ARTICLE

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The observation of a large *gauche* preference when 2-fluoroethylamine and 2-fluoroethanol become protonated

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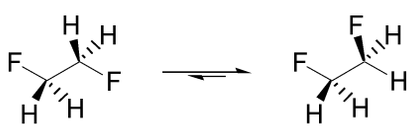
The energies of the *gauche* and *anti* conformers of 2-fluoroethylamine, 2-fluoroethanol and their protonated analogues are calculated using density functional theory. Unlike the non protonated systems, the protonated systems show a strong *gauche* effect where the C–F and the C–$^{+}NH_3$ or C–F and C–$^{+}OH_2$ bonds are *gauche* rather than *anti* to each other. Single crystal X-ray diffraction studies of 2-fluoroethylammonium compounds identify the same conformational preference.

1 Introduction

The preference for 1,2-difluoroethane **1** (Fig. 1) to adopt a *gauche* over an *anti* conformation has been widely reported[1–3] and the observation has emerged as a classical example of the '*gauche effect*'.[4] Values for this conformational preference have been calculated in the range of 0.5–1.0 kcal mol^{-1}.[5,6] The preference is contra-intuitive and appears to dominate over lone pair repulsion between the fluorine atoms and their increased steric influence relative to hydrogen.

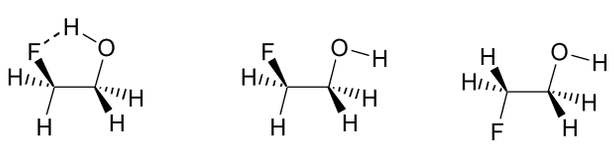


1a *anti* **1b** *gauche*

Fig. 1 The *gauche* over *anti* conformational preference found in 1,2-difluoroethane is a classical example of the *gauche* effect.

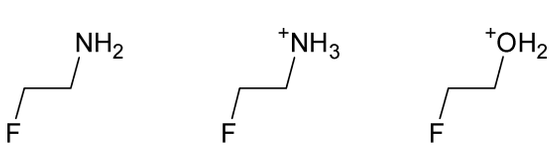
Gauche effects are apparent in other organofluorine systems when the second C–F bond is replaced with other polarised bonds. For example, we have recently highlighted a fluorine-amide *gauche* effect[7,8] in which the C–F bond is vicinal to the C–N(CO) bond of an *N*-2-fluoroethylamide, such as **2**. Similarly, a less pronounced but significant effect occurs in *O*-2-fluoroethyl ester systems, where we have reported solid state and theoretical calculations describing a fluorine-ester *gauche* effect,[9] in which the C–F bond is vicinal to the C–O(CO) bond in an *O*-2-fluoroethyl ester, such as **3**. There is no evidence that these effects benefit from an intramolecular F ··· H bond and their origins are attributed to a stereoelectronic *gauche* preference.

Since the electronegativity of oxygen is second only to fluorine,[10] the potential influence of a *gauche* effect in 2-fluoroethanol has been the subject of several studies. Compared to 1,2-difluoroethane, 2-fluoroethanol has the additional capacity to enter into intramolecular (O)H ··· F hydrogen bonding *via* the hydroxyl group. Dixon and Smart calculated the energies of different minimum conformations of 2-fluoroethanol **4**.[11] They calculated the energies of structures **4a**, **4b** and **4e**. A clear preference for *gauche* structure **4a** of about 2.0 kcal mol^{-1} emerged, over *gauche* structure **4b** which does not have an intramolecular (O)H ··· F. But notably **4b** had a similar energy to the *anti*-structure **4e**, and the preference for **4a** could be attributed almost entirely (1.9 kcal mol^{-1}) to an intramolecular (O)H ··· F bond rather than a through-bond stereoelectronic effect. The *gauche* effect, as measured by the relative energies of **4b** and **4e**, was only 0.1 kcal mol^{-1}.



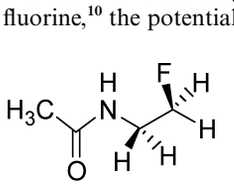
4a **4b** **4e**

In this study we have investigated the *gauche* effect in 2-fluoroethylamine **5** and its protonated form, 2-fluoroethylammonium **6**. The latter system has bio-organic relevance as amines are protonated at physiological pH, and organofluorine compounds have found wide utility in bio-organic studies.[12]



5 **6** **7**

Calculations were also carried out on the oxygen analogues 2-fluoroethanol **4** and protonated 2-fluoroethanol **7**. A number of 2-fluoroethylammonium derivatives were prepared by synthesis and their solid state structures determined by single crystal X-ray analysis. These structures are reported and their conformations discussed in the context of the *gauche* effect.



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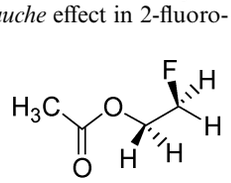

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Table 1 DFT derived absolute energies of conformational minima of structures **5** and **6** with F–C–C–N dihedral angles

Structure	Dihedral angle (°)	Total energy (Hartree)	Structure	Dihedral angle (°)	Total energy (Hartree)	*gauche* − *anti* (kcal mol^{-1})
gauche-NH_2			*anti*-NH_2			
5a	69.8	−234.338996	**5d**	178.3	−234.340450	+0.9
5b	61.5	−234.342092	**5e**	180.6	−234.340615	−0.9
5c	66.7	−234.342000	**5f**	181.7	−234.340450	−1.0
NH_3^+			NH_3^+			
6a	52.7	−234.685112	**6b**	181.0	−234.675825	−5.8

2 Results and discussion

2.1 Computational details

All calculations were performed using Kohn–Sham density functional theory (DFT) with the recently developed B97-2 hybrid exchange-correlation energy functional.[13] To check the validity of this method, we have also performed calculations using the widely-used B3LYP hybrid functional and the MP2 correlated wavefunction method; all three methods yield quantitatively similar results. The TZ2P[14] basis augmented with an additional s and p diffuse function on non-H atoms (with exponents determined using a simple geometric progression) was used. For each molecule, fully optimised *gauche* and *anti* conformations were determined using analytic first derivatives (forces). Harmonic vibrational frequencies were determined from finite differences of analytic first derivatives at perturbed geometries. These frequencies were used to confirm that the stationary points corresponded to minima on the potential energy surface. They were also used to determine zero-point vibrational energies. All relative energies quoted in this study include zero-point vibrational corrections. All calculations were performed using the CADPAC program.[15]

2.2 Theoretical studies on 2-fluoroethylamine 5 and 2-fluoroethylammonium 6

DFT calculations were carried out on 2-fluoroethylamine **5** to establish the extent of a *gauche* preference in this neutral system. Although fluoroethanol has been studied in some detail,[11] we are unaware of any previous calculations on the conformational preference of 2-fluoroethylamine **5**. The energies of the three optimised *gauche* conformers **5a**–**c** (Fig. 2 and Table 1) were calculated relative to their corresponding *anti* conformers **5d**–**f**. The *gauche* conformer **5a** is 0.9 kcal mol^{-1} *higher* in energy than the corresponding *anti*-conformer **5d**.

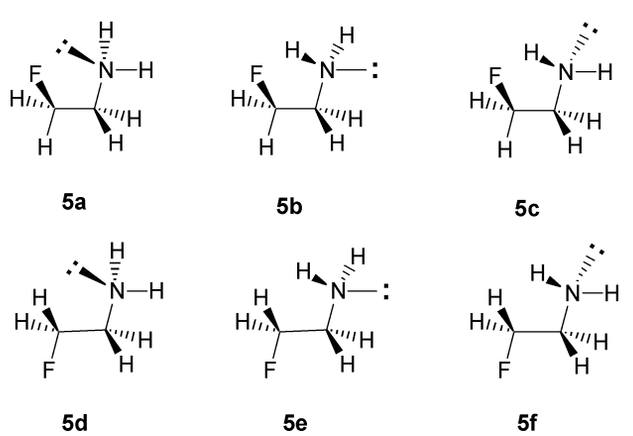
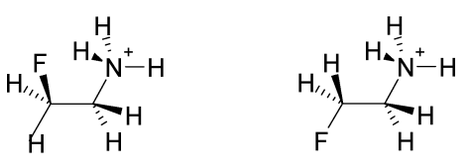


Fig. 2 Calculated minimum conformations of 2-fluoroethylamine **5**.

There is no apparent *gauche* effect in this compound, but instead the electrostatic repulsion between F and the nitrogen lone pair in **5a** is overriding any *gauche* stabilisation. By contrast, the *gauche* structures **5b** and **5c** are 0.9 and 1.0 kcal mol^{-1} lower in energy than their corresponding *anti* structures **5e** and **5f**. As with fluoroethanol, this clearly suggests stabilisation *via* intramolecular F ··· H bonding of between 1.0–2.0 kcal mol^{-1}.

The study was then extended to the 2-fluoroethylammonium system **6**. A number of considerations emerge. An enhanced stereoelectronic *gauche* effect can be expected in **6** as there is an increased polarisation of the C–N^+ bond due to the positive charge on the nitrogen. Furthermore, the prospect also exists for optimal intramolecular F ··· H bonding due to proximity and the increased acidic nature of the ammonium hydrogen atoms. There is only one minimum *gauche* **6a** and one minimum *anti* structure **6b** in this system. Both were evaluated by DFT calculations (Table 1) and it emerged that the *gauche* structure **6a** is more stable than the *anti* structure **6b** by 5.8 kcal mol^{-1}.



This *gauche* preference clearly arises as a combination of intramolecular (N)H ··· F bonding and a stereoelectronic *gauche* effect, however it is not straightforward to delineate the magnitude of each of these contributions.

2.3 Theoretical studies on 2-fluoroethanol 4 and protonated 2-fluoroethanol 7

With the data for the neutral and protonated fluoroethylamine in hand (Table 1) the study was extended to a consideration of the corresponding oxygen analogues. Initially 2-fluoroethanol **4** was examined, essentially as a control such that the current study could be compared to the previous study,[11] and in the event very similar results emerged. A *gauche* preference of ~2.0 kcal mol^{-1} was observed for conformation **4a** which contains an intramolecular F ··· H-bond, relative to the corresponding *anti* structure **4d** (Fig. 3). However the *gauche* structures **4b** and **4c** were only stabilised relative to their own *anti* structures **4e** and **4f** respectively, by 0.1–0.2 kcal mol^{-1}. Clearly **4a** is stabilised by intramolecular F ··· H bonding, rather than an inherent stereoelectronic *gauche* effect which is making only a small energetic contribution.

For protonated 2-fluoroethanol **7**, the appropriate structures are shown in **7a**–**f** (Fig. 4)and relative energies are given in Table 2. The *gauche* structure **7a** is more stable than the *anti* structure **7d** by 4.4 kcal mol^{-1}. This contrasts with the free amine **5a**/**5d** results, where lone pair repulsion reversed the relative energies of the *gauche* and *anti* structures, whereas in this case there is no such repulsion. This *gauche* preference does not have its origin in an intramolecular F ··· H bond and appears to arise from a true stereoelectronic *gauche* effect. The energy difference between *gauche* and *anti* structures increases further when structures **7b**/**7e** and **7c**/**7f** are considered. The

Table 2 DFT derived absolute energies and F–C–C–O dihedral angles of conformational minima for structures **4** and **7**

Structure	Dihedral angle (°)	Total energy (Hartree)	Structure	Dihedral angle (°)	Total energy (Hartree)	*gauche* − *anti* (kcal mol^{-1})
gauche-OH			*anti*-OH			
4a	65.3	−254.225123	**4d**	178.5	−254.222006	−2.0
4b	72.8	−254.222654	**4e**	180.5	−254.222198	−0.3
4c	64.9	−254.222054	**4f**	181.5	−254.222006	0.0
OH_2^+			OH_2^+			
7a	63.5	−254.509319	**7d**	175.9	−254.502339	−4.4
7b	48.2	−254.512994	**7e**	180.5	−254.501790	−7.0
7c	50.5	−254.513888	**7f**	184.1	−254.502339	−7.2

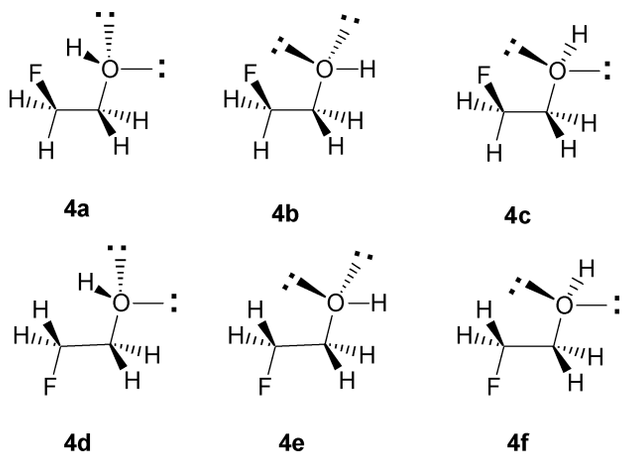


Fig. 3 Calculated minimum conformations of 2-fluoroethanol **4**.

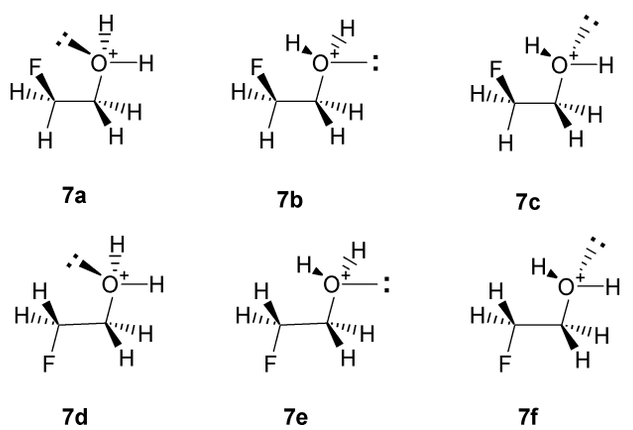


Fig. 4 Conformational minima of protonated 2-fluoroethanol **7**.

gauche conformations are now lower in energy by 7.0 and 7.2 kcal mol^{-1} respectively. Intramolecular F ⋯ H bonding clearly contributes more than 2.5 kcal mol^{-1} additional stabilisation energy in each case. A *gauche*/*anti* difference of greater than 7.0 kcal mol^{-1} is the largest calculated value for a fluorine *gauche* preference, which is contributed both from intramolecular H ⋯ F bonding (~2.6–2.8 kcal mol^{-1}) and a stereoelectronic *gauche* effect (~4.4 kcal mol^{-1}).

2.4 Solid-state studies on protonated fluoroethylamine 6

The Cambridge Structural Database (CSD)[16] is an excellent resource in which to examine the conformational preferences within set structural motifs, however a sub-structure search of the CSD did not reveal any structures containing the F–CH_2–C–$^+NR_3$ motif. It appeared appropriate in the context of the calculations described above to record the solid state structure of the parent 2-fluoroethylammonium system **6** and to prepare some specifically designed derivatives. In the first instance the hydrochloride salt of 2-fluoroethylamine was examined. Inspection of the X-ray crystal structure of **6** (Fig. 5) clearly shows

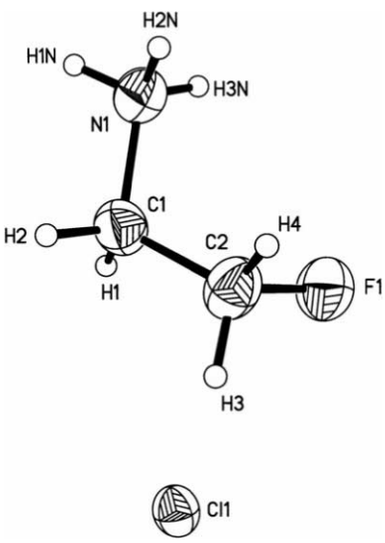


Fig. 5 X-ray crystal structure of 2-fluoroethylammonium chloride **6** showing the *gauche* relationship between C–F and C–N bonds.

that the C–F and C–N bonds adopt a *gauche* conformational preference in the solid state. The F–C–C–N dihedral angle is 67.83(1)°. The shortest intramolecular N–H ⋯ F distance in the structure of 2.73 Å is just beyond the van der Waals contact distance (2.7 Å) and not indicative of an intramolecular F ⋯ H hydrogen bonding interaction.[17,18]

Fig. 6 shows a stack plot with layers formed by two anti-parallel sheets of molecules of **6**. Within each sheet, there are 2 (N)H ⋯ Cl contacts, of around 2.3 Å, and between the sheets there are further (N)H ⋯ Cl contacts, also of around 2.3 Å, holding the sheets together to form the 'thick' layer shown in Fig. 6. The sheets and layers are perpendicular to the *c*-axis and parallel to the *ab* plane. The shortest N(H). . .F contact is also within each sheet. Clearly such crystal packing interactions may account for the variance in the F–C–C–N dihedral angle with that of the DFT calculation on **6a** (52.7°, Table 1).

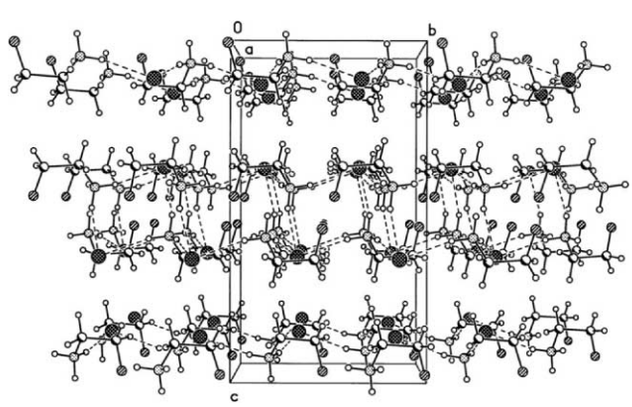
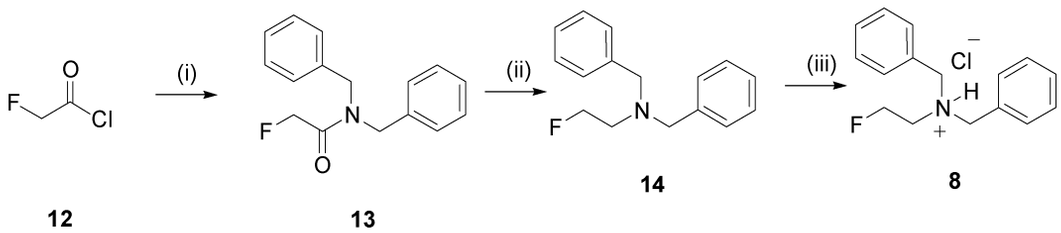


Fig. 6 X-ray crystal structure of 2-fluoroethylammonium chloride **6.Cl**.



12 13 14 8

Scheme 1 *Reagents and conditions*: (i) pyr, dibenzylamine, −78 °C to 25 °C, DCM, 36%; (ii) BH_3 in THF (1.0 M), reflux, 6 h, 66%; (iii) $HCl_{(g)}$ in THF (sat), 25 °C, 16 h, 97%.

2.5 Synthesis and X-ray structures of 2-fluoroethylammonium compounds 8–11

The dibenzylamine hydrochloride **8** was prepared by treating dibenzylamine with fluoroacetyl chloride **12** (generated from sodium fluoroacetate [TOXIC] *via* distillation in the presence of phthalyl dichloride)[19] in the presence of pyridine to generate amide **13** (Scheme 1). Subsequent reduction of amide **13** using a solution of borane in THF gave amine **14**, which was isolated as its hydrochloride salt **8** after treatment with acidic THF. Crystallisation of **8** from methanol and diethyl ether afforded crystals suitable for X-ray structure analysis.

Inspection of the X-ray crystal structure of **8** (Fig. 7) clearly shows that the C–F and C–N bonds align in a *gauche* arrangement relative to each other with a N(1)–C(15)–C(16)–F(17) dihedral angle of −81.9(11)° across the 2-fluoroethylammonium moiety. So again the structure displays a clear *gauche* preference. It is noteworthy in this case that there is no intramolecular F ··· H bonding as the C–F and N–H bonds are remote from each other and this may account for the relative widening of the dihedral angle.

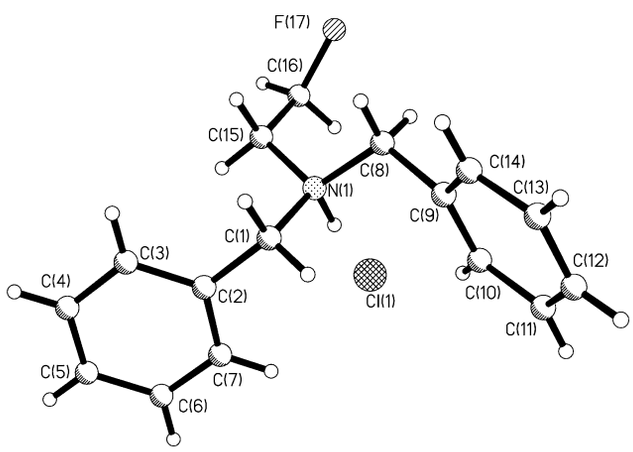
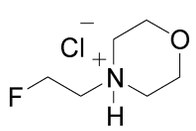


Fig. 7 The X-ray structure of the tertiary 2-fluoroethylammonium ion **8** showing a *gauche* relationship between C–F and C–N bonds.

In the crystal the packing interactions between the molecules are dominated by N–H ··· Cl hydrogen bonds (H ··· Cl 2.07(3) Å, N ··· Cl 3.025(9) Å, N–H. . ..Cl angle 166(9)°) which link the molecules together in chains.

4-(2-Fluoroethyl)morpholin-4-ium chloride **9** was prepared in a similar manner to that described for **8** using morpholine as the amine source.



9

Inspection of the X-ray structure of **9** (Fig. 8) shows that the C–F and C–N bonds also align in a *gauche* arrangement relative to each other with a N(1)–C(7)–C(8)–F(8) dihedral angle of −78.8(2)°. Again this is a relatively wide dihedral angle and there is no intramolecular F ··· H bonding apparent in the structure.

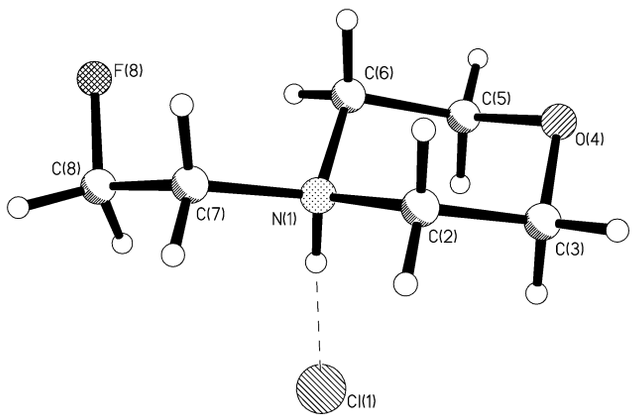
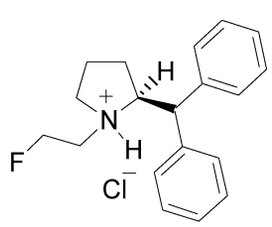


Fig. 8 The X-ray structure of morpholine derivative **9** showing the *gauche* relationship between C–F and C–N bonds.

In **9** the molecules in the crystal are linked together in chains with N–H ··· Cl hydrogen bonds (H ··· Cl 2.062(6) Å, N ··· Cl 3.036(2) Å, N–H ··· Cl angle 173(2)°) dominating the intermolecular packing.

N-2-Fluoroethylamine hydrochloride (*S*)-**10** was prepared from the enantiomerically pure amine (*S*)-2-(diphenylmethyl)-pyrrolidine[20] following the general strategy described above. A suitable crystal of (*S*)-**10** was selected for X-ray structure analysis.

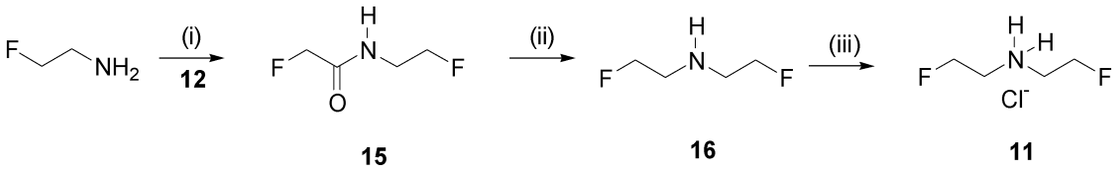


(*S*)-**10**

Inspection of the X-ray crystal structure of (*S*)-**10** (Fig. 9) clearly shows the C–F and C–N bonds aligning in a *gauche* arrangement relative to each other with a N(1)–C(6)–C(7)–F(7) dihedral angle of 74.1(5)° in the 2-fluoroethylammonium moiety. There are no significantly short intra- or intermolecular contacts between hydrogen and fluorine in the structure.

The packing in **(*S*)-10** is dominated by N–H ··· Cl hydrogen bonds (H ··· Cl 2.03(1) Å, N ··· Cl 3.00(1) Å, N–H–Cl angle 170(3)°).

Finally, the synthesis study was extended to the preparation of di(2-fluoroethyl)amine hydrochloride **11**. It was anticipated that such a system should accommodate two *gauche* interactions between the C–F bonds and the C–N bonds of this symmetric secondary amine hydrochloride. The preparation of **11** followed Scheme 2 again using the



Scheme 2 *Reagents and conditions*: (i) Py, **12**, −78 °C to 25 °C over 4 h in DCM, 67%; (ii) 1.5 M soln. borane in THF, reflux, 6 h, 74%; (iii) $HCl_{(g)}$ in THF (sat), 25 °C, 16 h, 96%.

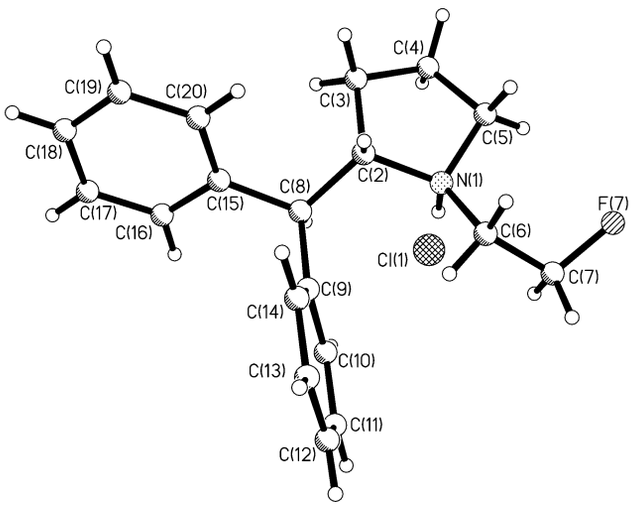


Fig. 9 The X-ray structure of amine hydrochloride (*S*)-**10** showing a *gauche* relationship between C–F and C–N bonds.

condensation of fluoroacetyl chloride **12** with 2-fluoroethylamine as the amine.

Inspection of the resultant X-ray crystal structure (Fig. 10) clearly shows the two C–F bonds aligning *syn* with respect to each other and *gauche* to both of the C–N bonds with F(1)–C(1)–C(2)–N(3) and N(3)–C(4)–C(5)–F(5) dihedral angles of 75.9(6)° and 74.2(6)° respectively. The shortest (N)H ··· F contacts are 2.82(1) Å for (N)H ··· F(1) and 2.65(1) Å for (N)H ··· F(5). A length of 2.7 Å for a F ··· H contact suggests a van der Waals contact and thus these interactions are at the edge or beyond the length that suggests significant stabilisation from intramolecular F ··· H bonding. Nonetheless the structure retains two clear *gauche* relationships in the solid state.

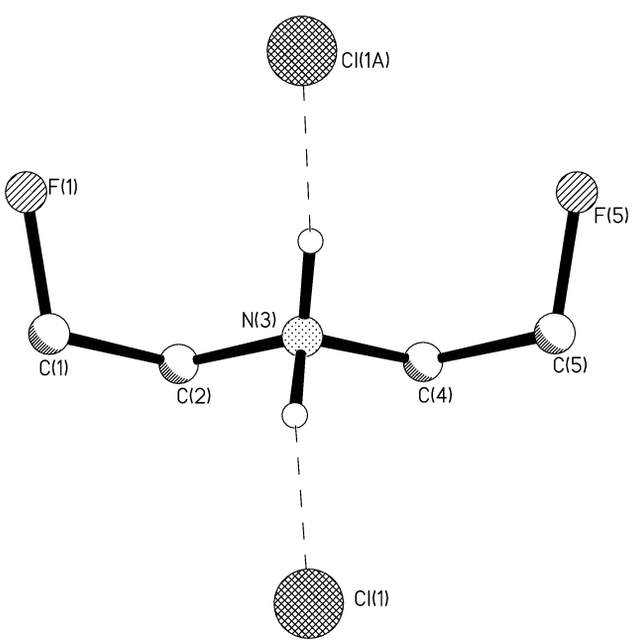


Fig. 10 The X-ray structure of **11** showing the *gauche* relationship between C–F and H–N bonds.

In **11** (Fig. 11) the molecules in the crystal are linked together forming chains along the *b* axis *via* N–H ··· Cl^- hydrogen bonds (H(3a) ··· Cl(1) = 2.134(8), N(3) ··· Cl(1) = 3.107(4) Å, N–H ··· Cl = 172(4)°; H(3b) ··· Cl(1a) 2.37(3), N(3) ··· Cl(1a) = 3.261(4) Å, N–H ··· Cl 151(5)°).

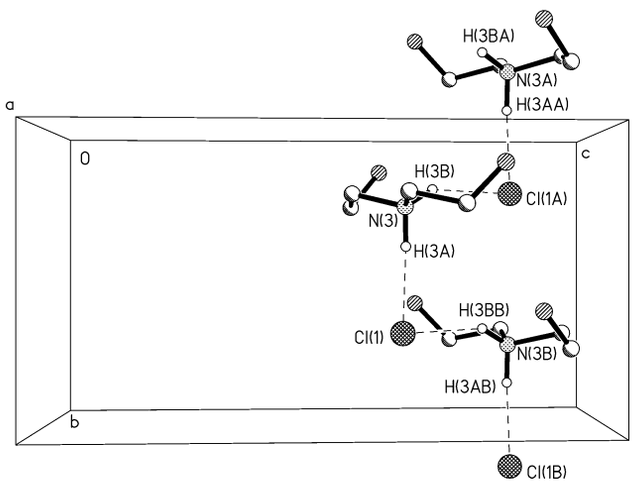


Fig. 11 The chain like structure of **11** in the crystal.

2.6 Discussion

DFT calculations were performed on 2-fluoroethylamine **5** and 2-fluoroethanol **4**. The data for 2-fluoroethanol **4** reinforced earlier calculations suggesting a *gauche* preference of ~2.0 kcal mol^{-1} with its origin only in intramolecular (O)H ··· F bonding. It is noteworthy that the *gauche* **4b/c** and *anti* **4e/f** pair of structures of 2-fluoroethanol, where the hydrogen is orientated away from an intramolecular contact, have similar energies and there is evidence only of a weak (≤ 0.3 kcal mol^{-1}) stabilising contribution from a stereoelectronic *gauche* effect. The situation is worse in 2-fluoroethylamine **5** where there is a clear *anti* preference when there is no bridging hydrogen bond. This is clear from the calculations, which indicate that structure **5a** is higher in energy by 0.9 kcal mol^{-1} than structure **5d**. However for the other two *gauche* structures **5b** and **5c**, the fluorine nitrogen repulsion is more than compensated for by intramolecular hydrogen bonding and these are more stable than the corresponding *anti* structures **5e** and **5f**. An examination of the conformational preference of *N*-2-fluoroethylammonium ion **6** has revealed a large *gauche* over *anti* preference of 5.8 kcal mol^{-1}. It is difficult to delineate contributions in this system from intramolecular F ··· H bonding and an inherent stereoelectronic *gauche* effect, as there is no structure where intramolecular F ··· H contacts are absent. Glusker[21] has calculated the stabilising interaction between fluoromethane and the ammonium (NH_4^+) ion in an *intermolecular* interaction and measured the N^+H ··· F stabilisation at 13.5 kcal mol^{-1}. This is a large value. The N^+H ··· F bond length was extremely short (1.65 Å) and the N^+HF angle almost 180° for this intermolecular interaction in the minimised structure, and such geometries are unobtainable in the intramolecular system studied here. Nonetheless, that study clearly indicates that a F ··· HN^+ electrostatic interaction can be significantly stabilising and may account in a large part for the magnitude of the *gauche* preference in **6**. However, it is also clear from the solid

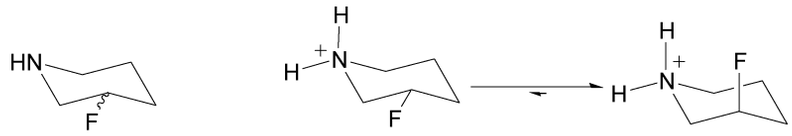
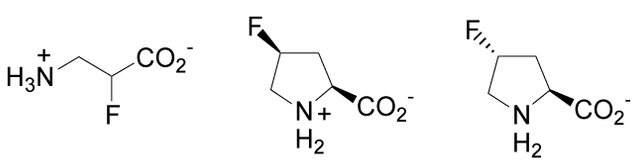


Fig. 12 3-Fluoropiperidine shows an axial preference for fluorine when protonated.

state structures that even in systems without intramolecular F ··· H contacts, the systems maintain a *gauche* preference. In spite of this, it is not easy to delineate these two contributions in **6**. In the context of this study it is noteworthy that 3-fluoropiperidine **17** as a free base displays no conformational preference in solution, whereas the corresponding 3-fluoropiperidinium system **18** has an absolute preference for the conformation **18b** with the fluorine in an axial configuration (Fig. 12).[22]

There is retrospective evidence that this *fluorine/ammonium gauche effect* also remains prominent in some amino acids in solution.[23,24] A study in 1977 reported[23] on the ^{1}H-NMR conformational analysis of 2-fluoro-3-aminopropionic acid **19** in water and revealed that the predominant conformer for the amino acids in solution had the C–F and C–NH_3^+ bonds *gauche* to each other. It was estimated that 77% of the rotamer population in solution at neutral pH was one of the two possible *gauche* conformers. Also the preferred conformations of *cis*-**20** and *trans*-**21** 4-fluoroprolines in solution were reported in 1973.[24] The authors suggested that the fluorines had a predisposition to occupy an axial orientation. This is entirely consistent with the maintenance of a *gauche* relationship between the C–F and C–N^+H_2R bonds. Thus, the observations made in this theoretical and solid state study for the 2-fluoroethylammonium system, are entirely consistent with observations in other systems in solution.



19 **20** **21**

The study was extended to exploring a *gauche* effect in protonated 2-fluoroethanol **7**, a system that was evaluated for the first time. A clear *gauche* preference was observed for **7**, with a greater *gauche*/*anti* differential than that calculated for **6**, consistent with the increased electronegativity of oxygen over nitrogen. The energy difference (4.4 kcal mol^{-1}) calculated between structures **7a** and **7d** is particularly striking as it is large and there is no intramolecular O$^+$H ··· F bond. The *gauche*/*anti* differential increases further (7.0–7.2 kcal mol^{-1}) when intramolecular O$^+$H ··· F bonding is allowed to take place, *e.g.* by comparison of **7b**/**7e** and **7c**/**7f**. In this system, unlike **6**, it is possible to delineate the contribution of the *gauche* preference from the *gauche* effect (~4.4 kcal mol^{-1}) and from intramolecular hydrogen bonding (2.6–2.8 kcal mol^{-1}). This is the largest value of a *gauche* effect calculated so far in an organo-fluorine system.

The X-ray structures of the hydrochlorides of the 2-fluoroethylammonium compounds **6** and **8**–**11**, all display a *gauche* preference. The F–C–C–N dihedral angles are all larger (67.8°–81.9°) than the one calculated for **6a** (52.7°). This difference must arise from weakened intramolecular (N)H ··· F bonding in the solid state and indeed, the dominating intermolecular interactions in the solid state structures were (N)H ··· Cl contacts. Nonetheless all of the structures prepared showed a *gauche* preference.

3 Experimental

General

All chemicals were purchased from Acros Organics Ltd. Pyridine was dried and distilled prior to use using standard literature procedures. The solvents used in reactions were dried, distilled using standard literature procedures and stored under nitrogen prior to use. Reactions were carried out under nitrogen atmosphere. FT-IR spectra were recorded using a Perkin-Elmer 2000 FT-IR as Nujol muls. NMR spectra were recorded on a Bruker Advance 300 MHz (^{1}H at 300.06 MHz, ^{13}C at 74.45 MHz, ^{19}F 282.34 MHz) spectrometer in $CDCl_3$. Mass spectroscopy data were recorded on a VG Autospec instrument. Elemental (C, H and N) analyses were obtained using a CE Instrument EA 1110 CHNS analyser. Fluoroacetyl chloride **12** was prepared from sodium fluoroacetate as previously described.[19] [**CAUTION: Sodium fluoroacetate and the product chloride* **12** are extremely toxic]

Synthesis of *N*,*N*-dibenzyl-2-fluoroacetamide 13. A solution of fluoroacetyl chloride[19] (2.0 g, 21.0 mmol) in DCM (10 ml) at −78 °C was added dropwise to a stirred solution of dibenzylamine (3.99 ml, 21.0 mmol) and pyridine (1.70 ml, 21.0 mmol) in DCM (10 ml) also at −78 °C. The resulting pale yellow solution was stirred and allowed to reach ambient temperature over a period of 4 h. The reaction mixture was quenched with water (10 ml) and extracted into DCM (3 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure to yield a pale yellow oil which was purified over silica (petrol and ethyl acetate (7 : 3)) to yield the title compound (1.94 g, 36%) as a pale yellow oil; ν_{max} (neat)/cm^{-1} 3087, 3063, 3030, 2939, 1674 (C=O), 1453, 1363, 1227, 1076, 1029; δ_H (300 MHz, $CDCl_3$) 4.25 and 4.50 (4H, s, Bn–CH_2), 4.96 (2H, d, $^2J_{H-F}$ = 47.1 Hz, CH_2F), 7.01–7.24 (10H, m, Ar–*H*); δ_F (282 Hz, $CDCl_3$) −225.0 (1F, t, $^2J_{H-F}$ = 47.1 Hz, CH_2F); δ_C (75 Hz, $CDCl_3$) 48.4 (d, $^4J_{C-F}$ = 35.9 Hz, Bn–CH_2), 53.0 (s, Bn–CH_2), 79.7 (d, $^1J_{C-F}$ = 179.7 Hz, CH_2F), 126.8, 128.0, 128.3 (s, Ar–*C*), 135.6 (s, Ar–*C*–CH_2), 167.2 (d, $^2J_{C-F}$ = 18.2 Hz, –*C*O); *m*/*z* (CI): 258 (MH^+, 100%), (Found: MH^+, 258.129827, $C_{16}H_{17}FNO$ requires: 258.129418 (−1.6 ppm)).

Synthesis of *N*,*N*-dibenzyl-2-fluoroethylamine 14. A solution of borane in THF (1 M, 9.73 ml, 64.0 mmol) was added dropwise to a cooled solution of *N*,*N*-dibenzyl-2-fluoroacetamide (8.33 g, 32.0 mmol) in THF (10 ml). The reaction was heated under reflux for a further 6 h and an aliquot of the reaction mixture was removed for ^{19}F NMR analysis to confirm the absence of starting material. The reaction was quenched with distilled water (10 ml) and the organic layer was separated. The residual aqueous layer was washed with DCM (3 × 25 ml) and the combined organic extracts were dried ($MgSO_4$), and concentrated under reduced pressure. The product was purified over silica (ethyl acetate and petrol (3 : 2)) to give the title compound (5.18 g, 66%) as a clear oil; ν_{max} (neat)/cm^{-1} 3347, 3028, 2944, 2831, 1495, 1454, 1029, 748, 700; δ_H (300 MHz, $CDCl_3$) 2.71 (2H, dt, $^2J_{H-H}$ = 5.1 and $^3J_{H-F}$ = 26.0 Hz, –CH_2NBn_2), 3.60 (4H, s, Bn–CH_2), 4.42 (2H, dt, $^2J_{H-H}$ = 5.1 and $^2J_{H-F}$ = 47.6 Hz, –CH_2F), 7.13–7.44 (10H, m, Ar–*H*); δ_F (282 Hz, $CDCl_3$) –219.3 (1F, tt, $^2J_{H-F}$ = 25.8 and $^3J_{H-F}$ = 47.4 Hz, –CH_2F); δ_C (75 Hz, $CDCl_3$) 52.9 (d, $^2J_{C-F}$ = 20.5 Hz, –CH_2NBn_2), 58.8 (s, Bn–CH_2), 82.9 (d, $^1J_{C-F}$ = 167.5 Hz,

–CH_2F), 127.0, 128.3, 128.7 (s, Ar–*C*), 138.4 (s, Ar–*C*–CH_2); *m*/*z* (EI): 243 (M^+, 30%), 210 ($M^+ - CH_2F$, 100), 152 ($M^+ - CH_2Ph$, 10), (Found: M^+, 243.142657. $C_{16}H_{18}FN$ requires: 243.142328 (−1.4 ppm)).

Synthesis of *N*,*N*-dibenzyl-2-fluoroethylammonium hydrochloride 8. A saturated solution of HCl gas dissolved in THF (10 ml) was added dropwise to a stirred solution of *N*,*N*-dibenzyl-2-fluoroethylamine (0.98 g, 4.03 mmol) in THF (10 ml). The reaction mixture was stirred for 16 h at ambient temperature. The excess solvent was removed under reduced pressure to give a viscous yellow oil which was re-crystallised from methanol and ether to yield the title compound (1.13 g, 97%) as a white crystalline solid, mp 182–184 °C (lit.,[25] 183–184 °C); ν_{max} (Nujol)/cm^{-1} 3073 (ammonium ion), 2923 (CH), 1458 (ammonium ion), 1216 (C–F); δ_H (300 MHz, $CDCl_3$) 3.17–3.50 (3H, m, –CH_2N and N*H*), 4.33 (4H, s, Bn–CH_2), 4.64–4.86 (2H, m, –CH_2F), 7.31–7.49 (10H, m, Ar–*H*); δ_F (282 Hz, $CDCl_3$) –221.8 (1F, tt, $^2J_{H-F}$ = 27.2 and $^3J_{H-F}$ = 47.1 Hz, –CH_2F); δ_C (75 Hz, $CDCl_3$) 53.2 (d, $^2J_{C-F}$ = 19.9 Hz, –*C*H_2NBn_2), 58.8 (s, Bn–*C*H_2), 66.7 (s, Bn–*C*H_2), 79.1 (d, $^1J_{C-F}$ = 166.4 Hz, *C*H_2F), 130.4, 131.2, 132.3 (s, Ar–*C*); *m*/*z* (CI): 244 ($MH^+ - Cl$, 100%), 210 ($MH^+ - CH_2F$, 6).

Synthesis of 2-fluoro-1-morpholin-4-ylethanone. A solution of fluoroacetyl chloride (2.66 g, 28.0 mmol) in DCM (10 ml) at −78 °C was added dropwise to a stirred solution of morpholine (2.0 ml, 23.0 mmol) and triethylamine (3.9 ml, 28.0 mmol) in DCM (10 ml) also at −78 °C. The resulting pale yellow solution was stirred and allowed to reach ambient temperature over a period of 4 h. The reaction mixture was quenched with water (10 ml) and extracted into DCM (3 × 25 ml). The combined organic extracts were washed with HCl (0.5 M, 1 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure to yield a pale yellow oil which was purified over silica (ethyl acetate and petrol (6 : 4)) to give the title compound (2.56 g, 76%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3553, 2970, 2863, 1651 (C=O), 1438, 1367, 1276, 1243, 1114, 1071, 1027, 848, 787; δ_H (300 MHz, $CDCl_3$) 3.46 (4H, m, 2 × –CH_2-N), 3.62 (4H, m, 2 × –CH_2–O), 4.92 (2H, d, $^2J_{H-F}$ = 47.1 Hz, –CH_2F); δ_F (282 MHz, $CDCl_3$) −225.7 (1F, t, $^2J_{F-H}$ = 45.4 Hz, –CH_2F); δ_C (75 MHz, $CDCl_3$) 41.9 (s, –*C*H_2–N), 44.9 (d, $^4J_{C-F}$ = 5.0 Hz, –N*C*H_2), 66.4 (s, –O*C*H_2), 79.7 (d, $^1J_{C-F}$ = 179.7 Hz, –*C*H_2F), 165.2 (d, $^2J_{C-F}$ = 17.7 Hz, –*C*O); *m*/*z* (CI) 148 (MH^+, 100%), (Found: MH^+, 148.077793. $C_6H_{11}FNO_2$ requires: 148.077382 (−2.8 ppm)).

Synthesis of 4-(2-fluoroethyl)morpholine. A solution of borane in THF (1.5 M, 29.9 ml) was added dropwise to a cooled solution of 2-fluoro-1-morpholin-4-ylethanone (2.20 g, 15.0 mmol) in THF (5 ml). The reaction mixture was stirred for a further 3 h at room temperature and an aliquot of the reaction mixture was removed for ^{19}F NMR analysis to confirm the absence of starting material. The reaction mixture was cooled in an ice bath before being quenched with water (10 ml), extracted into ether (3 × 25 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The crude material was purified over silica (ethyl acetate and petrol (7 : 3)) to yield the title compound (0.41 g, 21%) as a colourless oil. ν_{max} (neat)/cm^{-1} 2966, 2377, 1457, 1121, 1065, 880; δ_H (300 MHz, $CDCl_3$) 2.40–2.55 (4H, m, 2 × –CH_2N), 3.15 (2H, dt, $^2J_{H-H}$ = 4.4 Hz and $^3J_{H-F}$ = 28.8 Hz, –C$H_2$$CH_2$F), 3.56–3.72 (4H, m, 2 × –CH_2O), 4.99 (2H, dt, $^2J_{H-H}$ = 4.5 Hz and $^2J_{H-F}$ = 47.9 Hz, –CH_2F); δ_F (282 MHz, $CDCl_3$) −216.7 (1F, dt, $^2J_{F-H}$ = 47.4 Hz and $^3J_{F-H}$ = 28.9 Hz, –CH_2F); δ_C (75 MHz, $CDCl_3$) 58.6 (s, 2 × –N*C*H_2), 61.6 (s, 2 × –O*C*H_2), 64.3 (d, $^2J_{C-F}$ = 18.2 Hz, –*C*$H_2$$CH_2$F), 79.2 (d, $^1J_{C-F}$ = 166.4 Hz, –*C*O); *m*/*z* (CI) 134 (MH^+, 65%), (Found: MH^+, 134.098286. $C_6H_{13}FNO$ requires: 134.098117 (−1.3 ppm)).

Synthesis of 4-(2-fluoroethyl)morpholin-4-ium hydrochloride 9. A saturated solution of HCl in THF (10 ml) was added dropwise to a solution of 2-fluoro-1-morpholin-4-ylethanone (0.12 g, 0.88 mmol) in THF (5 ml) and stirred for 16 h at room temperature. The solvent was removed under reduced pressure to yield a viscous yellow oil which was re-crystallised from methanol and ether to give the title compound (0.14 g, 95%) as a white crystalline solid, mp 146–148 °C; (Found: C, 42.48; H, 7.72; N, 8.26. $C_6H_{13}FOCl$ requires: C, 42.07; H, 7.93; N, 8.47%); ν_{max} (Nujol)/cm^{-1}2699, 1645, 1459, 1269, 1130, 1106, 1038, 931, 911, 875; δ_H (300 MHz, CD_3OD) 4.14–4.86 (8H, m, 4 × –CH_2), 4.93–5.01 (2H, m, –CH_2), 5.73–5.93 (3H, m, –CH_2F and –N*H*); δ_F (282 Hz, CD_3OD) −222.4 (1F, dt, $^2J_{F-H}$ = 47.4 and $^3J_{F-H}$ = 27.8 Hz, –CH_2F); δ_C (75 Hz, CD_3OD) 53.7 (s, *C*H_2N), 58.4 (d, $^2J_{C-F}$ = 19.4 Hz, –N*C*H_2), 65.0 (s, *C*H_2N), 79.3 (d, $^1J_{C-F}$ = 169.1 Hz, –*C*H_2F); *m*/*z* (CI): 170 (MH^+, 100%).

Synthesis of (*S*)-2-benzhydryl-1-(fluoroacetyl)pyrrolidine. A solution of fluoroacetyl chloride (0.48 g, 4.94 mmol) in DCM (10 ml) at −78 °C was added dropwise to a stirred solution of (*S*)-2-benzhydrylpyrrolidine (0.98 g, 4.12 mmol) and pyridine (0.70 ml, 4.94 mmol) in DCM (10 ml) also at −78 °C. The resulting pale yellow solution was stirred and allowed to reach ambient temperature over a period of 4 h. The reaction mixture was quenched with water (10 ml) and extracted into DCM (3 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure. The residue was re-crystallised from ethyl acetate and petrol to give the title compound (0.95 g, 97%) as a clear crystalline solid, mp 165–167 °C; ν_{max} (Nujol)/cm^{-1} 2923, 1647 (C=O), 1491, 1459, 1354, 1207, 1074, 1031, 999, 755, 702; δ_H (300 MHz, $CDCl_3$) 1.48–1.57 (1H, m, –CH_2), 1.75–2.02 (3H, m, –CH_2), 3.38–3.55 (2H, m, –CH_2), 4.22–4.24 (1H, m, –C*H*Ph_2), 4.33–4.34 (1H, m, –C*H*), 4.83 (2H, dd, $^2J_{H-H}$ = 5.6 and $^2J_{H-F}$ = 47.4 Hz, CH_2F), 7.01–7.49 (10H, m, Ar–*H*); δ_F (282 Hz, $CDCl_3$) 225.2 (1F, t, $^2J_{H-F}$ = 47.1 Hz, –CH_2F); δ_C (75 Hz, $CDCl_3$) 24.2 (s, C-4), 31.0 (s, *C*-3), 45.8 (s, *C*HPh$_2$), 52.0 (s, *C*-5), 61.7 (s, –*C*H), 80.1 (d, $^1J_{C-F}$ = 180.8 Hz, –*C*H_2F), 126.7, 127.5, 127.7, 142.2 (Ar–*C*), 175.0 (d, $^1J_{C-F}$ = 23.0 Hz, –*C*O); *m*/*z* (CI): 298 (MH^+, 100%), (Found: MH^+, 298.161593. $C_{19}H_{21}FNO$ requires: 298.160718 (−2.9 ppm)).

Synthesis of 2-benzhydryl-1-(2-fluoroethyl)pyrrolidine. A solution of borane in THF (1.5 M, 5.85 ml, 3.9 mmol) was added dropwise to a cooled solution of 2-benzhydryl-1-(fluoroacetyl)pyrrolidine (0.4 g, 1.30 mmol) in THF (10 ml). The mixture was heated under reflux for 6 h and then cooled in ice. Water (10 ml) was added dropwise and the reaction mixture was extracted into DCM (3 × 20 ml), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was purified over silica (petrol and ethyl acetate (7 : 3)) to give the title compound (0.31 g, 76%) as a clear oil; ν_{max} (neat)/cm^{-1} 3350, 3030, 2950, 2830, 1490, 1450, 1020, 750, 700; δ_H (300 MHz, CD_3OD) 1.48–1.70 (3H, m, –CH_2), 1.79–2.0 (2H, m, –CH_2), 2.26–2.28 (1H, m, C*H*Ph_2), 2.70–2.94 (3H, m, –CH_2), 3.29 (2H, dt, $^2J_{H-H}$ = 4.2 and $^3J_{H-F}$ = 28.1 Hz, –C$H_2$$CH_2$F), 3.88–3.92 (1H, m, –C*H*), 4.19 (2H, dt, $^2J_{H-H}$ = 5.5 and $^3J_{H-F}$ = 47.5 Hz, –CH_2F), 7.11–7.34 (10H, m, Ar–*H*); δ_F (282 MHz, CD_3OD) −219.9 (1F, dtt, $^2J_{H-H}$ = 4.1, $^2J_{H-F}$ = 47.4 and $^3J_{H-F}$ = 22.7 Hz, –CH_2F); δ_C (75 Hz, CD_3OD) 23.0 (s, *C*-4), 29.2 (s, *C*-3), 54.7 (s, –*C*HPh_2), 55.0 (d, $^2J_{C-F}$ = 19.9 Hz, –*C*H_2F), 56.7 (d, $^1J_{C-C}$ = 2.8 Hz, -*C*-5), 67.3 (d, $^1J_{C-C}$ = 2.8 Hz, –*C*H), 82.6 (d, $^1J_{C-F}$ = 167.0 Hz, –*C*H_2F), 125.1, 127.1, 127.8, 142.6 (Ar–*C*); *m*/*z* (CI): 284 (MH^+, 100%), (Found: MH^+, 284.180974. $C_{19}H_{23}FN$ requires: 284.181453 (1.7 ppm)).

Synthesis of 2-benzhydryl-1-(2-fluoroethyl)pyrrolidinium hydrochloride 10. A saturated solution of HCl dissolved in THF (10 ml) was added dropwise to a stirred solution of 2-benzhydryl-1-(2-fluoroethyl)pyrrolidine (0.20 g, 0.71 mmol) in THF (5 ml). The reaction mixture was stirred for 16 h at ambient temperature. The excess solvent was removed under reduced pressure to yield a viscous yellow oil which was re-crystallised

from methanol and ether to give the title compound (0.19 g, 95%) as a white crystalline solid, mp 159–161 °C; ν_{max} (Nujol)/cm^{-1} 2390, 2330, 1160, 1030, 700; δ_H (300 MHz, CD_3OD) 1.66–1.83 (2H, m, 4-CH_2), 2.30–2.49 (2H, m, 3-CH_2), 2.58–2.66 (1H, m, 5-CH_2), 2.93–3.01 (1H, m, 5-CH_2), 3.26–3.37 (1H, m, –CH_2CH$_2$F), 3.60–3.72 (1H, m, –CH_2CH$_2$F), 3.67–3.73 (1H, m, –CH), 4.55–4.56 (1H, m, –CHPh$_2$), 4.68 (2H, dt, $^2J_{H-H}$ = 4.2 and $^3J_{H-F}$ = 48.1 Hz, –CH_2CH$_2$F), 3.88–3.92 (1H, m, –CH), 4.19 (2H, dt, $^2J_{H-H}$ = 5.5 and $^3J_{H-F}$ = 47.5 Hz, –CH_2F), 6.77 (1H, s (*br*), –NH), 7.11–7.34 (10H, m, Ar–H); δ_F (282 MHz, CD_3OD) −223.3 (1F, dtt, $^2J_{H-H}$ = 4.1, $^2J_{H-F}$ = 47.4 and $^3J_{H-F}$ = 22.7 Hz, –CH$_2F$); δ_C (75 Hz, CD_3OD) 19.3 (s, *C*-4), 23.7 (s, *C*-3), 45.0 (s, –*C*HPh$_2$), 50.6 (dd, $^1J_{C-C}$ = 2.4 Hz, *C*-5), 51.4 (d, $^2J_{C-F}$ = 28.0 Hz, –*C*H$_2$*C*H$_2$F), 67.1 (d, $^1J_{C-C}$ = 2.80 Hz, –*C*H), 74.2 (d, $^1J_{C-F}$ = 167.0 Hz, –*C*H$_2$F), 125.1, 127.1, 127.8, 142.6 (Ar–*C*); *m*/*z* (CI): 284 (MH$^+$ − HCl, 15%) (Found: MH$^+$ − HCl, 284.180740. $C_{19}H_{24}FN$ requires: 284.181453 (2.5 ppm)).

Synthesis of 2-fluoro-*N*-(2-fluoroethyl)acetamide 15. A solution of fluoroacetyl chloride (3.47 g, 36.0 mmol) in DCM (15 ml) at −78 °C was added dropwise to a stirred solution of 2-fluoroethylamine hydrochloride (3.0 g, 30 mmol) and pyridine (2.93 ml, 36.0 mmol) in DCM (15 ml) also at −78 °C. The resulting pale yellow solution was stirred and allowed to reach ambient temperature over a period of 4 h. The reaction mixture was quenched with water (10 ml), extracted into DCM (3 × 25 ml), dried ($MgSO_4$), and concentrated under reduced pressure to give a pale yellow oil which was purified over silica (petrol : ethyl acetate (4 : 6)) to yield the title compound (2.49 g, 67%) as a colourless oil. (Found: C, 39.03; H, 5.73; N, 11.38. $C_4H_7F_2O$ requires: C, 38.96; H, 5.72; N, 11.23%); ν_{max} (neat)/cm^{-1} 3316, 3092, 2964, 1765 (C=O), 1653, 1540, 1443, 1396, 1361, 1294, 1107, 1050; δ_H (300 MHz, $CDCl_3$) 3.59 (2H, dq, $^2J_{H-H}$ = 5.3 and $^3J_{H-F}$ = 27.8 Hz, –CH_2NH$_2$), 4.47 (2H, dt, $^2J_{H-H}$ = 4.7 and $^2J_{H-F}$ = 47.2 Hz, CH_2F), 4.77 (2H, d, $^2J_{H-F}$ = 47.2 Hz, CH_2F), 6.91 (1H, s (*br*), NH); δ_F (282 Hz, $CDCl_3$) –224.8 (1F, tt, $^2J_{H-F}$ = 47.4 and $^3J_{H-F}$ = 26.8 Hz, CH$_2F$), –226.1 (1F, t, $^2J_{H-F}$ = 47.4 Hz, –CH$_2F$); δ_C (75 Hz, $CDCl_3$) 39.1 (d, $^2J_{C-F}$ = 20.5 Hz, –*C*H$_2$NH), 79.9 (d, $^1J_{C-F}$ = 168.1 Hz, –*C*H$_2$F), 82.2 (d, $^1J_{C-F}$ = 150.4 Hz, –*C*H$_2$F), 168.1 (d, $^2J_{C-F}$ = 17.1 Hz, *C*O); *m*/*z* (EI): 123 (M$^+$, 50%); 103 (M$^+$ − HF, 60); 90 (M$^+$ − CH$_2$F, 100).

Synthesis of bis(2-fluoroethyl)amine 16. A solution of borane in THF (1.0 M, 6.0 ml, 60.0 mmol) was added to an ice cool solution of 2-fluoro-*N*-(2-fluoroethyl)acetamide (2.49 g, 20.0 mmol) in THF (10 ml) and the reaction heated under reflux for 6 h. An aliquot of the reaction mixture was removed for ^{19}F NMR analysis to confirm the absence of starting material. The reaction mixture was quenched by the dropwise addition of water (10 ml) and the organic layer separated. The aqueous layer was extracted into diethyl ether (3 × 25 ml) and the combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. The product was purified over silica gel (ethyl acetate and petrol (6 : 4)) to yield the title compound (1.63 g, 74%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3374 (NH), 2945, 2833, 2527, 2045, 1666, 1451, 1115, 1031; δ_H (300 MHz, CD_3OD) 3.26–2.79 (4H, m, 2 × –NCH_2), 4.19 (1H, s (*br*), NH), 3.26–2.79 (4H, m, 2 × –CH_2F); δ_F (282 Hz, CD_3OD) −225.9 (1F, tt, $^2J_{F-H}$ = 47.1 and $^3J_{F-H}$ = 23.7 Hz, –CH$_2F$); δ_C (75 Hz, CD_3OD) 56.0 (d, $^2J_{C-F}$ = 19.4 Hz, –N*C*H$_2$), 79.1 (d, $^1J_{C-F}$ = 165.9 Hz, *C*H$_2$F); *m*/*z* (CI): 110 (MH$^+$, 100%), (Found: MH$^+$, 110.077704. $C_4H_{10}F_2N$ requires: 110.078131 (3.9 ppm)).

Synthesis of 2-fluoro-*N*-(2-fluoroethyl)ethylammonium chloride 11. A saturated solution of HCl gas dissolved in THF (10 ml) was added dropwise to a stirred solution of *N*,*N*-bis-(2-fluoroethyl)amine (0.61 g, 5.5 mmol) in THF (10 ml). The reaction mixture was stirred for 16 h at ambient temperature. The excess THF was removed under reduced pressure to yield a viscous yellow oil which was recrystallised from methanol and diethyl ether to yield the title compound (0.66 g, 96%) as a white crystalline solid, mp 190–192 °C (lit.,[26] 190–193 °C); (Found: C, 33.07; H, 6.93; N, 9.47. $C_4H_{10}F_2NCl$ requires: C, 33.00; H, 6.92; N, 9.62%); ν_{max} (Nujol)/cm^{-1} 3073 (ammonium ion), 2926 (C–H), 1458 (ammonium ion), 1216; δ_H (300 MHz, CD_3OD) 3.38 (4H, dt, $^2J_{H-H}$ = 4.7 and $^3J_{H-F}$ = 26.8 Hz, –NCH_2), 4.69 (4H, dt, $^2J_{H-H}$ = 4.7 and $^2J_{H-F}$ = 47.0 Hz, –CH_2F), 4.81 (2H, s (*br*), –NH_2); δ_F (282 Hz, CD_3OD) −226.7 (2F, tt, $^2J_{F-H}$ = 46.4 and $^3J_{H-F}$ = 26.8 Hz, 2 × CH$_2F$); δ_C (75 Hz, CD_3OD) 48.8 (d, $^2J_{C-F}$ = 21.6 Hz, –N*C*H$_2$), 79.4 (d, $^1J_{C-F}$ = 167.5 Hz, –*C*H$_2$F); *m*/*z* (CI): 110 (MH$^+$ − Cl, 100%).

Crystal data

General. Data for **9**, (*S*)-**10** and **11** were corrected for Lorentz, polarization and absorption effects, whilst **6** and **8** were not corrected for absorption. **8** was a curtailed data collection as a result of decomposition. The structures were solved by direct methods and refined by full-matrix least squares on F^2 for all data using SHELXTL software. In all structures non-hydrogen atoms were refined with anisotropic thermal parameters. In all structures except **6** the amine hydrogens were refined isotropically subject to a distance constraint (N–H = 0.98 Å) and all other hydrogen atoms were assigned riding isotropic thermal parameters and constrained to idealised geometries. In **6** all hydrogen atoms were freely refined.

6: C_2H_7ClFN, M = 99.54, Orthorhombic, space group *Pbca*, a = 7.621(1), b = 8.543(1), c = 14.830(2) Å, U = 965.4(2) Å^3, F(000) = 416, Z = 8, D_c = 1.370 Mg m^{-3}, μ = 0.643 mm^{-1} (Mo-Kα, λ = 0.71073 Å). The data were collected at T = 150(2) K, 10312 reflections ($2.75 \leq \theta \leq 30.29°$) were measured on a Bruker SMART-1K CCD diffractometer equipped with an Oxford Cryostream low-temperature device[27] (ω-scan, 0.3°/frame) yielding 1371 unique data (R_{merg} = 0.0290). Conventional R = 0.0265 for 1154 reflections with $I \geq 2\sigma$, GOF = 1.078. Final $wR2$ = 0.0688 for all data (74 refined parameters). The largest peak in the residual map is 0.454 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.†

8: $C_{16}H_{19}ClFN$, M = 279.77, Triclinic, space group $P\bar{1}$, a = 6.821(7), b = 10.177(9), c = 12.07(2) Å, U = 758.0(17) Å^3, F(000) = 296, Z = 2, D_c = 1.226 Mg m^{-3}, μ = 0.249 mm^{-1} (Mo-Kα, λ = 0.71073 Å). The data were collected at T = 293(2) K, 1605 reflections ($1.81 \leq \theta \leq 23.25°$) were measured on a Bruker SMART CCD diffractometer (ω-scan, 0.3°/frame) yielding 1602 unique data (R_{merg} = 0.2652). Conventional R = 0.0887 for 801 reflections with $I \geq 2\sigma$, GOF = 0.935. Final $wR2$ = 0.2708 for all data (177 refined parameters). The largest peak in the residual map is 0.221 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.†

9: $C_6H_{13}ClFNO$, M = 169.62, Monoclinic, space group $P2_1/n$, a = 7.340(2), b = 9.302(3), c = 12.025(4) Å, U = 820.6(5)Å^3, F(000) = 360, Z = 4, D_c = 1.373 Mg m^{-3}, μ = 0.419 mm^{-1} (Mo-Kα, λ = 0.71073 Å). The data were collected at T = 125(2) K, 3185 reflections ($3.20 \leq \theta \leq 23.30°$) were measured on a Bruker SMART CCD diffractometer equipped with an Oxford Cryostream low-temperature device[25] (ω-scan, 0.3°/frame) yielding 1131 unique data (R_{merg} = 0.0428). Conventional R = 0.0391 for 1029 reflections with $I \geq 2\sigma$, GOF = 1.027. Final $wR2$ = 0.1052 for all data (96 refined parameters). The largest peak in the residual map is 0.461 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.†

(*S*)-10: $C_{19}H_{23}ClFN$, M = 319.83, Orthorhombic, space group $P2_12_12_1$, a = 9.21(3), b = 12.66(4), c = 14.89(5) Å,

† CCDC reference numbers 221927–221931. See http://www.rsc.org/suppdata/ob/b3/b312188g/ for crystallographic data in.cif or other electronic format.

U = 1735(10) Å^3, F(000) = 680, Z = 4, D_c = 1.224 Mg m^{-3}, μ = 0.226 mm^{-1} (Mo-Kα, λ = 0.71073 Å). The data were collected at T = 293(2) K, 7243 reflections ($2.11 \leq \theta \leq 23.37°$) were measured on a Bruker SMART CCD (ω-scan, 0.3°/frame) yielding 2475 unique data (R_{merg} = 0.0917). Conventional R = 0.0475 for 1386 reflections with $I \geq 2\sigma$, GOF = 0.961. Final $wR2$ = 0.1007 for all data (204 refined parameters). The largest peak in the residual map is 0.158 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.†

11: $C_4H_{10}ClF_2N$, M = 145.58, Monoclinic, space group $P2_1/n$, a = 7.335(2), b = 6.9524(19), c = 13.170(4) Å, U = 670.3(3) Å^3, F(000) = 304, Z = 4, D_c = 1.443 Mg m^{-3}, μ = 0.509 mm^{-1} (Mo-Kα, λ = 0.71073 Å). The data were collected at T = 293(2) K, 3017 reflections ($3.10 \leq \theta \leq 23.41°$) were measured on a Bruker SMART CCD diffractometer (ω-scan, 0.3°/frame) yielding 914 unique data (R_{merg} = 0.0605). Conventional R = 0.0645 for 594 reflections with $I \geq 2\sigma$, GOF = 0.925. Final $wR2$ = 0.1775 for all data (82 refined parameters). The largest peak in the residual map is 0.892 e Å^{-3}. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre.†

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