Flustrates: an attractive challenge for organic chemists

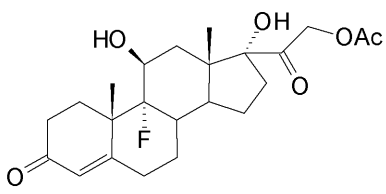
by Marcello Crucianelli

As witnessed by the large number of articles, reviews and books concerning fluoro-organic chemistry that have been published recently, the interest of scientific community toward this particular research field of synthetic organic chemistry has gone up. The present article does not cover a specific topic but rather intends to analyse some peculiar features typical of fluorine-containing compounds, in order to catch laymen attention toward the fascinating and still mysterious world of organofluorine chemistry.

Organofluorine chemistry has undoubtedly known an astonishing growth during recent years and especially in the last decade. What are the reasons to explain this restless state of activity, that moved Seebach to coin a new term such as "flustrates" in order to emphasize the unexpected and generally unusual reactivity and biological activity of *flu*orine-containing sub*strates* [1]?

Why fluorine is not merely a substituent?

First of all it must be pointed out that fluorine is an element with so many unique properties and unpredictable behaviour, that also Nature failed to handle it. Indeed Nature, that has synthesized a large number of halogen-containing natural products, produced only a dozen fluorinated molecules which mostly are very toxic for living creatures (typical is the toxicity of fluoroacetic acid: see below): a limited number of higher plants and bacteria are the only living organisms able to metabolise inorganic fluoride [2]. Fluoroorganic compounds can therefore be regarded as practically xenobiotic substances.
In spite of this, since the pioneering work of Fried concerning the preparation of 9α-fluoro-hydrocortisone acetate [3],



9α-Fluoro-hydrocortisone acetate

Marcello Crucianelli, Dipartimento di Chimica, Ingegneria Chimica e Materiali - Università dell'Aquila -Via Vetoio - 67100 L'Aquila - cruciane@univaq.it.

the selective introduction of a fluorine atom or a fluorinated residue into a biologically active molecule has become an extremely effective tool for modifying its physicochemical properties and consequently its physiological behaviour. In fact if inserted in a molecule this halogen can induce a huge variety of biological properties, varying from the complete inertness to any metabolic process (this is the case of perfluorinated fluids used as oxygen carriers) to the highest and most specific affinity for a given receptorial site (for example the selectively fluorinated amino acids used as enzyme inhibitors). Moreover fluorine can considerably alter both the chemical and stereochemical outcome of reactions well established for analogous unfluorinated compounds [4].
A rationale to the above described features lies in the peculiarities of this halogen. The *van der Waals radius* of fluorine (1.47 Å) is situated between oxygen (1.52 Å) and hydrogen (1.20 Å), and thus it appears to have a close isosteric relationship to oxygen while being larger than hydrogen. However, as seen in solid state X-ray structures, fluorine and hydrogen often interchange, suggesting a very close isosteric relationship between the two atoms. In fact the steric impact of replacing hydrogen by fluorine in a bioactive molecule is never too great, and binding of analogues to target proteins is not normally inhibited [5].
In other words, despite the different size, hydrogen and fluorine act as "bioisosteric". As a consequence, sometimes fluorinated analogues of biologically active compounds are able to follow the metabolic pathway of the parent hydrogen molecule (often involving mechanisms where stringent steric requirements are imposed), finally leading to their incorporation into the organism. This is strictly true for monofluorinated compounds, while the situation is different in di- and trifluoro derivatives or perfluorinated ones.

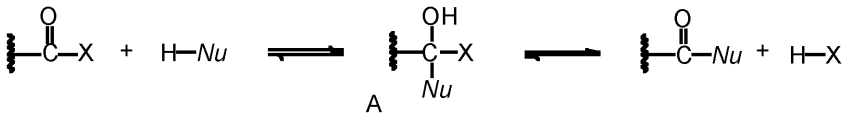


Figure 1

From a survey of literature data, it can be established that the *van der Waals molar volume* of the trifluoromethyl group (21.3 cm^3/mol) is almost the same as the isopropyl group, and the perfluoroisopropyl group has almost the same volume of the *t*-butyl group [6]. Thus the substitution of one, two, and three hydrogen atoms on carbon, by fluorine causes a sensible distortion in maintaining an isogeometric profile between the fluoro- and hydro-carbon series.
Fluorine is a first row π donor and, at the same time, *the most electronegative* element. This interplay of π-donation and σ-withdrawal makes the behaviour of fluorine-containing compounds sometimes astonishing but always interesting and challenging. So, the acidity, basicity and non-bonding interactions of neighbouring groups, close to the fluorinated site prove to be altered and the effects can be impressive (see for instance the pKa values of CH_3COOH: 4.76 and CF_3COOH: 0.52 [7]). As a consequence the chemical and enzymatic reactivity of surrounding functionalities is affected, and the conformation of the whole molecule may be changed due to dipole interactions.
Moreover the *strength of carbon-fluorine bond* (485.7 kJ/mol) frequently makes the substrate relatively more resistant to metabolic transformations, if compared with parent hydrocarbon. This is the reason why, even more frequently, in medicinal chemistry man-made fluorinated organo-compounds have been exploited in attempt to prolonge the action of a drug by blocking the sites involved in oxidative degradation.
In order to increase the biological activity of a drug it is necessary to raise its effective concentration in the target tissue, by improving the ability of the molecule to penetrate lipid bilayers. This may be obtained by increasing its lipophilicity, that is a property that often controls absorption, transport and delivery of a drug to its biological target. If introduced in a molecule, fluorine may alter its *lipophilic character.* The logarithm of octanol/water partition coefficients (log *P*) is the most common quantitative measure of lipophilicity. Fluorination clearly increases lipophilicity and its effect can be very large, when heteroatoms are present. The sulfone $C_6H_5SO_2CF_3$, for instance, is 150 times more lipophilic than $C_6H_5SO_2CH_3$. Aromatic fluorination invariably increases lipophilicity (even when it significantly increases acidity and hydrogen-bonding capability), as also makes fluorination of C adjacent to atoms with π-electrons, as well as of systems like C=C bonds.
The situation is more complex for fluorinated aliphatic carbonyl compounds: indeed α-fluorinated ketones or aldehydes commonly form stable hydrates (*gem*-diols) and ketals or acetals and their *apparent* lipophilicities depend on the choice of partitioning solvents [8]. The tendency of α-fluorinated carbonyl derivatives to exist in equilibrium with its hydrate form (i.e. a fluorinated residue in particular a CF_3, due to its strong electron withdrawing effect, tends to stabilize an α- sp^3 hybridized carbon) is the key to understand the large use of fluorinated molecules as potent inhibitors of esterases and proteases.
Indeed, as it is known, ester or amide hydrolysis, and the corresponding reverse reactions (ester and amide formation), follow an addition-elimination mechanism (Figure 1). If the enzyme is able to lower the energy level of the tetrahedral intermediate **A** by binding it preferentially, then the nucleophilic exchange will be accelerated. When the intermediate **A** behaves as a chemically stable species, neither a forward nor a backward transformation is any longer possible and the substrate jams in the enzyme, thus deactivating it [9].
A simple means to produce stable intermediates of type **A** is to introduce fluorine atoms in the α-position of carbonyl compounds.
Some examples of fluorinated compounds devised to interfere with enzymatic hydrolysis processes are depicted in Figure 2: **B** and **D** as acetylcholesterinase inhibitors, **C** as juvenile hormone esterase inhibitor.
Despite one extra lone pair, the higher electronegativity and lower polarizability of fluorine attenuate its electrostatic influence in comparison with oxygen. So, despite their apparent similarity in size, electrostatic effects emerge as a significant factor underlying the limited ability of fluorine to act as an oxygen surrogate (e.g. an OH mimic): the capacity of organically bound fluorine to enter into *hydrogen bonding* as an acceptor has been widely discussed. If the hydrogen difluoride anion $[F\cdots H\cdots F]^-$ is notorius for its symmetrical exceptionally tight (40 kcal/mol) hydrogen bond [10], all other cases of inter- or intramolecular hydrogen bonding involving covalent fluorine should be valued carefully.
Recent theoretical calculations have measured the strength of an optimum F····H bond (1.9 Å) to be 2.38 kcal/mol in an adduct between fluoromethane (CH_3F) and water. F····H contact strength can be estimated to be up to 4 kcal/mol, while generally O····H hydrogen bonds range from 5 to 10 kcal/mol [11]. There are numerous examples demonstrating total or significant loss of biological activity when a hydroxy group is replaced by fluorine. On the other hand, there are many proven cases of biological activity being maintained despite the replacement of hydroxy by fluorine substituents, as in the case of the muscarine-like activity of 4-fluoro-4-deoxy analogues **E** (X = H, eight

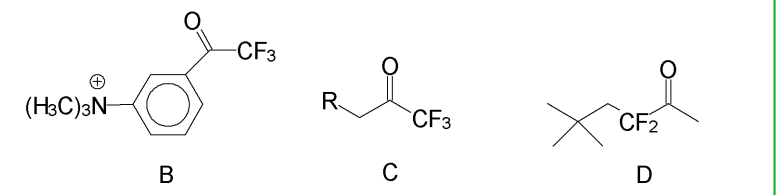
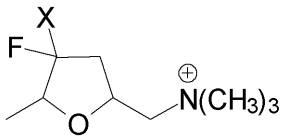


Figure 2

stereoisomers) and even of 4,4-difluoro-4-deoxy analogues **E** (X = F, four stereoisomers) [12].



E

The *NMR properties of* ^{19}F (100% natural abundance) make it a particularly useful probe for the study of both structure and activity mechanism of fluorine-labeled biomolecules, including peptides and proteins. ^{19}F has a spin number *I* of 1/2 (no electrical quadrupole moment) and equally high sensitivity to ^{1}H nucleus (0.83 times as sensitive as ^{1}H); it has a much higher chemical shift range than does ^{1}H; chemical shifts are particularly sensitive to environment and, of special importance, there are no endogenous signals present. There has been extensive use of fluorine-labeled peptides using ^{19}F NMR spectroscopy to probe such parameters as local environments of individual amino acid residues, effects of ligands on chemical shifts in fluorine-labeled receptors, intramolecular communications, and others [13].

In addition fluorine has a useful short-lived isotope, fluorine-18 (^{18}F), which decays by positron emission. Positron emission tomography (PET) is a practical noninvasive technique used for the survey of living tissue, which complements more traditional methods such as X-ray studies, by allowing real time analysis of metabolic processes. In order to gain these particular informations it is necessary to introduce ^{18}F-labeled materials into living tissue. ^{18}F PET has been used, for example, in the brain imaging of Parkinson's disease patients [14].

Additional interest, fascination and scientific challenge stem from the discovery of the unique *stereocontrolling properties* of fluorine substituents. There is a certain number of examples which demonstrate the abilities of fluorine and fluorine-containing groups to play the role of enantiodirecting factors inverting the stereochemical results of reactions. Thus, many of the methods established for asymmetric synthesis of fluorine-free compounds do not work or give impractical outcomes when applied to preparing fluorine-containing targets, and new synthetic strategies may be necessary in order to obtain chiral nonracemic fluorinated organic molecules.

Antimetabolite formation by means of fluorine introduction

From a reviewal of some peculiar properties of fluorine till now described, it is possible to get an answer to the initial question about the intriguing, exciting and often unforeseeable reactivity and biological activity of fluoro-organic compounds used for therapeutic ends.

Working in the field of medicinal chemistry the basic idea is always the same. Researchers generally attempt to alter molecular properties such as reactivity, metabolic stability and lipophilicity of a drug without changing the molecular dimensions. By replacing a hydrogen atom located at a critical site with a fluorine atom, one falsifies the original chemical information. As long as the biological sensors check the incoming material only by monitoring shape and size, they will be fooled until it is too late [15]. As suitable example may be chosen the molecular mechanism explaining the high toxicity of fluoroacetic acid (Figure 3), which was the first fluoroorganic substance isolated *inter alia* from leaves of the native South African gifblaar (*Dichapetalum cymosum*) shrub.

Fluoroacetic acid, not enzymatically recognized as a xenobiotic compound, is able to mimic so accurately acetic acid, to replace it in the Krebs cycle, by forming fluoroacetyl-CoA which then combines with oxalylacetic acid to give (2*R*,3*R*)-2-fluorocitric acid.

The latter specifically inhibits aconitase (the enzyme which dehydrates citric acid to aconitic acid) blocking the Krebs cycle, and more generally prevents citrate transport across mitochondrial membranes. The organism then anabolizes fluoroacetic acid into an antimetabolite which blocks irreversibly a vital process. This phenomenon has been designed by Peters as "lethal synthesis" [16].

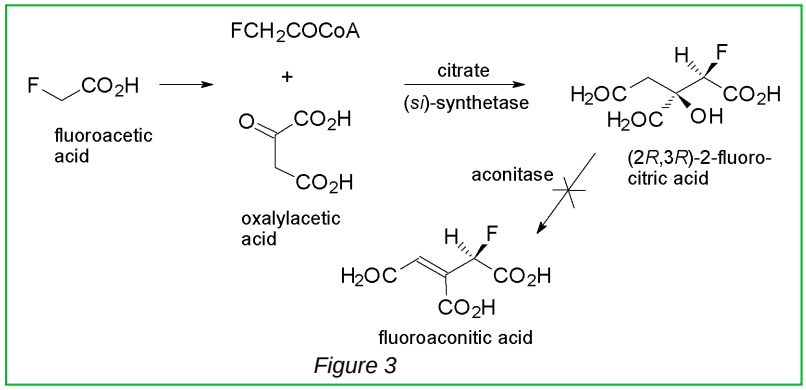


Figure 3

The comprehension of the molecular mechanism for fluoroacetate toxicity, gave a great impulse to the rational design of enzyme inhibitors for chemotherapeutic aims, by selective fluorine introduction in a naturally occurring compound.

Hints on fluorination methods

Once avoided as a fluorinating agent because of its voracious, destructive reactivity with organic molecules, elemental fluorine has come to be recognized as a useful reagent in synthetic organic chemistry [17].

It is known that the destructiveness of elemental fluorine is due mainly to the ease with which the F-F bond homolytically cleaves to give F radicals. Having a small size and the most high electronegativity, fluorine radicals attack organic molecules indiscriminately, breaking almost any C-H or C-C bond.

This peculiar reactivity was exploited during '70s and '80s in J.L. Adcock's and R.J. Lagow's laboratories in USA, in order to synthesize perfluorinated compounds by replacing all the hydrogen atoms in certain types of organic molecules with fluorine.

Now, the taming of molecular fluorine has been achieved by careful control of several factors, including the concen-

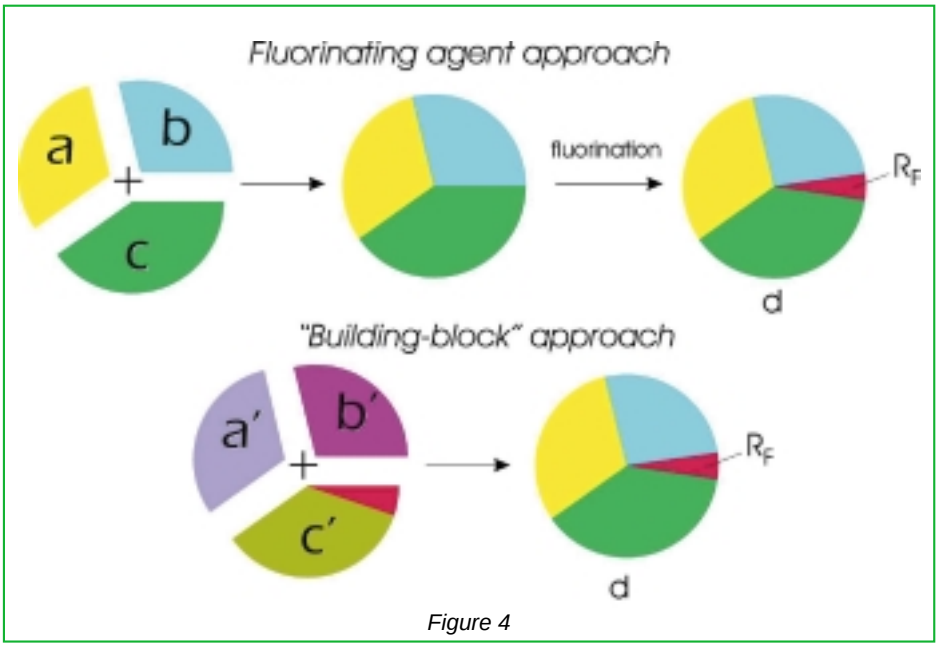


Figure 4

tration of fluorine in the reaction vessel, the reaction temperature and the choice of solvent.

Anyway to get stereocontrolled syntheses of fluorinated analogues of biologically active compounds, it is still difficult if not impossible to exploit elemental fluorine just as, in order to perform the selective fluorination of easily available non-fluorinated "chiral pool" substrates such as amino acids, carbohydrates, etc.

It is known that, according to severe FDA (Food and Drug Administration) guidelines, in modern pharmaceutical research the availability of *enantiomerically pure* molecules has become a basic requirement, in order to test their potential "receptor site" directed biological activity. Indeed, in recent years it has been finally acknowledged that two enantiomers of a chiral compound should be recognized as different substrates, one of which (eutomer) can display the desired biological activity, whereas the other (distomer) could possess opposite biological properties, be less effective or inactive, or, at worst, toxic.

Unfortunately the "chiral pool" does not provide any chiral fluorinated molecule, and so two strategies are by far followed in order to obtain chiral non racemic selectively fluorinated compounds **d** (see Figure 4, in which R_F=fluorinated residue): insert the C-F bond(s) required at a convenient stage using a fluorinating agent, or purchase a starting material already containing the C-F bond(s) needed (the "building-block" approach). Depending on the target molecule, either or both approaches may have to be employed [18].

By using the asymmetric fluorination (first strategy) for the introduction of new fluoro-containing stereocentres into prochiral molecules the three basic strategies currently used in asymmetric synthesis may be employed: (a) *reagent controlled stereoselectivity*, where the fluorine stereogenic centre is created by reacting a chiral reagent not covalently attached to the substrate with a prochiral unit; (b) *auxiliary controlled stereoselectivity*, in which the fluorine stereocentre is introduced by means of a covalently bound chiral moiety which in turn is removed in a late step; (c) *substrate controlled diastereoselectivity*, where the new fluorine stereocentre is generated by exploiting the presence of a covalently bound chiral unit, retained in the final target [19].

On the other hand the "building-block" approach, that is, the construction of complex molecular frameworks containing new stereogenic centres and functional groups around a fluorinated chiral building block [20], has been deeply investigated only in recent years due to the above mentioned lacking availability of fluorinated synthons in enantiomerically pure form.

In conclusion, judging by the large number of reviews and scientific reports published during last decade [21], it is possible to work out that the current knowledge level on fluorine chemistry is noticeably improved. However it is clear that future studies and investigations will be necessary in order to further expand aims and targets of this very promising field of chemistry.*

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[20] In this context, a considerable scientific growth to the chemistry which exploits the sulfinyl group as chiral auxiliary derived, during ‘80s and ‘90s, from the research groups of Prof. Bravo and Prof. Resnati at the Politecnico di Milano. By following the “building-block” approach, this useful and versatile stereogenic sulfoxide has been used in original synthetic methodologies devoted to the synthesis of a plethora of enantiomerically pure fluorinated analogues of biologically active compounds containing oxygen and nitrogen functionalities: for a comprehensive review see P. Bravo, M. Zanda, “Asymmetric Synthesis of Fluoro-Organic Compounds *via* Chiral Sulfoxide Chemistry” in [6], page 107.
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