Protonated 3-Fluoropiperidines: An Unusual Fluoro Directing Effect and a Test for Quantitative Theories of Solvation[1]

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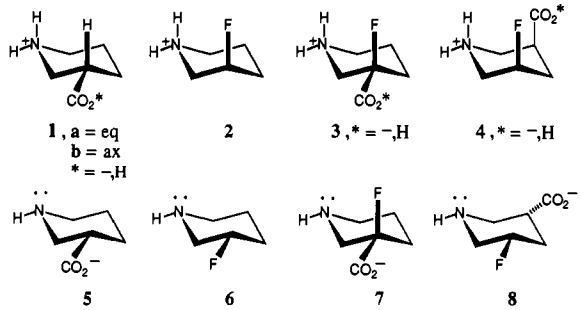
The ability to predict the energetics of molecules immersed in solvent is the principle that unites the theory and practice of solution chemistry. For neutral, polar, and some singly charged species, the resource-demanding free energy perturbation method with explicit treatment of solvent has yielded impressive results.[2] Solvent implicit parametric methods based on generalized Born electrostatics,[3,4] reaction fields[5] and molecular surfaces[6] are likewise capable of quantitative or semiquantitative assessment of solvated species. Exceptionally demanding are cases of highly polar or multiply charged compounds with conformational or fluxional freedom in the condensed phase. Many drugs at physiological pH,[7] ionic aggregates, metal complexes, and zwitterions sample the range of possibilities.

To provide a test for current and emerging solvent-based theoretical methodology, we have prepared a series of singly and doubly charged (zwitterionic) piperidines and analyzed their conformational profiles in water by NMR. An unprecedented fluoro-directed conformational effect has been observed. In addition, series **1–8** has been subjected to evaluation by several aqueous solvation treatments. The conformational profiles of piperidines **1–4** in water (D_2O) were determined by 1- and 2-D NMR. A summary of conformer populations as derived by NMR and modeling is given in Table I. The proton NMR spectrum of 3-carboxypiperidine (nipecotic acid), **1**, in D_2O (pH ca. 6, zwitterion, * = –) exhibits couplings between H-2 and H-3 ($^3J_{H\text{-}2ax/H\text{-}3}$ = 9.4 Hz and $^3J_{H\text{-}2eq/H\text{-}3}$ = 3.9 Hz) that demonstrate a 65–75% population of the equatorial conformer consistent with earlier studies[8] using the *J*-value method as applied to piperidines.[9]



In 1 N DCl/D_2O (**1**, * = H) the conformer population shifts to 60–70% equatorial ($^3J_{H\text{-}2ax/H\text{-}3}$ = 8.8 Hz), whereas in base (1 N NaOD/D_2O) **1** is converted to the free-amine carboxylate ion, **5**, present to the extent of 85–95% as the equatorial isomer ($^3J_{H\text{-}2ax/H\text{-}3}$ = 11.1 Hz). In sharp contrast, the proton NMR spectrum of 3-fluoropiperidine hydrochloride, **2**,[10] in D_2O reveals the presence of a single conformer with C(3)-F occupying an axial orientation. The latter was assigned by analysis of chemical shifts and coupling constants, the key diagnostic couplings occurring between H-3 and H-2_{ax}, H-2_{eq} ($^3J_{H\text{-}2ax/H\text{-}3}$ = 1.6 Hz and $^3J_{H\text{-}2eq/H\text{-}3}$ = 4.5 Hz, respectively) and between F(3) and H-2_{ax}, H-2_{eq}, H-4_{ax}, and H-4_{eq} ($^3J_{H\text{-}2ax,F}$ = 38.7, $^3J_{H\text{-}2eq,F}$ = 9.7, $^3J_{H\text{-}4ax,F}$ = 44.5, and $^3J_{H\text{-}4eq/H\text{-}3}$ = 9.3 Hz, respectively, $\delta_{^{19}F}$ = –250.8).[11] Dissolved in 1 N NaOD/D_2O, **2** is converted reversibly to free-base **6** ($^2J_{H\text{-}3,F}$ = 48 Hz).[12] The compound appears to exist entirely as the ring-inverted equatorial conformer. The ^{13}C-NMR spectrum of **6** displays long-range ^{19}F coupling to C-5 ($^3J_{C\text{-}5,F}$ = 4.5 Hz) consistent with equatorial orientation of fluorine. This three-bond long-range coupling is completely absent in the C-13 spectrum of the corresponding HCl salt **2** where fluorine is axial.[13]

The NMR spectra for 3-carboxy-3-fluoropiperidine, **3**,[10] substantiate the presence of a single common F-axial conformation in D_2O (zwitterion, * = –), 1 N DCl/D_2O (monocation, * = H), and 1 N NaOD/D_2O (free-base **7**) by virtue of the magnitude of the unchanged 1 H and ^{19}F coupling constants (e.g., zwitterion: $^3J_{H\text{-}2ax,F}$ = 34.3 Hz, $^3J_{H\text{-}2eq,F}$ = 10.2 Hz, $^3J_{H\text{-}4ax,F}$ = 44.4 Hz, and $^3J_{H\text{-}4eq,F}$ = 10.6 Hz; $\delta_{^{19}F}$ = –164.3). Finally, the proton NMR spectra of 3-carboxy-5-fluoropiperidine, **4**,[10] in D_2O (zwitterion, * = –) or in 1 N DCl/D_2O (monocation, * = H) are essentially the same. Examination of the ^1H, ^1H couplings ($^3J_{H\text{-}3/H\text{-}2ax}$ = 3.6 Hz, $^3J_{H\text{-}3/H\text{-}2eq}$ = 3.0 Hz) and the ^1H, ^{19}F couplings ($^3J_{H\text{-}6ax/F}$ = 35.5 Hz in D_2O and 37.5 Hz in 1 N DCl/D_2O; $^3J_{H\text{-}4ax/F}$ = 44.4

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Table I. Zwitterion and Piperidinium Salt Conformer Populations and E_{rel} and E_{solv} (298 K, kcal/mol)

			populations, %						
	exptl NMR[a]		gas phase		"H_2O"			solvation E's AMSOL	
	H	F	PRDDO[b]	AMBER[c]	AMBER[c,d]	AMSOL[e]	AMBER/FEP[d,f]	$\Delta G°$(aq)	$\Delta\Delta G°$(aq)
1a									
% ax	30		100	100	16	93	0.4	−37.2	
% eq	70		0	0	84	7	99.6	−51.8	14.6
ΔE	−0.5		36.2	10.7	−1.0	1.5	−3.2		
2									
% ax	100	96	99.6	99.9	99.6	87	82	−57.2	
% eq	0	4	0.4	0.1	0.4	13	18	−59.0	1.8
ΔE		−1.9	−3.3	−4.3	−3.3	−1.1	−0.9		
3									
% ax[F]	97	96	0	0	99	38	99.8	−51.3	
% eq	3	4	100	100	1	62	0.2	−38.8	−12.5
ΔE	−2.1	−1.9	29.5	8.8	−2.8	0.3	−3.8		
4									
% ax	93	96	100	100	99.7	95	100	−41.1	
% eq	7	4	0	0	0.3	5	0	−52.9	11.8
ΔE	−1.5	−1.9	−32.1	−14.6	−3.5	−1.8	−6.2		

[a] Experimental ratios were obtained by the J-value method using extreme values $^3J_{aa}$ = 12.2 Hz, $^3J_{ee}$ = 3.0 Hz for proton–proton coupling (cf. ref 9) and $^3J_{aa}$ = 46.0 Hz, $^3J_{ee}$ = 12.0 Hz for proton–F coupling (cf.: Berthelot, J.-P.; Jacquesy, J.-C.; Levisalles, J. *Bull. Soc. Chim. Fr.* **1971**, 1896). The F-derived quantities can be regarded as a lower limit. The J-value method generally provides populations within ±5%. Populations are Boltzmann at 299 K. [b] Halgren, T. A.; Kleier, D. A.; Hall, J. H., Jr.; Brown, L. D.; Lipscomb, W. N. *J. Am. Chem. Soc.* **1978**, *100*, 6595. Throckmorton, L.; Marynick, D. S. *J. Comput. Chem.* **1985**, *6*, 652. [c] Reference 3; The N^+–C–C–F torsional potential was derived with the 6-311G* basis set in Gaussian 92 (ref 14) for use in MacroModel 3.5a (ref 3); $V_1/2$ = −1.3405, $V_2/2$ = −0.3166, $V_3/2$ = 0.5709. For AMBER these values apply for phase angles of $\gamma_1 = \gamma_3 = 0.0$, and $\gamma_2 = 180.0$. [d] Each of the structures was supplemented with STO-3G electrostatic potential derived charges obtained by the Merz–Singh–Kollman scheme as implemented in Gaussian 92 (ref 14). [e] Reference 4. [f] AMBER, ref 2c; STO-3G ESP charges; 6-31+G* ESP charges for **1b** and **2** yielded ΔE's of −3.0 and −0.8 kcal/mol.

Hz in D_2O and 1 N DCl/D_2O; $\delta_{^{19}F}$ = −183.4 in D_2O) establishes that *both* the fluorine and the carboxyl group are almost exclusively axial. Under basic conditions (1 N NaOD/D_2O) zwitterion **4** is transformed reversibly to the free amine carboxylate displaying exclusively the diequatorial form **8**. This was confirmed in the ^{13}C NMR spectrum of **8**, as for **6**, by the presence of long-range three-bond coupling between C(5)-F and C-3 ($^3J_{C\text{-}3,F}$ = 6.0 Hz; $\delta_{^{19}F}$ = −177.4).

The unusual conformational variation within the series **1–4** can be understood primarily as a delicately balanced competition between electrostatic and solvation effects. Axial piperidinium species **1b** and **2** are strongly favored in the gas phase (Table I) as a consequence of unmitigated charge–charge ($NH^+ \cdots CO_2^-$) and charge–dipole ($NH^+ \cdots F^{\delta-}–C^{\delta+}$) attraction, respectively. AMSOL aqueous free energies of solvation (Table I) for **2** transferred to aqueous solution suggest a moderate $\Delta\Delta G_s°$(ax–eq) = 1.8 kcal/mol relative stabilization for equatorial F, insufficient to overcome the axial Coulombic effect. For nipecotic acid, **1**, however, AMSOL posits eq-CO_2^- to experience a solvation stabilization of nearly an order of magnitude greater than ax-CO_2^- ($\Delta\Delta G_s°$(ax–eq) = 14.6 kcal/mol) in spite of the method's underestimate of the equatorial population. Application of this solvation estimate to the observed $\Delta\Delta G$(ax–eq) = 0.5 kcal/mol for **1** (* = –) implies that differential solvation and intramolecular charge neutralization effects (ca. 15 kcal/mol) nearly cancel.

Placement of both F and CO_2^- at C-3 (**3**) maximizes the stabilizing factors for the ax-F/eq-CO_2^- conformation as is observed (90–100%). In the case of 3,5-substitution, it is noteworthy that hypothetical addition of fluorine γ and *syn* to the CO_2^- in the predominantly equatorial **1** promotes axial repositioning of both moieties on going to **4**, whereas similar addition of CO_2^- to fluoropiperidine **2** likewise giving **4** causes no conformational reorganization. The clear-cut stereochemical preference argues strongly that the axial $(N–H)^+ \cdots F^{\delta-}–C^{\delta+}$ charge–dipole association rather than the $NH^+ \cdots CO_2^-$ ionic interaction tips the conformational balance.

The unique blend of steric, Coulombic, and solvation effects evident within compounds **1–4** and their neutral and singly charged counterparts recommends series **1–8** as a challenging test suite for the qualitative and quantitative predictive ability of aqueous solvation treatments. For this reason we have employed a number of force fields (MM2, AMBER), charges (Mulliken, ESP), and quantum mechanics methods to predict the NMR populations for **1–8**. A representative sample for **1–4** is given in Table I. While gas-phase ax/eq ratios do not model experiment, the predicted "solution" values offer substantial improvement. The MacroModel AMBER GB/SA treatment draws closest to experiment when supplemented by an accurate N^+–C–C–F torsional potential and ESP charges (Table I), but misrepresents the ax/eq populations of **2** and **4** by overestimating the stability of the diaxial zwitterions by 1.4 and 2.0 kcal/mol, respectively. The MM2 GB/SA variant with a refined N^+–C–C–F torsion performs less satisfactorily. Given the lack of specific hydrogen bonding in these models, the level of agreement with experiment is encouraging. First solvation shell refinements within a continuum treatment might well eliminate the discrepancies. Surprisingly, the CPU-demanding AMBER free energy perturbation treatment with 650 explicit TIP3P water molecules matches experiment for **1–4** with less accuracy than the continuum models. For the conjugate acids (**1**, **3**, **4**, * = H) and bases **5–8**, the AMSOL aqueous models provide semiquantitative agreement with the NMR data (cf. supplementary material).

In summary, the novel diaxial zwitterion **4** (* = –) completes the deceptively simple series **1–4**. The position of the chair–chair conformational equilibria is recommended as a stringent test of the predictive ability of emerging treatments of aqueous solvation.

Supplementary Material Available: Table of neutral and conjugate acid/base salt conformer population for **5–8** and synthetic schemes for **2–4** (4 pages). Ordering information is given on any current masthead page.