The intramolecular β-fluorine···ammonium interaction in 4- and 8-membered rings

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The structures of 3-fluoroazetidinium hydrochloride and 3-fluoro-1,5-diazacyclooctane hydrobromide are explored both by X-ray diffraction analysis and DFT calculations, and the conformations of these molecules are shown to be significantly influenced by the through space C–F···N$^+$ interaction.

Snyder, Lankin *et al.* have reported[1] that 3-fluoropiperidinium **1** had a strong preference for fluorine in the axial **1a** over the equatorial **1b** conformation (see Fig. 1). Their studies[2–4] have extended to exploring the conformational preference of *cis*-3,5-difluoropiperidine **2** and again they conclude a very clear preference for both of the fluorines to lie axial **2a** rather than equatorial **2b**.

They have proposed a C–F···N$^+$ charge dipole orientating effect to account for this, rather than an intrinsic stereoelectronic *gauche* effect. The stereoelectronic *gauche* effect is observed in neutral vicinal difluorosystems, most classically in 1,2-difluoroethane,[5–7] but extends to systems such as amides of β-fluoroethylamine[8] and esters of fluoroethanol.[9] Generally the differences in *anti–gauche* energies in these neutral systems are in the range 1.0–2.0 kcal mol^{-1}, whereas the energy differences between equatorial and axial conformational preferences for C–F in the 3-fluoropyrimidiniums **1–3** are much larger, and thus the stabilising effect is considerably larger ($\sim$4.0–5.0 kcal mol^{-1}). We have investigated the conformation of β-fluoroethylamine hydrochloride **4**.[10] The X-ray derived structure of **4** shows a clear *gauche* conformational preference as in **4a** and density functional theory (DFT) calculations indicated a *gauche* **4a** over *anti* **4b** preference of $\sim$5.8 kcal mol^{-1}. In all of these cases the influence of intramolecular hydrogen bonding is *not* dominating. Both theoretical and X-ray derived structures do not reveal particularly short H···F contacts in these cases. Also the effect is retained in quaternary ammonium systems such as **3**, although in these cases some N$^+$–CH$_3$···F–C hydrogen bonding is implicated as the positive charge density from nitrogen extends to these hydrogens. None-the-less organic fluorine forms only weak hydrogen bonding interactions[11–13] and such stabilisation could only account for up to a few (2.0–3.0) kcal mol^{-1} in each case. In our study[10] on the fluoroethylammonium ion **4**, we found that the directionality of the hydrogen atoms towards fluorine did not significantly influence the stabilisation energy. These observations reinforce the charge–dipole interaction proposed by Snyder and Landkin as the dominant interaction in these systems.

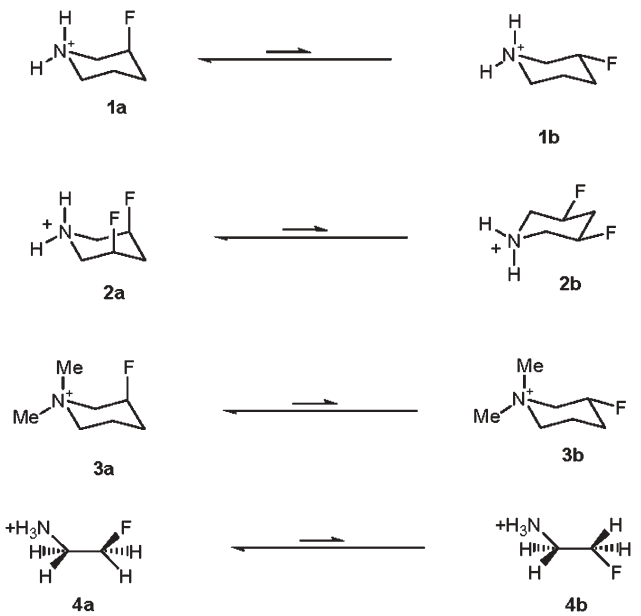

Fig. 1 Vicinal C–F···N$^+$ axial/*gauche* conformations are significantly favoured over the corresponding equatorial/*trans* relationships.

To explore the consequences of the interaction further, this *Communication* evaluates its influence in the 4-membered 3-fluoroazetidinium[14] **5** ring system, the smallest β-fluoroammonium ring system that can be constructed, and also the larger 8-membered 1,5-diaza-ammoniumcyclooctane **6** ring system (see Fig. 2).

In order to quantify and investigate the intramolecular effect, calculations were performed on isolated systems (*i.e.* non periodic), using Kohn–Sham DFT with the B97-2 hybrid exchange–correlation energy functional.[15] We have confirmed that qualitatively similar results are obtained with the widely used B3LYP DFT functional and with the computationally demanding MP2 correlated wavefunction-based method. All calculations were performed using the TZ2P basis set,[16] augmented with an additional s and p diffuse function on the non-H atoms, as in ref. 10. Molecular structures were optimised and analytic harmonic vibrational frequencies were calculated in order to confirm that the located stationary points are minima on the potential energy surface. Quoted energy differences include zero-point vibrational corrections determined using these harmonic frequencies. All calculations were performed using the Gaussian 03 program.[17]

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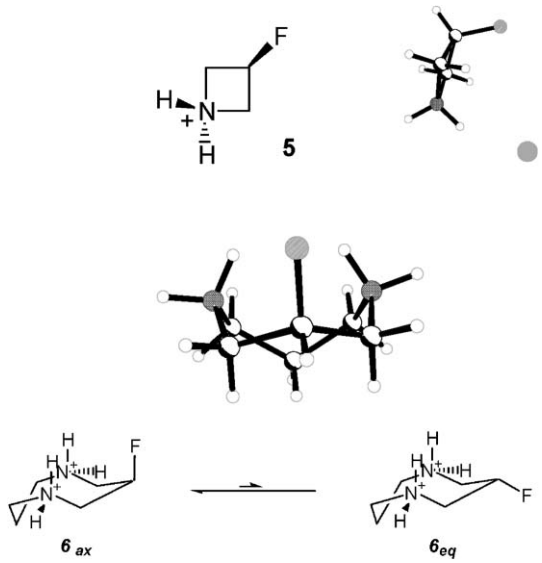


Fig. 2 X-Ray crystal structures of the **5** (Cl^-) and $\mathbf{6}_{ax}$ ($2Br^-$).†

We commenced by considering the 4-membered ring, **5**. In our previous study,[10] we quantified the influence of the C–F···N^+ interaction in the cation **4** by comparing the calculated electronic energies of the *gauche* and *anti* conformations **4a** and **4b**. Such an approach cannot be used for cation **5** due to the ring constraints where it is not possible to establish *gauche* and *anti* conformations. We have therefore taken an alternative strategy, which suppresses the interaction by removing the positive charge and/or the fluorine atom. We have also considered the influence of including the counterion in the calculations.

To investigate the influence of the net positive charge, we first compared the structure of the β-fluoroazetidinium cation **5** with the corresponding neutral amine **7** shown in Fig. 3. For the amine, stationary points were determined, commencing from a range of conformations. Three stationary points were located and the lowest energy structure is presented in Fig. 4. The C–F and N–H groups are spatially well separated, with F···H and F···N distances of 3.96 Å and 3.28 Å, respectively. The N–C–C–F torsion angle is 137.2°.

Next, we took the optimised structure of amine **7** and added a proton to obtain an approximate geometry for the β-fluoroazetidinium cation **5**. A full geometry optimisation was then performed, commencing from this structure. During the course of the optimisation the ring pucker inverted, relative to the F atom, causing the C–F and $^+$NH groups to approach one another more closely. The optimised structure is presented in Fig 4, together with the corresponding X-ray structure. The calculated F···H and F···N distances reduce to 3.10 Å and 2.95 Å, respectively and the N–C–C–F torsion angle reduces to 100.0°. Geometry optimisations commencing from alternative conformations also produced the same optimised structure. To further highlight the influence of

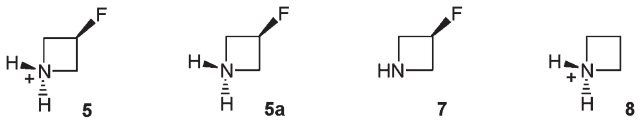


Fig. 3 The comparitive azetidine structures evaluated by DFT.

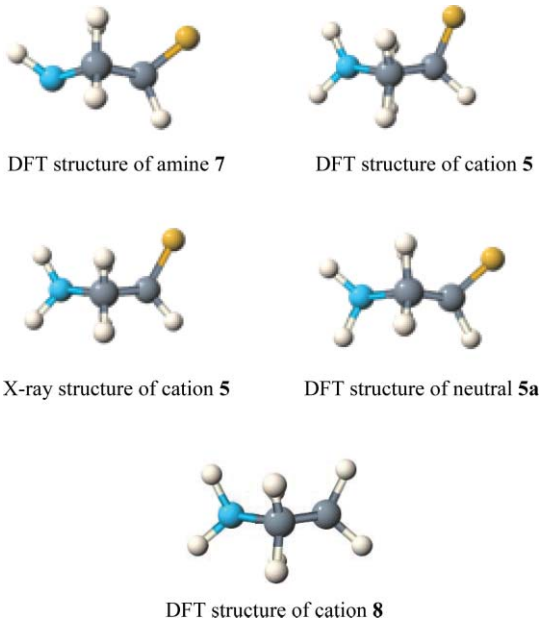


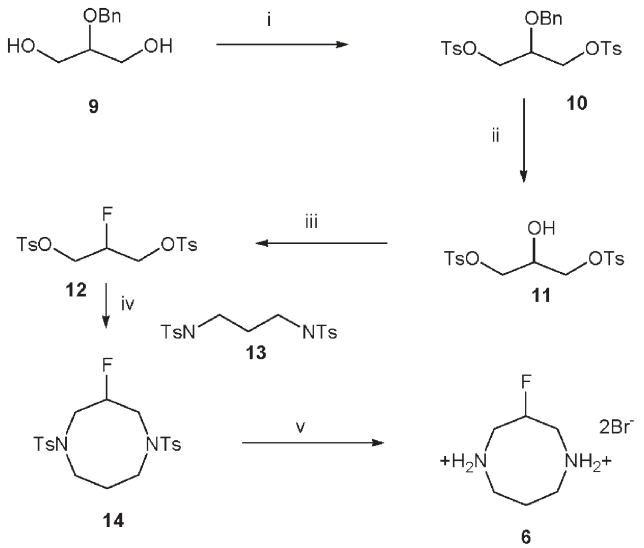
Fig. 4 X-ray and DFT optimized molecular conformations.

the positive charge, we then took the optimised structure of cation **5**, added an *extra electron* to the LUMO (which occupies the now HOMO molecular orbital with significant s character on the N and opposite-phase s character on the two bonded H atoms, together with p character on the bonded C atoms) and then re-optimised the structure of the resulting chemically non-intuitive neutral molecule **5a**. During the course of the optimisation, the ring pucker inverted to give the optimised structure of **5a** shown in Fig. 4, which closely resembles the amine structure **7**. The calculations clearly demonstrate that the positive charge has a pronounced effect on the structure—the observations are fully consistent with a favourable C–F···N^+ interaction.

To assess the influence of the F atom, we have performed calculations on the corresponding non-fluorinated, azetidinium ring **8**, obtained by replacing the F atom in **5** with a hydrogen atom. Fig. 4 shows the optimised structure of **8**. The dihedral angle, which was 100.0° in **5**, is now slightly wider, at 102.3° in **8**, which is consistent with the removal of the favourable C–F···N^+ interaction.

It was informative to include the Cl^- counter ion in calculations on **5**. We performed both an unconstrained optimisation and a second optimisation where the positions of the hydrogen on nitrogen and the Cl^- ion were constrained to correlate with their positions in the X-ray derived structure. The ring puckers in a similar manner to that found in the free amine **7** with a similar N–C–C–F torsion angle (134.1°), reflecting the strong electrostatic influence of the counterion, which clearly attenuates the C–F···N^+ interaction, consistent with an electrostatic interaction (structures not shown).

Optimised structures determined in the above manner are not directly comparable with X-ray structures, since they take no account of intermolecular effects. None-the-less we note that the X-ray structure of salt **5** in Fig. 2 and 4 is intermediate between the calculated structures of the free cation **5** and that with its counterion, with a ring puckering more closely resembling that determined for the free cation **5**.



Scheme 1 Reagents i. TsCl, NEt_3, DCM, 0 °C, 23 h, 97%; ii. $Pd(OH)_2$/C, H_2, EtOH, 23 °C, 99%; iii. Deoxofluor, DCM, 23 °C, 18 h, 67%; iv. **13**, NaH, DMF, 100 °C, 17 h, 36%; v. HBr (33%), phenol in AcOH, 90 °C, 96 h, 100%.

In this study we have also prepared the 3-fluoro-1,5-diazacyclooctane HBr salt **6**. This allowed an exploration of a conformationally flexible larger ring system, and in this particular case, the fluorine has the potential to participate in two intramolecular C–F···N^+ interactions. The synthetic route to **6** started from the glycerol ether **9** followed by tosylation, ether cleavage and then fluorination to generate **12**. Reaction of **12** with the bis-*N*-tosylamide **13** generated the desired ring system with **14**, and the HBr salt **6** was isolated after HBr treatment of **14**. These transformations are summarised in Scheme 1. It is obvious from the resultant X-ray structure shown in Fig. 2 that the C–F bond occupies an axial orientation. There was no evidence of any disorder in the structure and particularly of any molecules with the C–F bond lying in an equatorial conformation.

DFT absolute energy calculations comparing the $\mathbf{6}_{ax}$ and $\mathbf{6}_{eq}$ free cation structures indicate a preference for the axial conformational isomer of 9.2 kcal mol^{-1}. This energy difference is comparable to that found[2] for **2a** (8.9 kcal mol^{-1}), again reflecting the presence of two C–F···N^+ interactions.

In summary the intramolecular C–F···N^+ interaction has been explored in a small and a large ring system and in both cases it is significant in influencing the ring conformation. The magnitude of a single C–F···N^+ interaction is similar to that of a good hydrogen bond and it merits consideration in the design of biologically relevant amine analogues, where the C–F bond can be inserted as a strategic tool for influencing conformation without dramatically affecting the steric profile of a given molecule. In view of the fact that most aliphatic amines are protonated at physiological pH, fluorine incorporation β to amines will be expected to have a dramatic influence on the solution conformation of bio-active amines, through both pK_a modulation and the profound β-fluorine ammonium interaction.

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Notes and references

† *Crystal data for* **5**: C_3H_7ClFN, M = 111.55, monoclinic, space group $P2_1/n$, a = 6.583(3), b = 8.278(3), c = 9.052(3) Å, β = 97.556(12)°, U = 489.0(3) $Å^3$, $F(000)$ = 232, Z = 4, D_c = 1.515 Mg m^{-3}, μ = 0.645 mm^{-1}(Mo-Kα, λ = 0.71073 Å). The data were collected at T = 93(2) K, 2553 reflections ($3.35 < \theta < 25.33°$) were measured on a Rigaku Mercury CCD diffractometer yielding 843 unique data (R_{merg} = 0.0359). Conventional R = 0.0887 for 69 reflections with $I \geqslant 2\sigma(I)$, GOF = 1.000. Final w$R2$ = 0.0648 for all data (64 refined parameters). The largest peak in the residual map is 0.239 e $Å^{-3}$. CCDC 606604.*Crystal data for* **6**: $C_6H_{15}Br_2FN_2$, M = 294.02, monoclinic, space group $P2_1/c$, a = 7.0901(16), b = 12.250(3), c = 12.581(3) Å, β = 106.266(6)°, U = 1049.0(4) $Å^3$, $F(000)$ = 576, Z = 4, D_c = 1.862 Mg m^{-3}, μ = 7.691 mm^{-1}(Mo-Kα, λ = 0.71073 Å). The data were collected at T = 93(2) K, 6572 reflections ($2.37 < \theta < 25.37°$) were measured on a Rigaku Mercury CCD diffractometer yielding 1887 unique data (R_{merg} = 0.0333). Conventional R = 0.0284 for 1707 reflections with $I > 2\sigma(I)$, GOF = 1.026. Final w$R2$ = 0.0589 for all data (177 refined parameters). The largest peak in the residual map is 0.646 e $Å^{-3}$. CCDC 606605. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606334a

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