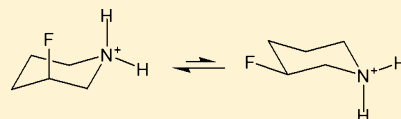


Gauche Preference of β -Fluoroalkyl Ammonium SaltsJosué M. Silla,[†] Wesley G. D. P. Silva,[†] Rodrigo A. Cormanich,[‡] Roberto Rittner,[‡] Cláudio F. Tormena,[‡] and Matheus P. Freitas^{*†}[†]Department of Chemistry, Federal University of Lavras, Lavras, MG 37200-000, Brazil[‡]Chemistry Institute, State University of Campinas, Campinas 13084-971, Brazil

Supporting Information

ABSTRACT: The strong gauche preference along with the F–C–C–N⁺ fragment in 3-fluoropiperidinium cation and analogues, in the gas phase, is dictated by electrostatic interactions, which can be both hydrogen bond F⋯H(N⁺) and F/N⁺ attraction. In aqueous solution, where most biochemical processes take place, electrostatic effects are strongly attenuated and hyperconjugation is calculated to be at least competitive with Lewis-type interactions.



1. INTRODUCTION

A strong gauche preference for some β -fluoroalkyl ammonium salts has been observed, whereas such predominance in the neutral form does not exist. This has influenced the conformation, reactivity, and biological properties of organic molecules.^{1–3} For example, the 3-fluoropiperidinium cation (**1**) was calculated to be more highly stable in its axial conformation than in the less sterically hindered equatorial form (Figure 1); on the other hand, the equilibrium between the axial and equatorial conformations for the neutral compound (3-fluoropiperidine, **2**) is more competitive (Table 1). Vicinal

Table 1. Conformational Energies (kcal mol^{−1}) of the 3-Fluoropiperidinium Cation (**1**) and 3-Fluoropiperidine (**2**), Calculated at the B3LYP/aug-cc-pVDZ Level in the Gas Phase and Implicit Water (PCM Model)^a

conformer	1		2	
	gas	water	gas	water
ax-1	0.0	0.0	0.0	0.0 (2.7, 2.7)
ax-2			0.5	0.3 (0.0, 0.0)
eq-1	4.7	1.8 (4.4)	0.2	0.0 (0.6, 1.5)
eq-2			0.0	0.1 (0.3, 0.8)

^aThe relative energy using two explicit waters is given in parentheses and, for **2**, the second value corresponds to MP2/aug-cc-pVDZ results. The level of theory was chosen upon basis set saturation tests (Supporting Information).

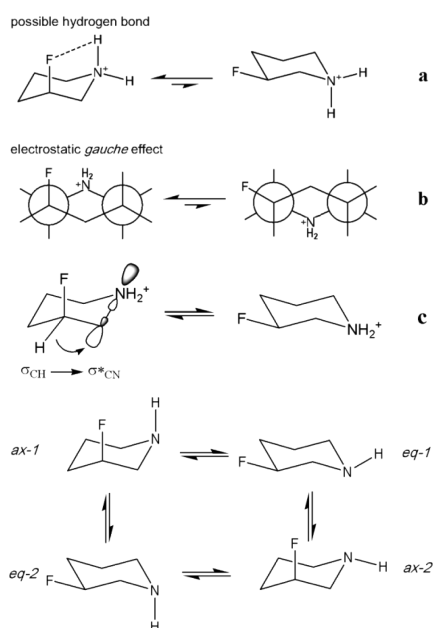


Figure 1. Preference for the axial conformation of 3-fluoropiperidinium cation (**1**), according to the hydrogen bond model (a), to the electrostatic gauche effect (b), and to the hyperconjugation approach (c). The conformers of 3-fluoropiperidine (**2**).

³J_{F,H} coupling constants give insight about the conformational preferences of **1** and **2**, because two large (³J_{Fax,Hax}) and two small (³J_{Fax,Heq}) values are expected for the axial conformer, whereas four small couplings (³J_{Feq,Hax} and ³J_{Feq,Heq}) should appear for the equatorial conformer (see calculated *J* in the Supporting Information). Experimentally, the axial predominance for both **1** and **2** in polar solution is consistent with the ³J_{F,H-2} coupling constants: 38.1 and 12.3 Hz (in D₂O), as well as 36.2 and 12.3 Hz (in CD₃OH) for **1**; 36.0 and 13.9 Hz (in CD₃OH), and 23.0 and 13.0 Hz (in DMSO-*d*₆, lesser amount of axial) for **2**.

The axial preference in **1** and derivatives has been attributed either to CF⋯HN charge-dipole orienting effect,⁴ which matches the intramolecular hydrogen bond (H-bond) of Figure 1a, or to the electrostatic gauche effect (Figure 1b).⁵ The large gauche preference in protonated (2-fluoroethyl)amine and 2-fluoroethanol has been ascribed as due to a mix of intramolecular H-bond and electrostatic attraction between F

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and N/O.⁶ Moreover, hyperconjugation effects are found to be the responsible factors for the gauche preference in organofluorine compounds;⁷ protonation of nitrogen in 3-fluoropiperidine to give the ammonium cation is expected to decrease the energy level of the low lying σ_{CN}^* orbital, facilitating electron transfer from the antiperiplanar σ_{CH} orbital in the axial conformation, whereas donation from σ_{CF} in the equatorial form to the σ_{CN}^* orbital would not be significantly affected, because such a bonding orbital is a poor electron donor, independently of the electron acceptor orbital (Figure 1c). Multinuclear magnetic resonance, natural bond orbital (NBO),⁸ quantum theory of atoms in molecules (QTAIM)⁹ and noncovalent-interaction (NCI)¹⁰ analyses were used to confront the possible explanations for the axial preference in the 3-fluoropiperidinium cation and to find out which is responsible for such a preference; this can be extended to a variety of biochemical systems containing the β -fluoroalkyl/arylammonium moiety.

2. EXPERIMENTAL AND COMPUTATIONAL DETAILS

The 3-fluoropiperidinium hydrochloride (**1**) was purchased from Sigma-Aldrich and used without further treatment. 3-Fluoropiperidine (**2**) was obtained by deprotonation of 3-fluoropiperidinium hydrochloride with zinc powder in CH_2Cl_2 .¹¹ The ^1H , ^{19}F , and ^{15}N NMR experiments were performed on a Bruker AVANCE III spectrometer operating at 600.17, 564.72, and 60.81 MHz, respectively, using ca. 20 mg mL^{-1} in CD_3CN , $\text{DMSO}-d_6$, D_2O or CD_3OH solutions.

All geometries were optimized at the B3LYP/aug-cc-pVDZ level¹² in the gas phase and using implicit solvent (CHCl_3 and CH_3CN) according to the polarizable continuum model (PCM) by Tomasi and co-workers.¹³ Frequency calculations were carried out to guarantee that imaginary frequencies were absent. Natural bond orbital (NBO)⁸ analyses were also performed (for the gas phase) at the same level of theory, including deletion of all antibonding and Rydberg-type orbitals. Spin–spin coupling constants were calculated at the BHandH/EPR-III level.¹⁴ Other levels discussed throughout the text were applied over some systems. All these calculations were carried out using the Gaussian 09 program.¹⁵ Quantum theory of atoms in molecules (QTAIM) calculations were performed to search for possible hydrogen bonds and their stabilities using the AIMAll program.⁹ The noncovalent interaction (NCI) method was carried out by using the NCIPLOT program.¹⁰

3. RESULTS AND DISCUSSION

NBO analysis at the B3LYP/aug-cc-pVDZ level does not indicate any significant $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$ interaction (“quantum” H-bond) either in the neutral or in the protonated molecule; a possible H-bond would be therefore expected to be of electrostatic rather than “quantum” origin. Surprisingly, protonation enhanced only modestly the antiperiplanar $\sigma_{\text{CH}_3} \rightarrow \sigma_{\text{CN}}^*$ interaction from 4.4 kcal mol^{-1} in **2** to 4.7 kcal mol^{-1} in **1** in the axial conformation, whereas the corresponding $\sigma_{\text{CF}} \rightarrow \sigma_{\text{CN}}^*$ interaction in the equatorial form varied from 1.6 kcal mol^{-1} in **2** to 2.3 kcal mol^{-1} in **1**.

According to NBO calculations in Table 2 (upon deletion of interactions involving antibonding and Rydberg orbitals), the axial **1** is more stabilized than the equatorial conformer by 0.8 kcal mol^{-1} in the gas phase due to hyperconjugation and by 3.9 kcal mol^{-1} due to Lewis-type interactions, summing up 4.7 kcal mol^{-1} (the full energy of a molecule is the sum of non-Lewis

Table 2. Steric, Electrostatic, and Hyperconjugative Contributions (kcal mol^{-1}) for the Axial \rightarrow Equatorial Isomerization in **1** and **2**, Using NBO Analysis

compound	$\Delta E(\text{a-e})$	$\Delta E_{\text{steric}}(\text{a-e})$	$\Delta E_{\text{elect}}(\text{a-e})$	$\Delta E_{\text{hyperc}}(\text{a-e})$
1 (gas)	−4.7	11.8	−15.7	−0.8
1 (water _{implicit})	−1.8	8.5	−5.9	−4.4
1 (water _{explicit})	−4.4	2.9	−4.2	−3.1
2 (gas)	0.0	2.7	−0.7	−2.0
2 (water _{implicit}) ^a	0.0	6.5	−6.2	−0.3
2 (water _{explicit}) ^b	−0.3	1.4	5.5	−6.9

^aConsidering ax-1 and eq-1 conformations. ^bConsidering ax-2 and eq-2 conformations.

and Lewis-type interactions). The contributors for the Lewis-type energy can be estimated by using the STERIC keyword in NBO analysis, in the spirit of NEDA (natural energy decomposition analysis), because it is a sum of electrostatic (Coulombic) and steric effects; although the hyperconjugative contribution for the conformational energy is small and the steric effect in the axial form is ca. 11.8 kcal mol^{-1} larger than in the equatorial conformer, the electrostatic effect plays the predominant role for the preference of the axial orientation (by 15.7 kcal mol^{-1}), reinforcing the hypothesis of electrostatic gauche effect due to F/ N^+ attraction and/or H-bond (Table 2). For the neutral molecule **2**, contribution from all three terms (steric, electrostatic, and hyperconjugation) to the overall energy is lower, and the steric effect in the axial conformer is canceled out by electrostatic and hyperconjugative interactions.

Using an implicit solvent model (polarizable continuum model) to mimic aqueous solution, the axial **1** is calculated to be more stabilized by 4.4 kcal mol^{-1} due to hyperconjugation, but it is destabilized by 2.2 kcal mol^{-1} due to Lewis-type interactions. However, protonation does not impact the magnitude of the antiperiplanar $\sigma_{\text{CH}} \rightarrow \sigma_{\text{CN}}^*$ interaction. Possible dipolar interactions, like the attractive electrostatic interaction F/ N^+ and H-bond in the axial **1**, are expected to be attenuated in polar solution; this explains the significant decrease in ΔE from the gas to implicit water solution (from 4.7 to 1.8 kcal mol^{-1}). Because explicit water was found to affect the anomeric effect in 2-substituted tetrahydropyrans differently from implicit water,¹⁶ two water molecules were further introduced in the calculations for **1** (conformational search using Monte Carlo/AM1 distribution, followed by optimization of the two main systems at the B3LYP/aug-cc-pVDZ level). Despite the discrepancy between the relative energies obtained from these methods (implicit and explicit water), hyperconjugation was found to be preponderant over Lewis-type energies in both cases (Table 2).

For **2**, the calculated energies in implicit water (Table 1) are consistent with the experimental findings obtained from $^3J_{\text{F,H-2}}$ in the polar DMSO solution; i.e., the populations of axial and equatorial conformers are roughly similar, but the calculated energies are not in agreement with the NMR data obtained in CD_3OH , where the axial conformer was found to be highly prevalent. This behavior is better reproduced using an explicit solvation model (Figure 2), in which the water molecules (like methanol) would interact via an intermolecular hydrogen bond, not computed using the implicit model. The explicit model gives an F-axial conformer as the most stable form using both DFT and MP2 calculations (Table 1), which is consistent with $^3J_{\text{F,H-2}}$ of 36.0 and 13.9 Hz in CD_3OH . It is worth mentioning that the axial conformer of **2** is quite less stabilized by

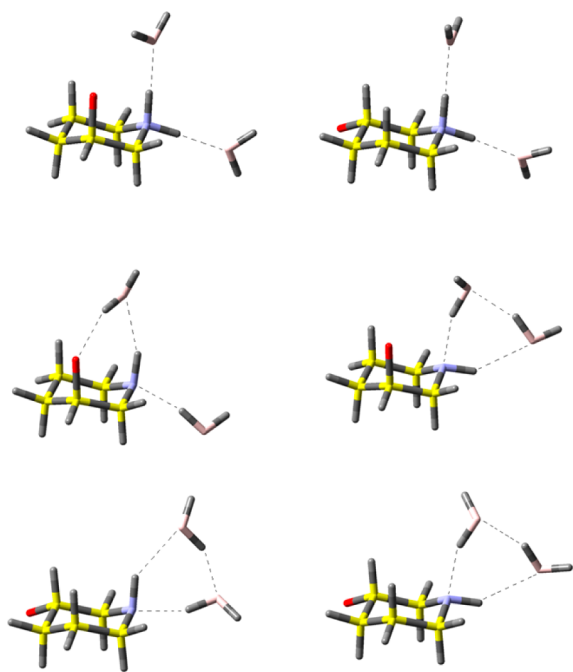


Figure 2. Axial and equatorial 1 and 2 using explicit water system.

electrostatic effects in water solution than in the gas phase, as expected from solvation considerations and, thus, the major contributor for the repulsive Lewis-type energy is the steric term. For the neutral molecule, according to the implicit model, a change in the medium does not affect the conformational energies; indeed, in implicit water, the higher steric effect in the axial conformation is practically canceled out by the electrostatic term, whereas hyperconjugation appears to be negligible. However, in explicit water, which better represents a protic medium, hyperconjugation slightly predominates over Lewis-type interactions, which are principally ruled by the electrostatic term (stronger electrostatic repulsion in the ax-2 form).

QTAIM has been found to be an useful tool to characterize hydrogen bonds and other intramolecular interactions: a bond path between F...H(N) was not found in 1 or 2 using a variety of theoretical levels (DFT B97-D, ϕ B97XD, B2PLYP-D, mP2PLYP-D, M06, and B3LYP-D3 functionals, as well as the ab initio CCSD/cc-pVTZ//MP2/aug-cc-pVTZ level), suggesting that the H-bond is weak or even absent in both species, in agreement with the NBO findings. Considering some controversial cases in the literature in which a BCP cannot be found for compounds where a H-bond is expected to be formed, we have applied the recently developed NCI method on the CCSD/cc-pVTZ//MP2/aug-cc-pVTZ wave function;^{10,17–19} NCI surfaces clearly indicate the formation of a F...H(N) H-bond in 1 (Figure 3). So, on the basis of the F...

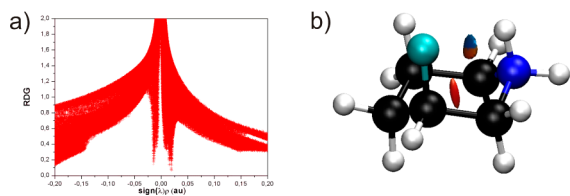


Figure 3. Reduced density gradient (RDG) vs $(\lambda)\rho$ (a) and NCI domains (b) for the axial isomer of 1. The NCI method indicates the formation of F...H(N) H-bond.

H(N) distance dependence with the theoretical method (the F...H(N) distance in these cases ranges from 2.28 to 2.41 Å, with the CCSD/cc-pVTZ/MP2/aug-cc-pVTZ geometry showing the shortest and the B3LYP/aug-cc-pVDZ the longest distances) and the NCI result, one may conclude that the QTAIM is not recovering the F...H(N) H-bond formation in this case.

NMR coupling constants have shown to be a probe to monitor H-bonds in fluoroalcohols;^{20,21} indeed, small coupling constants through hydrogen bonds have already been measured by means of 2D NMR contour maps.²² The calculated $J_{F,N}$ and $J_{F,H(N)}$ for 1 and 2 were +0.22 and −2.1 Hz (for 1), and −1.1 and −0.5 Hz (for 2), respectively, at the BHandH/EPR-III level. Similar results were obtained at the SOPPA/CCSD level ($J_{F,H(N)} = -0.4$ and $J_{F,N} = -1.8$ Hz for 1). To analyze how these couplings would behave if subjected to strong H-bond or F/N⁺ attraction, the $J_{F,N}$ and $J_{F,H(N)}$ dependence on shortening the N–C–C and C–C–F angles in (2-fluoroethyl)amine (3) and (2-fluoroethyl)ammonium cation (4) from the equilibrium structures was theoretically evaluated at the BHandH/EPR-III level. Both coupling constants were calculated to be negligible for the equilibrium geometry of 3; the calculated coupling constants for the cation 4 are larger (by a factor of roughly 2–5-fold). However, they increase when approaching the fluorine atom to H(N) and N, especially for 4 (Figure 4). Accordingly,

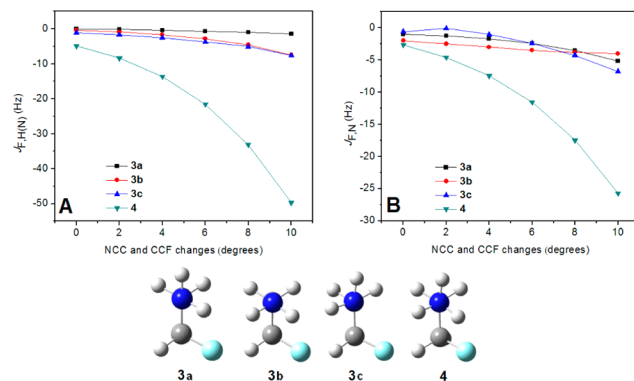


Figure 4. N–C–C and C–C–F angular dependence of $J_{F,H(N)}$ (A) and $J_{F,N}$ (B) coupling constants in (2-fluoroethyl)amine (3) and (2-fluoroethyl)ammonium cation (4), at the BHandH/EPR-III level.

small structural changes should impact the referred coupling constants, because the direct scalar component between the coupled (H-bonded) nuclei enhances, whereas the purely electrostatic interaction should not affect the contact term appreciably.²³

Experimentally, the ¹H NMR spectrum for 2 in CD₃CN solution did not show any measurable coupling between fluorine and H(N) (Supporting Information), indicating the expected absence of H-bond F...H(N) in the neutral compound. Interestingly, similar behavior was found for 1 in CD₃OH solution (the ammonium hydrogens readily exchanges in D₂O solution and the corresponding signal in DMSO-*d*₆ is somewhat broad, see the Supporting Information). In addition, no coupling is observed in the ¹H-decoupled ¹⁵N experiment in CD₃OH. Consequently, in polar solution (1 is not soluble in nonpolar and low polar solvent), both intramolecular hydrogen bond and the F/N⁺ interaction are weak or even absent.

4. CONCLUSIONS

The origin of the gauche effect and, therefore, the preference for the axial orientation of the fluorine atom in 3-fluoropiperidinium cation in the gas phase and possibly in low polar solution, which can also be extended to other β -fluoroalkyl ammonium salts, is electrostatic. The lack of any measurable $^1J_{\text{F,H(N)}}$ coupling constant in polar solution, together with calculations using implicit and explicit solvent (water) models, indicates that hyperconjugation (not any specifically) must be at least as dominant as Lewis-type interactions on the conformational equilibrium of **1** in polar solution. Because of the discrepancy between the conformational energies found in implicit and explicit solvent, and also because of the lack of any individual hyperconjugative effect ruling the gauche effect in **1**, we cannot assume that the preferred F-axial conformation in **1** is primarily governed by hyperconjugation rather than electrostatic effects in polar solution (where most of biochemical processes take place), but they are clearly quite competitive. Despite the absence of bond path between F and H(N⁺) according to QTAIM, the strong preference for the axial fluorine in 3-fluoropiperidinium cation indicates that electrostatic attraction between F and N⁺ and electrostatic H-bond (F...HN⁺) are roughly equivalent as the main causes of the gauche effect in **1** in the gas phase. Hyperconjugation was not found to play a relevant role for the gauche effect in the gas phase in this case, neither for the “quantum” H-bond, described as $n_{\text{F}} \rightarrow \sigma_{\text{NH}}^*$ interaction.

■ ASSOCIATED CONTENT

■ Supporting Information

Theoretical data (including basis set saturation tests, relative energies, F...H(N) distances, coupling constants) and NMR spectra. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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