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The influence of electronic perturbations on the Sulfur–Fluorine Gauche Effect

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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 ($\sigma_{C–H} \rightarrow \sigma^*_{C–F}$) and electrostatic ($F^{\delta-} \ldots S^{\delta+}$) 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 Despite the clear influence that the remote para-substituents have on conformer population, this is superseded by the oxidation state on sulfur (II, IV, VI), where an increased preference for the gauche conformer follows the trend: sulfide 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.

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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 (Fig. 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 stabilizing hyperconjugative interactions, to engage the low-lying anti-bonding orbital of the C–F bond (e.g. $\sigma_{C–H} \rightarrow \sigma^*_{C–F}$), 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 widespread application with second

period elements (N, O, F) [2], it was only recently extended to a third period element by this laboratory; a phenomenon termed the Sulfur–Fluorine Gauche Effect [3]. This extension to sulfur-based systems seemed highly prudent on account of the multiple oxidations states associated with sulfur (II, IV, VI). It was envisaged that sequential oxidation could be exploited as a mechanism by which the conformational equilibrium of the F-C1-C2-S(O)$_n$ fragment could be regulated.

Recently, a computational study by Aleksić et al. [4] delineated the origins of this unprecedented conformational preference and concluded that primarily electrostatic interactions are responsible for this phenomenon. Whilst in sulfur analogues of cyclic proline-derived systems the population of the gauche conformer increases noticeably following the trend sulfide < sulfone < sulfoxide, the effect of more subtle, remote electronic modulation has yet to be established and was the motivation for this investigation. By introducing para-substituted aryl sulfide, sulfoxide or sulfone units into the model systems (i.e. F-C1-C2-S(O)$_n$Ar), it was envisaged that the conformational population, as a function of sulfur oxidation state, could be further tuned by a remote handle. From the perspective of molecular design, this is an attractive strategy on account of the increased frequency with which fluorine stereoelectronic effects are finding application in catalysis and biomedical sciences [1b–d,5].
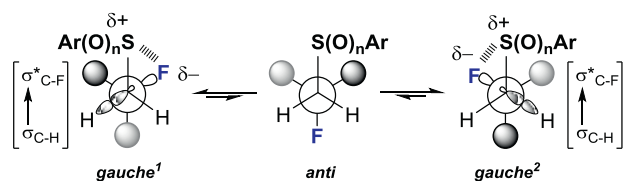
Fig. 1. Conformational equilibria in F-C1-C2-S(O)$_n$R systems: the Sulfur–Fluorine *Gauche* Effect [3].

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 (Fig. 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 = NH$_2$ (**a**), OH (**b**), OMe (**c**), Me (**d**), H (**e**), F (**f**), Cl (**g**), CO$_2$H (**h**), CO$_2$Et (**i**) and NO$_2$ (**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}; Fig. 2B).

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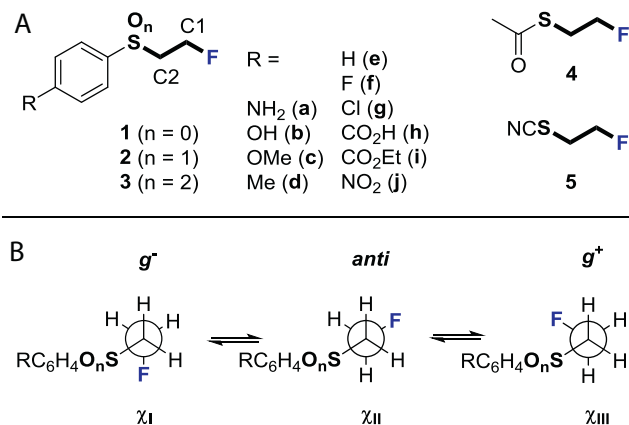
Despite the structural diversity of the systems **1–3** prepared, very few samples proved to be crystalline thereby precluding the use of crystallographic techniques for the conformational analysis.

The solution phase NMR analysis was performed with the precondition that only the three conformers partitioned by 120° would be considered: these include the two *gauche* (g^+/g^-) arrangements and the corresponding *anti* conformation (Fig. 2B). Furthermore, in the case of the sulfide (n = 0) and sulfone (n = 2), g^+ and g^- are equivalent and thus the sum of both is reported. The required NMR samples were prepared in CDCl$_3$ at concentrations between 0.1 and 0.2 mM and standard experiments ([1]H & [19]F) were conducted at ambient temperature.

The following population analysis was based on the experimental $<^3J_{HF}>$ coupling constants as summarized in Table 1 and theoretical values (J^{anti} and J^{gauche}), which were determined as previously described by Hamman et al. [8]. Hence, J^{anti} and J^{gauche} were calculated according to $J^{anti} = 65.75 - 7.52 \times \Sigma(\Delta E)$ and $J^{gauche} = 15.35 \times \exp(-0.266 \times \Sigma(\Delta E))$ here $\Sigma(\Delta E)$ represents the sum of the Huggins electronegativity differences between a substituent (SO$_n$R, 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 $\delta(CH_3) - \delta(CH_2)$ 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 SO$_2$Cl (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 = NH$_2$, σ_{para} = −0.66) and **1j** (R = NO$_2$, 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 $<^3J_{HF}>$ displayed a slightly broader distribution as determined by comparison of the data sets of the electronic extremes (R = NH$_2$; R = NO$_2$) 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 C$_2$ are diastereotopic, thus resulting in two experimentally distinct coupling constants $<^3J_{HF}>$. To translate these values into *gauche* conformer populations χ_I and χ_{III} the data was subjected to analysis using Eq. (1). The corresponding *anti* conformer population could be determined by simple extrapolation: $\chi_{II} = 1 - \chi_I - \chi_{III}$.

$$\chi_{I/III} = \frac{(<^3J_{HF}> - J^{gauche})}{J^{anti} - J^{gauche}} \qquad (1)$$

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 (Fig. 3). For the sulfoxide systems (n = 1), the conformer populations were also calculated independently based on the sets of experimental $<^3J_{HH}>$ coupling constants of each of the diastereotopic protons adjacent to sulfur: The values obtained

Fig. 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}).