An Analysis upon the Effect of the C-N$^+$------F-C Charge Dipole Interactions within Protonated Amines: Properties of Fluorine

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Abstract – Fluorine is the most chemically reactive of all the elements and combines directly (often with extreme vigor), at ordinary or elevated temperatures, with all the elements. Organo fluoro compounds and their place in pharmaceuticals and agrochemicals are introduced. The general properties of fluorine and the C-F bond are discussed. Describes the C-N+------F-C charge dipole interactions within protonated amines and explains the influence of a β fluorine on the conformation on various crystalline structures. A number of systems are synthesised which contain this charge dipole interaction. It was demonstrated that these provided a N+-C-C-F gauche torsion angle. However in the event a Grignard reaction on a fluoro cyclohexanone was found to provide an unexpected product where rearrangement followed by fluorine elimination had occurred.

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INTRODUCTION

Fluorine is the most abundant halogen in the earth's continental crust, where it occurs as fluoride in the form of minerals and rocks. In fact fluorine is the 13th most abundant element, at 544 ppm in crustal rocks. Despite its relatively high occurrence in the earth's crust, fluoride ion is the least bio-available of the halides. The availability of the halides in surface water differs considerably, with fluoride concentrations of about 1.2 ppm compared to bromide at 65 ppm and chloride at 19,000 ppm. The incorporation of fluoride into bio-molecules appears to be nearly non-existent. This can be explained by its low bioavailability and fluoride ion's high energy of solvation (-437 kJmol^{-1})[2], hydrogen bonding to water to generate F- $(H_2O)_x$ clusters. This solvation renders it unreactive as a nucleophile. It has however been shown that many plants accumulate fluoroacetate and the bacteria *Streptomyces cattleya* and *Streptomyces calvus*3 are capable of biosynthesizing organo-fluorine metabolites. In addition a few other naturally occurring fluorinated organic compounds have been isolated from plants.

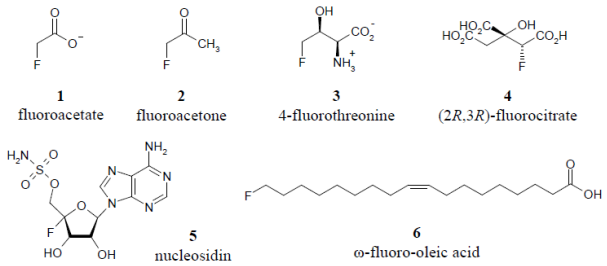


Figure 1 Natural products known to contain fluorine.

When a C-F bond replaces a C-H bond it can significantly influence the conformation of organic molecules. This paper has a particular focus on the influence of a fluorine atom positioned β to a charged nitrogen atom.

Lankin and Snyder have observed the preferred conformations of a number of fluoropiperidinium ring systems. Protonated 3-fluoropiperidine is found to prefer a conformation with the fluorine axial 51a, rather than equatorial 51b. In 51a, the C-F bond is *gauche* to the C-N$^+$ bond, and the preference for this conformation can be explained in terms of a C-F …… C-N$^+$ charge-dipole interaction.

Figure 2 3-Fluoropiperidinium 51 prefers conformer a with the fluorine axial.

The preferred conformation of the di-fluoro piperidinium analogue 64 has also been studied by ^{1}H NMR. The protonated hydrochloride exists predominantly in the di-axial conformation 64a, in a ratio of ~ 98 : 2, in water at RT.

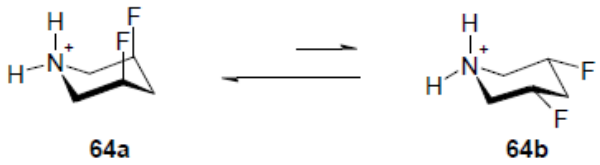


Figure 3 Piperidinium 64 prefers conformation 64a.

Lankin and Snyder then investigated 3 the effect of quarternary methyl substituents on the conformation of 3-fluoropiperidine salts. They carried out a computational analysis as well as X-ray crystallography and NMR studies on the di-methylated systems 65a and 65b. It was found that the fluorine adopts an axial preference, despite the increased steric influence of the methyl substituents. Again it appears that there is a favourable electrostatic interaction between the fluorine and the positively charged dimethylamine group.

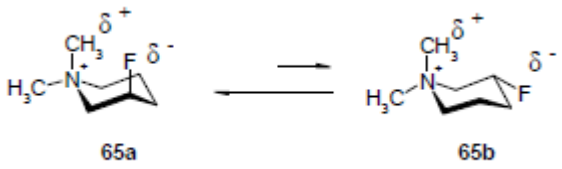


Figure 4. The preferred conformer 65a has the fluorine axial.

N-Dimethyl-4,4-diphenylpiperidinium 66 has been synthesised and the preferred conformation evaluated. Computational calculations suggest a higher population of the axial fluorine conformer 66a. X-ray crystallography also showed a clear axial preference and NMR studies in water agree with this.

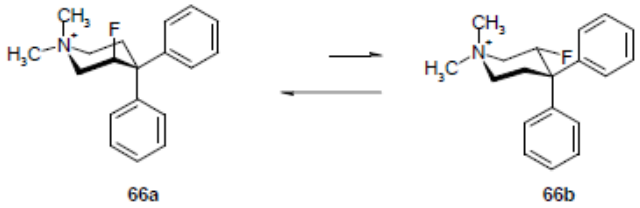


Figure 5 The axial conformer 66a was found to dominate.

Interestingly the neutral mono-methylated amine 67 shows an axial preference in the solid state as observed from X-ray diffraction studies, whereas computational and NMR studies suggest similar populations of the two conformers at equilibrium. Thus solid state packing effects must influence the ultimate solid state structure.

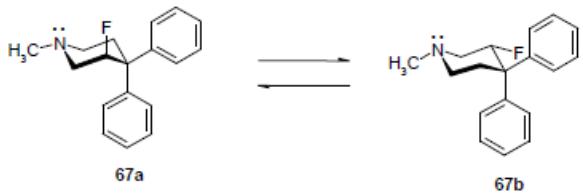


Figure 6 Conformers 67a and 67b are similar in energy.

The subsequent research develops from recent work at St Andrews 4 where the *gauche* preference in the hydrochloride salt of 2-fluoroethylamine 50 was explored. That study also extended to various 2-fluoroethylammonium salts such as 56. Both DFT and X-ray diffraction studies confirmed that there is a strong *gauche* preference (~5.8 kcal mol^{-1}) in the 2-fluoroethylammonium cation 50 and the origin is clearly similar to that rationalised by Lankin and Snyder for their piperidinium ring systems.

THE DISCOVERY OF FLUORINE

Fluorspar (fluorite, CaF_2) was known in the 15th century, where it was used as a flux (flußspat) in the German mining industry. It was not until the 1700's that it was used to produce hydrogen fluoride (fluoric acid) upon treatment of fluorspar with sulfuric acid. It was this observation which led to the development of an identification test for the mineral by the Swedish pharmacist, Karl Wilhelm Scheele which was reported in 1771. Later he showed hydrogen fluoride could also be generated by the addition of nitric or phosphoric acids to fluorospar.

Concentrated hydrofluoric acid, prepared by heating fluorspar and sulfuric acid, was reported by J. L. Gay-Lussac and L. J. Thénard in 1809.26 They also described its strong corrosive activity on the human skin. It was however later, in 1856 when anhydrous hydrofluoric acid was first obtained. Edmond Frémy achieved this by treating crude, wet hydrofluoric acid with potassium fluoride, which precipitated potassium hydrogen fluoride.

This was re-crystallised, removing potassium hexafluorosilicate, dried and then heated to give anhydrous hydrogen fluoride, which was condensed at low temperatures. Seventy-three years later, the French chemist Henri Moissan was more successful and in 1886 he prepared gaseous fluorine by electrolysing potassium hydrogen fluoride in anhydrous liquid hydrogen fluoride. He achieved this with use of platinum and iridium electrodes sealed into a platinum U-tube which was in turn sealed with fluorite tops. The equipment was cooled to -50 oC and hydrogen was produced at the anode and fluorine at the cathode. He also reported that the fluorine gas produced caused silicon crystals to burst into flames.

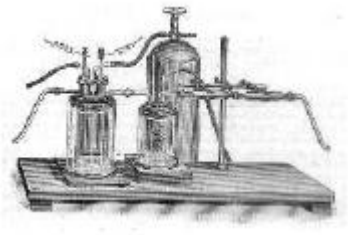


Figure 7 Henri Moissan's equipment, used to obtain gaseous fluorine.

Henri Moissan received various awards such as the Davy medal in 1896, and was awarded Fellowships with the Royal Society and The Chemical Society (London). In 1906 he was honoured with the Nobel Prize in Chemistry. His major works include *Le Fluor et ses Composés* (1900; 'Fluorine and its Compounds') and *Le Four électrique* (1897; 'The Electric Furnace').

FLUORINE PRODUCTION TODAY

Today a similar process is used for the production of gaseous fluorine which is distributed with and without nitrogen dilution. Fluorine is manufactured within a jacketed cell tub, filled with an electrolyte solution of potassium hydrogen difluoride. The temperature must be maintained at 74 oC for efficient F2 production. Should the temperature rise the corrosion rate increases (damaging the cell) and HF and KF.2HF contaminate the fluorine produced.27 If lower, the electrolyte solution solidifies, reducing the efficiency of the cell. The gas is removed by a fluorine flow system and delivered to the fluorine compartment which is purged with nitrogen. Hydrogen gas is generated at the cathode.

THE FLUORINE *GAUCHE* EFFECT

The 1,2-dihaloethanes - Alkanes, e.g. butane and haloalkanes such as 1,2-dibromoethane 34 in general have lower energy *anti* conformations, with a torsion angle X-C-C-X of ~ 180°. *Gauche* conformations (X-C-C-X = ~60°) have a higher energy and are thus less populated. There are however a number of compounds particularly containing fluorine, that exhibit a preference for a *gauche* conformation, and this observation has been coined the "*gauche effect*" byWolfe.

The most common example of the *gauche* effect in fluorinated compounds is that of 1,2-difluoroethane 32 which is often compared to other di-haloethanes such as 1,2- diiodoethane 35. More recently the crystal structures of 32 and 35 have been solved and their conformations discussed.69 Here two different phases of crystalline 1,2-difluoroethane 32 were obtained from cooling the liquid to near its melting point (169K) to 158K. X-ray diffraction of the two crystal phases showed similar *gauche* conformations with torsion angles near to 68°. 1,2-Diiodoethane 35 was also crystallised and an exact *anti* conformation, with a torsion angle of 180° was apparent.

Previously *ab initio* calculations and various techniques such as IR, Raman, microwave and electron diffraction have been used to show this *gauche* preference. The *anti*-conformer has been measured to 0.5 – 1.00 kcal/mol higher in energy than the *gauche* conformer in the gas phase.

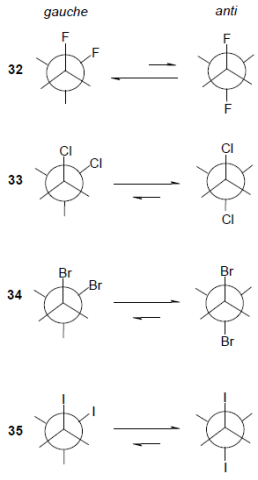


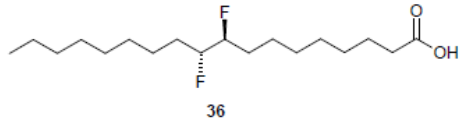
Figure 8 Conformational preferences for 1,2-dihaloethanes.

	% *Gauche*	% *Anti*	Energy difference (kcal/mol in the gas phase)
1,2-$C_2H_4F_2$	96	4.0	0.81
1,2-C_2H_4ClF	58	42	
1,2-$C_2H_4Cl_2$	27	73	1.05
1,2-$C_2H_4Br_2$	11	89	
1,2-$C_2H_4I_2$	12	88	2.0

Table 1 Conformational composition and energy differences for 1,2-dihaloethanes as measured by electron diffraction69 and IR.

The fluorine *gauche* effect in 9,10-difluorostearic acid - The *gauche* effect has been observed in systems other than 1,2-difluoroethane and 2,3-difluorobutane which are usually given as illustrative examples of the effect. *Erythro* 36 and *threo* 37 9,10-difluorostearic acids have very different physical properties. The *threo*

isomer has a melting point of 86-88 °C whereas the *erythro* isomer has a much lower melting point at 67-69 °C.74 Langmuir isotherm analysis was undertaken to examine more closely the conformational flexibility of the diastereoisomers. The results indicated that the *erythro* stearic acid has considerable conformational disorder whereas the *threo* isomer was comparable to normal stearic acid. In an extended anti-zig-zag conformation, the *threo* isomer 37 has two vicinal fluorines *gauche* to one another, enabling the fluorine *gauche* effect to stabilise the system. In the *erythro* stearic acid 36 the *gauche* 36b conformation is in competition with the anti-zig-zag extended conformation, providing a disordered system. This observation that the *gauche* effect can stabilise hydrocarbon chains may have an impact in the design of specialist materials within the liquid crystal industry.



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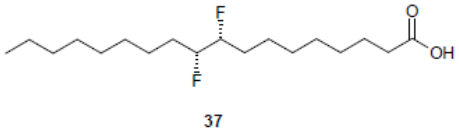
(±)-*erythro*-9,10-difluorostearic acid, mp = 67-69 °C



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(±)-*threo*-9,10-difluorostearic acid, mp = 86-88 °C

Figure 9 *Erythro* and *threo* isomers of 9,10-difluorosteric acid.

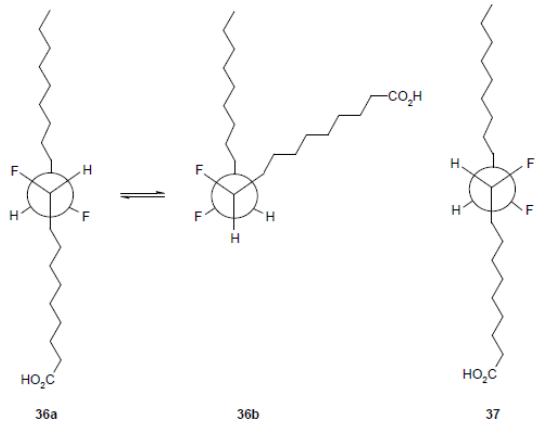

Figure 10 The *erythro* isomer of 36 exhibits disorder owing to competing *anti* and *gauche* conformations.

Fluorine in amides - Amides are an important functional group in pharmaceuticals as well as playing their significant role in peptides and proteins. The amide bond is planar but has rotational freedom around the XC-CO and N-C bonds.

SYNTHESIS OF NINE MEMBERED B-FLUORO AZA RINGS

cyclisation *via* putricine -

It was anticipated that a nine membered ring with *N*-benzyl protecting groups could be prepared by combination of a putricine derivative and a three carbon (C3) unit such as chloromethyl-oxirane or 1,3-dichloro-propan-2-ol as shown in Figure 11. Incorporation of fluorine could then follow by direct fluorination of the resultant secondary alcohol using a reagent such as DAST of Deoxofluor.

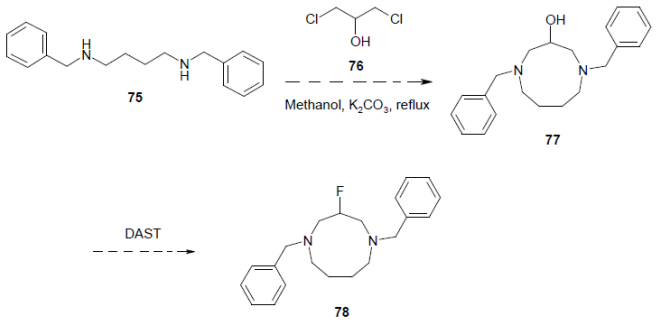

Figure 11 : Proposed route to diazonane 78.

With this strategy in mind, the synthesis of diazonane 78 was explored. Initially diamine 75 was generated by the

reaction of butane-1,4-diamine (putricine) 79 with two equivalents of benzylchloride. The reaction gave a relatively complex mixture with 75 as a minor component. The over-alkylated products, 81 and 82 predominated even when an excess of putricine was added and separating these benzylated amines by chromatography proved impractical.

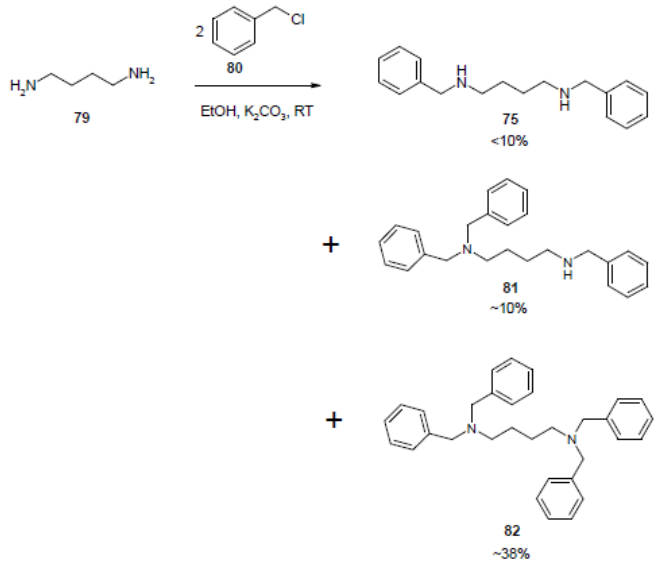

Figure 12 Reaction of putricine 79 with benzyl chloride gave a mixture of products.

In the main, this synthetic approach proved unsatisfactory and an alternative route to 75 was explored *via* 84. The preparation of amide 84 was accomplished in good yield by the reaction of putricine 79 with benzoyl chloride. The resultant diamide 84 was then treated with LiAlH4. This proved to be a straightforward reaction and di-benzylamine 75 was isolated in a reasonable yield. The strategy was very effective and did not give rise to any other benzylated products, unlike direct benzylation.

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