JOC The Journal of Organic Chemistry
Article
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Theoretical Evidence for the Relevance of n(F) → σ^*(C−X) (X = H, C, O, S) Stereoelectronic Interactions

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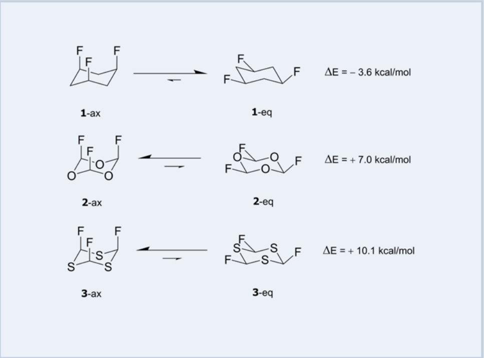
Supporting Information

ABSTRACT: Theoretical calculations on *r*-1,*c*-3,*c*-5-trifluorocyclohexane (**1**), *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trioxane (**2**), and *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trithiane (**3**) confirm the importance of n(F) → $\sigma^*(C{-}Y)_{gem}$, where Y = H, C, O, S, hyperconjugative interactions; that is, contrary to common wisdom, fluorine is a good lone pair electron donor toward geminal sigma bonds. This conclusion is in line with the recent observations reported by O'Hagan and co-workers, who synthesized and examined all-*cis* 1,2,3,4,5,6-hexafluoro-cyclohexane (*Nat. Chem.* **2015**, *7*, 483−488).



INTRODUCTION

It is now widely accepted that, together with steric and electrostatic interactions, stereoelectronic effects determine the structure, the conformational behavior, and the reactivity of organic molecules.[1] Stereoelectronic stabilizing interactions arise from the electronic transfer between a high-energy occupied orbital into a low-energy unoccupied (or partially empty) orbital. Particularly important are interactions that arise when the best donor orbital (lone pair or bond) is oriented antiperiplanar to the best acceptor orbital.[2]

Well identified consequences of stereoelectronic interactions in conformational equilibria are the anomeric effect[3] and the *gauche* effect,[4] and the accumulated evidence suggests the importance of n(X) → $\sigma^*(C{-}Y)_{app}$ and σ(C−H) → $\sigma^*(C{-}F)_{app}$ stereoelectronic interactions, respectively (Scheme 1).

From different studies in this area it has been established that *donor orbitals* in decreasing order of donor ability are[2,5]

$$\begin{aligned} &N(C^-) > n(N) > n(O) > \sigma(C{-}C) \sim \sigma(C{-}H) \\ &\qquad > \sigma(C{-}X)\ (X = N > O > S > \text{halogen}) \end{aligned}$$

Interestingly, while orbitals associated with lone pairs of electrons at the electronegative elements nitrogen and oxygen turn out to be rather good donor orbitals, fluorine usually exhibits poor lone pair donating power.[6] Nevertheless, O'Hagan and co-workers have recently provided structural and theoretical evidence for significant n(F) → $\sigma^*(C{-}X)_{gem}$ stereoelectronic interactions in geminal F−C−H and F−C−C segments present in all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane.[7]

In the present work we report theoretical calculations of the conformational behavior of *r*-1,*c*-3,*c*-5-trifluorocyclohexane (**1**-ax ⇌ **1**-eq, Scheme 2), *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trioxane (**2**-ax ⇌ **2**-eq, Scheme 2), and *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trithiane (**3**-ax ⇌ **3**-eq, Scheme 2). As it turned out, the existence of n(F) → $\sigma^*(C{-}X)_{gem}$ stereoelectronic interactions in **1**−**3** is confirmed and the relevance of "anomeric" n(X) → $\sigma^*(C{-}F)_{app}$ (X = O, S) stereoelectronic interactions in heterocycles **2** and **3** is also exhibited.

COMPUTATIONAL METHODS

The package of Gaussian 09 programs was used to carry out all calculations.[8] Energy minima were fully optimized at the MP2/6-311+G(*d*,*p*) level of theory. Potential hyperconjugative interactions were evaluated with Natural Bond Orbital analysis, using the NBO program (version 3.1).[9,10]

RESULTS AND DISCUSSION

A. *r*-1,*c*-3,*c*-5-Trifluorocyclohexane. The optimized geometries of axial and equatorial **1** at the MP2/6-311+G(*d*,*p*) level of theory are presented in Figure 1 and Table 1.

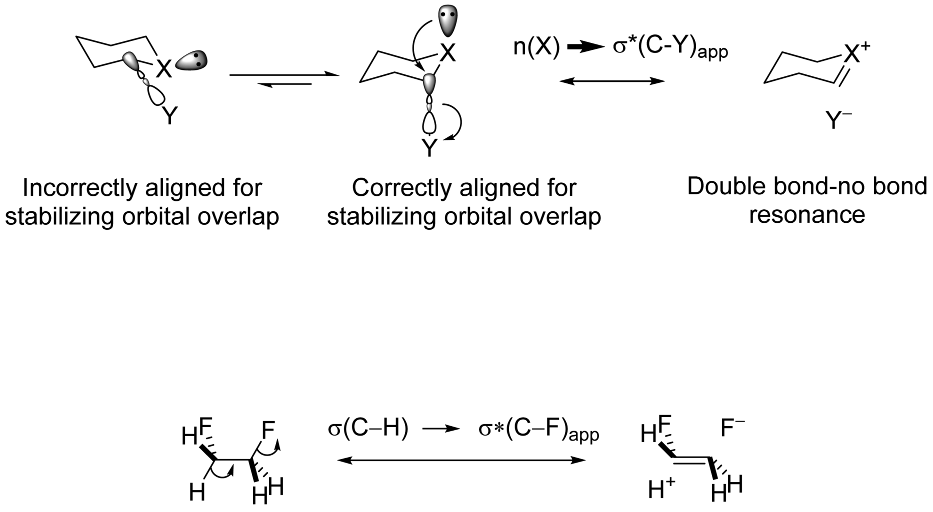
As it can be anticipated in terms of the strong dipole−dipole repulsion originated from 1,3-diaxial orientation of the C−F bonds, **1**-axial is calculated to be 3.6 kcal/mol higher in energy than **1**-equatorial. This value agrees quite well with the value calculated by Schaefer et al. (ΔE = 3.45 kcal/mol).[11,12]

On the other hand, no significant differences are calculated for all bonds in **1**-ax and **1**-eq. Nevertheless, as emphasized by Alabugin and co-workers,[9e] the NBO method developed by Weinhold and co-workers is very useful for the study of

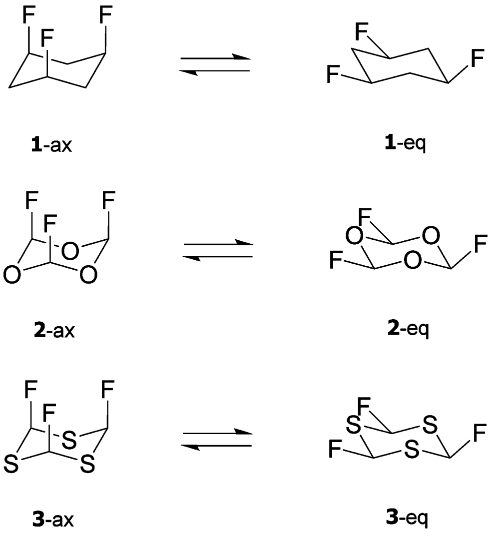
Received: November 28, 2015
Published: January 15, 2016

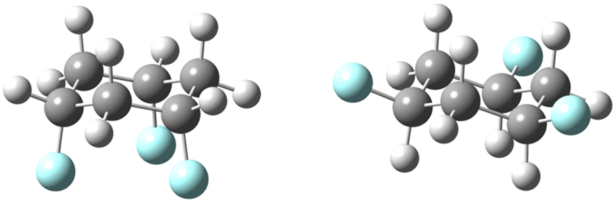
DOI: 10.1021/acs.joc.5b02718
J. Org. Chem. 2016, 81, 1192−1197

Scheme 1. Stereoelectronic Interactions Involved in the Anomeric Effect and the *Gauche* Effect



Scheme 2. Fluorinated Compounds Examined in the Present Study, *r*-1,*c*-3,*c*-5-Trifluorocyclohexane (1-ax ⇌ 1-eq), *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trioxane (2-ax ⇌ 2-eq), and *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trithiane (3-ax ⇌ 3-eq)





1-ax | **1**-eq

E = -532.407073 Hartrees (3.6 kcal/mol) | *E* = -532.412849 Hartrees (0.0)

Figure 1. MP2/6-311+G(*d*,*p*)-optimized structures of *r*-1,*c*-3,*c*-5-trifluorocyclohexane, in conformation axial, **1**-ax, and equatorial, **1**-eq.

hyperconjugative interactions.[14] Particularly useful is the fact that NBO analysis provides an estimate of the magnitude of the interaction energies between the participating donor and acceptor orbitals.

Table 1. MP2/6-311+G(*d*,*p*)-Optimized Geometrical Parameters of *r*-1,*c*-3,*c*-5-Trifluorocyclohexane, in Conformation Axial, 1-ax, and Equatorial, 1-eq (Bond Distances in Å)

	1-axial	**1**-equatorial
$C-F_{ax}$	1.395	–
$C-F_{eq}$	–	1.397
C–C	1.522	1.521
$C-H_{ax}$	1.098	1.096(1.097)[a]
$C-H_{eq}$	1.094 (1.096)[a]	1.094

[a] H geminal to F.

Table 2 lists the interaction energies (*E*(2)) and the corresponding energy gaps (Δ*E*) for the main hyperconjugative interactions in trifluorocyclohexanes **1**-ax and **1**-eq. Table 2 includes also the energy difference between the donor and acceptor orbitals of interest. As anticipated, an inverse relationship between energy gap between donor and acceptor orbitals and the magnitude of the two-electron/two-orbital hyperconjugative interaction is observed.

Table 2. Selected Hyperconjugative Interactions in *r*-1,*c*-3,*c*-5-Trifluorocyclohexane, 1-ax and 1-eq

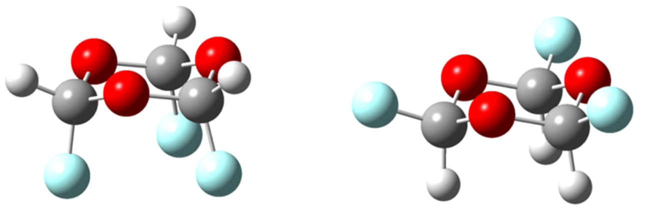
	1-axial		**1**-equatorial	
	E(2)/kcal/mol	Δ*E*/Hartrees	*E*(2)/kcal/mol	Δ*E*/Hartrees
$nF_{ax} \rightarrow \sigma^*(C-H_{eq})$	9.17	1.23	–	–
$nF_{eq} \rightarrow \sigma^*(C-H_{ax})$	–	–	8.93	1.22
$\sigma(C-H_{ax}) \rightarrow \sigma^*(C-F_{ax})$	6.12	1.19	–	–
$nF_{ax} \rightarrow \sigma^*(C-C)$	5.21	1.24	–	–
$nF_{eq} \rightarrow \sigma^*(C-C)$	–	–	4.82	1.25
$\sigma(C-H_{eq}) \rightarrow \sigma^*(C-C)$	3.59[a] 3.38[b]	1.33[a] 1.31[b]	3.22	1.31
$\sigma(C-H_{ax}) \rightarrow \sigma^*(C-H_{ax})$			3.50[c] 3.29[d]	1.27[c] 1.32[d]
$\sigma(C-C) \rightarrow \sigma^*(C-F_{eq})$	–	–	3.55	1.33

[a] H_{eq} geminal to F_{ax}. [b] H_{eq} geminal to H_{ax}. [c] H_{ax} geminal to H_{eq}. [d] H_{ax} geminal to F_{eq}.

Most relevant observations are the following, (1) $n(F_{ax}) \rightarrow \sigma^*(C-H_{eq})_{gem}$ with an interaction energy of 9.17 kcal/mol,

$n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})_{gem}$ with an interaction energy of 8.93 kcal/mol, $n(F_{ax}) \rightarrow \sigma^*(C{-}C)_{gem}$ with an interaction energy of 5.21 kcal/mol, and $n(F_{eq}) \rightarrow \sigma^*(C{-}C)_{gem}$ with an interaction energy of 4.82 kcal/mol confirm, as emphasized by O'Hagan et al.[7] the donor character of the fluorine lone pair toward the geminal sigma bonds. In this regard, $\sigma^*(C{-}H)$ is estimated to be a better acceptor orbital relative to $\sigma^*(C{-}C)$. (2) As it could be anticipated on the basis of the accepted interpretation of the *gauche* effect (see the Introduction), the calculations also show quite strong $\sigma(C{-}H_{ax}) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ hyperconjugative interactions, worth 6.12 kcal/mol.

B. *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trioxane. The optimized geometry of axial and equatorial **2** at the MP2/6-311+G(*d*,*p*) level of theory are presented in Figure 2 and Table 3.



2-ax — $E = -640.054446$ Hartrees — (0.0)

2-eq — $E = -640.043235$ Hartrees — (7.0 kcal/mol)

Figure 2. MP2/6-311+G(*d*,*p*)-optimized structures of *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trioxane, in conformation axial, **2**-ax, and equatorial, **2**-eq

Table 3. MP2/6-311+G(*d*,*p*)-Optimized Geometrical Parameters of *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trioxane, in Conformation Axial, 2-ax, and Equatorial, 2-eq (Bond Distances in Å)

	2-axial	**2**-equatorial
$C{-}F_{ax}$	1.363	–
$C{-}F_{eq}$	–	1.334
C–O	1.390	1.395
$C{-}H_{ax}$	–	1.099
$C{-}H_{eq}$	1.086	–

In dramatic contrast with the conformational energies estimated for *r*-1,*c*-3,*c*-5-trifluorocyclohexane, the all-axial conformer **2**-ax is predicted to be 7.0 kcal/mol more stable than the equatorial isomer **2**-eq. That is, replacement of the methylene groups in **1** for oxygen atoms in **2** results in 10.6 kcal/mol stabilization of the axial conformer, in spite of the strong dipole−dipole interactions between syn-diaxial C−F bonds.[6] Most likely, this conformational effect arises from $n(O) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ and $\sigma(C{-}H_{ax} \rightarrow \sigma^*(C{-}F_{ax})_{app}$ stereoelectronic interactions. Support for this interpretation may be found in the structural data estimated for the optimized structures of **2**-ax and **2**-eq (Table 3). Indeed, the axial C−F bonds are significantly longer (1.363 Å) than the equatorial C−F bonds (1.334 Å), as anticipated in terms of the above interactions that weaken the axial C−F bonds.[1−5,15]

Application of the NBO analysis gives evidence for the salient hyperconjugative interactions (Table 4). Quite significant are the rather large interaction energies involving fluorine as a lone pair donor.

Table 4. Selected Hyperconjugative Interactions in *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trioxane, 2-ax and 2-eq

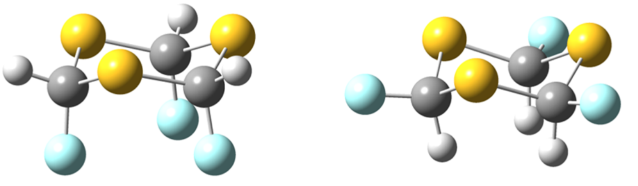
	2-axial		**2**-equatorial	
	E(2)/ kcal/mol	Δ*E*/ Hartrees	*E*(2)/ kcal/mol	Δ*E*/ Hartrees
$n(O) \rightarrow \sigma^*(C{-}F_{ax})$	19.07	1.03	–	–
$n(O) \rightarrow \sigma^*(C{-}F_{eq})$	–	–	6.88	1.39
$n(F_{ax}) \rightarrow \sigma^*(C{-}O)$	10.75	1.19	–	–
	4.04	1.19		
$n(F_{eq}) \rightarrow \sigma^*(C{-}O)$	–	–	11.03	1.19
			4.34	1.19
$n(F_{ax}) \rightarrow \sigma^*(C{-}H_{eq})$	9.24	1.24	–	–
$n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})$	–	–	10.20	1.20
$n(O) \rightarrow \sigma^*(C{-}O)$	7.10	1.08	13.10	1.08
	3.71	1.39		
$\sigma(C{-}H_{eq}) \rightarrow \sigma^*(C{-}O)$	3.92	1.31		
$n(O) \rightarrow \sigma^*(C{-}H_{ax})$	–	–	7.58	1.08
$n(O) \rightarrow \sigma^*(C{-}H_{eq})$	3.46	1.43	–	–
$\sigma(C{-}O) \rightarrow \sigma^*(C{-}F_{ax})_{gem}$	1.24	1.65	–	–
$\sigma(C{-}O) \rightarrow \sigma^*(C{-}F_{eq})_{gem}$	–	–	2.48	1.66

Salient observations are the following: (1) the strongest hyperconjugative interaction results from $n(O) \rightarrow \sigma^*(C{-}F_{ax})_{app}$, with 19.07 kcal/mol interaction energy. (2) Quite relevant is also hyperconjugation involving the fluorine lone electron pairs: $n(F_{ax}) \rightarrow \sigma^*(C{-}O)_{gem}$ (10.75 kcal/mol interaction energy) and $n(F_{eq}) \rightarrow \sigma^*(C{-}O)_{gem}$ (11.03 kcal/mol interaction energy). (3) Regarding the donor role of the n(F) orbital, the $\sigma^*(C{-}H)$ orbital shows lower acceptor capability than the $\sigma^*(C{-}O)$ orbital; see, for example: $n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})_{gem}$ with 10.20 kcal/mol interaction energy. (4) Very important is also the "anomeric-type" $n(O) \rightarrow \sigma^*(C{-}O)_{app}$ hyperconjugative interaction, with 10.30 kcal/mol interaction energy.

Donation from the F lone pair to the $\sigma^*(C{-}O)_{gem}$ and $\sigma^*(C{-}H)_{gem}$ orbitals are almost identical in the all axial and all equatorial conformers of trifluoro-1,3,5-trioxane (Table 4). This probably indicates that fluorine is much more effective stereoelectronic donor than oxygen (and should be even more the case with nitrogen) due to the presence of multiple lone pairs.

C. *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trithiane. The optimized geometry of axial and equatorial **3** at the MP2/6-311+G(*d*,*p*) level of theory are presented in Figure 3 and Table 5.

Most interesting is the very large preference for **3**-axial relative to **3**-equatorial. The calculated structural data, in



3-ax — $E = -1607.781349$ Hartrees — (0.0)

3-eq — $E = -1607.765301$ Hartrees — (10.1 kcal/mol)

Figure 3. MP2/6-311+G(*d*,*p*)-optimized structures of *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trithiane, in conformation axial, **3**-ax, and equatorial, **3**-eq

Table 5. MP2/6-311+G(*d*,*p*)-Optimized Geometrical Parameters of *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trithiane, in Conformation Axial, 3-ax, and Equatorial, 3-eq (Bond Distances in Å)

	3-axial	3-equatorial
$C{-}F_{ax}$	1.351	–
$C{-}F_{eq}$	–	1.339
C–S	1.804	1.815
$C{-}H_{ax}$	–	1.080
$C{-}H_{eq}$	1.080	–

particular the longer $C{-}F_{ax}$ (1.351 Å) by comparison with $C{-}F_{eq}$ (1.349 Å), as well as the shorter C–S bond in **3**-axial (1.804 Å) relative to the same bond in **3**-equatorial (1.815 Å) suggest a manifestation of $n(S) \rightarrow \sigma^*(C{-}F)_{app}$ hyperconjugation.[16]

Application of the NBO analysis gives evidence for the salient hyperconjugative interactions (Table 6). Most significant is the rather large $n(S) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ stereoelectronic interaction, worth 15.38 kcal/mol. While the magnitude of this anomeric interaction involving sulfur is smaller than the correspondig one with oxygen [$E(2)$ = 19.07 kcal/mol, Table 4], it contrasts rather strongly with early theoretical studies suggesting that sulfur is an ineffective donor in S–C–X anomeric segments.[17]

Table 6. Selected Hyperconjugative Interactions in *r*-2,*c*-4,*c*-6-Trifluoro-1,3,5-trithiane, 3-ax and 3-eq

	3-axial		3-equatorial	
	$E(2)$/ kcal/mol	ΔE/ Hartrees	$E(2)$/ kcal/mol	ΔE/ Hartrees
$n(S) \rightarrow \sigma^*(C{-}F_{ax})$	15.38	0.82	–	–
$n(S) \rightarrow \sigma^*(C{-}F_{eq})$	–	–	1.06	1.28
$n(F_{ax}) \rightarrow \sigma^*(C{-}S)$	8.31	0.98	–	–
	2.91	1.02		
$n(F_{eq}) \rightarrow \sigma^*(C{-}S)$	–	–	6.96	0.99
			2.66	1.01
$n(F_{ax}) \rightarrow \sigma^*(C{-}H_{eq})$	9.84	1.24	–	–
$n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})$	–	–	9.53	1.23
$n(S) \rightarrow \sigma^*(C{-}S)$	5.41	0.72	9.74	0.73
	3.38	1.18		
$\sigma(C{-}H_{eq}) \rightarrow \sigma^*(C{-}S)$	1.82	1.10		
$n(S) \rightarrow \sigma^*(C{-}H_{ax})$	–	–	4.24	0.94
$n(S) \rightarrow \sigma^*(C{-}H_{eq})$	0.83	1.39	–	–
$\sigma(C{-}S) \rightarrow \sigma^*(C{-}F_{ax})_{gem}$	1.50	1.29	–	–
$\sigma(C{-}S) \rightarrow \sigma^*(C{-}F_{eq})_{gem}$	–	–	2.18	1.27

The data gathered in Table 6 also support the existence of quite significant interaction energies involving fluorine as a lone pair donor in $n(F_{ax}) \rightarrow \sigma^*(C{-}S)_{gem}$, $n(F_{eq}) \rightarrow \sigma^*(C{-}S)_{gem}$, $n(F_{ax}) \rightarrow \sigma^*(C{-}H_{eq})_{gem}$, and $n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})_{gem}$ stereoelectronic interactions.

The interpretations advanced above are supported by deletion of the key NBO interactions followed by reoptimization of the geometries with these interactions switched off (NBODEL). The results are summarized in Table 7. In all cases, application of NBODEL while switching off the key hyperconjugative interactions led to the anticipated structural changes.

Table 7 provides a wealth of structural data that seem to confirm the various stereoelectronic interactions advanced in the above discussion. Nevertheless, for the sake of space, we will highlight only those interactions most closely related to the previous discussion.

*Equatorial r-1,c-3,c-5-Trifluorocyclohexane, **1**-eq.* Relative to the delocalized system (without NBODEL), switching off the geminal $n(F_{eq}) \rightarrow \sigma^*(C{-}C)_{gem}$ interaction in **1**-eq leads to substantial lengthening of the $C{-}F_{eq}$ bond length (1.372 Å versus 1.428 Å, Table 7), and this observation is in line with expectation in terms of $n(F) \rightarrow \sigma^*(C{-}C)_{gem}$ hyperconjugation. By the same token, "switching off" the geminal $n(F_{eq}) \rightarrow \sigma^*(C{-}H_{ax})_{gem}$ interaction in **1**-eq results in significant bond length shortening of the $C{-}H_{ax}$ bond (1.085 Å versus 1.078 Å).

*Axial r-2,c-4,c-6-Trifluoro-1,3,5-trioxane, **2**-ax.* Support for the importance of $n(O) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ hyperconjugative interaction in **2**-ax is evident when the $C{-}F_{ax}$ bond length is compared in the delocalized system versus the localized system, with the interaction $n(O) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ turned off. Indeed, the O–C bond becomes longer (1.426 Å versus 1.370 Å) while simultaneously the axial C–F bond becomes shorter (1.310 Å versus 1.337 Å, Table 7).

The relevance of the geminal $n(F_{ax}) \rightarrow \sigma^*(C{-}O)_{gem}$ hyperconjugative interaction is confirmed by comparison of the $C{-}F_{ax}$ bond length in the delocalized (1.337 Å) versus the localized (1.416 Å) system. Thus, the significant length increase upon switching off of the $n(F_{ax}) \rightarrow \sigma^*(C{-}O)_{gem}$ interaction is in line with anticipation.

By the same token, switching off the $n(F_{ax}) \rightarrow \sigma^*(C{-}H_{eq})_{gem}$ stereoelectronic interaction results in a substantial length increase of the C–F bond: 1.337 Å in the delocalized system versus 1.369 Å when the hyperconjugative interaction is turned off (Table 7).

*Axial r-2,c-4,c-6-Trifluoro-1,3,5-trithiane, **3**-ax.* Most relevant are the calculated bond lengths of $C{-}F_{ax}$ with and without $n(S) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ hyperconjugative interaction: 1.351 and 1.331 Å (Table 7). The longer bond in the delocalized system is in line with the expectation of the above-mentioned interaction that weakens the axial C–F bond and strengthens the S–C bond, 1.805 Å in the delocalized system versus 1.874 Å in the localized system (increased double bond character in the hyperconjugated case).

Evidence supporting the importance of geminal $n(F_{ax}) \rightarrow \sigma^*(C{-}S)_{gem}$ is found by comparison of the C–F and C–S bond lengths: the former becomes longer (1.351 Å versus 1.425 Å) while the latter becomes shorter (1.804 Å versus 1.778 Å) upon electronic localization (Table 7).

Finally, manifestation of the participation of the fluorine lone pair in $n(F_{ax}) \rightarrow \sigma^*(C{-}H_{eq})_{gem}$ hyperconjugation is found in the comparison of the C–F and C–H bond lengths: the former becomes longer (1.351 Å versus 1.356 Å) while the latter gets shorter (1.080 Å versus 1.074 Å) when the stereoelectronic interaction is turned off (Table 7).

■ CONCLUSIONS

Theoretical calculations seem to confirm the donor capability of fluorine lone pairs in hyperconjugative interactions involving geminal sigma bonds as acceptors. This is in line with the recent discovery of O'Hagan and co-workers while examining the structural characteristics of all-*cis* 1,2,3,4,5,6-hexafluorocyclohexane.[7] In particular, compelling evidence supporting the importance of $n(F) \rightarrow \sigma^*(C{-}C)_{gem}$, $n(F) \rightarrow \sigma^*(C{-}H)_{gem}$, $n(F) \rightarrow \sigma^*(C{-}O)_{gem}$, and $n(F) \rightarrow \sigma^*(C{-}S)_{gem}$ was gathered from the present study of *r*-1,*c*-3,*c*-5-trifluorocyclohexane (**1**), *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trioxane (**2**), and *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trithiane (**3**).

Table 7. Comparison of Structural Parameters in the Optimized Geometries, at the HF/6-31G(*d*) Computational Level, of 1-ax, 1-eq, 2-ax, 2-eq, 3-ax, and 3-eq with Those Optimized Geometries Obtained by NBODEL, When Switching Off Key NBO Interaction

r-1,*c*-3,*c*-5-Trifluorocyclohexane, **1**

Bond	without NBODEL		n(F) → σ^*(C−C)		n(F) → σ^*(C−H)	
	axial	equatorial	axial	equatorial	axial	equatorial
$\mathrm{C{-}F_{ax}}$	1.371	–	1.427	–	1.374	–
$\mathrm{C{-}F_{eq}}$	–	1.372	–	1.428	–	1.407
$\mathrm{C{-}H_{ax}}$	1.088	1.086	1.091	1.086	1.091	1.085
$\mathrm{C{-}H_{ax}}$	–	1.085	–	1.084	–	1.078
$\mathrm{C{-}H_{eq}}$	1.084	1.084	1.084	1.085	1.075	1.084
$\mathrm{C{-}H_{eq}}$	1.083	–	1.083	–	1.074	–
C−C	1.523	1.521	1.510	1.511	1.534	1.519

r-2,*c*-4,*c*-6-Trifluoro-1,3,5-trioxane, **2**

Bond	without NBODEL		n(O) → σ^*(C−F)		n(O) → σ^*(C−O)		n(F) → σ^*(C−O)		n(F) → σ^*(C−H)	
	axial	equatorial	axial	equatorial	axial	equatorial	axial	equatorial	axial	equatorial
$\mathrm{C{-}F_{ax}}$	1.337	–	1.310	–	1.329	–	1.416	–	1.369	–
$\mathrm{C{-}F_{eq}}$	–	1.316	–	1.309	–	1.329	–	1.401	–	1.348
$\mathrm{C{-}H_{ax}}$	–	1.085	–	1.079	–	1.077	–	1.079	–	1.079
$\mathrm{C{-}H_{eq}}$	1.072	–	1.071	–	1.071	–	1.069	–	1.068	–
C−O	1.370	1.373	1.426	1.404	1.394	1.366	1.361	1.360	1.366	1.368

r-2,*c*-4,*c*-6-Trifluoro-1,3,5-trithiane, **3**

Bond	without NBODEL		n(S) → σ^*(C−F)		n(S) → σ^*(C−S)		n(F) → σ^*(C−S)		n(F) → σ^*(C−H)	
	axial	equatorial	axial	equatorial	axial	equatorial	axial	equatorial	axial	equatorial
$\mathrm{C{-}F_{ax}}$	1.351	–	1.331	–	1.340	–	1.425	–	1.356	–
$\mathrm{C{-}F_{eq}}$	–	1.349	–	1.346	–	1.342	–	1.415	–	1.382
$\mathrm{C{-}H_{ax}}$	–	1.080	–	1.079	–	1.078	–	1.081	–	1.076
$\mathrm{C{-}H_{eq}}$	1.080	–	1.075	–	1.078	–	1.082	–	1.074	–
C−S	1.804	1.815	1.874	1.825	1.837	1.850	1.778	1.793	1.825	1.812

The Natural Bond Orbital (NBO) method developed by Weinhold[14] and co-workers is a very useful theoretical method for the study of hyperconjugative interactions present in **1**−**3**. In particular, NBO analysis provided the energies of the delocalizing interactions that weaken the acceptor bonds. In particular, comparison of structural parameters in the optimized geometries, at the HF/6-31G(*d*) computational level, of delocalized **1**-ax, **1**-eq, **2**-ax, **2**-eq, **3**-ax, and **3**-eq with those optimized geometries obtained by NBODEL, when switching off key hyperconjugative interactions, is in line with the anticipated structural changes.

MP2/6-311+G(*d*,*p*) calculations on the conformational equilibria of **1**−**3** indicate that **1**-ax ⇌ **1**-eq is shifted to the right by 3.6 kcal/mol, while **2**-ax ⇌ **2**-eq and **3**-ax ⇌ **3**-eq equilibria strongly favor the axial isomer by 7.0 and 10.1 kcal/mol, respectively. The strong axial preference for **2**-ax and **3**-ax originates from dominant n(X) → $\sigma^*(\mathrm{C{-}F})_{app}$ hyperconjugative interactions, where X = O or S.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b02718.

NBO hyperconjugative interactions in **1**-ax, **1**-eq, **2**-ax, **2**-eq, **3**-ax and **3**-eq (Table S-1). MP2/6-311+G(*d*,*p*)-optimized Cartesian coordinates of the compounds studied in this work (Table S-2) (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from Consejo Nacional de Ciencia y Tecnología, CONACYT Grant Number 220945, is gratefully acknowledged. The useful comments provided by the reviewers are also appreciated.

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(16) It is interesting to compare the 10.1 kcal/mol preference of the all axial conformer of *r*-2,*c*-4,*c*-6-trifluoro-1,3,5-trithiane, **3**-ax, with the *A*-value of fluorine, ca. 0.25 kcal/mol in the gas phase.[13] The nearly 11.0 kcal/mol "counterbalancing" preference for the axial conformation arises from $n(S) \rightarrow \sigma^*(C{-}F_{ax})_{app}$ anomeric stabilization in the axial isomer. According to NBO calculations (Table 6) this stereoelectronic interaction is worth 15.38 kcal/mol.

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