Understanding organofluorine chemistry. An introduction to the C–F bond†

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Fluorine is the most electronegative element in the periodic table. When bound to carbon it forms the strongest bonds in organic chemistry and this makes fluorine substitution attractive for the development of pharmaceuticals and a wide range of speciality materials. Although highly polarised, the C–F bond gains stability from the resultant electrostatic attraction between the polarised $C^{\delta+}$ and $F^{\delta-}$ atoms. This polarity suppresses lone pair donation from fluorine and in general fluorine is a weak coordinator. However, the C–F bond has interesting properties which can be understood either in terms of electrostatic/dipole interactions or by considering stereoelectronic interactions with neighbouring bonds or lone pairs. In this *tutorial review* these fundamental aspects of the C–F bond are explored to rationalise the geometry, conformation and reactivity of individual organofluorine compounds.

1. Introduction

The success of organofluorine compounds in all aspects of the chemicals industry (materials, pharmaceuticals, agrochemicals, fine chemicals) is striking. Because fluorine containing compounds usually emerge from broad chemical screening programmes, the influence of the fluorine is generally considered retrospectively. This *tutorial review* aims to provide some commentary in the area of interpreting organofluorine compounds and places a particular emphasis on understanding from the C–F bond, the fundamental unit of organofluorine chemistry. It is a relatively short and focused account but it takes evidence from both experimental and theoretical work and attempts to highlight key aspects of the C–F bond which may assist in interpreting the behaviour of organofluorine compounds. A key emphasis highlights that the C–F bond is polarised with significant electrostatic character, and the consequences of that go a long way to understanding organofluorine molecules. It is a personal summary, however I am very much aware of a number of recent excellent books in the area, that review organofluorine chemistry much more comprehensively, particularly those of Dick Chambers,[1] Peer Kirsch,[2] Kenji Uneyama,[3] and Daniele Bonnet-Delpon and Jean-Pierre Bégué.[4]

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† The HTML version of this article has been enhanced with colour images.

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Professor David O'Hagan was born in Glasgow and studied chemistry at the University of Glasgow (1982). He moved to the University of Southampton to carry out a PhD (1985) with John A. Robinson and then he spent a postdoctoral year at the Ohio State University with Heinz G. Floss. In 1986 he was appointed to the University of Durham where he established a strong interest in organofluorine chemistry, influenced particularly by Dick Chambers FRS. He remained at Durham until 2000, before moving to his current position at the University of St Andrews. He has wide ranging research interests in organofluorine chemistry. He was a founding member and a recent past Chair of the Royal Society of Chemistry, Fluorine Subject Group and one of the Vice-Presidents of the RSC Organic Division. He was awarded the RSC Malcolm Campbell Memorial Prize in Medicinal Chemistry in 2005 and was a recipient of the RSC Tilden Medal in 2006/2007.

2. The C–F bond is highly polarised

The high electronegativity of fluorine has a number of obvious consequences leading to polarisation imparting a less covalent and more electrostatic character to the C–F bond. This leads to a relatively large dipole and the dipole interacts with other dipoles that come close and thus the preferred conformations of organofluorine compounds can often be interpreted by considering these electrostatic interactions. Perhaps unexpectedly the polarised bond does not result in a good donor ability of the fluorine. The three lone pairs on fluorine are held tightly due to the high electronegativity of the atom and, unlike oxygen or nitrogen, they are reluctant to get involved in resonance or interact as hydrogen bonding acceptors. However, when the fluorine in a C–F bond does interact with its environment it is usually through electrostatic/dipole interactions and these aspects are discussed below.

2.1 Electronegativity and bond strength

Pauling assigned fluorine an electronegativity value of $\chi = 4$, the highest of all of the elements.[5] This was derived after

consideration of bond strengths and the degree of covalent/ionic character in the bonding of heteronuclear diatomic systems. If the energies required to dissociate two non polar covalent bonds A–A and B–B are E_{AA} and E_{BB} respectively, then Pauling found that the energy required to dissociate A–B could be expressed as:

$$E_{AB} = \tfrac{1}{2}E_{AA} + \tfrac{1}{2}E_{BB} + \Delta^2$$

Where Δ is the difference in electronegativity between A and B. From this analysis the Pauling value of $\chi = 4$ emerged for fluorine, which sits well (although not in absolute terms) with the earlier electronegativity calculations of Mulliken for fluorine which were based on an average of the ionisation energy I and electron affinity E_{ea} of a given element (but in this case fluorine) *i.e.* Fig. 1.

I	$F^+ + e \rightarrow F$	401.2 kcal mol^{-1}
E_{ea}	$F + e \rightarrow F^-$	78.3 kcal mol^{-1}
	$\chi^a = \tfrac{1}{2}(I + E_{ea})$	

Fig. 1 Mulliken derivation of electronegativity.

An appreciation of electronegativity in this way is helpful in understanding the extreme case for fluorine. Fluorine ($1s^2$, $2s^2$, $2p^5$) has the smallest atomic radius of the Period 2 elements, a contraction which arises because of its high(est) nuclear charge (nine protons) except for the noble gas neon. So, removal of an electron (I energy) from a fluorine atom to generate F^+ is extremely difficult (endothermic, -401.2 kcal mol^{-1}) as the 2p electrons are held more closely by the nuclear charge than *e.g.* oxygen (-312.9 kcal mol^{-1}). The fluorine atom can readily accept an electron, with the most exothermic E_{ea} of the Period 2 elements (+78.3 kcal mol^{-1}). This electron fills the 2p orbital, in a compacted atom, and the resultant negative charge is stabilised by the electropositive nucleus to a greater extent than electrons in more expanded valence orbitals with smaller nuclear charges such as those in oxygen with a much lower E_{ea} (+33.6 kcal mol^{-1}). Clearly, as we move down the halogens to chlorine, then the valence electrons are in the 3p shell and not so close to the nucleus, thus chlorine is less electronegative than fluorine and so on (Table 1).

2.2 The size of fluorine

The fluorine atom (and C–F bond length) is intermediate in size (and length) between hydrogen and oxygen but closer to oxygen. Bondi's atomic radii are generally quoted to substantiate this, with fluorine at 1.47 Å (Table 2) (the earlier Pauling value of 1.35 Å, although sometimes still quoted, is an underestimate).

Fluorine is often used to replace hydrogen in medicinal chemistry programmes, where C–H to C–F is the most conservative substitution for hydrogen on steric grounds. However, such a replacement has significant electronic consequences and can dramatically change the properties of a molecule, *e.g.* pK_as of adjacent functional groups, often to advantage. Replacement of F for O is a much more neutral change in that one electronegative atom replaces another and there is a closer size match, however a C–F or CF_2 replacement for C=O involves a hybridisation change (at carbon) and is generally an unsatisfactory substitution on the basis of shape, and a C–F for C–OH replacement involves the loss of the acidic hydrogen and its potential hydrogen bonding donor ability. The substitution of C–F for C–OH has emerged as an excellent tool in exploring the roles of C–OH hydrogen bonding relative to the inherent polarity of the C–O bond in biological systems. For example, important insights into the structure of collagen have been revealed, showing the importance of the polar nature of the C–OH bond rather than hydrogen bonding interactions (by replacing ((4*R*)-hydroxyproline residues with (4*R*)-fluoroproline residues) in stabilising the collagen triple helical structure.[7,8] Also, the interactions of carbohydrate binding to proteins, have benefited from exploiting this '*polar hydrophobic*'[9] aspect of the C–F bond relative to C–OH.

Table 1 Electronegativities of selected elements on the Pauling scale[5]

H (2.1)				
Li	C	N	O	**F**
1.0	2.5	3.0	3.5	**4.0**
Na	Si	P	S	Cl
0.9	1.8	2.1	2.5	3.0
K				Br
0.8				2.8
Cs				I
0.7				2.5

2.3 Hybridisation and geometry at carbon

Pauling[5] was the first to substantially draw attention to the polar nature of the C–F bond, when relating heats of bond formation to electronegativity as described above.

The C–F bond is the strongest in organic chemistry (105.4 kcal mol^{-1}). This is compared with other common bonds in Table 3. How can we account for the strength of the C–F bond? Wiberg has made significant contributions to this discussion.[10,11] The fluorine atom, as the most electronegative, has the greatest propensity to attract electron density. Accordingly, the C–F bond is highly polarised, with the electron density substantially on fluorine. The particular strength of the bond can thus be attributed to significant electrostatic attraction between $F^{\delta-}$ and $C^{\delta+}$ rather than the

Table 2 The van der Waals radii (Bondi)[6] and average C–X bond lengths of some common elements

Van der Waals radii/Å	H (1.2) Si (2.1)	C (1.70) P (1.8)	N (1.55) S (1.8)	O (1.52) Cl (1.74)	**F (1.47)**
Bond lengths/Å	C–H (1.09) C–Si (1.85)	C–C (1.54) C–P (1.84)	C–N (1.47) C–S (1.82)	C–O (1.43) C–Cl (1.77)	**C–F (1.35)**

Table 3 Bond dissociation energies of common covalent bonds. Fluorine forms the strongest covalent bond to carbon

Bond	Bond dissociation energy/kcal mol^{-1}
C–F	105.4
C–H	98.8
C–O	84.0
C–C	83.1
C–Cl	78.5
C–N	69.7

more classical electron sharing of a covalent bond. This argument can be used to rationalise the progressive bond shortening as we proceed from fluoromethane through to tetrafluoromethane.[10] Tetrafluoromethane in the extreme, can be considered as carbon ($C^{4\delta+}$) neutralised by four partial fluoride ions. The progressive positive charge density on carbon has been calculated to increase linearly by about 0.5^{+} of a charge unit on carbon as we progress from CH_3F to CF_2H_2, to CF_3H to CF_4 and the negative charge density remains the same for successive fluorines ($\sim 0.6^{-}$) through the series. Thus, each fluorine is attracted towards an increasingly positive carbon centre which leads to a progressive bond shortening due to electrostatic attraction, as we proceed from fluoromethane to tetrafluoromethane (Table 4).

This polarisation of the C–F bond leads to geometric changes in hydrocarbons.[12] For example, as we go from methane to fluoromethane and then to difluoromethane the H–C–H angle widens. This follows directly from the electron density shifts in the bonds due to the polarised C–F bonds. This can be rationalised by different models including *v*alence *s*hell *e*lectron *p*air *r*epulsion theory (VSEPR) theory.[13] The fluorine pulls valence electron density towards it and this relaxes the electron repulsion between the electron rich C–H bonds, so they spread out a little. In methane all the H–C–H angles are 109.5°, in fluoromethane the H–C–H angle widens to 110.2° and the F–C–H angle actually narrows to 108.7°. This is contrary to what might be expected on the basis of sterics and lone pair repulsion, where the fluorine is larger than hydrogen and might be expected to compress the H–C–H angle and widen the F–C–H angle, but this does not happen. The situation develops further for difluoromethane where the H–C–H angle widens to 113.8° and the angle between the two fluorines compresses to 108.4°, despite steric effects and lone pair repulsion. Alternatively these trends can be viewed as the C–F bond pulling p-orbital electrons from the sp^3 carbon to fluorine, due to fluorine's low lying 2p orbital, and the carbon therefore becomes more sp^2 in character, widening most obviously in difluoromethane (113.8°).

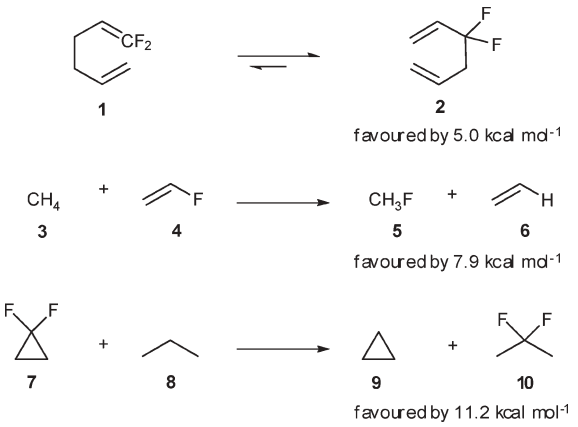


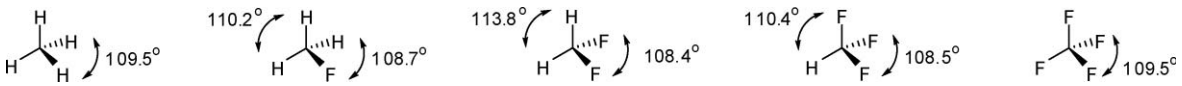
Fig. 2 Isodesmic reactions illustrating the preference for fluorine to bond to an sp^3 rather than an sp^2 hybridised carbon.

Extending the concept of fluorine attracting p-electron density, it follows that fluorine will prefer to bond to sp^3 rather than sp^2 hybridised carbon atoms. This is revealed in the case of the Cope rearrangement of 1,1-difluoro-1,5-hexadiene **1**, which thermodynamically favours the sp^3-CF_2 product **2** (entry 1 Fig. 2).[14] Such a preference is also revealed in the isodesmic calculations interconverting methane **3** and vinylfluoride **4**[15] with fluoromethane **5** and ethylene **6** (entry 2, Fig. 2) and *gem*-difluorocyclopropane **7** and *n*-propane **8** with cyclopropane **9** and *gem*-difluoropropane **10** (entry 3, Fig. 2).[11] In each case the products with sp^3 bound C–F are favoured. For the difluoropropane/difluorocyclopropane reaction both hybridisation and increased angle strain in the difluorocyclopropane **7** where the C–CF_2–C bond is wider than that in propane (*vide infra*) contribute to the overall large energy in favour of difluoropropane. This preference towards sp^3 bonded C–F is also observed in the favoured products in Diels–Alder reactions with appropriate fluorinated substrates.[16]

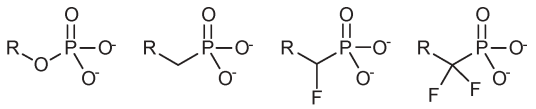
These changes in geometry/sp^3 hybridisation at carbon, influence the properties of CF_2 alkanes where the C–CF_2–C angle widens from $\sim 111°$ in the alkane to $\sim 116°$ in the difluoroalkane (*e.g.* 116.8° for 2,2-difluoropropane).[11] The introduction of a CF_2 into long chain alkanes such as stearic acids, leads to significant conformational disorder, due to this angle widening.[17]

The same effect has contributed to CF_2-phosphonates emerging as better phosphate mimics than CH_2-phosphonates, because the C–CF_2–P angle widens to 116.5°, and is more similar to that of the C–O–P angle in the phosphate of 118.7°

Table 4 Bond lengths, angles and physical properties of fluoromethanes



	CH_4	CH_3F	CH_2F_2	CF_3H	CF_4
C–F bond length/Å	—	1.39	1.36	1.33	1.32
C–F bond energy/kcal mol^{-1}	—	107	109.6	114.6	116
Boiling point/°C	−161	−78	−52	−83	−128
Dipole moment (μ)/D	0.0	1.85	1.97	1.65	0.0



angle C-X-P	118.7°	112.1°	113.3°	116.5°
pKa^2	6.4	7.6	6.5	5.4

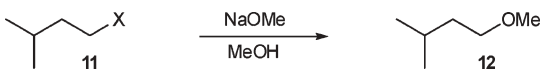
Fig. 3 Geometric and pK_a^2 properties of a phosphate and their phosphonate analogues.[18]

(Fig. 3). Of course, increasing fluorine substitution also increases the acidity (pK_a^2) of the mono- and difluorophosphonate relative to the phosphonates, rendering them better phosphate mimics both geometrically and electronically.[18]

2.4 Fluoride as a leaving group

Fluoride ion is a poor leaving group in organic chemistry, particularly in S_N2 reactions. For example, the rates of reactions of methoxide in methanol with iodo-, bromo-, chloro- and fluoro-isoamyl halides **11** are shown in Table 5 and fluoride is clearly a very poor leaving group.[1]

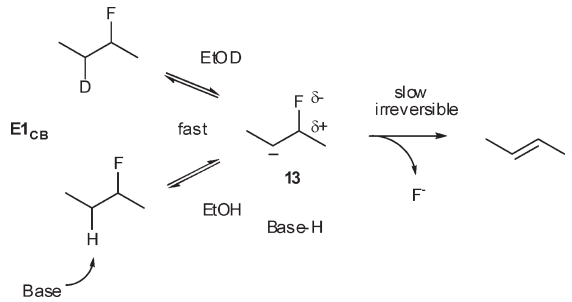
Table 5 Rates of halide ions as leaving groups in an S_N2 reaction



Halide ion	Relative reaction rate
F^-	1
Cl^-	71
Br^-	3500
I^-	4500

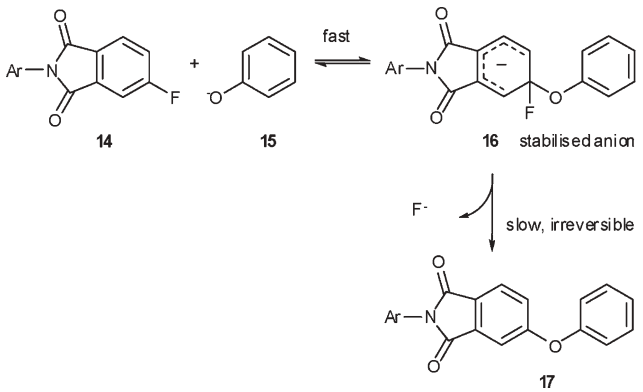
One might expect the leaving group ability to be the opposite. The C–F carbon has a significant positive charge density to attract the nucleophile, and the polarised C–F bond should be well on its way to fluoride ion. However, as discussed above, this bond is the strongest in organic chemistry due to its substantial ionic component, arising from fluorine's extreme electronegativity. The electrostatic stabilisation is sufficiently strong to resist polarisation towards free fluoride ion. So fluorine (and to some extent chlorine) show poor polarisability and direct displacement is difficult.

Nonetheless the elimination of fluoride ion under basic conditions is often problematic in synthesis. This occurs because the polarised C–F bond promotes an $E1_{CB}$ elimination process. Deprotonation β to the fluorine results in anion **13** (Scheme 1) which is stabilised by inductive withdrawal by fluorine. This anion then moves to neutralise the electropositive carbon of the $C^{\delta+}$–F^{δ} bond and eliminate fluoride ion in an irreversible process. The elimination process is rate limiting. For example, deuterium will exchange into the β-position, in *e.g.* EtOD, prior to elimination, so even under these circumstances, with an adjacent negative charge, the propensity for fluoride to leave is still slow.[19] Fluoride ion can be a useful leaving group in nucleophilic aromatic substitution reactions, another two step process, where the nucleophile attacks an electron deficient aromatic ring and then, in a slow



Scheme 1 Fluorine promotes $E1_{CB}$ elimination reactions.

irreversible rate limiting step, fluoride ion is eliminated. Such addition–elimination reactions are common with fluorinated aromatics (*e.g.* Scheme 2), and the fluorine contributes stabilisation to the intermediate anion *e.g.* **16**. So, although examples of C–F bond cleavage are rare by S_N2 reactions, fluorine will promote $E1_{CB}$ elimination reactions and the most frequent situation in which we find C–F bond cleavage is in nucleophilic aromatic substitution reactions.



Scheme 2 Example of a nucleophilic aromatic addition–elimination reaction with C–F bond cleavage.

2.5 Dipole–dipole interactions

The substantial ionic nature of the C–F bond gives rise to a large dipole moment (μ). In fluoromethane this is 1.85 D and in difluoromethane the value increases to 1.97 D (Table 4). The dipole of the C–F bond plays a significant part in determining the conformational behaviour of organofluorine compounds. For example, α-fluoroamides **18** and **19** have a very strong conformational preference (*syn–anti* 7.5 kcal mol^{-1}) for the C–F bond to lie *anti*-planar to the amide carbonyl, with the amide and C–F dipoles opposing each other (Fig. 4).[20] This conformational preference reduces steadily as we move to esters **20**,[21] ketones **21**[22] and then aldehydes **22**,[23] which have progressively weaker dipoles.

Perhaps surprisingly vinylfluorides have emerged as reasonable steric and polar hydrophobic mimetics of the amide bond, despite the removal of hydrogen bonding capacity. The success here appears to be due to the vinylfluoride dipole which, although weaker (~0.97 D *versus* 3.7 D),[24] is orientated similarly to the amide dipole (Fig. 5), and these analogues has been used successfully in medicinal chemistry studies.[25]

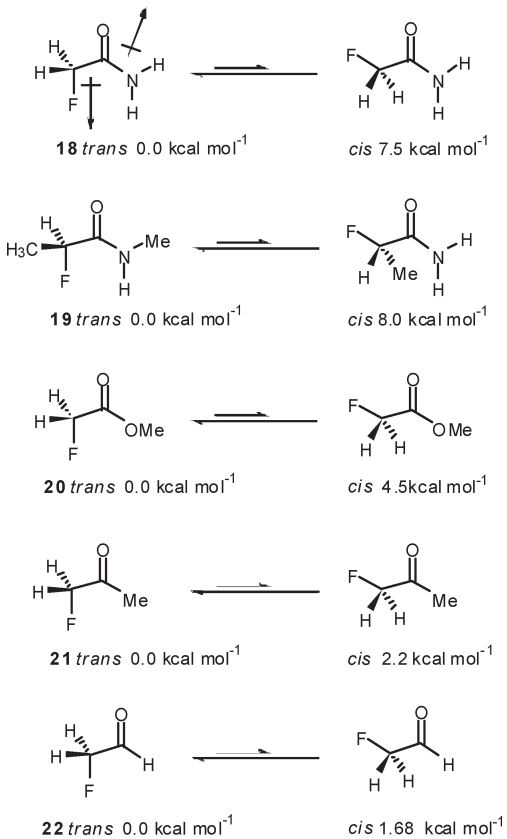


Fig. 4 Calculated energy difference between the *trans* and *cis* conformers of selected α-fluoroacyl species. The energy difference increases from aldehydes to amides approximately with increased electrostatic repulsion and dipolar relaxation.

The lower dipole moment suggests that shape compatibility must also play a significant role. A similar situation occurs with Kool and Sintim's studies using difluorotoluene,[26] which is demonstrated to be a good analogue of the DNA base thymine when used as a deoxynucleoside. When selectively positioned into DNA oligonucleotides, the difluorotoluene moiety acts as a good substrate for DNA replication by DNA polymerase enzymes and successfully directs adenine incorporation into the new complementary DNA sequence. Given

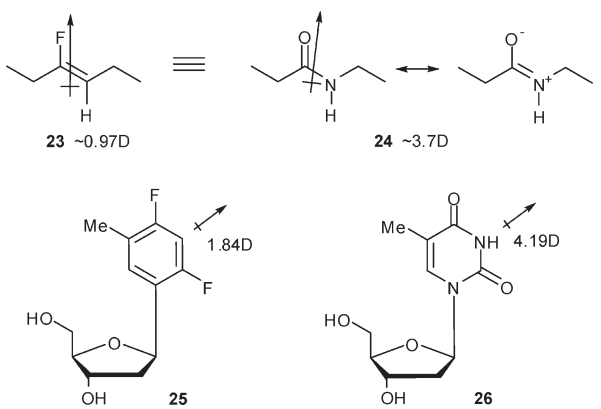


Fig. 5 Vinyl fluorides and difluorotoluene have been used as polar hydrophobic analogues of amides and thymine respectively.

the substantially weaker dipole of the toluene moiety relative to thymine, and weak hydrogen bonding acceptor ability of the C–F bond, shape compatibility emerges as an important factor in controlling sequence specificity, and these observations have opened up a discussion on the role of shape compatibility more generally on Watson–Crick DNA replication.[26]

Significant observations on dipole–dipole interactions involving C–F have been made by Mueller, Diederich *et al.*,[27,28] where they have searched the protein structure data base, (PSDB) and scanned the orientation of fluorinated drugs (mostly aromatic fluorine compounds) on their target proteins. The number of protein structures available now, with bound fluorinated compounds, is sufficient for a statistical analysis of such interactions. An overriding conclusion to emerge from this analysis is the propensity of the C–F bond dipole to adopt a Burgi–Dunitz type trajectory to amide carbonyls on the peptide backbone as illustrated for **27** in Fig. 6.

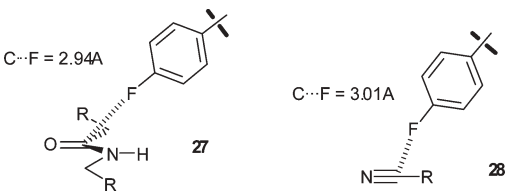


Fig. 6 Crystallographic analysis of drug–protein interactions has revealed a tendency of fluorinated aromatics to orientate towards protein backbone amides in dipole–dipole interactions. Such interactions are also found to other functional groups *e.g.* nitriles.

Although this electrostatic effect is weak relative to the other protein–ligand binding interactions, in this respect the C–F bond dipole contributes to optimising how drugs orientate at the binding site of their target enzyme/protein. This same statistical phenomenon is observed for the alignment of the C–F bonds to nitriles, *e.g.* **28**, and other polarised functional groups in small molecule X-ray structures more generally.

2.6 Charge dipole interactions C–F···X$^+$

A very much larger interaction in energy terms is experienced between the polarised C–F bond and a formal charge. This was first discussed by Lankin, Snyder *et al.* after the observation of the large axial preference (5.4 kcal mol^{-1}) for fluorine in 3-fluoropiperidinium ring systems **29** and **30**[29] (Fig. 7). It is also important in the large *gauche* preference for protonated fluoroethylamine **31** and protonated fluoroethanol **32**.[30] The *gauche* conformations of these systems result in short CF···HN$^+$ contacts (~2.4–2.5 Å), indicative of hydrogen bonding interactions, however, they are much more reasonably described as charge–dipole[29] or dipole–dipole[31] interactions. Fluorine hydrogen bonds are weak electrostatic interactions, but this situation gives rise to the strongest interactions of this kind. The interaction is strong even without a hydrogen, but as long as there is a formal charge. This is revealed by the strong *gauche* preference (~3.8 kcal mol^{-1}) observed for the fluoroethylpyridinium cation **33**,[32] a system that cannot accommodate intramolecular hydrogen bonding. So a more general description of this interaction is a charge–dipole interaction as described by Lankin, Snyder *et al.*[29]

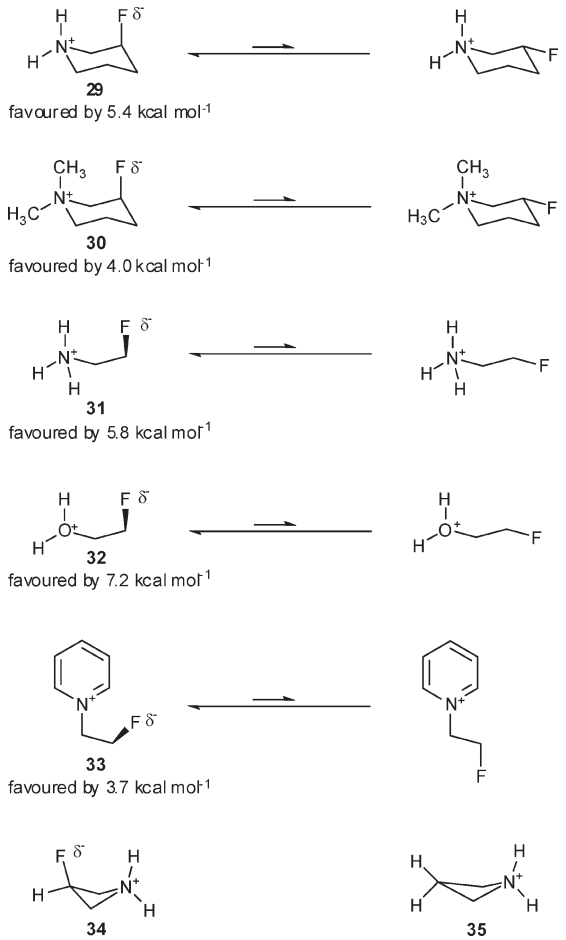
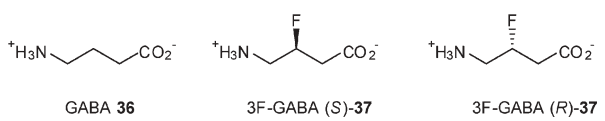


Fig. 7 The strongest intermolecular interactions of the C–F bond are found in charge–dipole interactions between C–F and a formally charged heteroatom.

The conformation of the four-membered ring 3-fluoroazetidinium cation **34** favours[32] a more puckered structure with the C–F bond approaching the N^+ atom, compared to the almost planar azetidinium cation **35** (Fig. 7).

This charge–dipole interaction has recently been exploited using 3-fluoroGABA enantiomers (*R*)-**37** and (*S*)-**37** as analogues of the neurotransmitter GABA **36**.[33] It emerges that each enantiomer has a similar interaction with $GABA_A$ receptors, but a very different interaction with the metabolising enzyme, GABA transaminase. This suggests that 3-fluoroGABA **37** (and therefore GABA **36**) binds $GABA_A$ receptors in the extended *anti*-zigzag conformation **B**, because both enantiomers can equally access a *gauche* conformation. However, for GABA transaminase the (*S*)-**37** enantiomer has a much higher affinity for the enzyme than the (*R*)-**37** enantiomer, suggesting conformation **A** as the binding mode. In this latter conformation, the (*R*) enantiomer cannot achieve a *gauche* relationship between C–F and $C–^+NH_3$ and would have to adopt the disfavoured high energy conformation (boxed in Fig. 8).



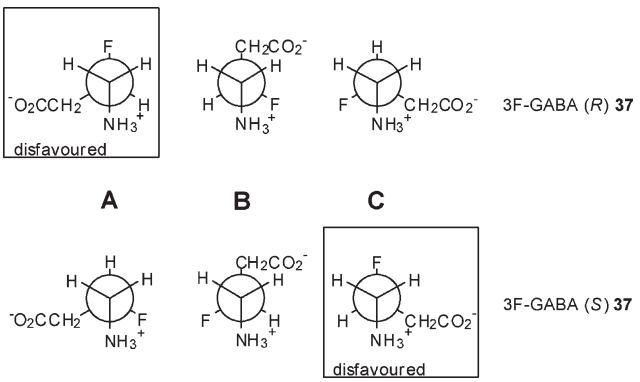


Fig. 8 The staggered conformations around C3–C4 of the enantiomers of 3-fluoroGABA **37**. Conformations where the C–F and the $C–^+NH_3$ bonds are *anti* are disfavoured, whereas the *gauche* conformers are much lower in energy and dominate in solution.

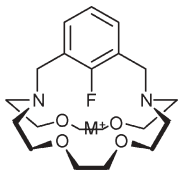
Thus this charge–dipole interaction of the C–F bond has potential as a means for exploring the binding conformations of protonated amines on target proteins.

2.7 Organic fluorine as a hydrogen bond acceptor

We have seen from the above that the C–F bond is highly polarised ($C^{\delta+}–F^{\delta-}$) This polarisation, and the presence of three lone pairs, might suggest that the fluorine will act as a good hydrogen bond acceptor. But the evidence is poor on this and organic fluorine compounds form only weak hydrogen bonds.[34,35] There are a few instances in the crystallographic literature where the fluorine in a C–F bond forms short intramolecular contacts to an acidic hydrogen atom of HX (X = N, O). The shortest CF···HX contacts observed are around 2.0–2.2 Å and calculations indicate that they are maximally about 25% of the strength of a typical hydrogen bond (*e.g.* ROH···O=C ~1.9 Å, 5–10 kcal mol^{-1}), however these are so infrequent that they attract attention as special cases. They are usually contributed to by other factors such as optimal coordination/entropy effects. Much more typical are CF···HX contacts in X-ray structures, of between 2.5–3.0 Å, just at or beyond the van der Waals contact distance between F and H (~2.65 Å). The high electronegativity of fluorine and the strong electrostatic nature of the $^{\delta+}C–^{\delta-}F$ bond hold the lone pairs (poor polarisability) and, unlike oxygen or nitrogen, render organic fluorine a poor donor and hydrogen bonding acceptor. The residual weak interactions arise almost exclusively due to through space electrostatic attraction between $^{\delta+}C–^{\delta-}F$ bond and the $^{\delta+}H–^{\delta-}X$, akin to the neutral dipole interactions discussed above in Section 2.5 for C–F protein interactions. For the very weakest interactions, *e.g.* between fluoromethane and carbon bound hydrogens, then the interaction has been deconstructed and shown to be a combination of a weak electrostatic interaction between $^{\delta+}C–^{\delta-}F$ and $^{\delta+}H–^{\delta-}C$, and also the particular form of van der Waals interaction known as 'dispersion' (London forces).[36] In these cases the C–F···H–C interaction gets stronger (0.4 to 1.7 kcal mol^{-1}) progressing from HC-sp (*e.g.* acetylene) to HC-sp^3 (methane) bound hydrogen due to an increasing electrostatic interaction as the C–H bond becomes more polarised.

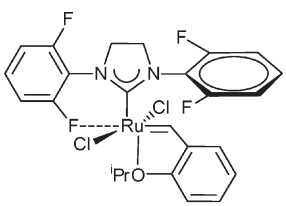
2.8 Organic fluorine as a metal ion coordinator

Although organic fluorine is a poor hydrogen bond acceptor, there is however a lot of evidence that the C–F bond will coordinate metal cations much more preferably. The interaction is an electrostatic one, again involving a charge–dipole interaction, and this is where we find the C–F bond maximising its (poor) coordination potential. The coordination of individual metals ions has been explored systematically with cryptands such as F-[2.2.1]-cryptand **38**.[37]



F-[2.2.1]-cryptand **38**

The C–F···M^+ interactions are strongest with hard cations (*e.g.* Li^+, Na^+, K^+) as expected, but extend to softer cations *e.g.* Ca^{2+}. It is also found that highly polarised metal centres (*e.g.* $TiCl_4$ and $Al(O^iPr)_3$) will coordinate C–F, particularly when the metals have highly electronegative ligands and the F–M bond dissociation energy is high (*i.e.* where F–M is a strong bond). This is the case for Al and Ti. Yamazaki *et al.*[38] have demonstrated in the synthetic arena that a fluoromethyl group can induce diastereoselectivity (82–90% de) in the methylation reactions of **39**–**41** as illustrated in Scheme 3. In this case the system distinguishes methyl and fluoromethyl to determine this diastereoselectivity, consistent with the fluorine coordinating potassium in the bicyclo[3.3.0] intermediate enolate **42**. Recently Grubbs has reported a fluorine coordination acceleration effect in the metathesis catalyst **46**.[39] So we can expect the C–F bond to participate in coordination to metal ions in a wide variety of situations.



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2.9 Is the fluorine in C–F a π-bond donor?

It has been argued above that the weak coordinating power of the C–F bond can be understood in terms of its high polarity and low polarisability (poor lone pair donating power). So to what extent can the fluorine in the C–F bond act as a π-donor?[40,41] Nitrogen and oxygen are defined by the ability of their lone pairs to enter into resonance (*e.g.* esters, amides, enol ethers *etc.*), however, fluorine only contributes lone pairs for conjugation in the most extreme case of a full positive charge.

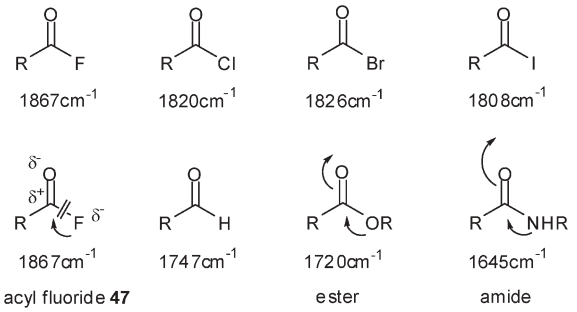
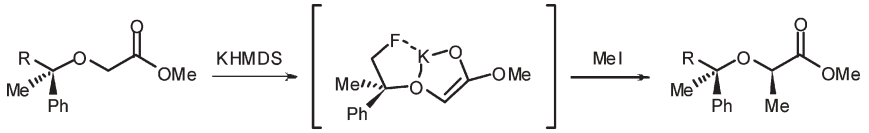


Fig. 9 IR wavenumbers of a range of carbonyl compounds do not support conjugative π-donor ability of fluorine lone pairs in acyl fluorides **47**.

If we consider the IR absorption for carbonyl compounds in Fig. 9, acyl fluorides have the highest wavenumber at 1867 cm^{-1}, indicative of a short, strong carbonyl bond. The other acyl halides have lower values (acyl chloride at 1820 cm^{-1}, acyl bromide at 1826 cm^{-1} and acyl iodide at 1808 cm^{-1}). It is useful in this discussion to compare the acyl fluorides with aldehydes, esters and amides. There is a significant difference in the IR wavenumber along this series. The aldehyde, at 1747 cm^{-1}, has no resonance possibilities and can be taken as a reference point for the absence of resonance. It is generally appreciated that there is oxygen lone pair donation into the carbonyl in an ester, and conjugation of the nitrogen lone pair is a characteristic of amides, which consequently have a low IR wavenumber (1645 cm^{-1}), yet acyl fluorides **47** have a significantly higher wavenumber (1867 cm^{-1}) than the aldehyde. The high value offers little evidence of fluorine lone pair donation in the ground state, and has to be rationalised as a consequence of the polarisation of the C–F bond, increasing the positive charge density on carbon, and pulling the carbonyl oxygen closer to it. The relative stability and higher wavenumber of acyl fluorides **47** is attributed therefore to the electrostatic stability of the C–F bond, not resonance. Another example compares the IR (C=O) wavenumbers of ethyl cinnamate and ethyl 3-fluorocinnamate (Fig. 10). The higher value for the fluorocinnamate does not support π-donor ability from the fluorine lone pairs.[42]

Although the evidence is poor for fluorine acting as a π-donor in ground state neutral systems as described above, it



Scheme 3 The C–F bond will coordinate K^+ and direct aldol reactions.

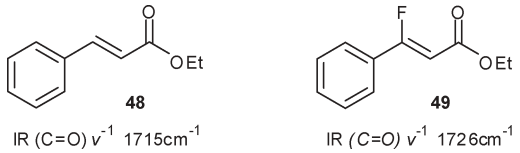


Fig. 10 The higher IR wavenumber of ethyl *E*-3-fluorocinnamate **49** over ethyl cinnamate **48** does not support the conjugative π-donor ability of fluorine in the ground state.

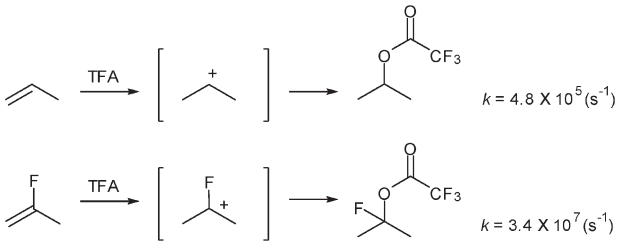


Fig. 11 Relative rates of electrophilic addition to propene and 2-fluoropropene.

appears to act as a weak donor only in fully (positively) charged carbocation systems. It is informative to compare electrophilic aromatic substitution (EAS) of fluorobenzene with chlorobenzene and toluene as summarised in Table 6.[43] For fluorobenzene the predominant and often exclusive isomer in such reactions is the *para*-substituted product and fluorobenzene undergoes EAS reactions just slower than or at a similar rate to benzene and at least an order of magnitude faster than chlorobenzene. Chlorobenzene also gives rise to minor but significant levels of *ortho*-products, whereas toluene reacts two to three orders of magnitude faster and often gives predominantly *ortho*-products (despite competing steric effects). In the intermediate σ-complexes **50** (Wheland intermediates) the 2p–2p carbocation–fluorine lone pair interaction is perfectly matched, whereas there is a mismatch (2p–3p) for chlorine, and thus, despite the highly polarised C–F bond, some back donation appears to take place, particularly to compensate a positively charged σ-complex. In fluorobenzene the strong polarisation of the C–F bond suppresses reactivity at the *ortho*-positions by inductive destabilisation. Also the strong inductive effect from fluorine alternately polarises the ring carbons such that the *meta*-carbon is δ− and this in turn supports the *ortho* positive charge of the σ-complex. This, coupled with some resonance from the fluorine lone pairs into the charged system, can account for the reactivity and product profile of fluorobenzene. It should be noted however that a very small contribution at this point can have a large effect. For example, a charge transfer of only 0.01 e from F to the *ipso*-carbon during aryl protonation is anticipated to stabilise protonation of the aromatic by 3.0 kcal mol^{-1}, and this would lead to a rate acceleration by two orders of magnitude.[40] This is the case, for example, in the addition of trifluoroacetic acid to propene *vs*. 2-fluoropropene, where there is a rate acceleration of about 100-fold (Fig. 11).[1]

The observed experimental rates in EAS are much less than this (comparing benzene and fluorobenzene), indicating very little charge transfer actually occurs from fluorine. Toluene ($PhCH_3$) behaves much more classically, with the methyl group promoting *o*/*p* substitution by hyperconjugative stabilisation, and at a much faster rate. Thus, fluorine is significantly worse than –Me as an activator, and in view of the fact that –Me is generally considered to be a weak activator in EAS, so fluorine must be considered as a very weak π-donor overall.

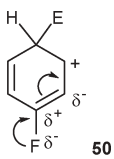
3. Hyperconjugation and the C–F bond

So far we have a picture of a C–F bond that is strong and unreactive, and that interacts only weakly through dipoles and electrostatic interactions to other molecules or functional groups. However, a consequence of the highly polarised aspect of the C–F bond is the presence of a low lying σ^*_{C-F} antibonding orbital, similar to that found for the C–O bond. Thus, electron density in the form of stereoelectronically aligned electron rich (*e.g.* C–H and π) bonds, oxygen/nitrogen lone pairs or nucleophiles can be accommodated by the σ^*_{C-F} orbital to stabilise conformations, intermediates or transition states. It is less easy to bring experimental proof to support the importance of such hyperconjugative interactions, and much of the evidence is theory based. The following sections summarise the more widely discussed stereoelectronic aspects of the C–F bond.

3.1 The σ^*_{C-F} antibonding orbital

The C–F bond has a low energy σ^*_{C-F} antibonding orbital. In this regard there are close similarities with the C–O bond and

Table 6 Product distribution and relative rates (relative to benzene) in electrophilic aromatic substitution reactions[49]



50

most favoured sigma-complex

	Nitration				Chlorination				Benzoylation				Protonation			
	Relative rate	*o*	*m*	*p*	Relative rate	*o*	*m*	*p*	Relative rate	*o*	*m*	*p*	Relative rate	*o*	*m*	*p*
$PhCH_3$	24.5	57	3.2	40	3400	59	4	37	110	9.3	1.4	89	NA	66	3.0	31
PhF	0.15	12	0.0	87	0.74	9	0	91	0.25	0.0	0.0	100	1.6	13.2	0.0	86.8
PhCl	0.03	30	1.9	69	0.1	30	1	69	0.012	0.0	0.0	100	0.12	30.4	0.0	69.6

an obvious parallel is anomeric stabilisation. In the classical case, the OMe substituent of 2-methoxypyran **51** prefers an axial rather than an equatorial conformation (Fig. 12). This violates preferred conformational effects for substituents on cyclohexane, which prefer equatorial orientations to avoid 1,3-diaxial interactions when they are placed in an axial orientation. Fluorocyclohexane has only a small equatorial preference ($\sim$0.2–0.3 kcal mol^{-1}) due to the small size of fluorine.[44] The clear axial preference in *e.g.* 2-methoxypyran **51**, is rationalised by lone pair (HOMO) donation from the ether oxygen into the σ^*_{C-O} orbital (LUMO) of the bond (*endo* anomeric effect) as shown in Fig. 12. The axial preference and anomeric stabilisation extends to 2-fluoropyran (Δeq–ax $\approx$ 2.8–2.9 kcal mol^{-1}), consistent with oxygen lone pair donation into the σ^*_{C-F} orbital. This is supported by O–C bond shortening, C–O/F$_{ax}$ bond lengthening and O–C–F angle widening in theory calculations comparing the axial relative to the equatorial conformers. It is important to recognise however that there is a reduction in the dipole moment (μ) of **52** ($\Delta\mu_{eq-ax} \approx$ 1.12 D) in going from the equatorial to the axial conformer and this reduction also contributes to axial stabilisation; however, hyperconjugative effects appear to be the dominant contributor.

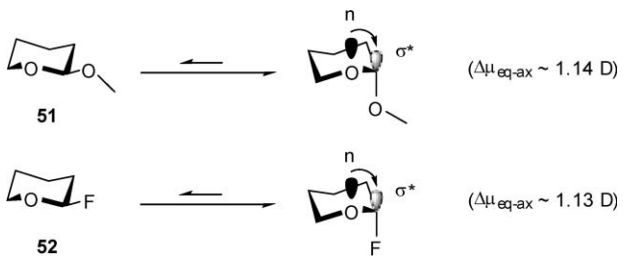


Fig. 12 The anomeric effect involving n–σ^*_{C-F} interactions operates both for C–O and C–F bonds in *e.g.* α-substituted pyrans.

It is interesting to note that α-fluoropyrans are relatively stable and the most chemically stable of the F > Cl > Br series. This to some extent is contradictory to the idea that as the most electronegative element, its antibonding σ^*_{C-F} orbital will be closest in energy to overlap with the oxygen lone pairs, and its propensity to leave as fluoride ion should be straightforward. But this n–σ^* overlap does not have the destabilising effect that might be expected, and again we have to consider the large ionic component of the C–F bond. The electrostatic attraction between $F^{\delta-}$ and $C^{\delta+}$ gives this system unusual stability. Population of a molecular orbital involving the σ^*-antibonding orbital only decreases the covalent character and increases the ionic character of the bond, and thus, of the halogens, the electrostatic attraction between $X^{\delta-}$ and $C^{\delta+}$ is greatest for fluorine. A similar argument was discussed above to rationalise the stability of acyl fluorides **47** over the other acyl halides. Acyl fluorides **47** are the most chemically stable of the series, which is unexpected on the basis of the electronegativities of the halogens. However, again the electrostatic attraction between $F^{\delta-}$ and the acyl carbonyl carbon (O=$C^{\delta+}$) strengthens the bond (see also the IR discussion, Fig. 9).

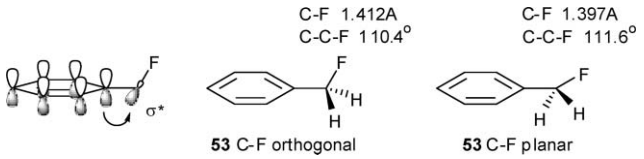


Fig. 13 The preferred orthogonal conformer of benzyl fluoride **53** benefits from a π–σ^*_{C-F} interaction, which narrows the C–C–F angle and lengthens the C–F bond relative to the planar conformer.

Another example of the σ^*_{C-F} antibonding orbital accepting electron density is revealed in the preferred conformer of benzyl fluoride **53**.[45] The rotational energy barrier is quite low at $\sim$0.4 kcal mol^{-1}, as π-donation is a weaker effect than lone pair donation, however, the lowest energy structure revealed by NMR spectroscopy, has the C–F bond orthogonal to the aromatic ring as illustrated in Fig. 13. Bond lengths and angles have been calculated for these two structures at a high level of theory and it emerges that in the orthogonal conformer, the C–C–F angle is narrower and the C–F bond longer, consistent with aromatic π-orbital donation into the σ^*_{C-F}-orbital, as a stabilising feature of the orthogonal conformer.

3.2 1,2-Fluorine bond attraction; the *gauche* effect

It is well known that 1,2-difluoroethane prefers a *gauche* rather than an *anti* conformation (Fig. 14). Various gas phase calculations and experimental observations support a *gauche* preference of about 0.5–0.9 kcal mol^{-1}. For 1,2-dichloro- and 1,2-dibromoethanes the *anti* conformers are lower in energy as expected. This observation is perhaps counterintuitive as one might predict that the fluorine atoms would repel each other, favouring an *anti* conformation. This must happen to some extent, but it is overridden by other stabilising effects. The most convincing explanation for the fluorine *gauche* effect in 1,2-difluoroethane **54** is hyperconjugation.

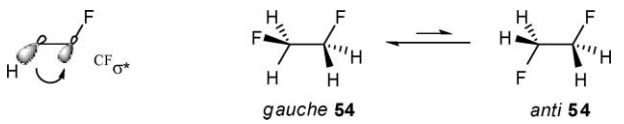


Fig. 14 1,2-Difluoroethane prefers a *gauche* over an *anti* conformation. This can be rationalised by hyperconjugation.

In the hyperconjugation model (Fig. 14), the *gauche* conformer supports two stabilising $\sigma_{C-H}\cdots\sigma^*_{C-F}$ interactions. In the case of the *anti* conformer, then an electron deficient C–F bond is now *anti* to the σ^*_{C-F} orbital and hyperconjugation does not occur. An alternative and reinforcing hypothesis for the *gauche* effect has been presented by Wiberg *et al.*[46] This is the 'bent bond' analysis, which argues that geometric changes of the σ-bonds (C–C and C–H) on carbon are due to the highly polarised C–F bond. The C–C and C–H bonds are electron rich with electron density in the middle of the bond, whereas the electron deficient C–F bond has most of its electron density on the fluorine atom. Thus, the electron density trajectory from each carbon atom towards the C–C bond is bent towards the fluorines (see VSEPR discussion on hybridisation and geometry in Section 2.3). For the *gauche*

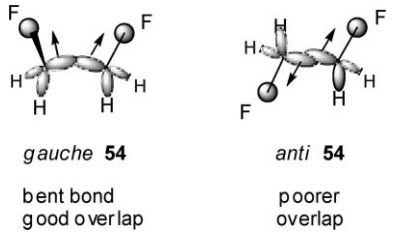


Fig. 15 Wiberg's bent bond analysis to rationalise the *gauche* effect in 1,2-difluoroethane **54**.

conformer there is good overlap in the C–C bond, but for the *anti* conformer electron density is skewed in different directions towards each fluorine with resultant poorer C–C bond overlap as illustrated in Fig. 15.

The relative contributions of hyperconjugation and bent bonds for rationalising the *gauche* preference in 1,2-difluoroethane **54** have been widely presented, and the current consensus is in favour of hyperconjugation as the greater contributor.[47]

In the case of *trans*-1,2 difluorocyclohexane **55** the energy difference between the ax/ax (*anti*) and eq/eq (*gauche*) conformers is very small.[48,49] The two conformers shown in Fig. 16 are essentially isoenergetic. In solution the eq/eq conformer dominates. The ax/ax conformer benefits from dipolar relaxation which dominates over *gauche* effect stabilisation, however, in solvents with increasing polarity then dipolar repulsion is shielded and the eq/eq *gauche* conformer predominates. For *gauche* effect stabilisation in this case, hyperconjugation comes from less efficient C–C rather than C–H σ-bond overlap with the σ^*_{C-F} orbitals and thus is less stabilising in the gas phase than that found for 1,2-difluoroethane **54**.

	Energy (Kcal mol^{-1}) eq/eq- - ax/ax
gas phase	0.1
methylcyclohexane	-0.57
dibutyl ether	-0.78
THF	-1.3
acetone	-1.51

Fig. 16 In *trans*-1,2-difluorocyclohexane **55** the ax/ax conformer is favoured in the gas phase, whereas the eq/eq is favoured in solution.

3.3 1,3-C–F bond repulsion

Vicinal fluorines appear to weakly attract each other, with a *gauche* preference often predominating as discussed above for **54** and **55**; however, when two fluorine atoms are placed 1,3- on a hydrocarbon chain, then they repel each other. This has been explored most comprehensively in 1,3-difluoropropane **56**.[50] There are four reasonable staggered conformers and both experimental evidence and theory indicate their relative stabilities as GG < GA < AA < GG′, as illustrated in Fig. 17. The order can be rationalised by considering hyperconjugative interactions, assuming that the C–H bond is a better donor[51] than the C–CF bond. Conformer GG has two C–H to σ^*_{C-F} hyperconjugative interactions, GA has one and AA has none. Anomalously, the highest energy conformer GG′ has two C–H to σ^*_{C-F} interactions, however, the overriding destabilising interaction in this conformer involves dipole repulsion between the parallel C–F bonds. This GG′ conformer is 3.33 kcal mol^{-1} higher in energy than the GG conformer.

Combinations of the 1,2-*gauche* effect and 1,3-dipolar repulsion reveal themselves in the lowest energy conformations of all-*syn* multivicinal fluorinated chains.[52] The favoured conformer for all *syn*-2,3,4,5-tetrafluorohexane motifs **57** has a helical arrangement of the C–F bonds, rather than an extended *anti*-zigzag structure (Fig. 18). The helical structure preserves the 1,2-*gauche* relationships between the C–F bonds, but avoids 1,3-dipolar repulsions. It is perhaps surprising that the 1,3-repulsive effect is so strong through space (~3.0 kcal mol^{-1}), beyond the van der Waals contacts, and this indicates that the negative electrostatic field associated with the C–F dipole is significant, despite the compression of its lone pairs. It is interesting to speculate on the conformation of longer multivicinal fluorinated alkane chains or polymers such as **58**, which should have a helical arrangement of the C–F bonds along the molecular axis.

3.4 π-Facial selectivity

The polarity of the C–F bond should reasonably influence the face of attack at a carbonyl or double bond adjacent to the fluorine *e.g.* the diastereoselectivity of nucleophilic addition to α-fluoroaldehydes or ketones. Early theoretical studies by Paddon-Row and Wong[53] explored cyanide attack to α-fluoropropionaldehyde **59** to generate the diastereoisomers of **60** and revealed a favoured transition state structure **61** where the nucleophile approaches *anti* to the C–F bond (Fig. 19). This outcome supported the molecular orbital ideas of Anh and Eisenstein,[54] who argued that a nucleophile (HOMO) will

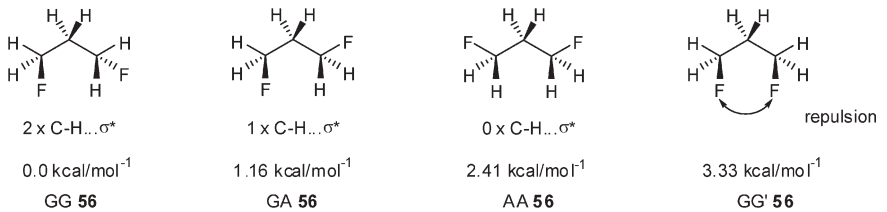


Fig. 17 The relative energies of the conformers of 1,3-difluoropropane **56**, indicating stabilising C–H to σ^*_{C-F} interactions and 1,3-repulsion in the GG′ conformer.

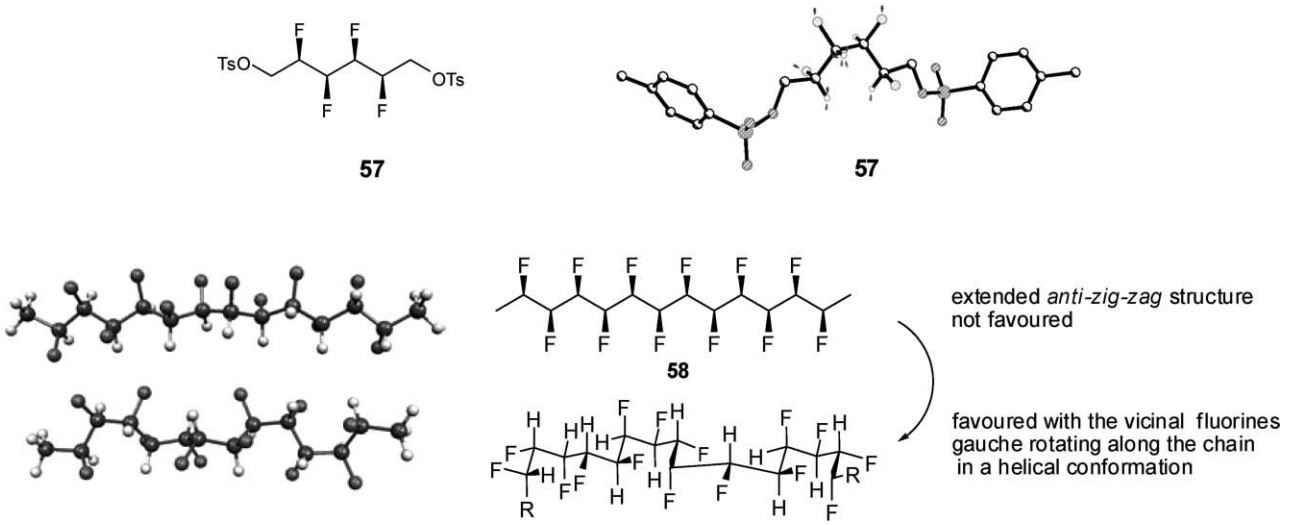


Fig. 18 The conformation of all-*syn* multivicinal fluorinated alkanes accommodates 1,2-*gauche* interactions and avoids 1,3-repulsive interactions, leading to a helical structure. The X-ray structure of a tetravicinal motif **57** is shown and a computationally derived structure of an oligomer **58** reveals a helical arrangement of fluorine along the chain.

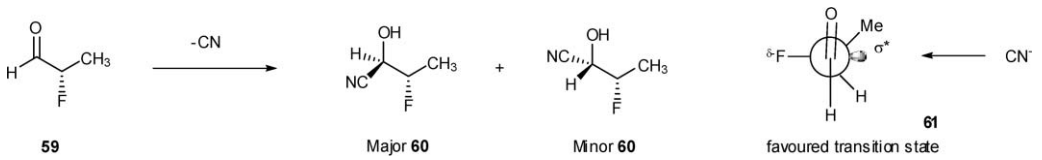


Fig. 19 Nucleophiles tend to approach α-fluorocarbonyls *via* a trajectory opposite to the fluorine atom.

approach a carbonyl back side to an adjacent C–X bond, where X is electron withdrawing, to enable electron density donation from the nucleophile (HOMO) into the carbonyl LUMO, a MO that is stereoelectronically aligned to and mixes with the σ^*_{C-X} orbital. However, as was also noted by Anh and Eisenstein,[54] a much more straightforward interpretation involves minimising electrostatic repulsion between the fluorine and the incoming nucleophile, and this appears to be the prevailing consideration in such situations.

More recently the $LiAlH_4$ reduction of axial and equatorial orientated *tert*-butyl fluorocyclohexanones $\mathbf{62}_{ax}$ and $\mathbf{62}_{eq}$ has been explored and this gives rise to the product ratios shown in Fig. 20.[55] During the reduction of $\mathbf{62}_{ax}$ the nucleophile approaches *anti* rather than *gauche* to the fluorine with a large preference of 10 : 1. There has been some debate over

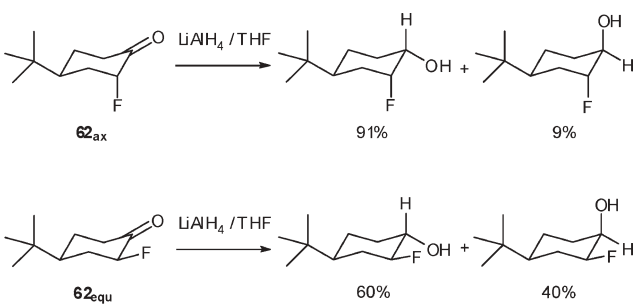


Fig. 20 Nucleophiles tend to approach α-fluorocarbonyls *via* a trajectory opposite to the fluorine atom.

competing frontier orbital hypotheses (*e.g.* Ciplak *vs.* Anh and Eisenstein) in interpreting nucleophilic attack to substituted cyclohexanones, but for fluorine the most persuasive rationale, across a wide spectrum of situations, involves electrostatic repulsion between the nucleophile and the bound fluorine. So again we can usefully interpret outcomes in organofluorine chemistry by recognising the highly polar nature of the C–F bond.

4. Conclusions

This review has focused on some relatively widely discussed aspects of the C–F bond. It has tried to emphasise that many of the properties of organofluorine compounds can be rationalised by appreciating that the C–F bond is highly polarised and that it derives its unusual stability from a significant electrostatic $C^{\delta+}$–$F^{\delta-}$ component. The C–F dipole interacts (repulsive or attractive) with other approaching dipoles or charges (*e.g.* N^+, O^+, M^+) in electrostatic interactions. In C–F the fluorine lone pairs are held by the nucleus (electronegativity) and the adjacent partially charged ($^{\delta+}$C) carbon, so they are not easily polarised and are not good hydrogen bonding acceptors or π-donors. In this respect the interaction of the fluorine with its environment is mainly through electrostatic interactions. The polarised C–F bond results in a low lying σ^*_{C-F} antibonding orbital. Hyperconjugative interactions into the low lying σ^*_{C-F} antibonding orbital from stereoelectronically aligned lone pairs or electron rich bonds can assist in rationalising the

favoured conformations of organofluorine molecules, *e.g.* as discussed for the *gauche* and anomeric effects, however, these effects are generally small. This *tutorial review* is rather descriptive and cursory and it is hoped that the reader will use it as a point of contact to delve deeper into the appropriate literature.

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