 22.0$, $^3J_{\text{HH}} = 5.6$, H-C2) ppm; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 139.5$ (C3), 134.2 (C6), 129.5 (2C, C4), 128.2 (2C, C5), 77.2 (d, $^1J_{\text{CF}} = 173.1$, C1), 56.9 (d, $^2J_{\text{CF}} = 21.5$, C2) ppm; $^{19}\text{F NMR}$ (282 MHz, CDCl_3) $\delta = -221.42$ (1F, tt, $^2J_{\text{HF}} = 46.5$, $^3J_{\text{HF}} = 22.0$, F-C1) ppm; **IR** (ATR) $\tilde{\nu} = 2932\text{w}$, 1447m, 1389w, 1319m, 1292m, 1246w, 1184w, 1142s, 1088m, 1065m, 999m, 961w, 768m, 729s, 687s, 594m cm^{-1} ; **HRMS** (ESI): m/z : 211.0209 ($[\text{M}+\text{Na}]^+$, calcd. for $\text{C}_8\text{H}_9\text{FO}_2\text{SNa}^+$: 211.0199)

S-(2-Fluoroethyl) ethanethioate (4)^[7]

2-Fluoroethane tosylate (0.4 g, 1.8 mmol, 1.0 eq.) and potassium thioacetate (0.25 g, 2.2 mmol, 1.2 eq.) were suspended in acetone (6 mL) and heated to 70 °C for 4 h. The reaction mixture was filtered and the residual was washed with copious amounts of acetone. The brown filtrate was concentrated under reduced pressure. Subsequently, the residual was partitioned between H_2O and Et_2O and the organic layer was dried over MgSO_4 and concentrated under reduced pressure. Fractional distillation (40 mbar, 50 °C) afforded the title product as a colourless liquid (0.1 g, 44%). Spectroscopic data in agreement with previously published ones.^[6]

$^1\text{H NMR}$ (400 MHz, CDCl_3) $\delta = 4.50$ (2H, dt, $^2J_{\text{HF}} = 46.9$, $^3J_{\text{HH}} = 6.2$, H-C1), 3.19 (2H, dt, $^3J_{\text{HF}} = 21.5$, $^3J_{\text{HH}} = 6.2$, H-C2), 2.36 (3H, s, H-C4) ppm; $^{13}\text{C NMR}$ (101 MHz, CDCl_3) $\delta = 195.0$ (C3), 81.9 (d, $^1J_{\text{CF}} = 170.7$, C1), 30.7 (C4), 29.3 (d, $^2J_{\text{CF}} = 22.1$, C2) ppm; $^{19}\text{F NMR}$ (282 MHz, CDCl_3) $\delta = -213.95$ (1F, tt, $^2J_{\text{HF}} = 46.9$, $^3J_{\text{HF}} = 21.6$, F-C1) ppm; **IR** (ATR) $\tilde{\nu} = 2963\text{w}$, 1694s, 1686s, 1420w, 1385w, 1354m, 1134m, 1115m, 1065m, 1015m, 995m, 967m, 810w, 683w, 621s cm^{-1} ; **GC-MS** (EI): $t_R = 4.35$ min, m/z 122.0 (M^+).

1-Fluoro-2-thiocyanatoethane (5)^[7]

A mixture of 2-fluoroethane tosylate (218 mg, 1.0 mmol, 1.0 eq.) and NaSCN (122 mg, 1.5 mmol, 1.5 eq.) in H₂O (0.2 ml) was heated to 100 °C for 5 h. After reaching rt, the mixture was diluted with H₂O (5 ml) and extracted with Et₂O (3 x 5 ml). The combined organic layers were dried over Na₂SO₄ and most of the Et₂O was removed under reduced pressure. The obtained brown oil was purified *via* fractional distillation (12-35 mbar, 33 °C) to give the desired product as a colourless liquid (40 mg, 38%).

¹H NMR (400 MHz, CDCl₃) δ = 4.74 (2H, dt, $^2J_{\text{HF}}$ = 46.4, $^3J_{\text{HH}}$ = 5.6, H-C1), 3.24 (2H, dt, $^3J_{\text{HF}}$ = 21.4, $^3J_{\text{HH}}$ = 5.6, H-C2) ppm; **¹³C NMR** (101 MHz, CDCl₃) δ = 111.2 (C3), 80.7 (d, $^1J_{\text{CF}}$ = 174.7, C1), 33.8 (d, $^2J_{\text{CF}}$ = 22.3, C2) ppm; **¹⁹F NMR** (282 MHz, CDCl₃) δ = -217.07 (1F, tt, $^2J_{\text{HF}}$ = 46.4, $^3J_{\text{HF}}$ = 21.4, F-C1) ppm; **IR** (ATR) $\tilde{\nu}$ = 2963w, 2901w, 2156m, 1404m, 1296m, 1196w, 1065m, 1015s, 953m, 822m, 633m cm⁻¹; **GC-MS** (EI): t_{R} = 4.10 min, m/z 105.1 (M⁺). Spectroscopic data are in agreement with previous literature.^[14]

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