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REVIEW

FLUORINE CHEMISTRY: PAST, PRESENT AND FUTURE

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In this paper, some of the discoveries and accomplishments of the fluorine chemistry, in its past, present and future will be reviewed. The dramatic changes that the field of fluorine-containing compounds has undergone over the last 70 years, from the discovery of **Freon** in 1930s to the positron emission technology (**PET**) are discussed. The future of fluorine chemistry appears to be bright and new perspectives are expected in the most important areas of technology in the new millennium.

INTRODUCTION

On June 28, 1886, the August French Academy of Sciences heard the news chemist has been hoping for since the beginning of the nineteenth century. Henri Moissan, a 34-years old French chemist, had finally isolated the element fluorine. This was the "Fluoric radical" that Antoine-Laurent Lavoisier, the "father" of modern chemistry, had predicted in 1789 when he produced the first precise definition of a chemical element.

Fluorine (from L. *fluere*, meaning "to flow"), "the gas of Lucifer", is a pale greenish-yellow gas. It occurs naturally within some fluorite crystals. Dark violet fluorite from Wölsendorf in Bavaria is called antozonite because the smell of ozone is apparent when crystals are fractured or crushed. Violet crystals from Quincie, dep. Rhône, France are similar. In both cases the ozone is generated by the release of free fluorine from the crystal lattice. The fluorine reacts with water vapour in the air, forming hydrogen fluoride and ozone. A nasty combination.

This element was not isolated for many years after this due to its extreme reactivity - it is separated from its compounds only with difficulty and then it immediately attacks the remaining materials of the compound. Finally, in 1886 fluorine was isolated by Henri Moissan after almost 74 years of continuous effort. It was an effort which cost several researchers their health or even their lives. The conclusive experiments were carried out in June 1886. A solution of potassium fluoride in dry hydrogen fluoride was electrolyzed on a rater exotic piece of equipment. To resist the extraordinarily corrosive fluorine gas produce, Moissan made his electrolytic cell body out of platinum. The conducting Electrodes were fabricated from an alloy of platinum and iridium, and were fitted into fluorspar stoppers. With this costly equipment, elemental fluorine was isolated for the first time.

Henri Moissan received the Noble Prize in chemistry in 1906 for his contributions to inorganic chemistry. He did not live long to enjoy his fame. He died in 1907 at the age of fifty-four, and it seems likely that he too was a martyr to the effects of fluorine and its compounds.

It can be said that the field of fluorine chemistry was born with Henry Moissan's first isolation of elemental fluorine in 1886.

During World War II fluorine was used for very special purposes**:** in 1940 Germany´s IG Farbenindustrie developed a secret project of the Oberkommando des Heeres (German Army High Command) for manufacturing a new incendiary agent, chlorine tri-fluoride".[2]

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The first large scale production of fluorine was needed for the atomic bomb Manhattan project in World War II where the compound uranium hexafluoride (UF_6) was used to separate the ^{235}U and ^{238}U isotopes of uranium. The enriched radioactive uranium was used for the construction of the first atomic bombs, which went down on Hiroshima and Nagasaki in 1945.[3] Today both the gaseous diffusion process and the gas centrifuge process use gaseous (UF_6) to produce enriched uranium for nuclear power applications. Uranium refining for nuclear energy is still one of the major uses for elemental fluorine.

Fluorine is the most electronegative and the most reactive of all the elements. It forms compounds with essentially all the other elements (with the exception of the lighter noble gases, helium, neon and argon). Fluorine is also the smallest substituent (other hydrogen or hydrogen's isotopes).

This high reactivity can be attributed to a combination of the very weak F-F bond and the very strong bonds of fluorine to most other elements. The strength of C-H, C-C and C-F bonds in highly fluorinated compounds gives rise to the extraordinary thermal and oxidative stability that generally characterized fluorine-containing organic compounds. Of all types of bonds in organic chemistry, the carbon-fluorine bond is the most inert and the most resistant to oxidative degradation. In addition, fluorocarbons have exceptional and unique physical and chemical properties, and have found a widespread use in practical applications such as refrigerants, aerosol propellants, plastics, pharmaceuticals, oils, pesticides, etc. Several new published "reviews" about fluorine chemistry, in particular, those of Powel et al.,[4] Hiyama,[5] Kirsch,[6] Chambers,[7] Uneyama,[8] and a special issue of *Chemical Reviews,*[9] present a perspective of fluorine chemistry at the beginning of the 21th century.

NATURALLY OCCURRING COMPOUNDS CONTAINING FLUORINE

"Even Nature finds fluorine chemistry difficult, so no wonder the element is a challenge for chemists", say two famous fluorine chemists, David O'Hagan (University of St Andrews, UK) and Graham Sandford (University of Durham, UK).

In spite of the fact that fluorine is a very common element in the earth's crust (13th most abundant), nature has found it difficult to incorporate fluorine into naturally occurring molecules, owing to the very strong energy of solvation of fluoride ion in water. As a result, they are few naturally occurring fluorine-containing compounds and *none* containing more than one fluorine atom. In the Fig. 1 are presented the short list of natural occurring fluoroorganic compounds[10].

THE FIRST FLUORINATING ENZYME

Although fluorine is the thirteenth most abundant element in the Earth's crust, fluoride concentrations in surface water are low and fluorinated metabolites are extremely rare.[11,12] The fluoride ion is a potent nucleophile in its desolvated state, but is tightly hydrated in water and effectively inert. Low availability and a lack of chemical reactivity have largely excluded fluoride from biochemistry: in particular, fluorine's high redox potential precludes the haloperoxidase-type mechanism[13] used in the metabolic incorporation of chloride and bromide ions.

But fluorinated chemicals are growing in industrial importance, with applications in pharmaceuticals, agrochemicals and materials products.[14]

The fluorine atom is a small and compacted atom and sterically it sits between H and O. It can often replace H or O in an enzyme substrate without a significant change in the shape, and it is often recognised by the target enzyme.

Reactive fluorination reagents requiring specialist process technologies are needed in industry and, although biological catalysts for these processes are highly sought after, only one enzyme that can convert fluoride to organic fluorine has been described. *Streptomyces cattleya* can form carbon-fluorine bonds and must therefore have evolved an enzyme able to overcome the chemical challenges of using aqueous fluoride.

When grown in the presence of F^- ions, *S. cattleya* secretes fluoroacetate and 4-fluorothreonine, demonstrating its ability to biosynthesize organofluorine metabolites. This organism contains an enzyme with a relative molecular mass (Mr) of 32,200 that has been shown to catalyze the formation of a C-F bond by combining S-adenosyl-L-methionine (SAM) and F^- to generate 5'-fluoro-5'-deoxyadenosine (5'-FDA) and

L-methionine. In 2003, O'Hagan et al., of the University of St. Andrews, reported the discovery[15], and the structural characterization[16] of a bacterial fluorinating enzyme, 5'-fluoro-5'-deoxyadenosine synthase (**5'-FDA synthase**), which provides the means to allow the reaction of fluoride ion with S-adenosyl-L-metionine (**SAM**) to form 5'-fluoro-5-deoxyyadenosine (**5'-FDA**). The authors report the sequence and three-dimensional structure of the first native fluorination enzyme, 5'-fluoro-5'-deoxyadenosine synthase, from this organism. Both substrate and products have been observed bound to the enzyme, enabling the authors to propose a nucleophilic substitution mechanism for this biological fluorination reaction (Scheme 1).

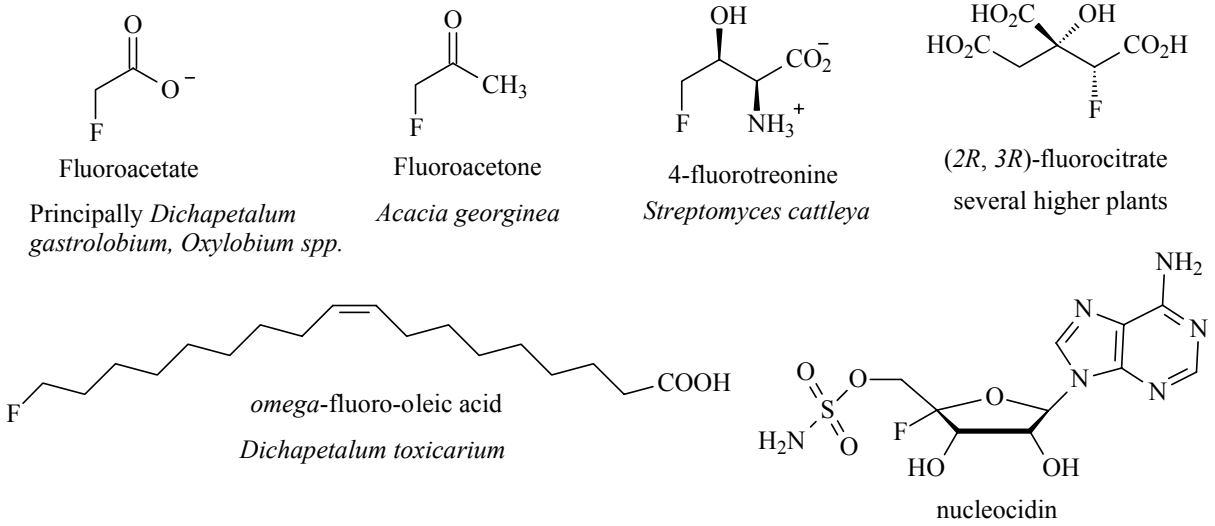
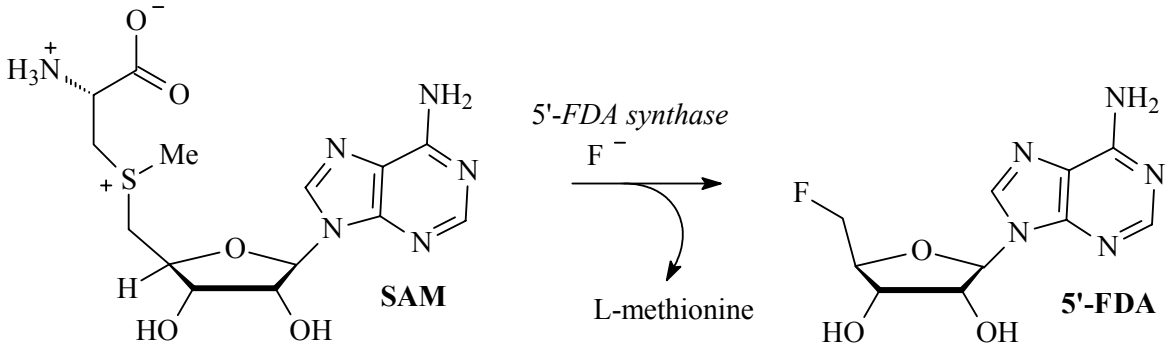


Fig. 1 – Natural occurring fluoroorganic compounds.



Scheme 1

LEVELS IN HUMANS

Fluorine as fluoride (F^-) is probably an essential element for humans and certainly is for some molluscs. In 1981, John Emsley at King's College, London, England, report findings on the hydrogen bonding properties of fluoride ion that shed considerable light on the problem of the mechanism of fluoride toxicity.[17] On the basis of experimental and theoretical data, it was demonstrated the existence of an unusually strong hydrogen bond between the fluoride ion and amides (RCONHR') that may be involved in how fluoride interferes with normal biological functioning. Whereas the fluoride ion is comparatively stable in aqueous solution and not very reactive in normal covalent bond-forming and bond-breaking reactions, "its strong hydrogen bonding potential toward the NH group of amides and related biomolecules," provides, in the words of Emsley, "an explanation of how this reputedly inert ion could disrupt key sites in biological systems."

ORGANOFLUORINE CHEMISTRY – A SYNTHETIC FIELD

The introduction of fluorine substituents into an organic molecule can radically change the physico-chemical properties of that molecule. Try substituting fluorine for hydrogen in some compounds and the consequences can be dramatic. Take for example vinegar, more formally known to chemists as acetic acid, CH_3COOH. Insert a fluorine atom and you have fluoroacetic acid**,** CH_2**F**COOH - one of only a handful of fluorine-containing compounds found in Nature. Fluoroacetic acid is highly poisonous; found among other places in plants of the South African veldt, it is responsible for numerous deaths among the cattle that graze there.

High performance materials and polymers, vectors for drug delivery, anesthetics, fluorine-containing drugs, perfluorinated solvents for organic reactions are only a few examples of the practical uses of fluorinated molecules.

But introducing fluorine atoms can impart many desirable properties too. Polytetrafluoroethylene (PTFE) is the basis of the non-stick coating Teflon, as well as the breathable waterproof fabric Goretex. Perfluoropolyethers such as Krytox are universally used for lubricating high performance jet engines for commercial, military and space flight. Both types of polymer contain strong C-F bonds and are thermally stable, chemically inert and 'non-stick', because of the low affinity of fluorine for other materials.

In the pharmaceutical and agrochemical sectors, selectively fluorinated products are increasingly common. Introducing F and CF_3 substituents often improves lipophilicity, and supresses metabolic detoxification processes to increase the *in vivo* lifetime of drugs. Examples of selectively fluorinated drugs include the antimalarial drug **Larium**, several antibacterial agents based on 6-fluoroquinolones, and linezolid, which represents the first new class of antibiotic for 30 years. The antidepressant **Prozac** contains a CF_3 group, while **Efavirenz** possesses a CF_3 group at a chiral centre.

Elemental fluorine is generally too reactive for use in direct reactions with organic compounds, but favorable results could be achieved through the choice of specific reaction conditions (degree of dilution, temperature, the nature of solvent). The energy, which is liberated at the fluorination, and leads to unselective substitution, carbonisation, etc. is removed by working at a low temperature. For example, the direct addition of F_2 to olefins at –72 °C leads to the respective vicinal difluorides in good yields.[18] Fluorinations with the very diluted F_2 (with N_2 or Ar) at low temperature were also extensively studied. Fluorinations with F_2 in polar solvents like water (in 1961, Grakauskas[19] succeeded in the fluorination of urea dissolved in water to *N*,*N*-Difluorourea, $F_2NC(O)NH_2$), CH_3COOH, or $CH_3COOH/CFCl_3$ mixture were also performed.[20]

Organofluorine chemistry is virtually a completely man-made branch of organic chemistry. Since none of the natural C-F compounds are isolated for utilisation, synthetic routes to a wide variety of fluoro-organic molecules have been developed, and an impressive array of reagents exists for creating a C-F bond (the strongest single bond involving carbon). Today more than one million compounds containing one or more carbon-fluorine bonds are known.

As concerning the basic strategy in the synthesis of fluorinated compounds, two approaches are open to planning routes to novel fluoro-organic targets: **1. chemical methods** and **2. electrochemical methods**.

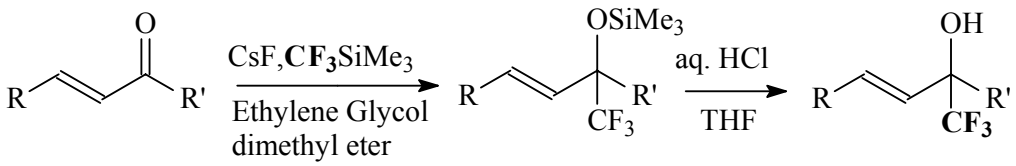
1. Chemical methods. By chemicals methods, partially fluorinated organic compounds are prepared by two different approaches:

(i) by insertion of a group already containing C-F bonds into an existing molecule
(the 'building-block' approach), or

(ii) by creating new C-F bonds by fluorination ('en route fluorination')**.**

The 'Building Block' method.[21] This is an effective methodology for a preparation of complex molecules based on multiple molecular conversions of commercially available fluorinated compounds such as CF_3COCF_3, CF_3COMe, CF_3COEt, TMS-CF_3 and CF_2Br_2. The disadvantages of this method are: (a) the limitation of commercially available fluorinated compounds; (b) the shortage of monofluorinated precursors, and (c) that fluorinated substrates are always costly.

For example, a facile synthesis of *trans*-α-trifluoromethyl allylic alcohols was performed by the CsF-catalyzed nucleophilic trifluoromethylation of enones with TMS-CF_3 (Scheme 2).[22]



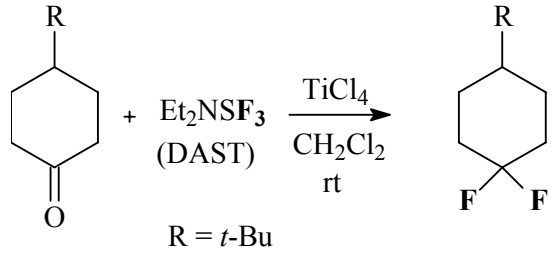
Scheme 2

The Direct fluorination ('en route fluorination'). Direct substitution of hydrogen by fluorine generally requires the handling of elemental fluorine, either in a direct reaction with the substrate or in the preparation of fluorinating reagents. This method is used generally when introduction of a single fluorine (sometimes two) into a molecule is desired.

The fluorinating reagents are nucleophilic or electrophilic ones.

Nucleophilic fluorinating reagents: $\mathbf{F}^-$ is a poor nucleophile and highly toxic. To overcome these problems, the most commonly used nucleophilic reagents are HF, BrF_3, XeF_2, SF_4, SiF_4, alkali metal fluorides, AgF, HgF_2, CuF_2, ZnF_2, Et_2NSF_3 (DAST) and $R_3N.nHF$.

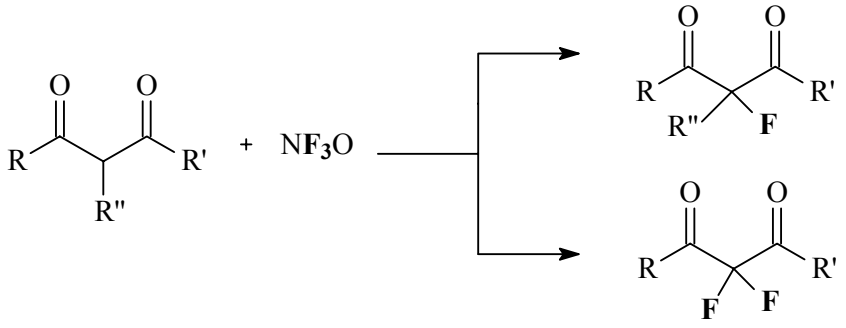
For example, reaction of 4-*t*-butylcyclohexanone with diethylaminosulfur trifluoride (DAST) in CH_2Cl_2 containing $TiCl_4$ (0.3 mmol) as catalyst, at room temperature, gave a 99% conversion of starting material to products and a 67% yield of 1,1-difluoro-4-t-butylcyclohexane after 6 h (Scheme 3).[23]



Scheme 3

Electrophilic fluorinating reagents. The ability of fluorine to beave as an electrophile ($\mathbf{F}^+$) is not easily achieved, since fluorine is the most electronegative element. Ingenious ways for overcoming this problem have been achieved by either withdrawing electronic charge from fluorine through inductive effects or by the presence of an excellent leaving group adjacent to fluorine. Examples of electrophilic reagents are F_2 and fluoroxy compounds such as $FClO_3$, CF_3COOF, CsSO4F, CF_3OF, $CF_3C(O)OF$ or NF_3O. The main disadvantages of these methods are: (a) the difficulties in handling the hazardous or troublesome fluorinating reagents; and (b) the lack of selectivity (regio- and stereoselectivity).

In Scheme 4 is shown the preparation of monofluoro- and difluoro-diketones (or ketoesters) using NF_3O as a powerful and manageable electrophilic agent.[24]



Scheme 4

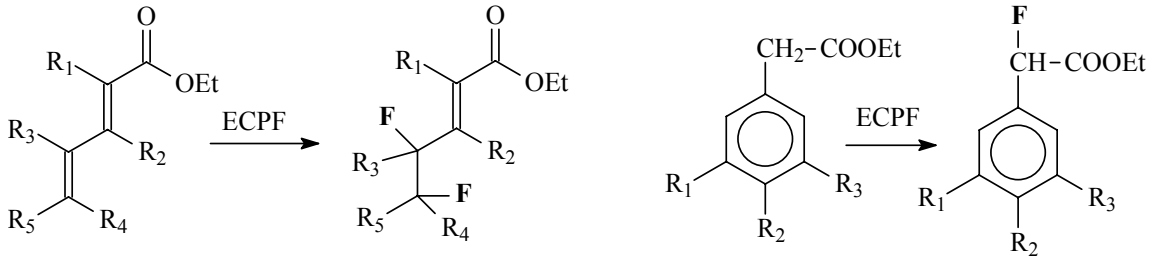
2. Electrochemical methods. On the contrary, electrolytic fluorination methodology proved to be highly attractive and more promising than the above-mentioned methods and, consequently, it serves as a

new tool in fluoro-organic synthesis.[25-27] Compared with the conventional chemical fluorination methods, electrolytic fluorination has the following advantages: (a) hazardous or toxic reagents are not required, less corrosive fluoride salts are used; (b) fluorination can be carried out in relatively simple equipment under mild conditions; (c) fluorination processes can be easily controlled by the applied potential, current and electricity; (d) it is a type of green chemistry, where the secondary pollution can be avoided because electricity is used as an oxidising reagent.

Electrochemistry has for almost 50 years made a significant contribution in the area of fluorination of organic compounds with the development and commercialization of the Simons process[28] in 1949. By this route, it is possible to produce perfluorinated compounds (compounds in which all the hydrogen atoms are replaced by fluorine) and at the same time some functional groups are unaffected. For conversion of all C-H to C-F bonds, anhydrous HF (AHF) is the most common reagent used in electrochemical perfluorination. AHF is, however, an extremely hazardous substance due to its low boiling point and high toxicity, in addition to giving poor yields of products. For this reason, in the last decades, HF combined wit organic bases to form fluoride salts such as $Et_3N{\cdot}nHF$ or $Et_4NF{\cdot}nHF$, (n = 2-5), have been widely used as fluorine sources and supporting electrolytes for the selective partial fluorination (ECPF) of organic compounds.[29]

The ECPF of organic compounds using $Et_3N{\cdot}nHF$ (n = 2-3) and $Et_3N{\cdot}5HF$, as fluorine sources and supporting electrolytes has been quickly developed in the last few years.[30,31]

V. Dinoiu and Japanese co-workers[32-34] reported the selective electrochemical partial fluorination of conjugated dienesters (Scheme 5), electrophilic alkenes or styrenic derivatives (Scheme 5).



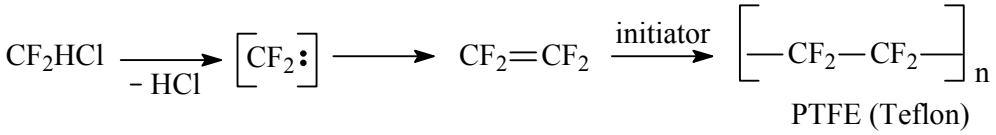
Scheme 5

Caution: All chemists working with fluorine and its compounds need to know about the hazards arising from contact with hydrogen fluoride (perhaps produced inadvertently); liquid HF (bp 19.5 ^{o}C), its vapour (to a lesser degree) and aqueous HF (hydrofluoric acid) can cause serious skin burns and sensible prior arrangements must be made for medical treatment.

FLUORINATED MATERIALS

Because of a hugely important properties of thermal and oxidative stability, fluorinated materials play an important role in the development of new areas of material science, including, Fluoropolymers, Liquid crystals and Fire extinguishants.

Fluoropolymers. The serendipitous discovery of polytetrafluoroethylene (**PTFE**), the original TEFLON, at Du Pont by Roy Plunkett[35] in 1938, along with the almost simultaneous discovery report of the preparation of polychlorotrifluoroethylene (**PCTFE**)[36], revolutionized the industrial world and opened up the largest commercial application of organofluorine chemistry, the field of fluoropolymers (Scheme 6).



Scheme 6

Dr. Roy Plunkett accidentally discovered this white waxy solid in 1938. Upon checking a frozen, compressed sample of tetrafluoroethylene, he and his associates discovered that the sample had polymerized

spontaneously into a white, waxy solid to form polytetrafluoroethylene (**PTFE**). PTFE is inert to virtually all chemicals and is considered the most slippery material in existence.

Recent developments in the field of fluoropolymers lead to new amorphous fluorinated resins such as Teflon AF, used in microchip manufacture and fiber optics, and ionomers such as Nafion that are used in fuel cells.[37]

Liquid crystals. In recent years, liquid crystal displays (**LCDs**) have become an indispensable part of our daily life. Full-color, flat-screen displays capable of high resolution graphics, as seen in computer monitor, "hang-on-the-wall" TV screens, are the most rapidly growing applications. Owing to its special properties, the presence of fluorine in a liquid crystal exerts a large influence on permittivity causing minimum change in molecular shape. Some fluorinated compounds[38] used as liquid crystals are shown in Fig. 2.

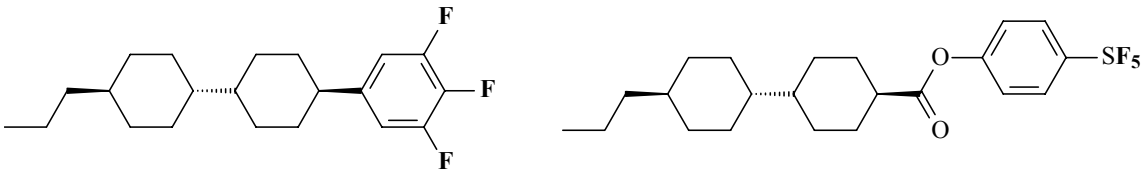


Fig. 2

Fire extinguishants. Halons, such as CF_3Br and CF_2ClBr exhibit exceptional fire-extinguishing properties being electrically nonconductive and leaving no residues dangerous for human exposure.[39] From 2003, they are replaced by other highly fluorinating materials, such as heptafluoropropane, CF_3CHFCF_3.

CHLOROCARBONS AND FLUOROCARBONS (FREON)

The discovery of SbF_3-facilitated conversion of chlorocarbons to chlorofluorocarbons (**CFCs**) and fluorocarbons at the end of 19th century[40] was in fact the starting point of synthetic organofluorine chemistry (scheme 7).

The "Milestone" Swartz process:

$$\text{Hydrocarbons} \xrightarrow{Cl_2} \text{Chlorocarbons} \xrightarrow{SbF_3} \text{Fluorocarbons}$$

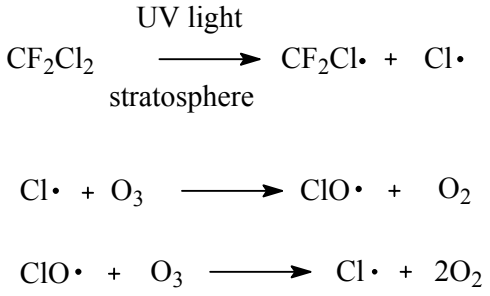
The discovery of Thomas Midgley:

$$CCl_4 + SbF_3 \xrightarrow[\text{cat.}]{} CF_2Cl_2 \text{ (\textbf{Freon 12})}$$

Scheme 7

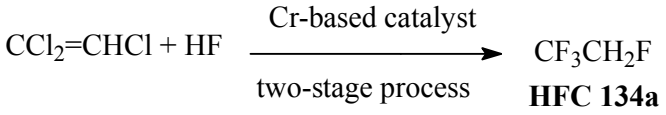
The revolutionary scientific discovery of Thomas Midgley, (Frigidaire Corporation), concerning the application of $\mathbf{CF_2Cl_2}$ (Freon 12) as refrigerators and air conditioners, constituted the first commercial application of organic fluorides. For the ozone-depletion hypothesis in 1974[41], Molina and Rowland were awarded with Nobel Prize in 1995. Their hypothesis was accepted in all the world and claimed that the exceptional stability of the Freon (widely used as an ideal product for more 40 years) caused a depletion of the ozone layer in the stratosphere (Scheme 8).

Their success as refrigerants and, later, as convenient, non-toxic, non-inflammable aerosol propellants endeared them to people. They also found industrial applications as foam-blowing agents, degreasing agents and solvents. A related compound, bromochlorodifluoromethane, CF_2ClBr (a bromo-chloro-fluorocarbon) is perhaps the best fire-fighting agent for petrol or other solvent fires that has ever been invented.



Scheme 8

When chemists recognised the damage that these compounds do to the ozone layer, in 1987 it was signed Montreal Protocol and US Clean Air Act in 1990 to ban clorofluorocarbons and many researchers were involved in searching of environmentally friendly-alternatives to CFCs. These efforts leaded to the synthesis of commercially HFC 134a, (**CF_3CH_2F**), based on the use of a "chromium-based" catalyst in gas-phase chlorine-fluorine exchange reactions (Scheme 9).[42]



Scheme 9

MEDICINAL FLUORINE CHEMISTRY-BIOLOGICALLY ACTIVE FLUOROCHEMICALS

Since the fluorine atom is not much larger than a hydrogen atom, it can be introduced into carbon-hydrogen compounds in almost any position. The fluorine atom, being very electronegative, changes quite drastically the charge distribution in compounds into which it is placed, thereby altering their biological effects. Consequently, fluorine is a component of a wide range of modern drugs including anti-cancer and anti-viral agents, anti-inflammatory drugs, antibiotics, central nervous system agents, diuretics and antihypertensive agents, and antiarrhythmic heart drugs.

In the area of medicinal chemistry, incorporation of fluorine into organic compounds have had an exceptionally impact. The incorporation of fluorine into a biologically active compound alters the electronic, lipophilic and steric parameters and can critically increase the intrinsic activity, the chemical and metabolic stability, and the bioavailability. The positive effects of fluorine on the biological efficiency is outlined by three examples: in the chemical class of herbicidal thiatriazines, the presence or the absence of fluorine leads to dramatic effects on the biological activity; the metabolic stability and the pharmacokinetics of aminopyrazinone acetamide thrombin inhibitors were improved by the introduction of fluorine, and in a novel class of insecticides/acaricides any modification of the gem-difluorovinyl group results in a strong decrease of biological activity. The famous Uracil is a compound containing nitrogen, oxygen, carbon, and hydrogen. It is one of the basic components of RNA. When a particular one of its hydrogen atoms is replaced by fluorine, the compound that results is toxic. It is especially toxic to rapidly growing cancer cells, and thus fluorouracil is an effective chemotherapeutic agent for some types of cancer.

Hundred of organic chemists who worked in fluorine chemistry in the last 35 years, so called Modern age of Fluorine Chemistry, turned their talent in the designed synthesis of partially fluorinated compounds, commercially available, with excellent applications in medicine. Today, about 30 percent to 50 percent of all pharmaceuticals now contain fluorine.

One of the most important contributions of fluorine chemistry to the quality of human life has been the creation of compounds that induce **anaesthesia**. Modern inhalation anaesthetics are almost entirely dependent on fluorine chemistry.

Diethyl ether, used until 1950, was successfully replaced first with Fluoroxene ($CF_3CF_2OCH=CH_2$) leading to the "fluorine revolution" in this field. Other fluorinated anesthetics followed, including Halothane ($CF_3CHClBr$), an ozone depleter, used in 70-80% of all anaesthesias for a long time. In recent years it has

been replaced by a new class of fluorine-containing chemicals called fluoro-ethers, which are not only not damaging to the ozone layer but also have none of the side effects such as the post-operative nausea experienced by many who were treated with Halothane: Isoflurane ($CF_3CClOCHF_2$), Sevoflurane ($(CF_3)_2CHOCH_2F$), and the most performed, Desfluorane ($CF_3CHFOCHF_2$) (Fig.3). This new class that revolutionized the field of anaesthesiology owing to their low blood-gas partition coefficients and their minimal level of metabolism, which minimized side effects and thus shortened the recovery time of patients.[41] Desfluorane has the most rapid onset and offset of the volatile anaesthetic drugs used for general anaesthesia due to its low solubility in blood. Sevoflurane (2,2,2-trifluoro-1-(trifluoromethyl) ethyl ether), also called fluoromethyl, is a sweet-smelling, non-flammable fully-fluorinated methyl isopropyl ether. It was introduced into clinical practice initially in Japan in 1990.

Halothane and Isoflurane are still widely used in veterinary surgery and the Third World because of their lower cost.

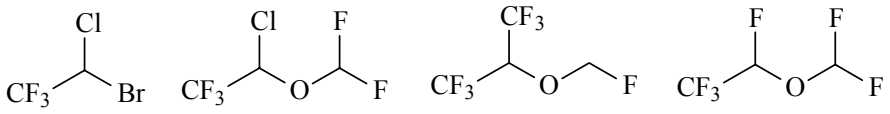


Fig. 3

Fried and Sabo (1954) reported the synthesis of 9-*alpha*-fluorohydrocortisone acetate and showed that it exhibited glucocorticoid activity 11 times greater than that of the corresponding hydrocarbon (cortisol acetate).[43,44] The enhanced activity has been attributed to the lower pK(sub-alpha) of the 11beta-hydroxyl group and its increased ability to donate a hydrogen bond, as well as its increased resistance to metabolic inactivation by oxidation. Fried's discovery led to the development of at least six commercial **antiinflammatory agents**. More importantly, his demonstration of the extraordinary potential of fluorine substitution to alter and enhance the pharmacological properties of organic molecules became the basis of a powerful strategy for synthetic drug development in the pharmaceutical industry (Biologically active fluorochemicals). At present, there are 128 fluorinated compounds with US trade names, including 9 of 31 new drugs approved in 2002, according to the World Drug Index.[45]

The small size of the fluorine substituent, combined with its high electronegativity and its impact upon bond strengths give rise to the observed distinctive effect of fluorine substituents upon biological activity of compounds. In the area of medicinal chemistry, incorporation of fluorine plays a significant role in the development of new anti-cancer and anti-viral agents, anti-inflammatory and anti-hyperintensive agents, anti-fertility drugs and central nervous system drugs. In the area of modern crop protection, fluoro agrochemicals include herbicides, insecticides and fungicides.[46] Fluorine affects the biological activity of compounds in a number of important ways. The presence of fluorine at a particular position in a molecule can enhance its metabolic stability or modulate its physicochemical properties, such as its lipophilicity, acidity or basicity. Fluorination can increase a molecules binding affinity to a target protein, and by a combination of factors interfere with specific enzyme action. As a result, fluorine plays a huge role in the current areas of pharmaceutical chemistry and agrochemistry, with many of the most important new drugs and agents containing propitiously placed fluorine, trifluoromethyl, difluoromethyl or other fluorinated groups.

Two well-known examples of fluorine-containing drugs are given in Fig. 4.

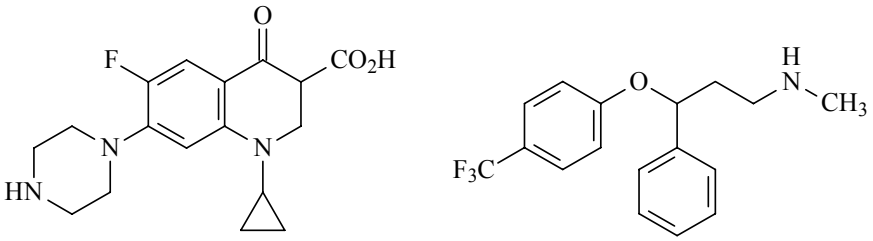


Fig. 4

The famous Fluorouracil (5-FU) is a drug that is used in the treatment of cancer. It is a pyrimidine analog and it belongs to the family of drugs called antimetabolites. The newest synthesized anti-cancer drugs are presented in Fig. 5.[47]

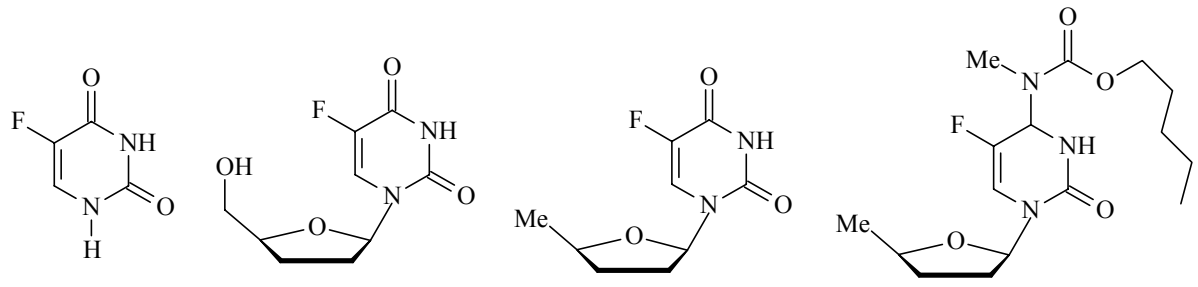


Fig. 5

Another important application of fluorine-containing compounds is the use of ^{18}F radioisotope (a radioactive isotope that emits positrons because of its half-life of 110 minutes) in **positron emission tomography** (**PET**). The availability of ^{18}F and specifically ^{18}F-fluorodeoxy-D-glucose (**FDG**) (Fig. 6), has allowed for the studying biochemical transformation, pharmacodynamics, and recently (**EF5**) the superior diagnostic scanning technique to survey living tissue in human bodies.[48,49] A further limitation arises from the high costs of cyclotrons needed to produce the short-lived radionuclides for PET scanning (for example ^{18}F). Few hospitals and universities are capable of maintaining such systems. PET scanning with the tracer (^{18}F) fluorodeoxyglucose is widely used in clinical oncology.

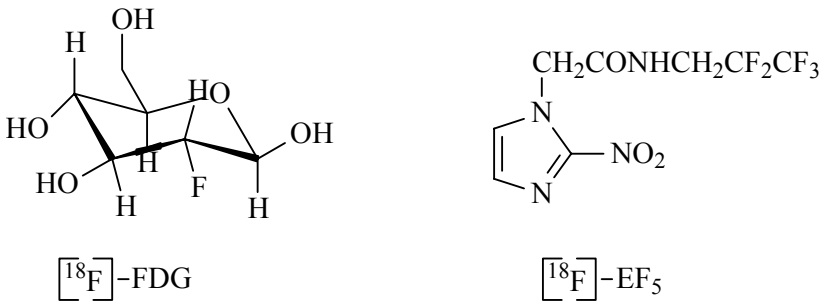


Fig. 6

CONCLUSION-THE FUTURE

On the basis of early fluorine-chemistry research, which so often left its practitioners dead or maimed, no-one could have predicted the central role it has now taken in the evolution of much contemporary industrial and academic research or its wide application in contemporary life.

Fluorine and its chemistry often have been described by the adjectives i.e. exciting, exotic, unusual, unexpected, novel, highly reactive and challenging. Fluorine chemistry has lived up to all these adjectives and remains for all the chemists an exciting field of synthetic and structural challenges.

The future of fluorine chemistry appears bright, with a significant role in the most important areas of technology in the 21st century. New perspectives are required in applications, in continuing the creative organic synthetic work of hundred of chemists in all the world. In the field of medicine, fluorine chemistry holds a number of promises for the future.

Fluorocarbon liquid emulsions containing perfluorodecalin, $C_{10}F_{18}$, or perfluotri-n-propylamine, $(n\text{-}C_3F_7)_3N$, can dissolve and carry oxygen and are already being exploited in assisting the survival of prematurely born babies and offer the prospect of application as **artificial blood**.

The importance of fluorine extends into many other areas; it continues to be crucial in the extraction of aluminium, it has a significant role in the polymer industry and its applications in modern medicine, pharmaceuticals and agriculture continue. It also underpins microelectronics and computing where it is found in modern optical fibres, etchants for microchips and degreasing agents for circuit boards.

Currently, a new way of carrying out catalytic conversions more efficiently is being investigated. Given that it is estimated that 30% of the GNP for an industrial nation depends on catalysis, this could have far-reaching consequences. Thus, fluorine can aptly be described as an important enabling element for contemporary advanced technology.

Fluorine chemistry will keep its fundamental role in this new millennium. Entirely novel chemistry results and an ever increasing role in industry is developing. The special issue[50] of Journal of Fluorine Chemistry from 2003 presents the importance of this very interesting chemistry of fluorine from this point of view.

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REFERENCES

1. H. Moissan, "Das Fluor und seine Verbindungen'', German Edition, Verlag von M. Krayn, Berlin, 1900.
2. H. E. Karr, "Elemental Fluorine. IG Farbenindustrie Leverkusen", Technical Industrial Intelligence Agency, 1946.
3. S. H. DeWolf, "Atomic energy for military purposes. The official report on the development of the atomic bomb under the auspices of the United States Government, 1940 – 194", Princeton University Press, 1946.
4. R. L. Powel: in R.E. Banks (Ed.), "Fluorine Chemistry at the Millennium", Elsevier, Amsterdam, 2000, p. 339-384.
5. T. Hiyama, "Organofluorine Compounds: Chemistry and Applications", Springer, Berlin, 2000.
6. P. Kirsch, "Modern Fluoroorganic Chemistry", Wiley-VCH, Weinheim, 2004.
7. R. D. Chambers, "Fluorine in organic Chemistry", Blackwell Publishing, Oxford, 2005.
8. K. Uneyama, "Organofluorine Chemistry", Blackwell Publishing, Oxford, 2006.
9. *Chem. Rev*., **1996**, *96*, 555-1823.
10. X. -H. Xu, *J. Nat. Prod*. **2003**, *66*, 285-288.
13. K. H. vanPee, *Annu. Rev. Microbiol.* **1996**, *50*, 375-399.
14. G. Sandford, "Organofluorine Chemistry", Phil. Trans. R. Soc. Lond. A 358, 2000, p. 455-471.
15. D. O'Hagan, *Proceedings of the International Symposium on Fluorine in the Life Sciences Bürgenstock*, **2003**.
16. D. O'Hagan and D. B. Harper, *J. Chem*., **1999**, *100*, 127-133.
17. J. Emsley, *J. Am. Chem. Soc*, **1981**, *103*, 24-28.
18. W. T. Miller, J. D. Stoffer, G. Fuller and A. C. Currie*, J. Am. Chem. Soc*., **1964**, *86*, 51.
19. V. Grakauskas, *Am. Cem. Soc*. 140. National Meeting, Chicago, Sept. 1961.
20. S. Rozen and J. Menahem, *J. Fluorine Chem*., **1980**, *16*, 19.
21. J. T. Welch, *Tetraedron,* **1987**, *43*, 3123.
22. R. Sing, R. L. Kirchmeier and J. M. Shreeve, *Organic Letters*, **1997**, *1*, 1047-1049.
23. U.S. Patent 6222064, **2001**
24. O. D. Gupta and J. M. Shreeve, *Tetrahedron Letters*, **2003**, *44*, 2799-2801.
25. T. Fuchigami, S. Higashiya, S. Hou and K. Dawood, *Rev. Heteroat. Chem*. **1999**, *19*, 67.
26. T. Fuchigami, "Advances in Electron-Transfer Chemistry", Mariano P. S. Ed., JAI: Greenwich, CT, 1999; Vol 6.
27. T. Fuchigami in "Organic Electrochemistry", 4th ed. Lund, H., Hammerich,O., Eds.; Dekker: New York, 2001; p. 1035-1050.
28. U.S. Pat. No. 2,519,983, **1949**.
29. N. Yoneda, *J. Fluorine Chem.,* **2000**, *105*, 205
30. N. Yoneda, *Tetrahedron,* **1991**, *47*, 5329.
31. T. Fuchigami, M. Shimojo and A. Konno, *J. Org. Chem*., **1995**, *60*, 7654.
32. V. Dinoiu, T. Fukuhara S. Hara and N. Yoneda, *J. Fluorine Chem.,* **2000**, *103*, 75.
33. V. Dinoiu, T. Fukuhara, K. Miura and N. Yoneda, *J. Fluorine Chem.,* **2003**, *121*, 227
34. V. Dinoiu, K. Kanno, T. Fukuhara and N. Yoneda, *J. Fluorine Chem.,* **2005**, *126*, 753.
35. R. J. Plunkett, U.S. Patent 2,230,654, **1941**.
36. British Patent 465,520, **1937**.
37. P. Kirsch and M. Bremer, *Angew. Chem. Int. Ed*., **2000**, *39*, 4216-4235.
38. J. Scheirs in Scheirs J. (Ed), "Modern Fluoropolymers", Wiley, Chichester, 1997, p. 435-485.
39. C. Wakselman and Lantz A. in Banks R.E., Smart B.E., Tatlow J. C. (Eds), "Organofluorine Chemistry: Principles and Commercial Applications", Plenum Press, New York, 1994, p. 177-194.
40. F. Swarts, *Bull. Acad. Roy. Belg.,* **1892**, *24*, 309-314.
41. M. J. Molina and F.S. Rowland, *Nature*, **1974**, 249-250.

42. D. F. Halpern in: R. E. Banks, B. E. Smart, J. C. Tatlow (Eds), "Organofluorine Cemistry: Principles and Commercial Applications", Plenum Press, New York, 1994, pp. 543-554.
43. J.H. Fried and E.F. Sabo, *J. Am. Chem. Soc*., **1954**, *76*, 1455–1456.
44. J.H. Fried, V. John, M.J. Szwedo, C.-K. Chen, C. O'Yang, T.A. Morinelli, A.K. Okwu and P.V. Halushka, *J. Am. Chem. Soc*., **1989**, *111*, 4510–4511.
45. H.-J Böhm, D. Banner, S. Bendels, M. Kansy, B. Kuhn, K. Müller, U. Obst-Sander and M. Stahl, *Chem. Biol. Chem.,* **2004**, *5*, 637–643.
46. P. Jeschke, *Chem. Biol. Chem.,* **2004**, *5*, 570–589.
47. C. Isanbor and D. O'Hagan, *J. Fluorine Chem*., **2006**, *127*, 303-313.
48. R. L. Whal, *Q. J. Nucl. Med.,* **1998**. *42*, 1-7.
49. M. E. Phelps, *Annals of Neurology*, **1979**, 6, 371-378.
50. B. E. Smart, *J. Fluorine Chem*., **2003**, *122*, 1.