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The Unexpected Diaxial Orientation of *cis*-3,5-Difluoropiperidine in Water: A Potent CF- - -NH Charge-Dipole Effect

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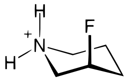
Conformational analysis of substituted and saturated six-membered rings teaches that unfavorable 1,3-diaxial interactions lead to equilibria favoring equatorial conformers.[1] A striking apparent exception[2] to this long-standing generalization has recently been shown to be erroneous.[3] By contrast, 3- and 4-substituted sulfoxides, sulfones,[4] and piperidines[5,6] represent systems in which lone-pair bearing functionalities, −X**:**, can promote mixtures favoring the axial form by as much as 95−98%. Intramolecular electrostatic effects[5d,6] and lone-pair → π^* or σ^* interactions[7] have been suggested as the source of the axial preferences. In previous work on piperidine salts **1**−**2** in aqueous solution, we noted that fluorine imparts a dramatic and unprecedented fluoro-directed axial stabilization even in the presence of CO_2^- at the 5-position (**2a**, >95%).[8] The result was interpreted as the outcome of a delicate competition between a $(N-H)^+$- - - - $(F^{\delta-})-(C^{\delta+})$ charge-dipole association and substituent solvation.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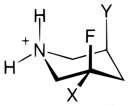
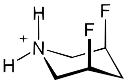


	X	**Y**
2a	H	CO_2^-
b	CO_2^-	H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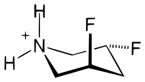
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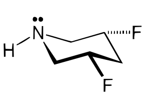
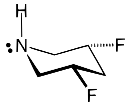
In the present contribution we describe NMR and computational results for the previously unknown and isomeric *cis*- and *trans*-3,5-difluoropiperidine hydrochlorides, **3** and **4**,[9] where equally dramatic effects are observed. Thus, in aqueous (D_2O) solution *both* the *cis*-hydrochloride salt, **3**, *and* the corresponding free base, **5**, exist almost exclusively in the diaxial fluorine chair conformation. In addition, we show that the latter is subject to an unexpected solvent-dependent conformational equilibrium.

The conformational profiles of piperidines **3**−**5** in water (D_2O) were determined by 1- and 2-D NMR at 400 MHz. The proton spectrum for *cis*-**3** exhibits H-4_{ax} as a doublet-of-triplet-of-triplets (δ 2.162) and displays diagnostic couplings between F-3/F-5 and H-2_{ax}/H-6_{ax}/H-4_{ax} and between H-3/H-5 and H-4_{eq}. Although all of the *J*-values have been determined (See Supporting Information), there are two key F/H interactions. Coupling of F-3/F-5 (δ $^{19}F = -183.4$) to the equivalent protons H-2_{ax} and H-6_{ax} (δ 3.410), which appear as a distorted (virtual coupling) doublet-of-doublets, occurs with $^3J_{H-2ax,F-3} = {}^3J_{H-6ax,F-5} = 40.1$ Hz; at H-4, $^3J_{H-4ax,F-3/5} = 46.3$ Hz. The latter resides firmly at the extreme for three-bond H,F coupling constants (47 Hz).[10,11] The result signals the presence of a single chair conformer in solution (≥98%) in which the $F-C-C-H_4$ moiety is trans and diaxial.[6,12,13]


5a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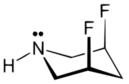
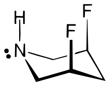

5c


5d

The free base **5**, generated from **3** ($NaOD/D_2O$, pH > 12), afforded a proton NMR spectrum with all coupling constants similar in magnitude to those observed for **3** (e.g. $^3J_{H-4ax,F} = 44.5$, $^3J_{H-2ax,F-3} = 39.3$, $^3J_{H-2eq,F-3} = 12.2$ Hz, δ $^{19}F = -182.1$; see Supporting Information). Acidification regenerates the spectrum of **3**. Unwilling to accept a diaxial free base, we initially believed that deprotonation had failed or rearrangement had taken place. Guided especially by the results of the computational solvation calculations described below, we ultimately turned to two additional NMR criteria to support the conclusion that, even as the free base, **5** retains the diaxial orientation of the fluorines (≥93%) in D_2O.

First, the ^{13}C signals of C-2 and C-6 carbons of **3** and the conformationally averaged homomers **4** are shifted 1.3−2.0 ppm downfield in strong base, consistent with the behavior of other piperidines.[14] Second, if we assume that **5** is conformationally homogeneous and that $^3J_{H-2ax,F-3} = 39.3$ and $^3J_{H-2eq,F-3} = 12.4$ Hz correspond to the totally axial isomer, we predict that the simple average (25.9 Hz) will match the measured value for neutralized and conformationally averaged **4**; namely, the corresponding free base **6** (22.2 Hz). The same calculation for salts **3**

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(9) (a) The fluoropiperidines **3** and **4** were prepared from a mixture (~1: 1) of the corresponding *N*-benzyl-protected diols (mixture of *cis* and *trans*, refs 9b−d) using diethylaminosulfurtrifluoride (DAST, refs 9e, f) followed by chromatographic separation and deprotection. The synthetic scheme and experimental details are provided in the Supporting Information. All new compounds afforded satisfactory microanalytical results and/or high resolution mass spectral analysis and were fully characterized by ^1H, ^{13}C, and ^{19}F NMR spectroscopy. (b) Kliegel, W.; Ahlenstiel, E. *Chem. Ber.* **1976**, *109*, 3547−3556. (c) Stetter, H.; Zoller, K. *Chem. Ber.* **1965**, *98*, 1446−1449. (d) Paul, R.; Tchelitcheff, S. *Bull. Soc. Chim. Fr.* **1948**, 896−900. (e) Wilkinson, J. A. *Chem Rev.* **1992**, *92*, 505−519. (f) Hudlicky, M. *Org. React.* **1988**, *35*, 513−637.

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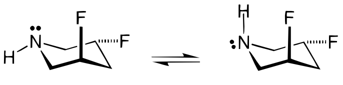
Table 1. *cis*-3,5-Difluoropiperidine Conformer Populations as Determined by NMR and ab Initio Calculation; Estimates of Conformer Energy Differences, Dipole Moments, and Solvation Energies

		populations (%, 298 K)[a] and E_{rel},[b] kcal/mol									
		NMR[c]				gas phase		H_2O		μ,D	E_{solv}[h]
		D_2O	$CDCl_3$	CD_2Cl_2	C_6H_{12}	3-21G[d]	6-311G* [e,f]	3-12G[g]	6-311G* [g]	6-311G*	6-311G*
3	**ee**						0		0		−47.3
		≤2					(8.9)		(17.6)		
3	**aa**	≥98					100		100		−56.1
							(0.0)		(0.0)		
5a	**eee**					92	78	17	4	2.4	−3.7
		7	36	39	72	(−2.6)	(−0.9)	(0.9)	(1.9)		
5b	**aee**					7	5	1	0	2.2	−3.8
						(−1.1)	(1.0)	(2.4)	(3.4)		
5c	**eaa**					0	0	0	4	4.7	−8.1
		93	64	61	28	(4.7)	(3.3)	(3.8)	(1.8)		
5d	**aaa**					1	17	81	92	3.2	−6.6
						(0.0)	(0.0)	(0.0)	(0.0)		

[a] Boltzmann populations, 25 °C. [b] Parenthetical values. [c] Determined with ^{1}H NMR at 400 MHz; population ratios by the *J*-value method (ref 12). [d] HF/3-21G//HF/3-21G, **eee** −445.451 49 hartree (1 hartree = 627.5 kcal/mol), ref 17. [e] HF/6-311G*//HF/6-31G*, **eee** −448.003 45, ref 17. [f] *E*(rel): MP2/6-311++G(d,p)//HF/6-311G* −0.3, 0.9, 3.6, 0.0 kcal/mol; Becke3LYP/6-311++G(d,p)//HF/6-311G*, −0.8, 0.3, 3.4, 0.0 kcal/mol. [g] Image approximation, 6-311G*(s)//6-311G*(g) **aaa** −448.012 45, ref 12. [h] ΔE(gas-"H_2O").

and **4** yields averaged coupling constants of 26.1 and 21.5 Hz, respectively. Both criteria are met, confirming that **5** has indeed been formed, and that it overwhelmingly sustains 3,5 diaxial fluorine substitutents.



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The basis for the axial fluorine preference of **3** and **5** in water was examined by computing the equilibria in terms of an aqueous continuum treatment. For salt **3**, AMBER/GB-SA(H_2O) molecular mechanics[15] with previously determined parameters[8] places the diequatorial conformer 4.9 kcal/mol higher in energy than the diaxial one. The ab initio dielectric continuum model based on the image approximation[16] at the HF/6-311G*//HF/6-311G* level[17] favors the diaxial form by 17.6 kcal/mol; both methods in complete accord with exclusive (≥98%) observation of **3**. Clearly, favorable charge-dipole interactions between NH and CF override any F- - -F repulsion.

To understand the extraordinary preference for diaxial fluorine in basic aqueous solutions of neutral **5** we first examined the four possible chair conformers **5a**−**d** in the gas phase. In the latter, the all-equatorial form **5a** is predicted to be the most stable (Table 1). Unlike calculations for 1,2-difluoroethane,[18,19] inclusion of electron correlation and/or diffuse functions (e.g., MP2/6-311++G-(d,p)//6-311G*; footnotes, Table 1) does not invert the eq/axial ratio, thereby ruling out an F to N gauche effect as a stabilizing factor. For **5**, it would appear that the F- - -F repulsion in the diaxial conformers coupled to a pair of stabilizing N−C−C−F anti relationships in the equatorial forms[20,21] causes the diequatorial preference.

By contrast, ab initio water models suggest a preponderance of **aaa** conformer **5d** (Table 1). The image approximation at the triple-ζ HF/6-311G*//HF/6-311G* level delivers close correspondence with experiment, i.e., **5c** + **5d** = 96%. The result can be interpreted by noting that **5c** (**eaa**) and **5d** (**aaa**) sustain dipole moments of 4.7 and 3.2 D, respectively, higher than for the diequatorial conformers **5a** (**eee**) and **5b** (**aee**) (Table 1). Consequently the more polar axial conformers **5c** and **5d** experience a significant solvation advantage estimated at $\Delta\Delta E_{solv}$ = 3−5 kcal/mol.

If this analysis, which provided the preliminary stereochemical assignment for **5**, is correct, then solvents of lower polarity should favor the equatorial forms. NMR analysis of **5** extracted into $CDCl_3$, CD_2Cl_2, and C_6D_{12} gave $^3J_{H-4ax,F-3} = {}^3J_{H-4ax,F-5}$ = 34.5, 33.5, and 22.0 Hz, respectively. These coupling constants translate into axial populations[12] of 64, 61, and 28%, respectively, as expected for values intermediate between the aqueous and gas phases (Table 1). Due to its insolubility, a similar study was not possible for salt **3**. However, the 6-311G* E_{rel}'s and populations for cationic **ee** and **aa** conformers suggest that solvent polarity will not mediate the equilibrium.

Finally, the forces responsible for stabilizing **3** and **5** deserve comment. Several recent reports have examined the nature of organic CF- - -HN hydrogen bonds.[22−24] Each has concluded that such noncovalent interactions are both weak (<2.5 kcal/mol) and rare. By geometric standards, the CF/HN interactions in **3** and **5** cannot be regarded as hydrogen bonds (HF/6-311G*: *r*(H- - -F) = 2.4−2.7 Å; θ(N−H- - -F) = 95−100°). However, the medium range and antiparallel N−H and C−F bond pairing, characterized by a strong charge-dipole reinforcement able to regulate conformer population, is a potent alternative to hydrogen bonding. The strength, geometric variation, medium influence, and applicability of the interaction is under active investigation.

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Supporting Information Available: ^{1}H and ^{13}C NMR data and synthesis details for **3**, **4**, and **5** are provided (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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