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Origin of Fluorine/Sulfur *Gauche* Effect of β-Fluorinated Thiol, Sulfoxide, Sulfone, and Thionium Ion

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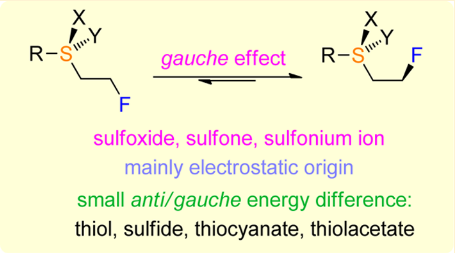
S *Supporting Information*

ABSTRACT: The well-known *gauche* preference in FCCX systems, where X is an electronegative element from Period 2, is widely exploited in synthetic, medicinal, and material chemistry. It is rationalized on the basis of $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation and electrostatic interactions. The recent report (Thiehoff, C.; et al. *Chem. Sci.* **2015**, *6*, 3565) showed that the fluorine *gauche* effect can extend to Period 3 elements, such as sulfur. The aim of the present work is to disclose factors governing conformational behavior of FCCS containing systems. We examine conformational preferences in seven classes of compounds by *ab initio* and DFT calculations and rationalize the results by quantitatively decomposing the *anti*/*gauche* isomerization energy into contributions from electrostatic, orbital, dispersion, and Pauli interactions, and energy spent on structural changes. The results show that the fluorine/sulfur *gauche* effect is primarily electrostatic (63−75%), while all orbital interactions contribute 22−41% to stabilizing interactions. Stereoelectronic effects, involved in orbital interactions, also play a role in *gauche* conformer stabilization.



INTRODUCTION

Molecular properties, their reactivity, and interactions with other molecules and biomolecules are influenced by their conformational behavior, which presents an interplay of classical electrostatic interactions and quantum-mechanical orbital interactions involving charge transfer stabilization and Pauli repulsion. A possibilty to have a control over molecular conformation has emerged as a valuable tool in chemistry and biochemistry.[1] One way to do that is to introduce fluorine β to an electronegative or (partially) positively charged substituent, which results in *gauche* preference over the *anti*. The classical example of this fluorine *gauche* effect[2] is 1,2-difluoroethane. The *anti*/*gauche* energy difference has been estimated as 0.5−1 kcal/mol in favor of the *gauche* conformer.[3] Explanations for this counterintuitive observation invoke $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ hyperconjugation,[3a,b,e−h,4] the C−C bond bending induced by the fluorine's high electronegativity,[5] and electrostatic effects involving interactions between all charges, rather than partial interaction between the C−F bond pair.[6] A vicinal difluorine motif can also affect conformational stability of longer chain alkanes.[7] The fluorine *gauche* effect persists in systems having a F−C−C−X fragment, where X = O, N, C, and has been extensively studied experimentally and theoretically.[3b,g,8] Of particular importance is its application in synthetic organic chemistry,[9] medicinal chemistry,[10] and material science.[11]

The effect of fluorine, β-positioned to a Period 3 element such as sulfur, on molecular conformation is almost unexplored. Though, a hint on the possible fluorine/sulfur *gauche* effect has been given in several reports. Early NMR studies of the conformational behavior of β-fluorinated sulfides,[12] sulfoxides,[12] sulfones,[12,13] and sulfonium salts[12] revealed the existence of conformers having a *gauche* orientation of sulfur and fluorine, influenced by steric and electrostatic effects involving sulfur, fluorine, and additional substituents. Two computational studies, done at the HF/3-21G[14] and MP2/6-31G(d,p)[15] levels, showed that 2-fluoroethanethiol prefers the *gauche* conformation around both FC−CS and CC−SH bonds. An X-ray analysis of β-difluorinated sulfoxide identified a *gauche* orientation of both fluorines with the sulfur atom.[16] In addition, crystal structures of fluorinated deoxy-4-thiopyrimidine nucleosides contain fluorine in a pseudoaxial position, which is *gauche* to the ring sulfur.[17] It is the very recent paper in which the fluorine/sulfur *gauche* effect has been examined for the first time as a means to achieve conformational control.[18] The authors studied the conformational stability of cyclic and acyclic β-fluorinated sulfides, sulfoxides, and sulfones, experimentally and theoretically. The experimental results showed the *gauche* arrangement of the F−C−C−S fragment in all compounds, both in the solid state and in solution. Computations were consistent with these findings, though only in the case of acyclic sulfides, no significant conformational preference was found. The observed fluorine/sulfur *gauche* effect was rationalized by the widely used hyperconjugation model, involving $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ charge transfer interactions. In addition, the magnitude of the $\Delta G_{anti/gauche}$ values increased when the sulfur atom was more electron-deficient.

The above-described, rather limited literature data have prompted this study. We were interested to identify what factors govern the conformational preferences in compounds

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containing the F−C−C−S motif, which is important in bioactive compounds. We are unaware of any other previous work on this topic. *β*-Fluorinated thiol **1**, sulfide **2**, sulfoxide **3**, sulfone **4**, thionium ion **5**, thiocyanate **6**, and thiolacetate **7** (Figure 1) were chosen as model systems for this study. To our knowledge, there is no experimental or theoretical study on conformations of *β*-fluorinated thiocyanate and *β*-fluoroethyl thiolester, and this work will theoretically predict their conformational equilibria. All sulfur-containing functional groups chosen for this study are present in various biologically important compounds or intermediates, the function of which depends on the conformation they adopt. A possible fluorine-induced conformational control and understanding of factors governing conformational behavior of F−C−C−S systems are thus important to address various questions in chemistry and biochemistry, and for further exploration and application of the fluorine *gauche* effect.

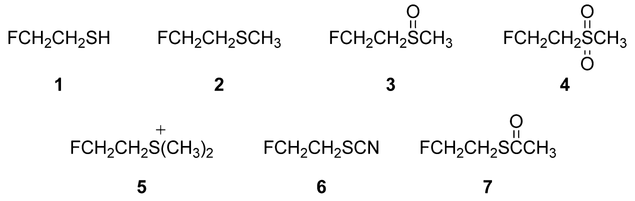

Figure 1. Structures of compounds examined in this work.

RESULTS AND DISCUSSION

Quantitative Decomposition of Isomerization Energies. *Theoretical Background.* Conformational isomerization energy ΔE_{iso} represents the energy change occurring when one conformer rotates into another one. In the performed conformational analysis, the starting/final conformer possesses the FCCS chain in an *anti*/*gauche* arrangement, while conformation around the C−S bond was kept constant. The isomerization energy can be decomposed into two main parts: interaction energy change ($\Delta\Delta E_{int}$) and deformation energy change ($\Delta\Delta E_{def}$) (eq 1).

$$\Delta E_{iso} = \Delta\Delta E_{int} + \Delta\Delta E_{def} \qquad (1)$$

The first energy term, $\Delta\Delta E_{int}$, reflects energy changes associated with changes in bonding nature, involving electrostatic and orbital interactions. One way to quantitatively decompose ΔE_{int} between two (or more) interacting fragments into its individual energy components is by using the localized molecular orbital energy decomposition analysis (LMOEDA), developed by Su and Li[19] and implemented in the Gamess program package.[20] The LMOEDA partitions the interaction energy into five components (eq 2).

$$\Delta E_{int} = \Delta E_{elstat} + \Delta E_{ex} + \Delta E_{rep} + \Delta E_{pol} + \Delta E_{disp} \qquad (2)$$

As interacting fragments, we have chosen two radicals $FH_2C\cdot$ and $\cdot CH_2Y$ having opposite spins (α and β superscripts in Scheme 1), which, when combined, form a molecule.

Scheme 1. Formation of Studied Compounds 1−7 from Two Radicals

$$FCH_2^{\alpha} + {}^{\beta}CH_2Y \rightarrow FCH_2{-}CH_2Y$$

$(Y = SH, SCH_3, SOCH_3, SO_2CH_3, {}^{+}S(CH_3)_2, SCN \text{ and } SCOCH_3)$

In eq 2, electrostatic energy (ΔE_{elstat}) represents the total attractive (nucleus−electron) and repulsive (electron−electron, nucleus−nucleus) electrostatic interactions between the two interacting fragments having geometry and position as in the conformer in question. It is usually stabilizing (negative energy contribution). The exchange energy (ΔE_{ex}) refers to the quantum mechanical exchange between the same-spin electrons and is simultaneously counteracted by the repulsion energy (ΔE_{rep}). Taken together, they form the exchange repulsion[21] or Pauli repulsion[22] of other energy decomposition analyses (EDA), which is a destabilizing interaction (positive energy contribution). Herein, we use the sum of ΔE_{ex} and ΔE_{rep} to represent the Pauli repulsion. Polarization energy ΔE_{pol} is an orbital relaxation energy accounting for the bond formation, charge transfer (donor−acceptor interactions between occupied orbitals on one fragment with empty orbitals on the other), and polarization (empty-occupied orbital mixing within one fragment due to the presence of another fragment). Herein, we change the original labeling ΔE_{pol}[19] into ΔE_{oi} to represent all orbital interactions. Dispersion energy ΔE_{disp} is associated with electron correlation and is available at DFT and post-HF levels. The latter two energy terms are stabilizing interactions. In our conformational analysis, changes in the mentioned individual energies are calculated as a difference between corresponding energies of final ($FCCS_{gauche}$) and starting ($FCCS_{anti}$) conformations and are denoted as the corresponding $\Delta\Delta E$ values.

The second energy term in eq 1, ($\Delta\Delta E_{def}$), reflects energy change due to structural changes within two fragments that follow the conformational isomerization. This energy is calculated as a two fragment ($FH_2C\cdot$ and $\cdot CH_2Y$) deformation energy (ΔE_{def}) in $FCCS_{gauche}$ vs their ΔE_{def} in $FCCS_{anti}$ (eq 3), where ΔE_{def} represents an energy required to deform two isolated radical fragments from their equilibrium geometry into the geometry they have in a conformer in question.

$$\Delta\Delta E_{def} = [\Delta E_{def}(CH_2F) + \Delta E_{def}(CH_2Y)]_{FCCS_{gauche}} - [\Delta E_{def}(CH_2F) + \Delta E_{def}(CH_2Y)]_{FCCS_{anti}} \qquad (3)$$

It is important to realize that structural changes also affect all interaction energy components. They take place in order to achieve a balance between repulsive (Pauli interactions) and attractive (electrostatic, orbital, and dispersion) forces such that a molecule attains an energy minimum structure.

Such an analysis of the interaction energy between two or more radical fragments constituting a molecule has been applied to study the torsional potential of ethane,[19,23] butane,[24] and group 13 elements (E = B−Tl),[25] conformational preferences in 1,2-difluoroethane,[6] 1-chloro-2-fluoroethane,[8e] (protonated) 2-haloethanol, and 2-haloethylamine (X = F, Cl),[8e] distortion to the trans-bent geometry in heavier ethylene homologues,[26] the isomerization energy of heterocyclic[27] and polycyclic[28] compounds, the strength of conjugation and hyperconjugation,[29] and the nature of covalent bonds.[30]

Computational Details. The EDA was done at the MP2/6-311++G(d,p) theory level[31] on gas-phase geometries optimized at the same level. The Gaussian 09 program package[32] was used for geometry optimizations. All stationary points were characterized as energy minima by the absence of imaginary frequencies. This level of theory was chosen to enable a comparison with our previous study on the fluorine/Period 2 elements *gauche* effect. Additionally, gas-phase conformational energies of **1** and **5−7** were also evaluated at the DFT level, using the B3LYP functional[33] and 6-311++G(d,p) basis set

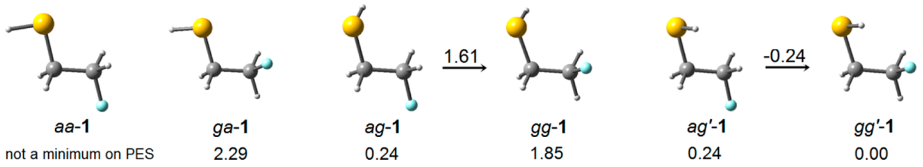

Figure 2. Optimized structures of conformers of **1**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

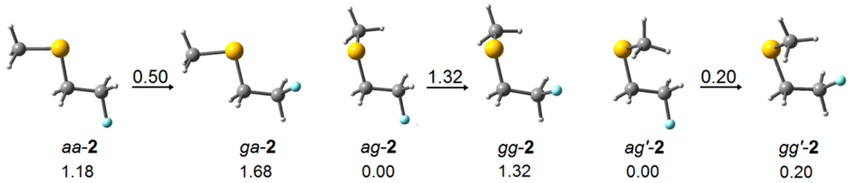

Figure 3. Optimized structures of conformers of **2**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

(DFT/B3LYP calculations have already been done for **2**–**4** in ref 18, and they were not repeated, herein). All conformational energies were also examined under solvent conditions, at both MP2 and DFT levels. Solvent effects were studied on structures reoptimized under solvent conditions, by using the integral equation formalism polarizable continuum model (IEFPCM, solvents = CH_2Cl_2, Me_2CO, H_2O).[34]

2-Fluoroethanethiol (1). At both theory levels employed, 2-fluoroethanethiol (**1**) exists as four energetically distinguishable conformers (Figure 2), denoted as *ag*, *ga*, *gg*, and *gg′*, where the first letter refers to the FCCS conformation and the second to the CCSH conformation. The *ag* and *ag′* conformers are mirror images and energetically indistinguishable. They are both included in the discussion to be compared with the corresponding *gg* and *gg′* forms. The *aa* conformation is a transition structure with an imaginary frequency, corresponding to rotation around the C–S bond. The MP2/6-311++G(d,p) relative energies of four conformers of **1** are shown in Figure 2 and in Table S1 in the Supporting Information, which also contains their relative enthalpies and free energies in the gas phase and in the solvent, at both MP2 and DFT levels. The MP2 and DFT values agree with each other qualitatively and show the same trend, so that only MP2 data will be discussed in the following.

The most stable conformer is *gg′*, which possesses the thiol hydrogen atom oriented toward the fluorine and the FCCS dihedral angle of 65.1°. Further rotation around the C–S bond to *gg* and *ga* forms increases the energy by 1.85 and 2.29 kcal/mol, respectively, while isomerization around the FC–CS bond to the *ag′* structure results in an energy rise by 0.24 kcal/mol. The EDA data in Table S2 reveal that the *anti* arrangement of the HSCC fragment in the *ga* form suffers from large deformation energy (ΔE_{def} = 18.71 kcal/mol) compared to the HSCC *gauche* conformation in *ag*, *gg*, and *gg′* (ΔE_{def} = 13.33–13.86 kcal/mol). Interaction energy in the former is more stabilizing, owing to the smaller Pauli repulsion and increased dispersion interactions, whereas electrostatic and orbital stabilization energies are smaller than in the case of the HSCC *gauche* conformation. This is also the case for sulfide **2** and thiocyanate **6**, as will be seen later. The calculated relative energetic stabilities of energy minimum conformations of **1** are in accord with previous calculations.[15] Thus, the isolated gaseous 2-fluoroethanethiol shows a very small *gauche* preference (−0.24 kcal/mol), which will be discussed by considering the *ag′* → *gg′* isomerization.

Data in Table S2 show that the most important stabilizing energy upon *ag′* → *gg′* rotation comes from electrostatic interactions (63%), a part of which originates from an attraction between the antiparallel C–F and S–H bond dipoles (φ_{FCSH} = −0.34°). Orbital and dispersion forces contribute 26% and 11%, respectively, to the *gauche* effect. The resulting, relatively favorable, $\Delta\Delta E_{\text{int}}$ = −0.78 kcal/mol is attenuated by the unfavorable deformation energy, $\Delta\Delta E_{\text{def}}$ = 0.54 kcal/mol. These results can be compared with our previous study on the oxygen analogue of **1**, 2-fluoroethanol (FE), which was done at the same theory level.[8e] The relevant values are included in Table S2, too. In contrast to **1**, FE shows a significant *gauche* effect of −2.54 kcal/mol, regarding the same *ag′* → *gg′* rotation. Although, sulfur is larger than oxygen, a much smaller *gauche* preference in **1** does not originate from an increased Pauli repulsion, $\Delta\Delta E_{\text{ex+rep}}$ = 0.85 kcal/mol for **1** and 5.77 kcal/mol for FE. It mostly comes from smaller magnitudes of $\Delta\Delta E_{\text{elstat}}$ and $\Delta\Delta E_{\text{oi}}$, a drop in the former being more pronounced. It is interesting to note that *ag*-FE → *gg*-FE isomerization results in electrostatic stabilization, $\Delta\Delta E_{\text{elstat}}$ = −1.28 kcal/mol, even though fluorine encounters the oxygen lone pair in the *gg* conformer and the CF and CO bond dipoles are in an unfavorable orientation. In the case of **1**, however, the same isomerization is followed by a decrease in electrostatic stabilization (positive $\Delta\Delta E_{\text{elstat}}$ value), by approximately the same amount. This comparison of **1** and FE provides an additional support of our previous conclusion that substitution of small, electronegative atoms from the Period 2 (F, O, N) by larger and less electronegative ones results in a decrease of *gauche* conformer electrostatic stabilization (relative to the *anti* form). Although it appears as counterintuitive, this drop in electrostatic stabilization can be considered as one cause for a decrease or loss of *gauche* preference for the third row elements. Another cause is the decrease in the magnitude of orbital interactions, as can be seen in Table S2 for **1** and FE.[35]

In all three solvents considered, the *gauche* preference of **1** does not exceed the discussed gas-phase value, at both levels of theory (Table S1).

2-Fluoroethyl Methyl Sulfide (2). 2-Fluoroethyl methyl sulfide (**2**) exists as five energetically distinguishable conformers, shown in Figure 3, along with their relative energies and energy changes accompanying conformational isomerizations. The second letter in the conformation label denotes the CCSC arrangement. The C_s symmetric *aa* structure

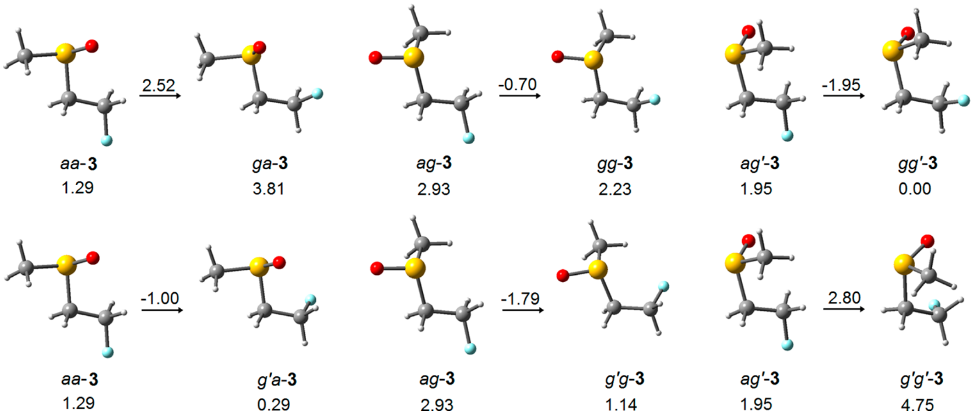

Figure 4. Optimized structures of conformers of **3**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

contained a small imaginary frequency, *i*42.1 cm^{-1}, so that it was reoptimized to the form having the FCCS dihedral angle of 166.9° and no imaginary frequencies. Relative enthalpies and free energies of optimized structures are given in Table S3 and EDA results in Table S4, in the Supporting Information.

In the case of **2**, there is no *gauche* preference and the most stable conformer is *ag*. Among the three *gauche* forms, the most stable one, *gg*′, contains a fluorine atom oriented toward the methyl group, with FCCS and CCSC dihedral angles of 68.4° and −78°, respectively. The other two *gauche* conformers, *ga* and *gg*, are by more than 1 kcal/mol higher in energy than *gg*′, primarily due to the less favorable electrostatic energy, though orbital interaction energy decreases, too, upon *gg*′ rotation around the C−S bond to *ga* or *gg* forms. The electrostatic stabilization of *gg*′-**2** can partly be ascribed to attraction between fluorine and positively charged hydrogens contained in the CH_3 group.

In this case, too (see discussion for **1**), the *anti* conformation around the $CH_3S{-}CC$ bond in *aa*-**2** and *ga*-**2** is of higher energy relative to CSCC *gauche* arrangement in *ag* and *gg*/*gg*′, respectively, just because of the large deformation energy (~20 kcal/mol for $CSCC_{anti}$ and ~13.5 kcal/mol for $CSCC_{gauche}$). The interaction energy is larger for the $CSCC_{anti}$ conformation, again, because of smaller Pauli repulsion and increased ΔE_{disp}, while electrostatic and orbital energies favor the $CSCC_{gauche}$ arrangement.

If we consider the two most stable *ag*/*g*′ and *gg*′ forms and their *ag*′/*gg*′ interconversion, there is a very small *anti* preference of 0.2 kcal/mol, slightly increased under solvent conditions: $\Delta E/\Delta H/\Delta G$ = 0.31/0.22/0.43 kcal/mol in CH_2Cl_2, 0.30/0.21/0.41 kcal/mol in acetone, and 0.30/0.20/0.39 kcal/mol in water (Table S3). The other two isomerizations are followed by a larger energy rise (0.5 and 1.32 kcal/mol, for the *aa* → *ga* and *ag* → *gg* isomerizations, respectively; Figure 3). In a solvent, conformational energies of *ga* and *gg* forms are significantly reduced with respect to the gas phase, and that of the *aa* form is somewhat increased. This leads to the smaller *anti* preference for the *ag*/*gg* interconversion, ~ 0.4 kcal/mol in CH_2Cl_2, ~ 0.3 kcal/mol in acetone, and ~0.2 kcal/mol in water, and a decrease in energy following the *aa* → *ga* conformational change, ~ 0.3 kcal/mol in CH_2Cl_2, ~ 0.4 kcal/mol in acetone, and ~0.5 kcal/mol in water. However, the latter should not be considered as a *gauche* effect since the *ga* conformer is of the highest energy among $FCCS_{gauche}$ forms, having a conformational energy > 0.7 kcal/mol with respect to the most stable *ag*/*g*′ form. Thus, no *gauche* preference was observed, and this is consistent with theoretical results of Thiehoff et al.[18] obtained by considering CH_2Cl_2 as a solvent.

The small positive energy change for *ag*′-**2** → *gg*′-**2** isomerization (ΔE_{iso} = 0.20 kcal/mol) compared to the also small, but negative, energy change for *ag*′-**1** → *gg*′-**1** isomerization (ΔE_{iso} = −0.24 kcal/mol) can be attributed to the increased Pauli repulsion (by 0.64 kcal/mol relative to the case of **1**) and less favorable dispersion interactions (by 0.42 kcal/mol relative to **1**), while both electrostatic and orbital interactions are sligthly strengthened compared to **1**. As a consequnce, the interaction energy change $\Delta\Delta E_{int}$ in **2** is close to zero and the small energy increase following the *ag*′-**2** → *gg*′-**2** isomerization originates from deformation energy. The other two *aa*-**2** → *ga*-**2** and *ag*-**2** → *gg*-**2** rotations benefit neither from $\Delta\Delta E_{int}$ nor from $\Delta\Delta E_{def}$ and increase the energy by 0.5 and 1.32 kcal/mol, respectively. The only *gauche* conformer stabilization in the former case comes from orbital and dispersion interactions, obviously not sufficient to overcome the increased Pauli repulsion and $\Delta\Delta E_{def}$ (change in electrostatic energy is negligible). Interestingly, in the latter case, the Pauli repulsion drops by 0.71 kcal/mol on account of less favorable electrostatic and orbital interactions.

*1-Fluoro-2-(methylsulfinyl)ethane (**3**).* Oxidation of sulfide **2** to sulfoxide **3** creates a stereogenic sulfur atom increasing the number of energy miniminum conformations to nine. They are shown in Figure 4 along with their relative energies and energy changes occurring during the conformational isomerizations. The second letter in the conformation label refers to the CCSC arrangement. Relative enthalpies and free energies are given in Table S5 in the Supporting Information, and EDA results are shown in Table S6.

In the gas phase, the most stable *gg*′ conformation contains a *gauche* arrangement around both FC−CS (φ = 80.7°) and CC−SC (φ = −68.5°) bonds, and this places the methyl group and fluorine in the 1,3-position, as well as O^- and hydrogen. As in the case of **2**, this orientation is particularly stabilized by electrostatic energy. Interestingly, the *g*′*g* conformer, also having 1,3-F/CH_3 interactions, is by 0.85 kcal/mol higher in energy than the *g*′*a* form in which fluorine encounters a sulfur lone pair. Our EDA results reveal that this is due to the release in Pauli repulsion in *g*′*a* by 2.15 kcal/mol and enhanced dispersion interactions, by 1.32 kcal/mol, while ΔE_{elstat}, ΔE_{oi}, and ΔE_{def} are less favorable in *g*′*a*-**3** than in *g*′*g*-**3**. The highest energy forms, *ga* and *g*′*g*′, contain unfavorable C−F and $S^+{-}O^-$

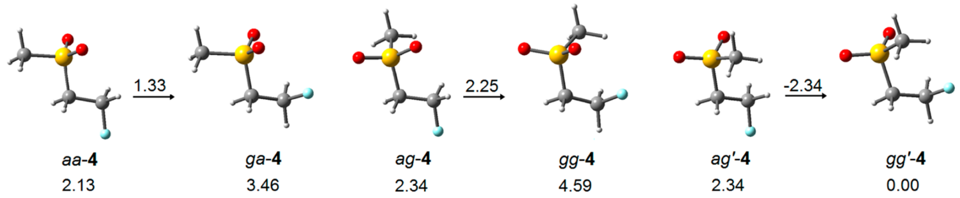

Figure 5. Optimized structures of conformers of **4**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

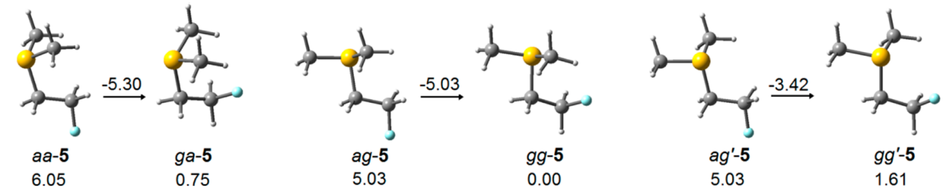

Figure 6. Optimized structures of conformers of **5**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

bond dipole orientations, which primarily affects their electrostatic energy. In order to reduce partial electrostatic repulsion, the molecule attains a geometry in which dihedral angles between C−F and S−O bonds are −26.4° and −54.3° respectively. It should be noted that Pauli repulsion is the largest when CH_3 and F are close to each other, that is, in the most stable *gg*′ conformer and in the *g*′*g* one (223.69 and 220.4 kcal/mol, respectively). Interestingly, the *ag*′ conformer suffers from similar Pauli destabilization as the *g*′*g* form (220.52 kcal/mol), even though fluorine is far from both sulfur substituents, CH_3 and oxygen. This repulsion is also the strongest among all three $FCCS_{anti}$ forms. This could be associated with the *gauche* interactions between both CH_3 and oxygen with the methylene group, not existing in *aa* and *ag* forms, while, in the case of *g*′*g*, it is the lone pair which encounters the methylene hydrogen atom. The *g*′*g*′ conformer, also having CH_3 and O *gauche* to the CH_2F group, somewhat escaped Pauli repulsion (215.34 kcal/mol) due to the above-mentioned geometry change.

Data in Table S5 show that all *anti* → *gauche* gas-phase conformational isomerizations are followed by an energy decrease, except the two leading to the 1,3-F/O interactions. However, both *ag* and *gg* forms are of high energy and would not contribute much to the *anti*/*gauche* energy change. Hence, *ag* → *gg* isomerization should not be considered as a manifestation of the *gauche* effect. The *g*′*g* conformer stabilization relative to the high energy *ag* form (*ag* → *g*′*g* rotation) results mainly from electrostatic energy (78%). Minor stabilization comes from orbital interactions (22%). Even though the *ag* conformer population should be very low, the *g*′*g* form contributes to the *gauche* effect in sulfoxide **3**. The remaining two isomerizations leading to the *gauche* conformer stabilization relative to the corresponding *anti* forms, that is, *aa* → *g*′*a* and *ag*′ → *gg*′, also benefit primarily from more favorable electrostatic energy, 52% and 63%, respectively. Then comes orbital energy stabilization, 41% and 31%, while dispersion interactions provide the smallest stabilizing energy contribution, 7% and 6%, respectively. In the case of *aa* → *g*′*a* rotation, the expected 1,3-F/lone pair electrostatic repulsion is obviously overcome by other attractive electrostatic interactions.

Inclusion of solvents into calculations reverses the relative stability of *gg*′ and *g*′*a* conformers; that is, the latter is the most stable form in all solvents considered (Table S5). This is in accord with DFT results of ref 18 in which the *g*′*a* form was found to be the most stable, in CH_2Cl_2 and in the gas phase, though, our MP2 data favor the *gg*′ form in the gas phase. Relative energies of other conformers in CH_2Cl_2 agree with the data of ref 18. In all three solvents, the sulfoxide **3** *gauche* effect ranges from 1.1 to 1.6 kcal/mol.

*1-Fluoro-2-(methylsulfonyl)ethane (**4**).* Further oxidation of sulfoxide **3** to sulfone **4** removes the stereogenic unit, decreasing the number of energetically distinguishable energy minima to five. They are shown in Figure 5 together with their relative energies. The relative enthalpies and free energies are listed in Table S7, and EDA values are given in Table S8 in the Supporting Information.

The sulfone **4** shows a significant *gauche* conformer stabilization, that is, the *gauche* effect of ΔE_{iso} = −2.34 kcal/mol regarding the *ag*′ → *gg*′ isomerization. With increasing polarity of the medium, this *gauche* preference decreases, but remains important even in water: $\Delta E/\Delta H/\Delta G$ = 2.04/2.15/1.95 kcal/mol in CH_2Cl_2, 1.97/2.09/1.84 kcal/mol in acetone, and 1.94/2.05/1.74 kcal/mol in water (Table S7). The calculated ΔG value in CH_2Cl_2 compares well with the DFT result of ref 18 (1.8 kcal/mol).

In the gas phase, the *gg*′ conformer (φ_{FCCS} = 70.8°, φ_{CCSC} = −74.2°) is also significantly more stable (by 2.13 kcal/mol) than the *aa* form, which comes next to *gg*′ according to energetic stability. This should be again attributed mostly to its large electrostatic stabilization, partly coming from F/CH_3 and O^-/H attraction. The other two *gauche* forms are obviously destabilized by the C−F/S−O dipolar repulsion, which is the main factor responsible for their significantly increased energy (>3 kcal/mol, Table S7) relative to *gg*′-**4**. In solvents, conformational energies of these two *gauche* forms are reduced, but exceed 1 kcal/mol for *ga* and 1.5 kcal/mol for *gg* in water, and are still larger in acetone and methylene chloride. Both $FCCS_{anti}$ forms are by 1−2.2 kcal/mol higher in energy than the *gg*′ conformer, in all three solvents (Table S7).

As data in Table S8 show, the sulfone **4** *gauche* effect is mainly electrostatic in origin (65%), which is followed by orbital interactions (35%). Magnitudes of both electrostatic and orbital stabilizing intearctions are larger than in the case of sulfoxide **3**.

*(2-Fluoroethyl)dimethylsulfonium Ion (**5**).* Five energy minima structures of sulfonium ion **5** are shown in Figure 6, with their relative energies and isomerization energies. In this

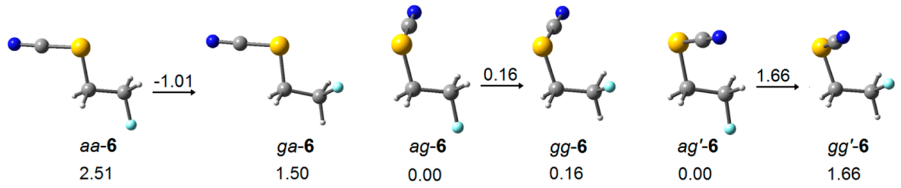

Figure 7. Optimized structures of conformers of **6**, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

case, the second letter in the conformer labeling refers to the C−C−S−lone pair conformation. Relative enthalpies and free energies, calculated at the MP2 and DFT levels, in the gas phase and in the three solvents are presented in Table S9 in the Supporting Information. The EDA results are shown in Table S10. As the results show, sulfur methylation in **2** reverses conformational preference to *gauche*, which is very large. The *ga* and *gg* conformers are by 5.30 and 5.03 kcal/mol more stable than their corresponding *anti* forms, at the MP2 level in the gas-phase. Even the *gg*′ conformation with a 1,3-F/lone pair interaction shows a significant *gauche* effect of 3.42 kcal/mol. Thus, this molecule would exist exclusively in the FCCS *gauche* arrangement. The FCCS dihedral angles are smaller than 60° and range from 48.8° to 56.6°, indicating a considerable F/$S(CH_3)_2^+$ attraction. DFT data are consistent with the MP2 ones, though *gauche* preference is slightly smaller at this level (5.12 kcal/mol, 4.88 and 2.98 kcal/mol for *aa* → *ga*, *ag* → *gg*, and *ag*′ → *gg*′ isomerizations, respectively; Table S9). The gas-phase *gauche* effect is reduced almost twice when methylene chloride is included as a solvent, $\Delta E/\Delta H/\Delta G$ = 1.9−2.6/2−2.8/1.3−2.9 kcal/mol, and further drops with increasing solvent polarity, 1.8−2.3/1.8−2.5/1.1−2.2 kcal/mol in acetone and 1.7−2.2/1.5−2.3/0.9−2.4 kcal/mol in water, but remains larger than that of sulfone **4**.

The gas-phase *gauche* effect of **5** is by ∼1.5 kcal/mol smaller than that calculated for 2-fluoroethylammonium ion (6.84 kcal/mol) and compares with the one calculated for 2-choroethylammonium ion (5.24 kcal/mol), at the same level of theory.[8e] The major part of *gauche* energy stabilization comes from electrostatic forces (64−75%), while stabilization by orbital interactions ranges from 25% to 30%. Dispersion forces play a role only when fluorine encounters a sulfur lone pair, as in the *gg*′ conformer. The magnitude of electrostatic stabilization is the largest compared to **1**, **3**, and **4**.

*1-Fluoro-2-thiocyanatoethane (**6**).* In the case of **6**, the C_s symmetric *aa* form contained a small imaginary frequency at the MP2 level, *i*31.3 cm^{-1}, and it was reoptimized to the C_1 structure having an FCCS dihedral angle of 174.8°. All energy minima structures and their relative energies are shown in Figure 7. Relative energies, enthalpies, and free energies at both MP2 and DFT levels are included in Table S11, and EDA results are presented in Table S12 in the Supporting Information.

At the MP2 level, the observed gas-phase *gauche* conformer stabilization (∼1 kcal/mol) in the case of *aa* → *ga* rotation is just a consequence of the high energy of the *aa* form and should not be considered as a manifestation of the *gauche* effect, since the *ga* form lies 1.5 kcal/mol above the most stable *ag*/*g*′ conformation. Thus, thiocyanate **6** shows a slight *anti* preference, by 0.16 kcal/mol, regarding the *ag*/*gg* conformational interconversion. Among the *gauche* forms, the *gg* conformer (φ_{FCCS} = 64.9°) is of lowest energy. The *gg*′ form, having 1,3-F/CN interaction, mainly suffers from an increased Pauli repulsion with respect to the *gg* structure, whereas an inreased energy of *ga* relative to *gg* results from deformation energy. Large ΔE_{def} is also the sole factor responsible for the high energy of *aa*-**6** relative to *ag*-**6**, and this compares with the already discussed results for **1** and **2**. Thus, ΔE_{int} favors the $RSCC_{anti}$ conformation (R = H, CH_3, and CN), whereas ΔE_{def} destabilizes it, leading to overall destabilization of $RSCC_{anti}$ compared to $RSCC_{gauche}$. We have checked an influence of solvent on conformation preference concerning the *ag* → *gg* isomerization, which occurs with the smallest energy change. All three solvents considered shift the conformational equilibrium to the *gauche* conformer, though the effect does not exceed 0.6 kcal/mol: $\Delta E/\Delta H/\Delta G$ = 0.35/0.45/0.39 kcal/mol in CH_2Cl_2, 0.41/0.52/0.46 kcal/mol in acetone, and 0.46/0.56/0.41 kcal/mol in water. In solvents, relative energies of *ag*/*g*′ and *gg*′ structures become close to each other (the first one is raised, the second one reduced), so that *ag*′/*gg*′ interconversion has no preference in CH_2Cl_2, but is slightly shifted toward the *gg*′ form in acetone and water (by ∼0.2 and ∼0.3 kcal/mol, respectively).

The EDA results, done for the gas-phase state, show that the slight *anti* preference in the case of *ag*/*gg* interconversion does not originate from interaction energy, which is more favorable in the *gg* conformer, but from energetically costly structural changes. In this case, $\Delta\Delta E_{int}$ benefits more from orbital (58%) than from electrostatic interactions (42%). In the case of *ag*′ → *gg*′ isomerization, an energy increase by 1.66 kcal/mol originates exclusively from Pauli repulsion, diminished by the (slightly) more favorable electrostatic and orbital interactions. If compared to sulfoxide **3**, sulfone **4**, and thionium ion **5**, the slight *anti* preference in gaseous **6** comes from a decreased magnitude of electrostatic and orbital attractive forces upon *anti* → *gauche* isomerization, while Pauli repulsion is smaller than in **3**−**5**, from smaller electrostatic and dispersion stabilization and somewhat increased Pauli repulsion compared to thiol **1**.

The situation is slightly different at the DFT level. In the gas phase, the *ag*/*g*′ and *gg* conformers become almost equal in energy, resulting in no conformational preference, while enthalpy and free energy slightly (∼0.1 kcal/mol) favor the FCCS *gauche* arrangement. With increasing polarity of the medium, the *gauche* preference increases and becomes comparable with that of 1,2-difluoroethane (0.5−1 kcal/mol):[3] $\Delta E/\Delta H/\Delta G$ = 0.57/0.70/0.73 kcal/mol in CH_2Cl_2, 0.64/0.77/0.80 kcal/mol in acetone, and 0.68/0.82/0.84 kcal/mol in water. The *ag*′ → *gg*′ isomerization also goes with the energy drop of ∼0.3 kcal/mol in CH_2Cl_2, ∼ 0.5 kcal/mol in acetone, and ∼0.6 kcal/mol in water. The *ga* form is the least stable among the $FCCS_{gauche}$ form, so that the large negative energy change (1.4−1.7 kcal/mol) that follows *aa* → *ga* isomerization should not be considered as the *gauche* effect. All in all, a possible *gauche* effect in *β*-fluorinated thiocyanates awaits further experimental studies.

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2-Fluoroethyl Thiolacetate (7). At both theory levels employed, optimizations of *aa* and *ga* conformations of 7 ended in *ag* and *gg* forms, so that 7 is characterized by three energetically distinguishable conformers, *ag*, *gg*, and *gg′*, shown in Figure 8, which also includes their relative energies and isomerization energies. Relative Δ*H*s and Δ*G*s are included in Table S13, and EDA results are collected in Table S14 in the Supporting Information.

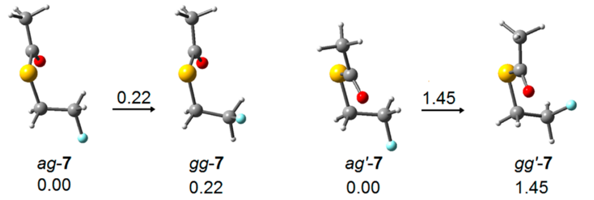

Figure 8. Optimized structures of conformers of 7, their relative energies and energy changes upon conformational isomerization (kcal/mol), calculated at the MP2/6-311++G(d,p) level of theory.

At the MP2 level, the most stable conformer *ag* is by 0.22 kcal/mol lower in energy than the *gg* form (φ_{FCCS} = 65.4°). Thus, there is a small *anti* preference regarding the *ag*/*gg* conformational isomerization. Rotation of *ag*/*g′* into the *gg′* form is followed by more rise in energy, ΔE_{iso} = 1.45 kcal/mol. Transfer of *ag* and *gg* conformers into solvent conditions resulted in almost no conformational preference: $\Delta E/\Delta H/\Delta G$ = 0.05/−0.05/−0.08 kcal/mol in CH_2Cl_2, 0.05/−0.06/−0.10 kcal/mol in acetone, and 0.04/−0.06/−0.11 kcal/mol in water.

The EDA data in Table S14 show that *ag* → *gg* rotation is followed by an increased electrostatic and orbital stabilization, the former constituting 54%, the latter 46%, of all attractive interactions. These stabilizing energies overcome somewhat increased Pauli repulsion and less favorable dispersion forces, thus making $\Delta\Delta E_{\text{int}}$ = −0.36 kcal/mol slightly negative. However, this is outweighed by unfavorable deformation energy, resulting in a small *anti* preference. Thus, as in the case of **6**, there is insuficient electrostatic and orbital stabilization in 7 to overcome energy spent on structural changes, increased Pauli repulsion, and less favorable dispersion interactions. It should be noted that, in the case of 7, the $\Delta\Delta E_{\text{ex+rep}}$ and $\Delta\Delta E_{\text{def}}$ (the latter with few exceptions) are less destabilizing than the corresponding energies in **1** and **3**−**5**, showing a *gauche* effect.

It is interesting to note that there is a slight decrease in electrostatic stabilization when *ag′* → *gg′* isomerization takes place, even though both sulfur and carbonyl carbon atoms carry a partial positive charge. This energy, along with an increased repulsion and energy gone on structural changes, makes ΔE_{iso} unfavorable.

At the DFT level, the *ag*/*gg* interconversion in the gas phase has no preference regarding Δ*E* and Δ*H*, while Δ*G* slightly favors the *gauche* form (by 0.27 kcal/mol). According to calculations, this small *gauche* effect decreases (CH_2Cl_2) or disappears (acetone and water) in a solvent: Δ*G* = −0.15 kcal/mol in CH_2Cl_2, 0.35 kcal/mol in acetone, and 0.02 kcal/mol in water.

Structural Changes That Follow $FCCS_{anti}$ *to* $FCCS_{gauche}$ *Isomerizations.* The EDA data show that almost all $FCCS_{anti}$ → $FCCS_{gauche}$ isomerizations are accompanied by positive deformation energies (exceptions are four conformational changes, that is, *ag*-**1** → *gg*-**1**, *aa*-**3** → *ga*-**3**, *aa*-**3** → *g′a*-**3**, and *ag′*-**6** → *gg′*-**6**, for which $\Delta\Delta E_{\text{def}}$ is insignificant, < 0.1 kcal/mol). These structural changes take place to minimize unfavorable Pauli and, in several cases, partial electrostatic repulsive interactions (particularly C−F/S−O), but to keep attractive forces as large as possible. It is interesting to note that the C−C, C−F, and C−S bond length changes do not exceed 0.01 Å in the majority of these isomerizations (the C−F and C−S bonds are elongated by 0.12−0.15 Å when sulfoxide **3** encounters 1,3-F/O interactions, and the C−F and C−S bonds become longer by 0.01−0.14 Å when thionium ion **5** rotates into the *ga* and *gg* conformers). The insensitivity of bond lengths on conformational changes can be a consequence of somewhat balanced effects of repulsive and attractive interactions, the former tending to elongate bonds, the latter

Table 1. Energies ($E(2)$, kcal/mol) of Vicinal *Anti* Hyperconjugative Interactions in Selected Conformers of 1 and 3−5 Estimated from the Second-Order Perturbation Approach on an NBO Basis at the HF/6-311++G(d,p) Level, Their Change ($\Delta E(2)_{anti}$), and Change of All Hyperconjugative Interactions ($\Delta E(2)_{anti+synclinal}$) upon $FCCS_{anti}$ → $FCCS_{gauche}$ Isomerization

	$E(2)$ energies of individual orbital interactions								
	C−H	C−F	C−S	C−H	C−H	C−F	C−S		
conformation	C−H*[a]	C−S*	C−F*	C−F*	C−S*	C−H*	C−H*	$\Delta E(2)_{anti}$	$\Delta E(2)_{anti+synclinal}$
ag′-**1**	−12.36	−2.13	−4.58						
gg′-**1**	−6.27			−5.89	−6.08	−1.17	−2.34	**-2.68**	**-2.42**
aa-**3**	−11.71	−1.74	−4.42						
g′a-**3**	−5.90			−5.34	−4.75	−1.29	−2.54	**-1.95**	**-2.07**
ag-**3**	−11.69	−1.81	−3.54						
g′g-**3**	−6.39			−6.26	−5.24	−1.13	−2.19	**-4.17**	**-3.33**
ag′-**3**	−11.58	−1.92	−3.67						
gg′-**3**	−5.55			−5.40	−5.10	−1.08	−2.13	**-2.09**	**-2.52**
ag′-**4**	−11.54	−1.92	−3.03						
gg′-**4**	−5.87			−5.60	−5.49	−1.14	−1.87	**-3.48**	**-3.44**
aa-**5**	−10.90	−2.71	−2.11						
ga-**5**	−5.86			−5.00	−7.25	−1.12	−1.56	**-5.07**	**-4.41**
ag-**5**	−10.75	−2.41	−2.56						
gg-**5**	−5.82			−4.60	−6.01	−1.24	−1.92	**-3.87**	**-3.29**
gg′-**5**	−5.59			−4.23	−5.93	−1.23	−1.79	**-3.05**	**-2.65**

[a] Sum of four interactions for $FCCS_{anti}$ isomers and sum of two interactions for $FCCS_{gauche}$ isomers.

Table 2. Contribution of Various Energy Components to the *Gauche* Effect in FCCX Systems (X = F, O, N, and S) or Small *Anti* Preference in Some FCCS Systems at the MP2/6-311++G(d,p) Level of Theory, in the Gas Phase (Values Are in kcal/mol)[a]

compound	ΔE_{iso}	$\Delta\Delta E_{def}$	$\Delta\Delta E_{int}$	$\Delta\Delta E_{elstat}$	$\Delta\Delta E_{ex+rep}$	$\Delta\Delta E_{oi}$	$\Delta\Delta E_{disp}$
$FCH_2CH_2OH_2^+$[b]	−8.23	0.81	−9.04	−12.32 (66%)	9.52	−5.40 (29%)	−0.84 (5%)
$FCH_2CH_2NH_3^+$[b]	−6.84	0.34	−7.18	−9.45 (72%)	5.96	−3.55 (27%)	−0.14 (1%)
$FCH_2CH_2S(CH_3)_2^+$	−5.30	1.37	−6.67	−8.83 (75%)	5.10	−2.98 (25%)	0.04
FCH_2CH_2OH[b]	−2.54	0.57	−3.11	−5.34 (60%)	5.77	−3.03 (34%)	−0.51 (6%)
$FCH_2CH_2SO_2CH_3$	−2.34	0.19	−2.53	−5.13 (65%)	5.23	−2.82 (35%)	0.19
$FCH_2CH_2SOCH_3$	−1.95	0.63	−2.58	−3.61 (63%)	3.17	−1.77 (31%)	−0.38 (6%)
$FCH_2CH_2NH_2$[b]	−1.39	1.93	−3.32	−1.46 (33%)	1.04	−1.62 (37%)	−1.28 (30%)
$FCH_2CH_2NH_2$[b]	−1.17	0.34	−1.51	−2.71 (69%)	2.43	−1.17 (30%)	−0.06 (1%)
FCH_2CH_2F[b]	−0.77	0.18	−0.95	−3.38 (40%)	7.57	−4.53 (53%)	−0.61 (7%)
FCH_2CH_2SH	−0.24	0.54	−0.78	−1.03 (63%)	0.85	−0.42 (26%)	−0.18 (11%)
FCH_2CH_2SCN	0.16	0.54	−0.38	−0.61 (42%)	1.00	−0.85 (58%)	0.08
$FCH_2CH_2SCH_3$	0.20	0.22	−0.02	−1.14 (65%)	1.49	−0.61 (35%)	0.24
$FCH_2CH_2SCOCH_3$	0.22	0.58	−0.36	−0.63 (54%)	0.44	−0.53 (46%)	0.36

[a] ΔE_{iso} = isomerization energy, $\Delta\Delta E_{def}$ = deformation energy, $\Delta\Delta E_{int}$ = interaction energy, $\Delta\Delta E_{elstat}$ = electrostatic energy, $\Delta\Delta E_{ex+rep}$ = exchange repulsion energy, $\Delta\Delta E_{oi}$ = orbital interaction energy, $\Delta\Delta E_{disp}$ = dispersion energy. Values in parentheses are percentage contribution to all attractive interactions. [b] Energy values are from ref 8e.

to shorten them. Bond angle changes are more pronounced: the CCF and CCS angles widening can reach 3.5°. Only in the case of thionium ion **5**, the CCS angles close upon *anti* → *gauche* rotation, by up to 1.2°. The most prominent structural change is related to CCSC and CCSO dihedral angles, which can alter by up to 42°.

Is Hyperconjugation Important for Fluorine/Sulfur *Gauche* Effect? The most commonly used explanation of the fluorine *gauche* effect is based on $\sigma_{\mathrm{C-H}} \rightarrow \sigma^*_{\mathrm{C-F}}$ hyperconjugative interactions, also invoked in ref 18. Our EDA revealed that electrostatic interactions actually play a more significant role in *gauche* conformer stabilization than total orbital interactions, though, the authors of ref 18 noted that the $\Delta G_{anti/gauche}$ values are larger when sulfur is more electron-deficient, particularly in sulfoxides. There remains a question on what is the effect of hyperconjugation on *anti*/*gauche* conformational equilibria, and what individual interactions are the most important. To answer the question, we have performed an NBO analysis, which provides information about the strength of charge transfer interactions betweeen filled (bonding) and empty (antibonding) orbitals. In this analysis, we used the second-order perturbative approach[36] at the HF/6-311++G(d,p) level and the NBO 6.0 version[37] linked to G09.

We calculated stabilizing energies, denoted as $E(2)$ values, of all vicinal hyperconjugative interactions (*synclinal* and *anti*) across the FC−CS bond and their influence on $\mathrm{FCCS}_{anti} \rightarrow \mathrm{FCCS}_{gauche}$ isomerizations. The results showed that, with one exception (see below), *anti* interactions contribute more than 80% to all vicinal hyperconjugation and they favor *gauche* isomers. By contrast, *synclinal* interactions are somewhat more pronounced in *anti* than in *gauche* forms, so that they diminish the stabilizing effect of *anti* interactions, but not more than 0.9 kcal/mol. Only in the case of rotations leading to *gg*′-**3** and *g*′*a*-**3** conformers, both *synclinal* and *anti* interactions favor *gauche* forms. An interesting case is *ag*′-**3** → *g*′*g*′-**3** isomerization, which occurs with *synclinal* hyperconjugative stabilization ($\Delta E(2)_{synclinal}$ = −2.59 kcal/mol), but overcome by less favorable *anti* interactions ($\Delta E(2)_{anti}$ = 2.85 kcal/mol), resulting in no stereoelectronic stabilization in the *gauche* form. This is a consequence of the significantly distorted geometry of *g*′*g*′-**3** (φ_{FCCS} = −91°), made such to diminish the C−F/S−O repulsion.

Thus, stereoelectronic effects work in favor of the *gauche* arrangement around the FC−CS bond, but what are the most important stabilizing interactions? In Table 1, we selected the stabilizing energies, $E(2)$, of individual *anti* hyperconjugative interactions in energy minima structures, the interconversion of which leads to the *gauche* effect, along with changes in *anti* ($\Delta E(2)_{anti}$) and all vicinal hyperconjugative interactions (sum of *synclinal* and *anti*, $\Delta E(2)_{anti+synclinal}$) upon $\mathrm{FCCS}_{anti} \rightarrow \mathrm{FCCS}_{gauche}$ isomerizations.

The largest stereoelectronic *gauche* effect is calculated for the *aa*-**5** → *ga*-**5** conformational isomerization ($\Delta E(2)_{anti}$ = −5.07 kcal/mol, $\Delta E(2)_{anti+synclinal}$ = −4.41 kcal/mol), which also shows the strongest *gauche* effect (Tables S9 and S10), 75% of which is owing to the electrostatic stabilizing energy. As data in Table 1 show, the stereoelectronic stabilization in *ga*-**5** primarily comes from the $\sigma_{C-H} \to \sigma^*_{C-S}$ interaction ($E(2) = -7.25$ kcal/mol); the $\sigma_{C-H} \to \sigma^*_{C-F}$ one takes the second place according to its importance ($E(2) = -5.00$ kcal/mol). The same order of stabilizing energies, $\sigma_{C-H} \to \sigma^*_{C-S} > \sigma_{C-H} \to \sigma^*_{C-F}$, is found in *gg*-**5** and *gg*′-**5**, having somewhat decreased stereoelectronic stabilization compared to *ga*-**5**. In the case of sulfone **4**, the energies of $\sigma_{C-H} \to \sigma^*_{C-S}$ ($E(2) = -5.49$ kcal/mol) and $\sigma_{C-H} \to \sigma^*_{C-F}$ interactions ($E(2) = -5.60$ kcal/mol) are comparable, now the latter one being slightly more pronounced. In all three FCCS_{gauche} conformers of sulfoxide **3**, the $\sigma_{C-H} \to \sigma^*_{C-F}$ interaction contributes more stabilizing energy than the $\sigma_{C-H} \to \sigma^*_{C-S}$ one by 0.3−1 kcal/mol. However, this changes for thiol **1**, where the $\sigma_{C-H} \to \sigma^*_{C-S}$ interaction is slightly more pronounced (by 0.19 kcal/mol) than the charge transfer into the C−F* antibonding orbital.

To rationalize these results, we discuss two factors affecting orbital interaction energy: (1) energy gap between the interacting orbitals and (2) amount of their overlap. In all *gauche* conformers, shown in Table 1, the energy gap between the interacting σ_{C-H} and σ^*_{C-X} (X = F, S) orbitals is smaller when X = S, which is more favorable for electron transfer interactions (the respective values are given in Table S15 in the Supporting Information). When going from **5** to **4** and **3**, the $\sigma_{C-H}/\sigma^*_{C-S}$ energy gap increases and $\sigma_{C-H}/\sigma^*_{C-F}$ energy difference decreases, thus reducing $\sigma_{C-H}/\sigma^*_{C-S}$ and enhancing $\sigma_{C-H}/\sigma^*_{C-F}$ orbital interactions. The largest $\sigma_{C-H}/\sigma^*_{C-F}$ energy gap in **5** is primarily related to the decreased energy level of the σ_{C-H} orbital, adjacent to the C−S bond, possibly due to an increased sulfur electronegativity. The latter can also be responsible for stronger $\sigma_{C-H}/\sigma^*_{C-S}$ overlap relative to $\sigma_{C-H}/\sigma^*_{C-F}$, only in the case of **5**. In **3** and **4**, the $\sigma_{C-H}/\sigma^*_{C-S}$ overlap is smaller and $\sigma_{C-H}/\sigma^*_{C-F}$ is larger. This, along with the reduced $\sigma_{C-H}/\sigma^*_{C-F}$ energy gap, increases the stabilizing energy associated with $\sigma_{C-H}/\sigma^*_{C-F}$ hyperconjugation with respect to the $\sigma_{C-H}/\sigma^*_{C-S}$ interaction, in **3** and **4**. What makes the $\sigma_{C-H} \to \sigma^*_{C-S}$ charge transfer in **1** slightly more important than the $\sigma_{C-H} \to \sigma^*_{C-F}$ interaction is just the smaller $\sigma_{C-H}/\sigma^*_{C-S}$ energy gap, while the $\sigma_{C-H}/\sigma^*_{C-F}$ orbital overlap is somewhat larger.[38]

On average, $\sigma_{C-H} \to \sigma^*_{C-H}$ interactions are comparable in *anti* and *gauche* forms, while stabilizing energies involving $\sigma_{C-F} \to \sigma^*_{C-S}$ and $\sigma_{C-S} \to \sigma^*_{C-F}$ charge transfer in *anti* forms are larger than energies corresponding to $\sigma_{C-F} \to \sigma^*_{C-H}$ and $\sigma_{C-S} \to \sigma^*_{C-H}$ interactions in *gauche* conformers (Table 1).

Comparative Analysis of F/X *Gauche* Effect (X = F, O, N, and S). Table 2 collects energy decomposition results for selected *anti* → *gauche* conformational isomerizations of various FCCX systems (X = F, O, N, and S) studied in the gas phase, at the MP2/6-311++G(d,p) level. The selected isomerizations are either those leading to the strongest *gauche* effect or those resulting in the smallest *anti* preference in compounds which do not show the *gauche* effect. In all isomerizations, the FCCX conformation changes, whereas that around the C−X bond remains the same. Data for the FCCS systems are from this work, and those for the Period 2 elements are taken from ref 8e. In the table, compounds are ordered according to a decreasing *gauche* effect, or increasing *anti* preference. In the case of 2-fluoroethylamine, data for two isomerizations are given, because their energy decompositions differ.

The first important note is that all *anti* → *gauche* isomerizations are followed by an increase in electrostatic stabilization, which, in some cases, opposes our traditional understanding of how electrostatic interactions affect conformational equilibria (for example, in the case of 1,2-difluoroethane). With just three exceptions (FCH_2CH_2F, FCH_2CH_2SCN, and one isomerization of $FCH_2CH_2NH_2$), contribution of electrostatic forces to all attractive interactions (54−75%) is larger than the contribution of all orbital interactions (25−46%), which is also always stabilizing. With one exception, the contribution of dispersion interactions is minor, negative, or positive. It is, thus, mainly the relative magnitude of stabilizing $\Delta\Delta E_{\mathrm{elstat}}$ and $\Delta\Delta E_{\mathrm{oi}}$ and destabilizing $\Delta\Delta E_{\mathrm{ex+rep}}$ that determines the amount of interaction energy stabilization ($\Delta\Delta E_{\mathrm{int}}$). Both attractive quantities, $\Delta\Delta E_{\mathrm{elstat}}$ and $\Delta\Delta E_{\mathrm{oi}}$, drop from the top to the bottom of Table 2, more or less regularly. The drop in the magnitude of electrostatic interactions is more pronounced (from 12.3 to 0.6 kcal/mol) than the drop in the magnitude of orbital interactions (from 5.4 to 0.4 kcal/mol). Thus, electrostatic forces play a more important role in determining the conformational equilibria in FCCX systems. As the magnitudes of $\Delta\Delta E_{\mathrm{elstat}}$ and $\Delta\Delta E_{\mathrm{oi}}$ decrease, $\Delta\Delta E_{\mathrm{int}}$ decreases, as well. Being counteracted by energy consuming $\Delta\Delta E_{\mathrm{def}}$, this drop results in a small *anti* preference, at the bottom of the table.

Data in Table 2 show that the strength of the *gauche* effect is the highest for positively charged species (>5 kcal/mol) and it decreases in the order O > N > S. Alcohol, sulfone, sulfoxide, and amine exhibit the *gauche* effect, which is still larger than 1 kcal/mol. Then, it drops to less than 1 kcal/mol for FCH_2CH_2F and FCH_2CH_2SH (for the former due to large Pauli repulsion), or small *anti* preference in thiocyanate, sulfide, and thiolester. For the latter four, the *anti*/*gauche* isomerization energy is rather small and could go in favor of *gauche* forms under solution conditions or in the solid state, as was experimentally shown for *β*-fluorosulfides.[12,17,18]

■ CONCLUSIONS

Conformational preferences around the FC−CS bond in simple systems in which a sulfur atom is part of a thiol, sulfide, sulfoxide, sulfone, thionium ion, thiocyanate and thiolacetate group have been analyzed by *ab initio* and DFT calculations. The largest *gauche* effect in the gas phase was found for thionium ion (ΔG = 2.7−4.5 kcal/mol), followed by that of sulfone (ΔG = 2.2 kcal/mol), sulfoxide (ΔG = 1−1.8 kcal/mol), and finally thiol (ΔG = 0.1−0.2 kcal/mol). The same trend is found in the three solvents considered: methylene chloride, acetone, and water. Sulfide showed small *anti* preference in both gas-phase and solvent conditions. Small gas-phase *anti* (*gauche*) preference in thiolacetate at the MP2 (DFT) levels changed into almost no preference in solvent conditions (DFT slightly favors *gauche* form). While thiocyanate slightly preferred the *anti* conformation (showed no preference) in the gas phase at the MP2 (DFT) levels, transfer to a solvent resulted in the *gauche* preference of 0.4−0.8 kcal/mol.

To gain an insight into the origin of these conformational preferences, the *anti*/*gauche* energy difference was partitioned into contributions from electrostatic, orbital, dispersion, and Pauli interactions, and energy spent on structural changes. It was found that, for all $\mathrm{FCCS}_{anti} \to \mathrm{FCCS}_{gauche}$ isomerizations, structural changes are energy costly or, in several cases, occur with an insignificant change in energy. The results showed that the most important *gauche* conformer stabilizing energy comes from electrostatic interactions, 63−75%, meaning that the fluorine/sulfur *gauche* effect has mainly an electrostatic origin. Orbital interactions, involving the C−C bond strength, charge transfer, and polarization, add 22−41% stabilizing contribution, and dispersion forces 6−11%. Stereoelectronic effects work in favor of *gauche* conformers, the most important interaction being $\sigma_{C-H} \rightarrow \sigma^*_{C-S}$ in thionium ion and $\sigma_{C-H} \rightarrow \sigma^*_{C-F}$ in sulfoxide, while both are of comparable strength in thiol and sulfone.

According to the current data, conformational control can be achieved by utilizing the fluorine/sulfur *gauche* effect in cases when sulfur is part of a sulfoxide, sulfone, and sulfonium ion. In the case of thiol, sulfide, thiocyanate, and thiolacetate, the *anti*/*gauche* isomerization energy is small and direct solute−solute and solute−solvent interactions in a real system could possibly shift the conformational equilibria toward *gauche* forms, which awaits further experimental studies. The lack of *gauche* effect in sulfide compared to the small *gauche* preference in thiol comes from an increased Pauli repulsion and smaller dispersion attraction in the former. In addition, there is insuficient electrostatic and orbital stabilization upon *anti* → *gauche* isomerization in sulfide, thiocyanate, and thiolacetate to overcome energy spent on structural changes and the Pauli repulsion, even though the latter two (with just a few exceptions) are less destabilizing than in molecules showing a *gauche* effect. This results in no *gauche* effect in these molecules, in the gas phase.

Comparative energy decomposition analysis of conformational preferences in various FCCX systems (X = O, N, S) showed that, with few exceptions, the most important energy responsible for the strength of the *gauche* effect is electrostatic energy, next coming orbital interaction energy.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01779.

> Tables S1−S14, the second-order perturbative analysis of donor−acceptor interactions, absolute energies, and *x*, *y*, *z* coordinates of optimized structures (PDF)

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Notes

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