Fluorine gas F_2 is the most powerful oxidizing agent known, reacting with practically all organic and inorganic substances. Except compounds formed already by its reaction

Fluorine ignites on contact with ammonia, phosphorus, silicon, sulfur, copper wire, acetone etc and many organic and inorganic compounds. It reacts with most compounds and often, violently.

Fluorine gas is corrosive to exposed tissues and to the upper and lower respiratory tract.

It can penetrate deeply into body tissues and will continue to exert tissue damaging effects unless neutralized. Fluorine reacts violently and decomposes to hydrofluoric

The name fluorine was coined by the French chemist amperé as ‘le fluor’ after its ore fluorspar.

•Since F_2 reacts with almost all the elements except a few rare gases, storage and transport of F_2 gas was also a challenge.
•Teflon is the preferred gasket material when working with fluorine gas.
•Equipments have to be kept dry as F_2 oxidizes water giving a mixture of O_2, O_3 and HF.
•The reaction between metals and fluorine is relatively slow at room temperature, but becomes vigorous and self-sustaining at elevated temperatures.
•Fluorine can be stored in steel cylinders that have passivated interiors, or nickel or Monel metal cylinders at temperatures below 200 °C (392 °F).
•Frequent passivation, along with the strict exclusion of water and greases, must be undertaken.
•In the laboratory, glassware may carry fluorine gas under low pressure and anhydrous conditions

Attempts to isolate fluorine gas (F_2) was one of the toughest tasks handled by chemists.

Scientists who were maimed and mauled to death by the **tiger of chemistry**

Humphrey Davy of England: poisoned, recovered.

George and Thomas Knox of Ireland: both poisoned, one bedridden 3 years, recovered.

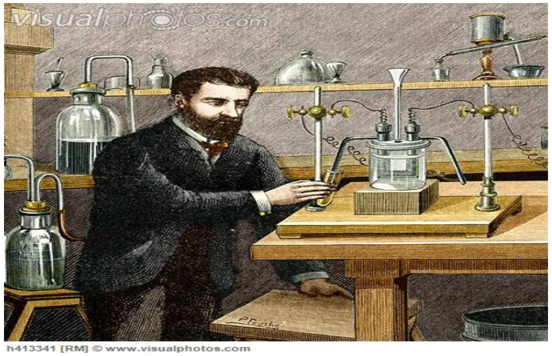
P. Louyet of Belgium: poisoned, died.

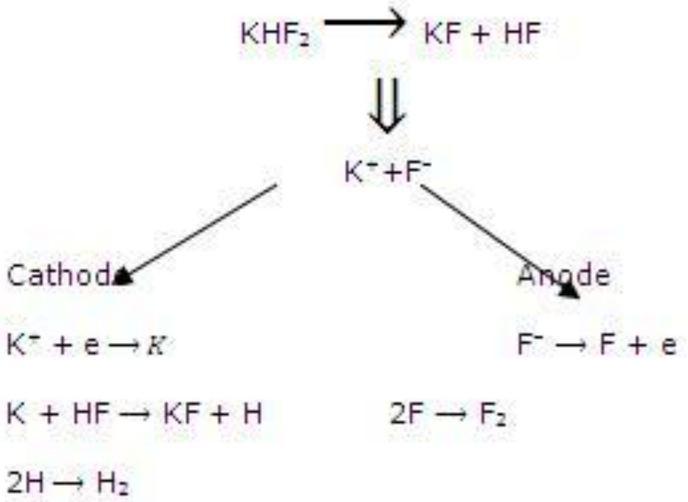
Jerome Nickels of Nancy, France: poisoned, died.

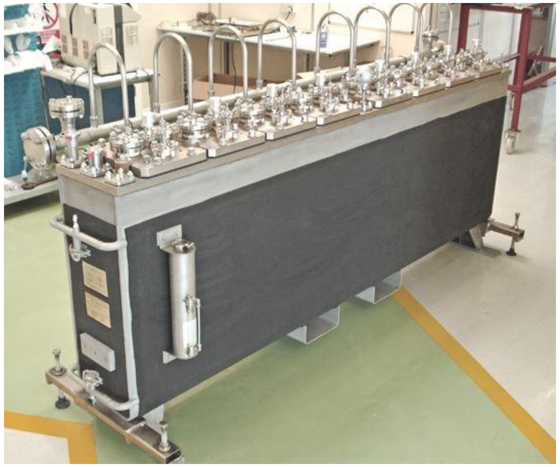
George Gore of England: fluorine / hydrogen explosion, narrowly escaped injury.

Henri Moissan : poisoned, success, but shortened lifespan.

1886
Henri Moissan
First isolation of fluorine







Henri Moissan prepared fluorine gas, F_2 by the electrolysis of a solution of potassium hydrogen difluoride in liquid hydrogen fluoride. **For this discovery he received the Nobel prize in 1906.** Two electrodes were made from an alloy of platinum and iridium. These were sealed into a platinum U-tube closed with caps made from the mineral fluorspar, the caps being covered with a layer of gum-lac. The U-tube was chilled to 10 degrees below zero Fahrenheit to reduce the rate of the action of the fluorine on the platinum. The first test made with the gas was to bring it in contact with the element silicon. There was an immediate burst of flame, a gaseous product being formed."

Ferdinand Frederic Henri Moissan died, aged 55, in 1907; a year after receiving the Nobel prize

Can fluorine be made in the laboratory by chemical reactions??

In 1986, 100 years after the discovery of the Moissan' procedure, Karl O. Christe came out with a simple laboratory method for the synthesis of small amounts of F_2 gas starting with $KMnO_4$ and HF. The synthesis is based on the fact that thermodynamically unstable higher oxidation state of transition metal fluorides can be stabilized by anion formation.

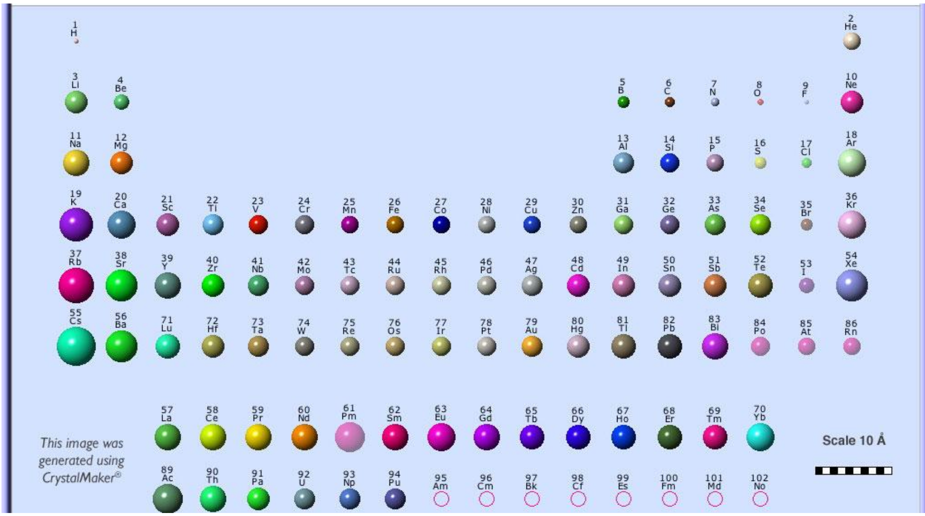
$$2\,KMnO_4 + 2\,KF + 10\,HF + 3\,H_2O_2 \longrightarrow 2\,K_2MnF_6 + 8\,H_2O + 3\,O_2$$

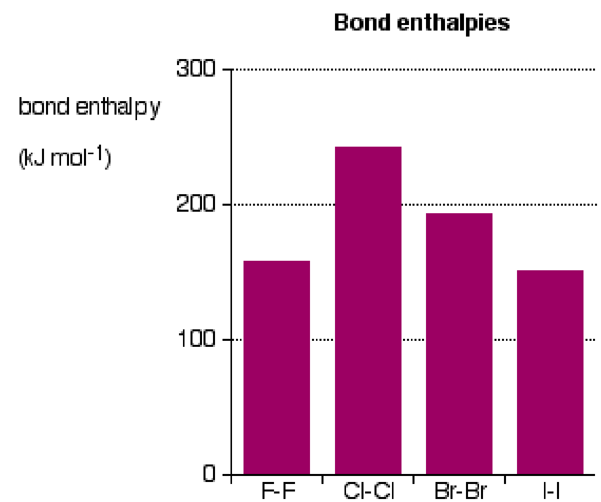
$$2\,K_2MnF_6 + 4\,SbF_5 \longrightarrow 2\,KSbF_6 + 2\,MnF_3 + F_2$$

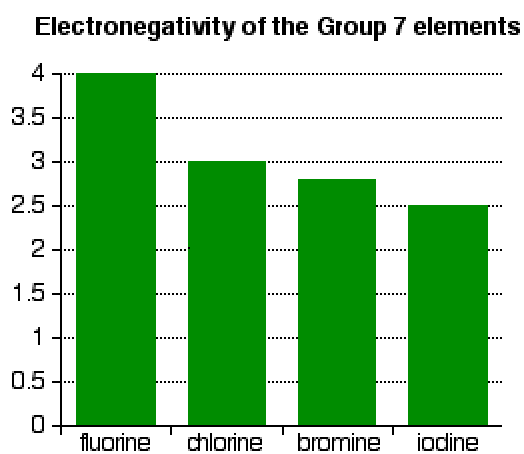
Also, weaker Lewis acids such as MnF_4 can be displaced from its salts by stronger Lewis acids such as SbF_5. MnF_4 is thermodynamically unstable and decompose to a lower fluoride MnF_3 with the elimination of fluorine gas. The formed F_2 gas has been ascertained by the formation of white solid HgF_2 on reaction with liquid mercury and by its characteristic pungent and unique odor.

Unique properties of fluorine

Fluorine is the most electronegative element and the second smallest substituent (covalent radius 0.72 Å) after hydrogen (0.37 Å). The F-F bond strength (38 kcal/mol) is the second lowest among dihalogen molecules.



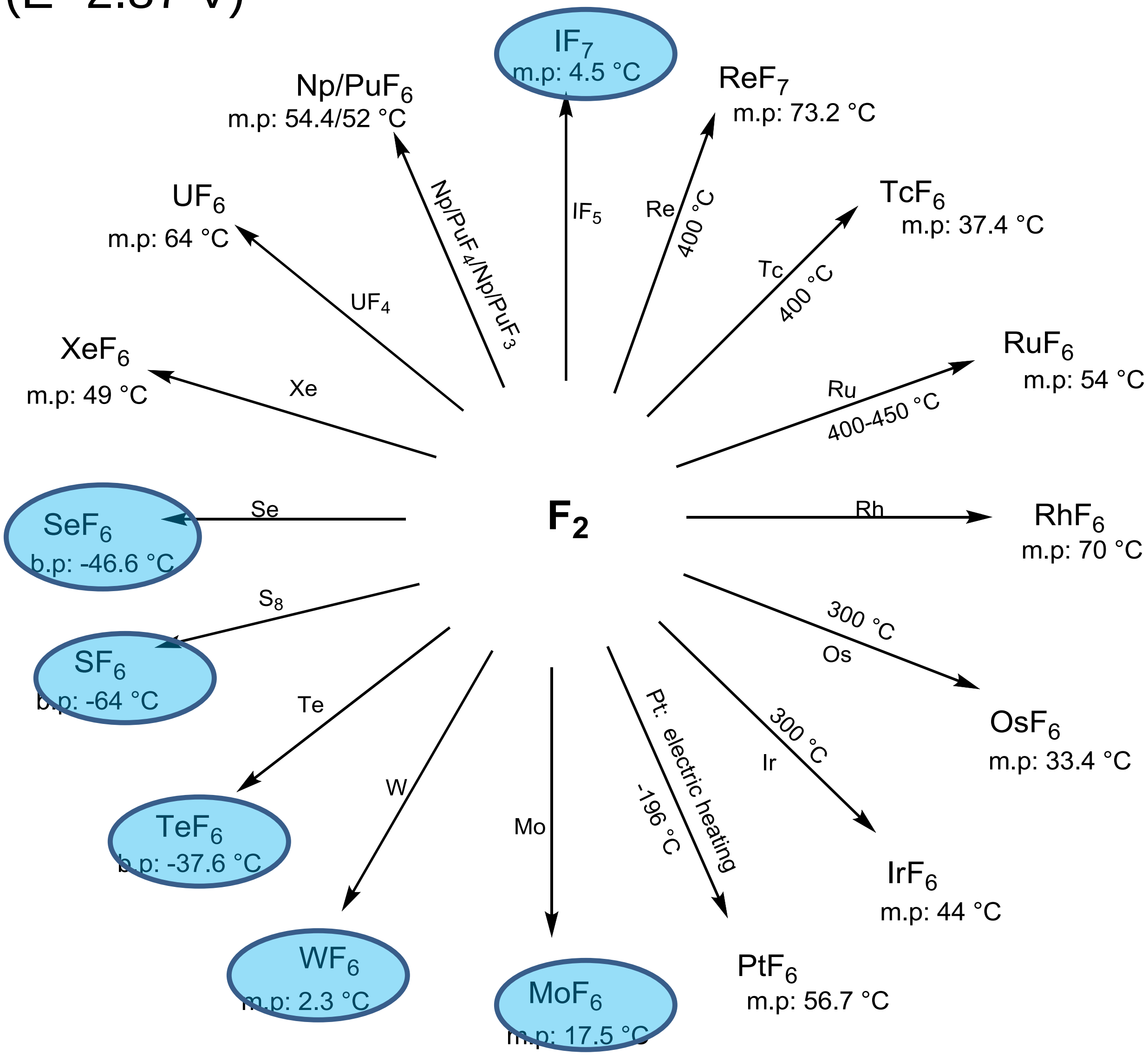




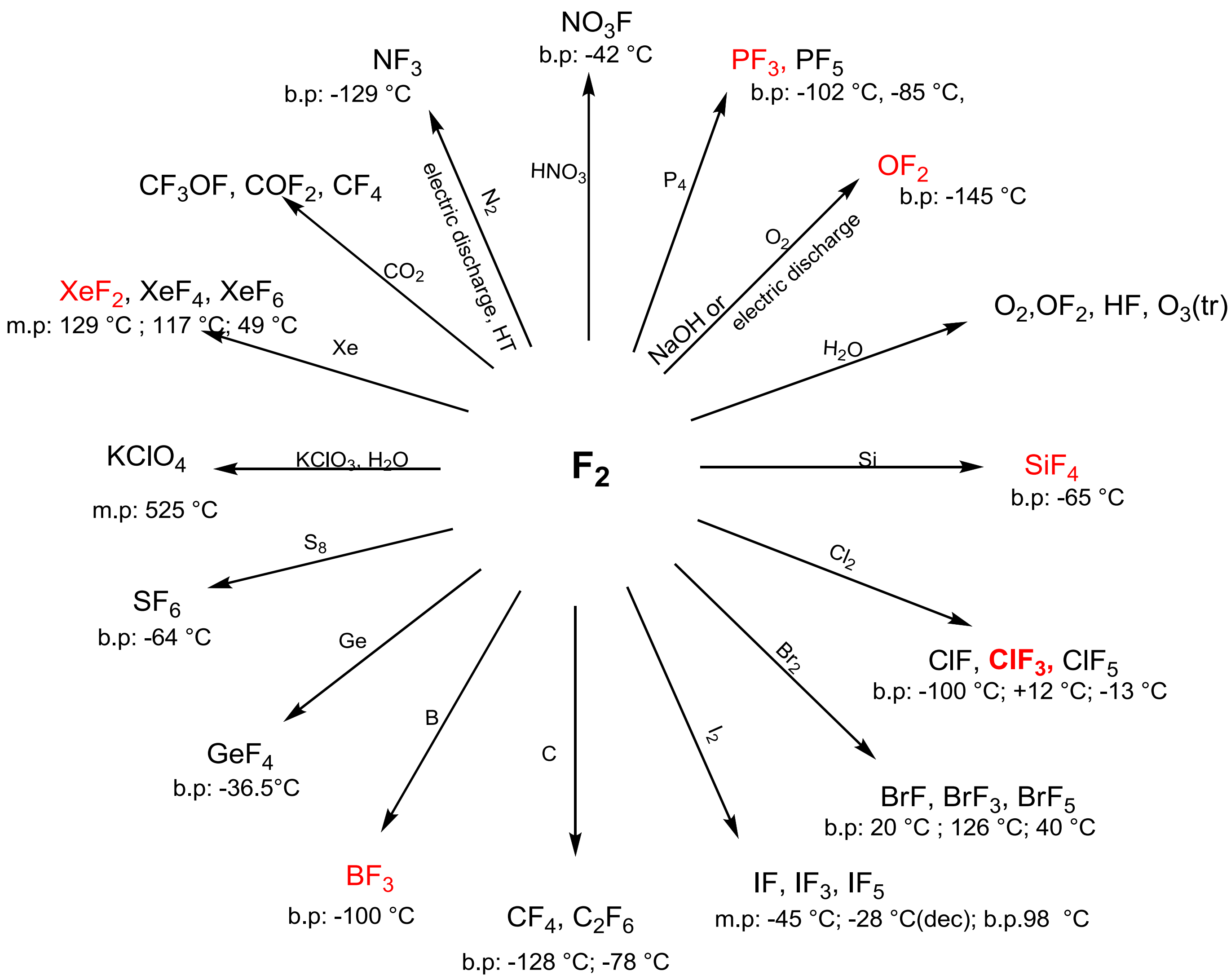
The bond enthalpies of the Cl-Cl, Br-Br and I-I bonds fall just as you would expect, but the F-F bond is different!
Because fluorine atoms are so small, you might expect a very strong bond - in fact, it is remarkably weak. There must be another factor at work as well.
Between the two atoms, each atom has 3 non-bonding pairs of electrons in the outer level - lone pairs. Where the bond gets very short (as in F-F), **the lone pairs on the two atoms get too close resulting in a significant amount of repulsion**.

Small size and high electronegativity helps fluorine to form **high oxidation state compounds** of many main group, transition metal and inner transition metals which other halogens do not form e.g. SF_6, WF_6 and UF_6. Strongest oxidizing element (E^0 2.87 V)

Low melting solids, liquid and gases



The extraordinary reactivity of F_2



Does F_2 occur free in nature ?

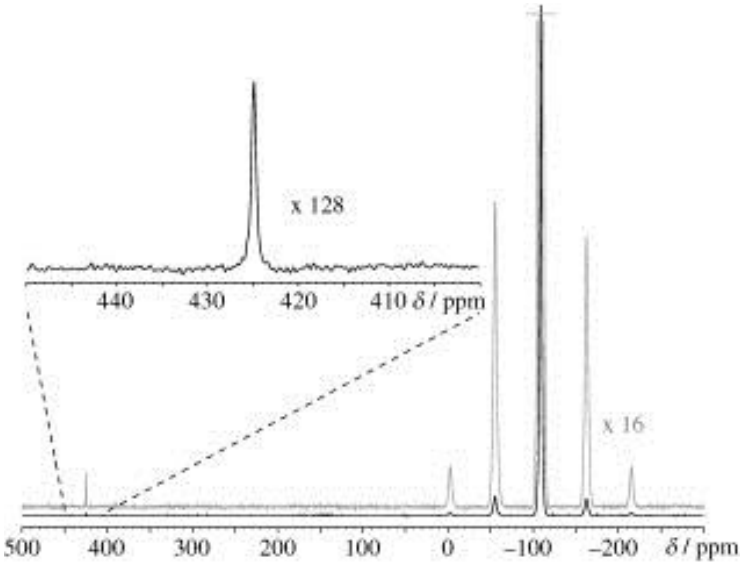
Antozonite known also as as Stinkspat, Stinkfluss, Stinkstein, Stinkspar and fetid fluorite) first found in Wölsendorf, Bavaria, in 1841

Pure Fluorite (CaF_2)

Prof. Dr. Florian Kraus , 2012 Philipps-Universität Marburg

Fluorine has a strong and characteristic odor that can be detected in very small amounts, **as low as 20 parts per billion**. But scientific community does not accept smell as evidence!

^{19}F solid-state NMR on pea-sized samples of antozonite. They detected a peak at **425 ppm** in the ^{19}F NMR spectra that corresponded to the range expected for molecular F_2 . Clearly, **F_2 does not react with CaF_2** and thus they were able to identify the fluorine gas non-destructively trapped in its natural environment.



How does one explain the presence of F_2 in the crystalline clusters of CaF_2?

The mineral antozonite also contains tiny amounts of radioactive uranium-238, which decays into β-emitting daughter nuclides. The rocks have been lying around for over 100 million years and separate experiments carried out earlier on directly exposing samples CaF_2 to β and γ radiation and high energy electron beams turned the mineral to violet color indicating formation of calcium clusters. Tiny bubbles of a gas were also found to form during such irradiations which were never analyzed earlier.

NATURE | NEWS

Stinky rocks hide Earth's only haven for natural fluorine

Chemists settle centuries-old debate about what causes 'fetid fluorite' to smell.

•Katharine Sanderson

11 July 2012

•J Schmedt auf der Gruenne, M Mangstl, F Kraus, Occurrence of difluorine F_2 in nature—In situ proof and quantification by NMR Spectroscopy, ***Angew. Chem. Int. Ed.* 2012, Vol. 51, 7847**

Periodic Table of Videos, FAZ-Online, Spiegel-Online, Die Welt-Online, Die Welt print, Deutschlandfunk, Hamburger Abendblatt, Berliner Morgenpost, derStandard.at, Chemical and Engineering News, Nature, Chemistry Times, Chemistry World (Royal Society), SpectroscopyNOW, Chemie.de, uni-online.de, Sci-News.com, Sciencedaily.com, Azomining, Phys.org, Eureka!, terradaily.com, C2WLabnews.nl, glas-koncila.hr, pcgames.de, extremnews.com, scinexx g-o.de, Lenta.ru, Delfi.lv, znanost.hr, z-moravec.net, hvg.hu, tlap.hu, scix.it

Fluorine based neutral Interhalogen compounds

ClF,	**ClF_3,**	ClF_5	
b.p: -100 °C	+12 °C;	-13 °C	
BrF,	BrF_3,	BrF_5	
b.p: 20 °C	126 °C	40 °C	
IF,	IF_3,	IF_5	IF_7
m.p: -45 °C;	-28 °C(dec)	b.p.98 °C	b.p 4.8 °C

$$ClF_3 \longrightarrow ClF + F_2$$

$$2BrF_3 \rightleftharpoons BrF_2^{+}\ BrF_4^{-}$$

Chlorine Trifluoride (ClF_3): The most reactive fluorinated compound

A ton of ClF_3 was accidentally spilled inside of a warehouse in the 1950s. The chemical burned straight through one foot of concrete and three feet of gravel of the warehouse flooring while releasing a deadly cloud of gas containing vapours that corroded every surface it came into contact with. The Nazis who discovered this compound were interested in its military applications. They were possibly fascinated by its property of melting concrete and reacting with water.

It is also well known that a fire made by ClF_3 cannot be put out as it does not require atmospheric oxygen and it burn down all fire fighting equipments and chemicals.

It was first reported in 1930 by Ruff and Krug

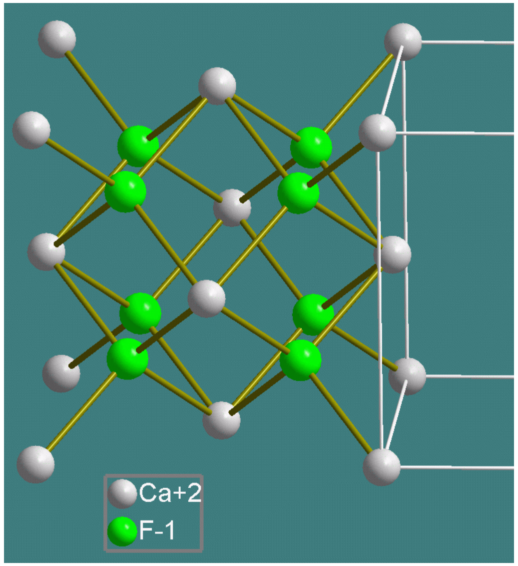
$$3F_2 + Cl_2 \xrightarrow{250\text{-}280\ °C} 2ClF_3$$

$$ClF_3 + H_2O \longrightarrow HF + HCl + OF_2$$

$$ClF_3 + 2\,H_2O \longrightarrow 3\,HF + HCl + O_2$$

$$ClF_3 \longrightarrow ClF + F_2$$

The famous American rocket fuel developer Dr. John D. Clark said about the best way to deal with chlorine trifluoride accidents- "**I have always recommended a good pair of running shoes**."

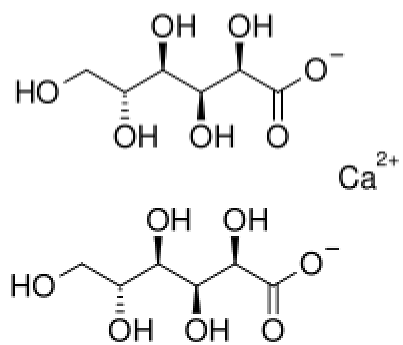


HF Acid burns

HF goes after Ca

Systemic toxicity occurs secondary to depletion of total body stores of calcium and magnesium, resulting in enzymatic and cellular dysfunction, and ultimately in cell death. Majority of deaths are resulting from cardiac problmes that were precipitated by hypocalcaemia and consequent hyperkalemia.

Antidote for HF burn:
calcium glauconate



Fluoride ion present in drinking water in the range of 0.7 to 1.5 ppm prevents dental decay by conversion of hydroxyapatite of the teeth to fluorapatite, the latter being resistant to attack by acids produced in the mouth. Cavity fighting toothpaste contains fluoride sources such as NaF, SnF_2 and sodium monofluorophosphate Na_2PO_3F

$$Ca_5(PO_4)_3OH_{(s)} + H^+_{(aq)} \rightarrow Ca_5(PO_4)_3^+{}_{(aq)} + H_2O_{(\ell)}$$

hydroxyapatite

$$Ca_5(PO_4)_3^+{}_{(aq)} + F^-_{(aq)} \rightarrow Ca_5(PO_4)_3F_{(s)}$$

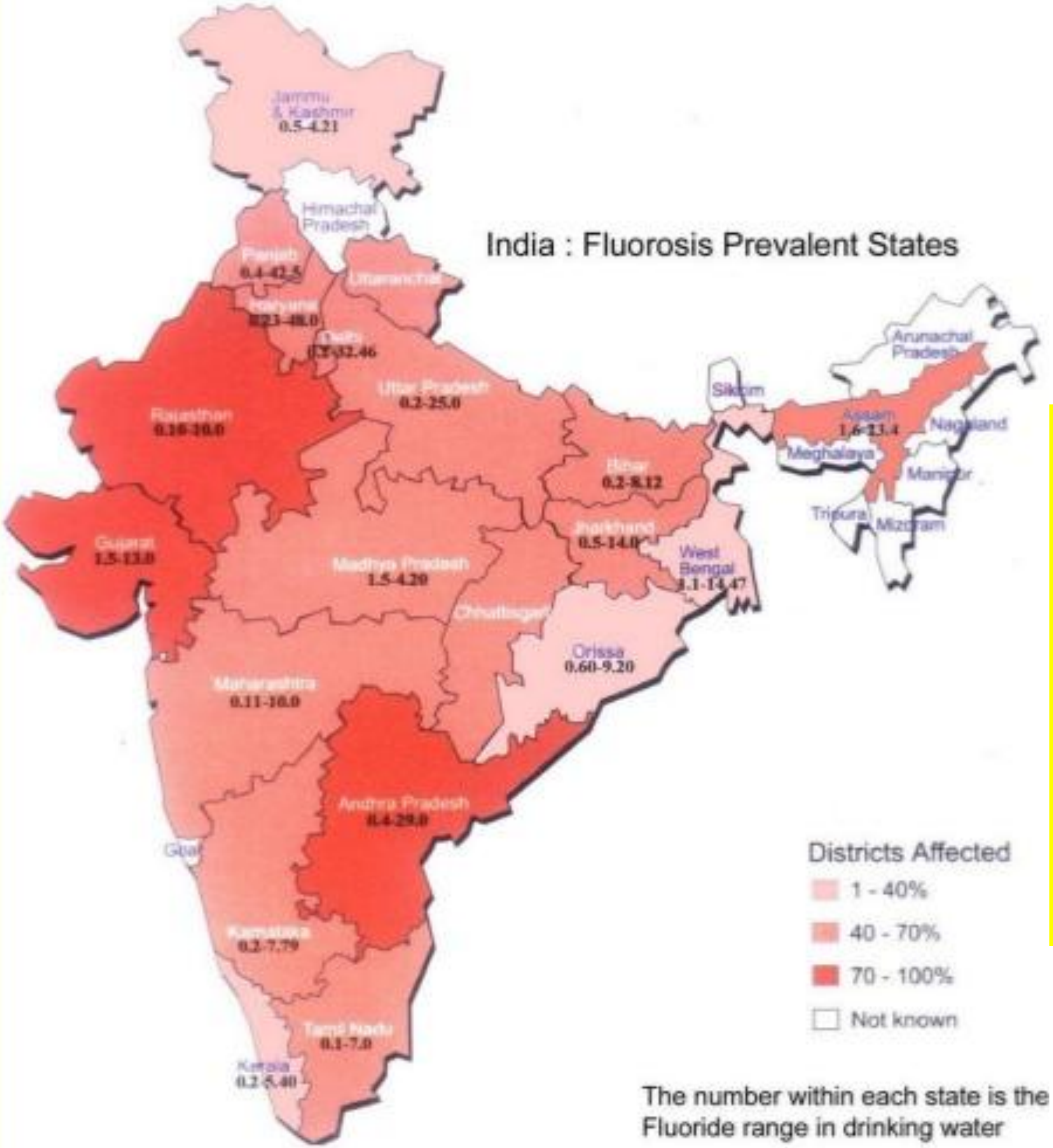
fluorapatite

MFP 0.76%

•**Fluoride ion, if present above 1.5 ppm in drinking water can lead to dental fluorosis, disfiguration of bones, and arthritis.**

Endemic fluorosis has been recognized as a major public health problem in 18 states of India and in certain regions of India, water contains fluoride up to 48 mg/L (ppm), which is extremely high compared to the maximum permissible limit. 17 out of 21 districts in the state of **Andhra Pradesh** of India are affected by fluorosis and the fluoride levels of **Nalgonda district** in this state range from 0.4 to 20 mg/L.

These are the deformities of limb bones, which are notably seen in weight bearing lower limbs in children in endemic areas of fluorosis. These occur only in poorly nourished children whose diet is **low in calcium intake**.



Source of information: 1) UNICEF State of Art Report, 1999
2) FR & RDF data bank

tolerable level 0.7 to 1.5 ppm

Ground water fluoride levels mg/L

Delhi	0.9 to 32.5 ppm
Haryana	0.2 to 48.0 ppm
Punjab	0.4 to 42.5 ppm
UP	0.2 to 25.0 ppm
Andhra Pradesh	0.4 to 29.0 ppm
Rajasthan	0.1 o 10.0 ppm
Kerala	0.2 to 5.40 ppm
Bengal	1.1 to 14.5 ppm

These changes are not seen in endemic regions in Punjab, haryana and adjacent Rajasthan where intake of dairy products containing calcium is higher. The average amount of calcium in the daily diet of Nalgonda Villager is 300 mg while it is 900 mg in residents of Punjab.

How does calcium help?

At birth the body content of calcium is 30 grams and in adults it is 1200 grams. 180 milligrams a day should be retained during growth. Calcium binds with fluoride in the Gastro Intestinal tract and compound formed is eliminated through the feces. A diet poor in calcium increases body's retention of fluoride. Fluoride increases bone metabolism and the diets deficient in calcium intake provokes parathyroid hyperactivity. This in turn mobilizes calcium from bone to keep the serum levels, which causes weakening of bones by causing osteoporosis. **Weight bearing lower limb bones suffers leading to grotesque deformities.** These deformities in lower limb bones are not seen in individuals living in high endemic regions of fluorosis in Punjab and Haryana since their diet contains adequate calcium.

Prevention

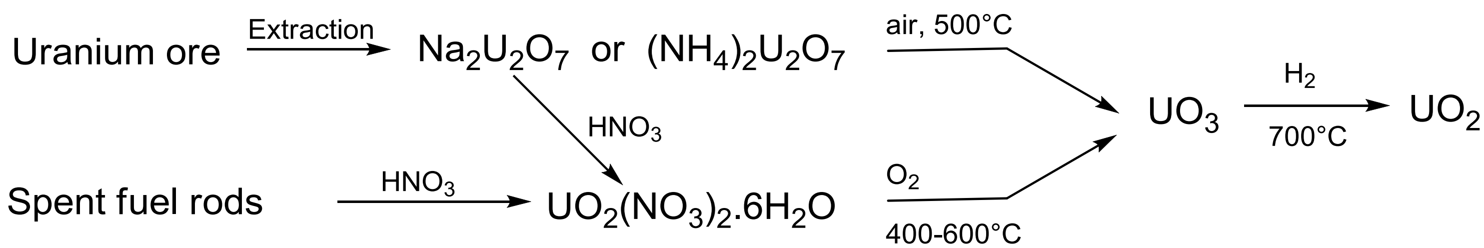
Avoid ground water for cooking and drinking

Use milk and milk products in plenty

Most important use of F_2 gas :Uranium purification for radioactive use

About 75% of F_2 gas produced in the world is used in uranium purification for nuclear reactions.

$$^{235}_{92}U \xrightarrow{^{1}_{0}n} {}^{144}_{56}Ba + {}^{89}_{36}Kr + 3\,{}^{1}_{0}n \qquad t_{1/2} = 704 \text{ million years}$$

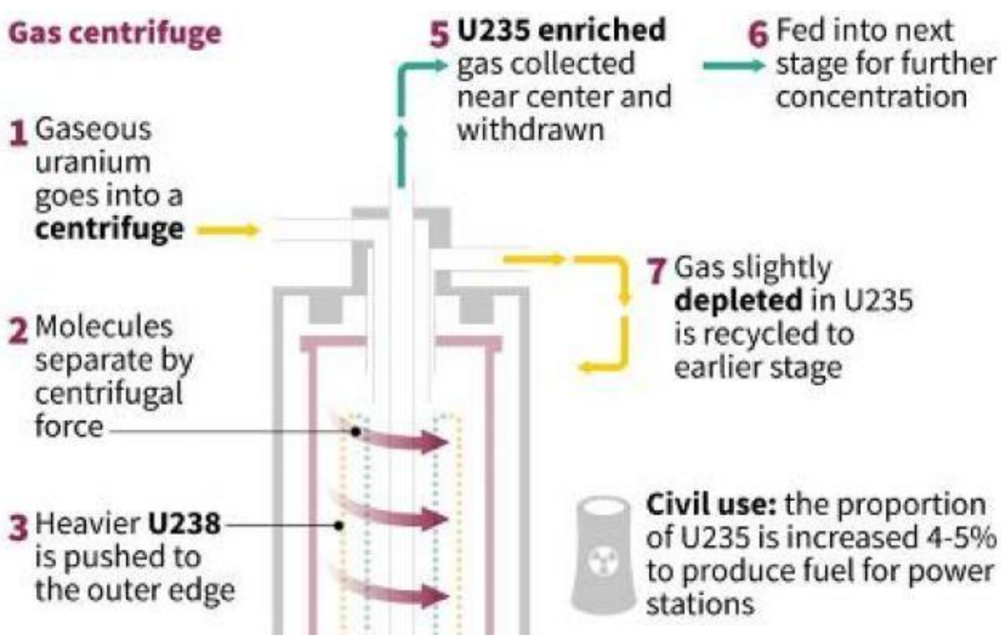


$$UO_2 \xrightarrow{\text{anhydrous HF}} UF_4 \xrightarrow{F_2 \text{ gas}} UF_6 \text{ (mixture of } {}^{235}U \text{ and } {}^{238}U)$$

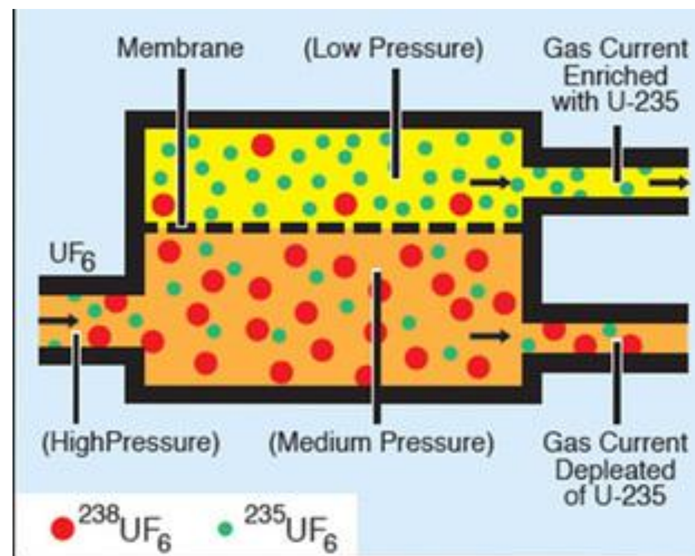
UF_6 is a white crystalline solid below 57 °C and a liquid at 64 °C and 1.5 atm pressure. It readily sublimes at atmospheric pressure above 57 °C. It is stable to dry air, O_2, N_2 and CO_2.

The enriched UF_6 having ^{235}U is separated from ^{238}U by diffusion, gas centrifugation and laser isotopic separation.

Countries which secretly process uranium are monitored by the sale of gas centrifuges

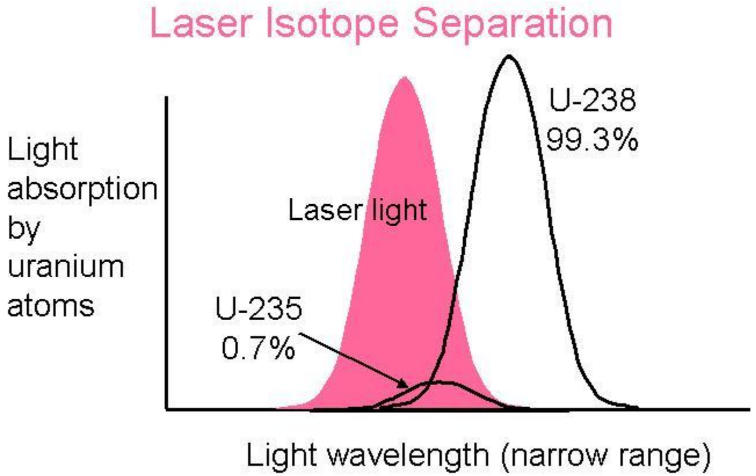


Separation using a semipermeable memberane

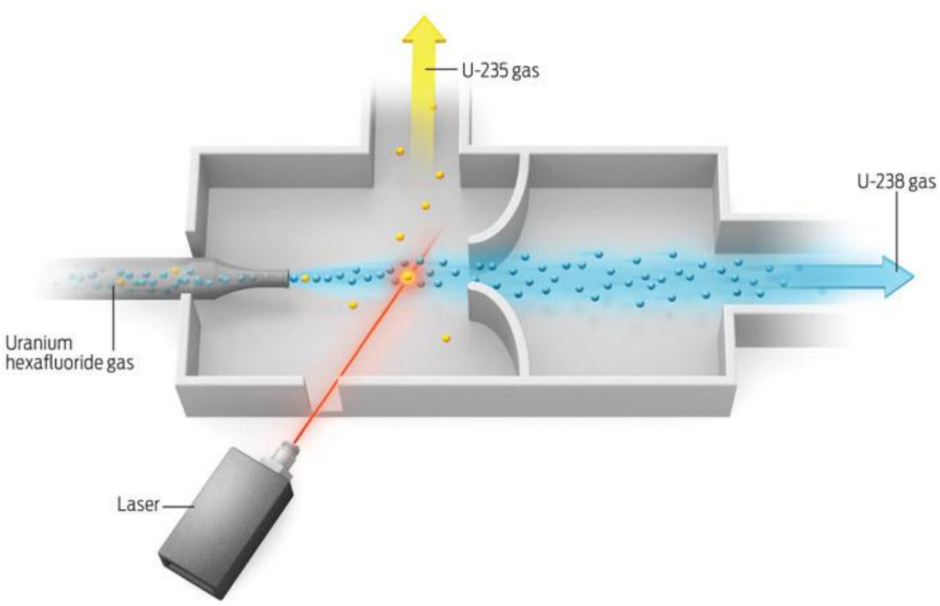


Laser method- SILEX Process

The laser separation process (also known as SILEX process) works on the principle of photo-ionisation, whereby a powerful laser is used to ionise particular atoms present in a vapor of uranium metal. The laser used is a CO_2 laser operating at a wavelength of 10.8 μm (micrometres) and optically amplified to 16 μm, which is in the infrared spectrum. Photo-dissociation of UF_6 to solid UF_5^+, using tuned laser radiation targeted to break the molecular bond holding one of the six fluorine atoms to a U-235 atom. (An electron can be ejected from an atom by light of a certain frequency.) The laser techniques for uranium uses frequencies which are tuned to ionize a U-235 atom but not a U-238 atom. The positively-charged U-235 ions are then attracted to a negatively-charged plate and collected.



U-235 absorbs the light and becomes reactive. It can then be separated out chemically.



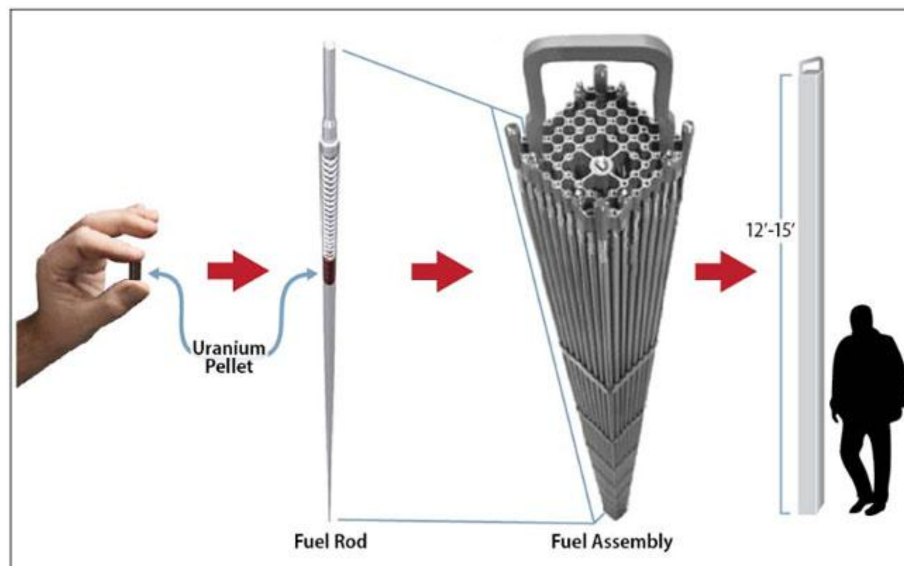
Normally for use as nuclear fuel, enriched uranium hexafluoride is converted into UO_2 powder through uranyl fluoride (UO_2F_2) which is then processed into a pellet form. The melting points of various uranium, oxides, fluorides and oxyfluorides given below indicates the reason for this conversion.

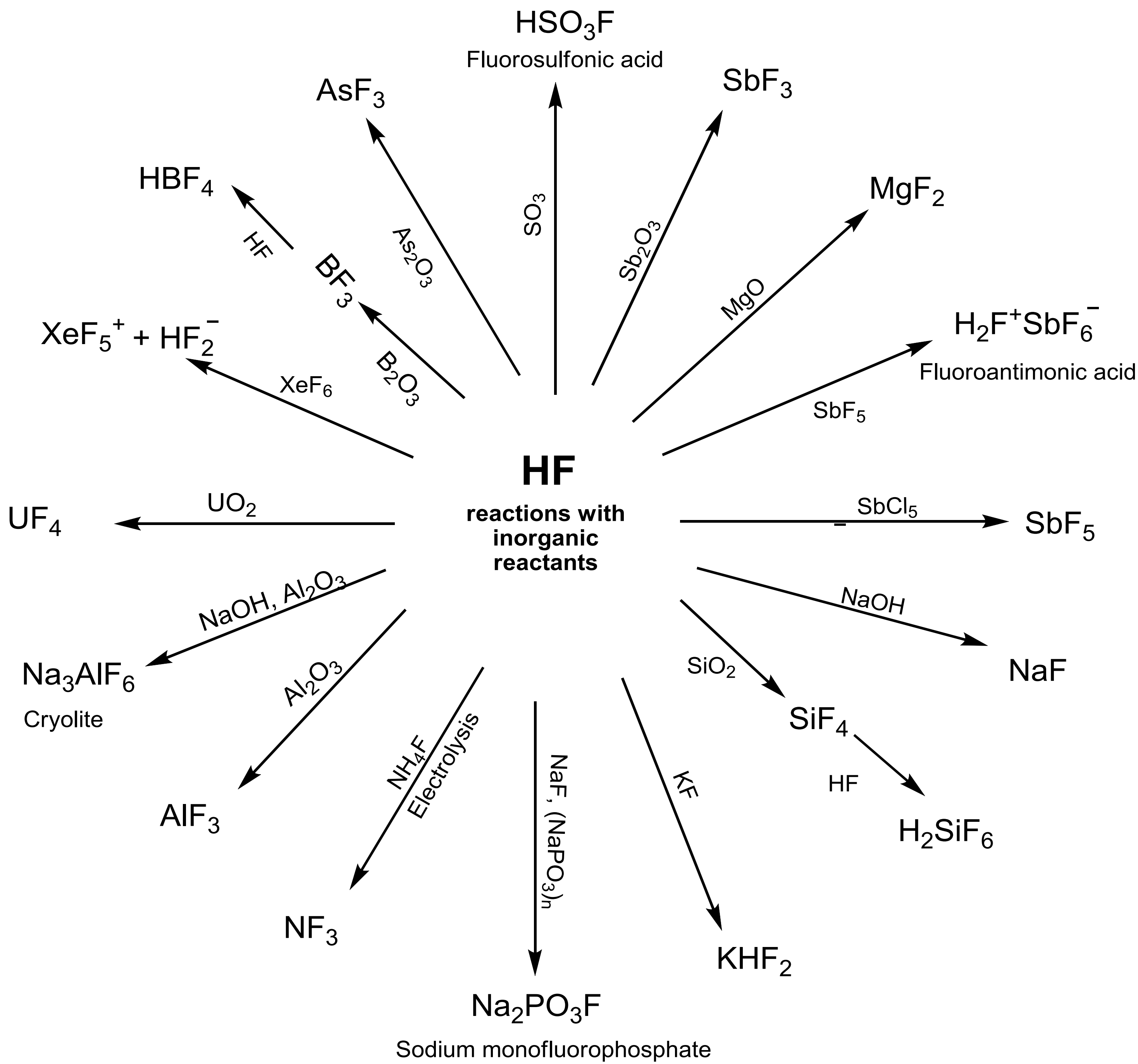
Compound	UO_3	UO_2	UO_2F_2	UF_4	UF_6	U_3O_8
M.P. (°C)	200-650	2865	300 (dec)	1036	57	1500

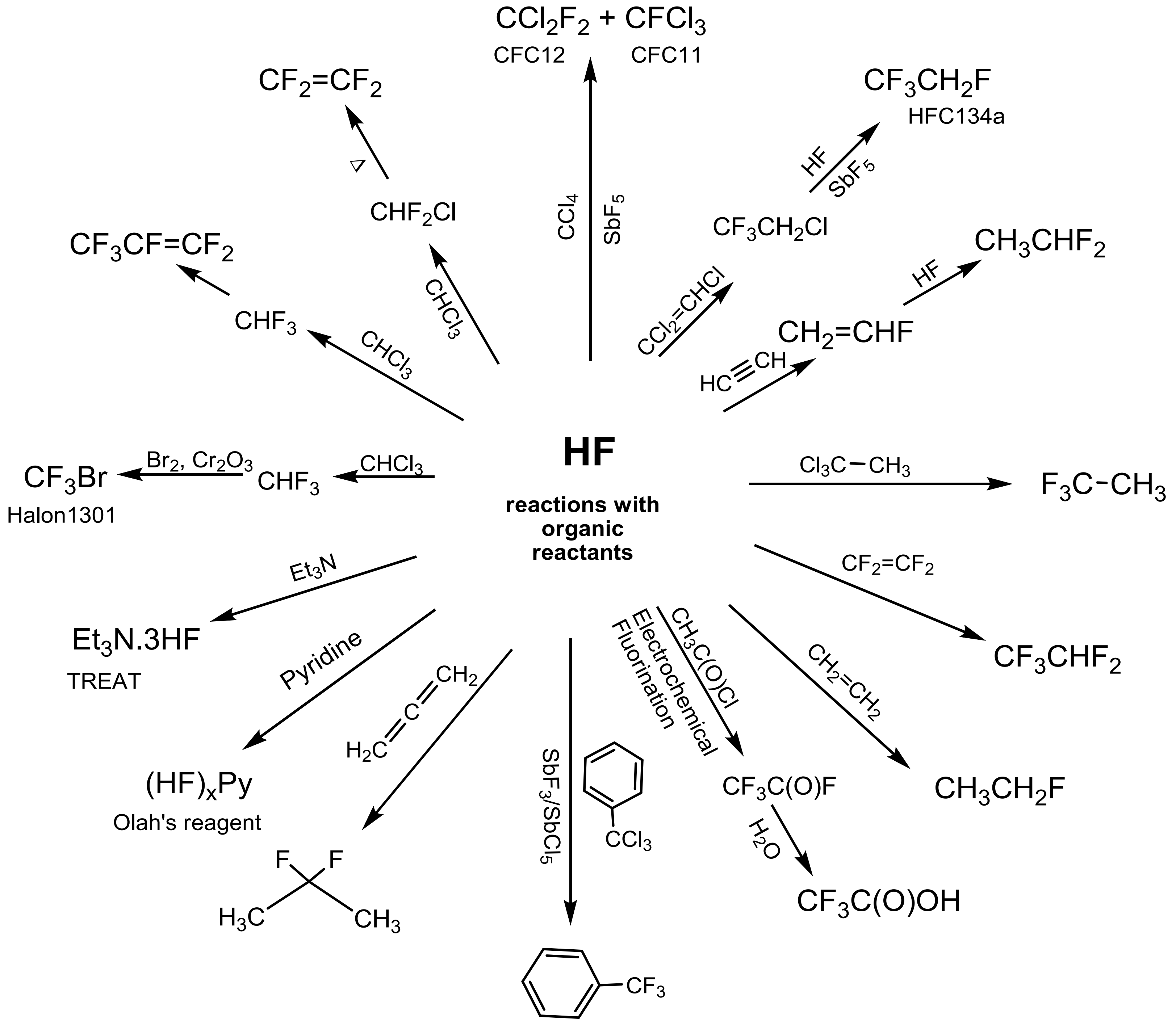
$$UF_6\,(g) + H_2O\,(\text{steam}) \longrightarrow UO_2F_2\,(s) + HF(g)$$

$$UO_2F_2\,(s) + H_2(g) \longrightarrow UO_2(s) + HF(g)$$

After sintering, these pellets are stacked into tubes made of corrosion-resistant alloys such as zirconium alloy. The tubes are sealed to contain the fuel pellets and these are called fuel rods. The finished fuel rods are grouped in special fuel assemblies that are then used to build up the nuclear fuel core of a power reactor.




HF
reactions with inorganic reactants
HSO$_3$F
Fluorosulfonic acid
SO$_3$
AsF$_3$
As$_2$O$_3$
SbF$_3$
Sb$_2$O$_3$
MgF$_2$
MgO
H$_2$F$^+$SbF$_6^-$
Fluoroantimonic acid
SbF$_5$
SbCl$_5$
SbF$_5$
NaOH
NaF
SiO$_2$
SiF$_4$
HF
H$_2$SiF$_6$
KF
KHF$_2$
NaF, (NaPO$_3$)$_n$
Na$_2$PO$_3$F
Sodium monofluorophosphate
NH$_4$F
Electrolysis
NF$_3$
Al$_2$O$_3$
AlF$_3$
NaOH, Al$_2$O$_3$
Na$_3$AlF$_6$
Cryolite
UO$_2$
UF$_4$
XeF$_6$
XeF$_5^+$ + HF$_2^-$
B$_2$O$_3$
BF$_3$
HF
HBF$_4$

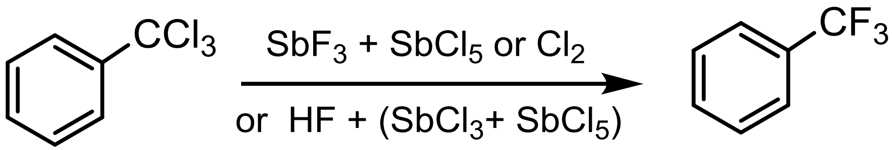

HF
reactions with organic reactants
CCl2F2 + CFCl3
CFC12
CFC11
CCl4
SbF5
CF2=CF2
CHF2Cl
CHCl3
CF3CF=CF2
CHF3
CF3CH2F
HFC134a
HF
SbF5
CF3CH2Cl
CCl2=CHCl
CH3CHF2
HF
CH2=CHF
HC≡CH
CF3Br
Halon1301
Br2, Cr2O3
CHF3
CHCl3
Cl3C−CH3
F3C−CH3
CF2=CF2
CF3CHF2
Et3N
Et3N.3HF
TREAT
Pyridine
(HF)xPy
Olah's reagent
H2C=C=CH2
F F
H3C CH3
SbF3/SbCl5
CCl3
CF3
Electrochemical Fluorination
CH3C(O)Cl
CF3C(O)F
H2O
CF3C(O)OH
CH2=CH2
CH3CH2F

Fluorination : Primary reactions

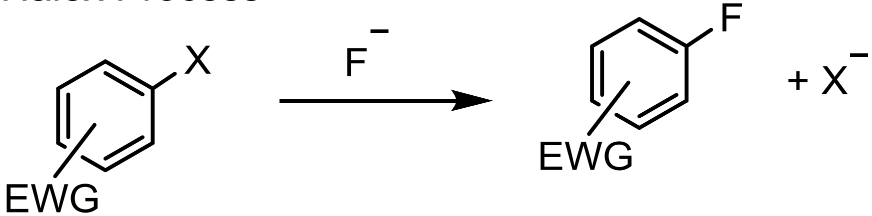
Balz-Schiemann reaction

$$ArN_2^+BF_4^- \xrightarrow{\Delta} Ar\text{-}F + N_2 + BF_3$$

Swarts Reaction



Halex Process



Simons Process (Electrochemical Fluorination)

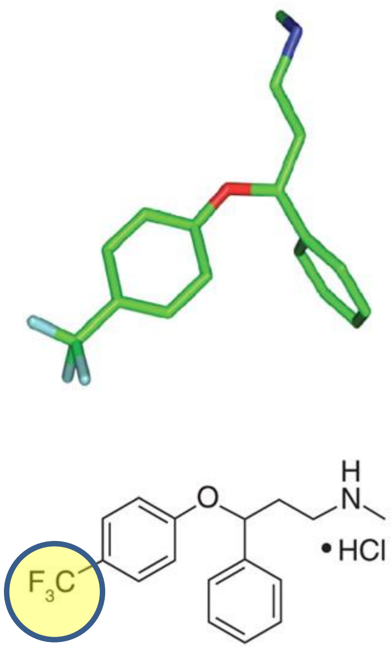
$$R_3CH + HF\ (\text{anhydrous}) \xrightarrow[\text{5-6 V}]{\text{electrolysis}} R_3CF + H_2$$

$$CH_3C(O)Cl + 4\ HF\ (\text{anhydrous}) \xrightarrow[\text{5-6 V}]{\text{electrolysis}} CF_3C(O)F + 3\ H_2 + HCl$$

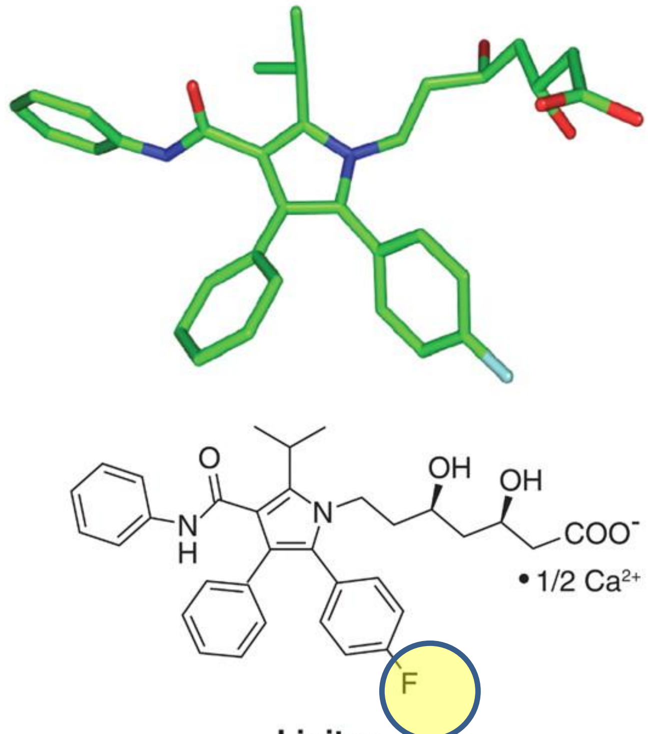
$$CF_3C(O)F + H_2O \longrightarrow CF_3C(O)OH + HCl$$

Fluorine in drugs

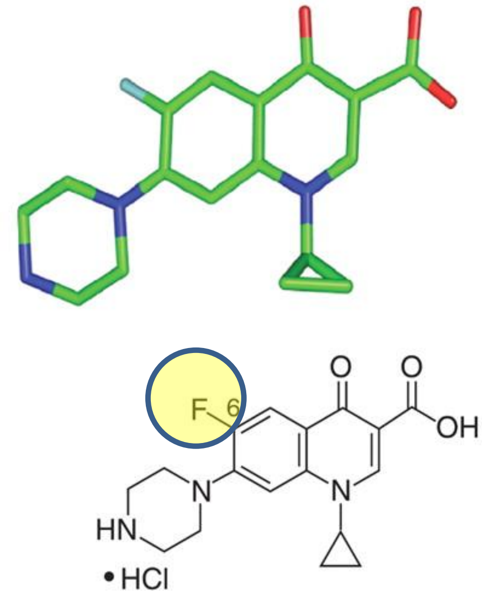
20% of all drug molecules approved by FDA has fluorine in it
40% of all herbicides have fluorine in it



Prozac



Lipitor



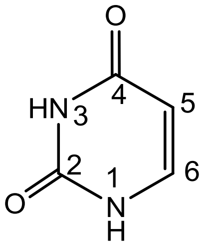
Ciprobay

Anti depressant
1 billion $/year

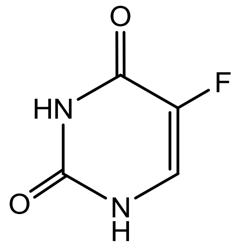
Atrovastatin
US$ 125 billion
1996-2012

Broad spectrum
anti microbial

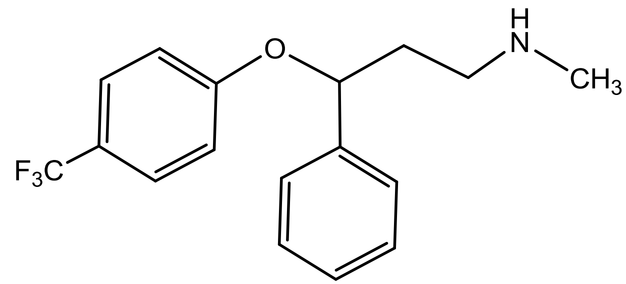
Fluorinated Drugs



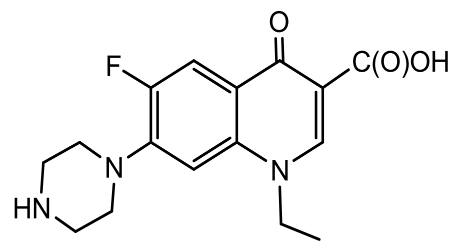
uracil



5-fluorouracil

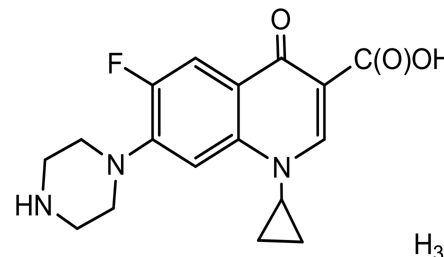


Fluoxetine (Prozac)



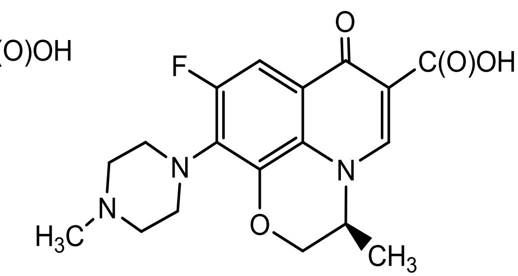
Norfloxacin

Anti bacterial



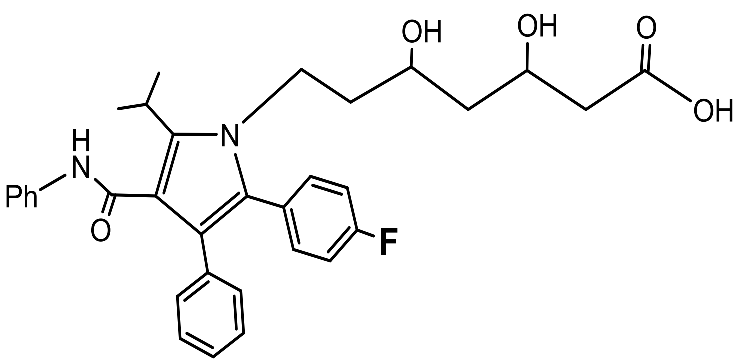
Ciploxacin

Broad spectrum antimicrobial



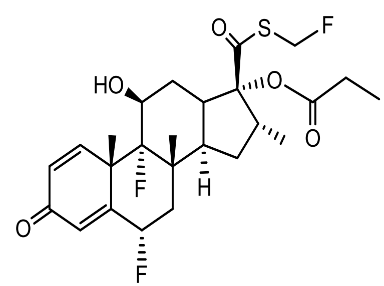
Levofloxacin

Broad spectrum antibiotic

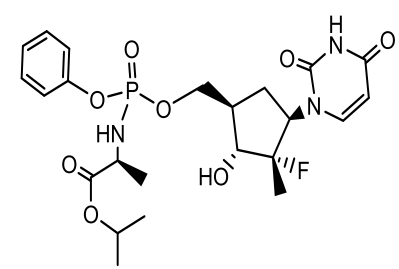


Atrovastatin (Lipitor) -anticholesterol drug sold by Pfizer

Worlds best selling drug of all times; US$ 125 billion in sales (1996-2012)



Fluticasone propionate (Advair)
A glucocorticoid; antiinflammatory
for nasal allergy etc.



Sofosbuvir (Sovaldi)
For hepatitis C virus infection

•Among carbon-halogen bonds, C-F bond has the highest bond dissociation energy making it stable for many uses. C-F bonds have very low polarisability, high dipole moment (1.50-1.85 D) (vs 0.30 D for C-H), low intermolecular dispersion interactions, are resistant to oxidative metabolism and have increased fat solubility.

Average Bond Energies (kJ/mol)

Single Bonds						Multiple Bonds	
H—H	432	N—H	391	I—I	149	C=C	614
H—F	565	N—N	160	I—Cl	208	C≡C	839
H—Cl	427	N—F	272	I—Br	175	O=O	495
H—Br	363	N—Cl	200			C=O*	745
H—I	295	N—Br	243	S—H	347	C≡O	1072
		N—O	201	S—F	327	N=O	607
C—H	413	O—H	467	S—Cl	253	N=N	418
C—C	347	O—O	146	S—Br	218	N≡N	941
C—N	305	O—F	190	S—S	266	C≡N	891
C—O	358	O—Cl	203			C=N	615
C—F	485	O—I	234	Si—Si	340		
C—Cl	339			Si—H	393		
C—Br	276	F—F	154	Si—C	360		
C—I	240	F—Cl	253	Si—O	452		
C—S	259	F—Br	237				
		Cl—Cl	239				
		Cl—Br	218				
		Br—Br	193				

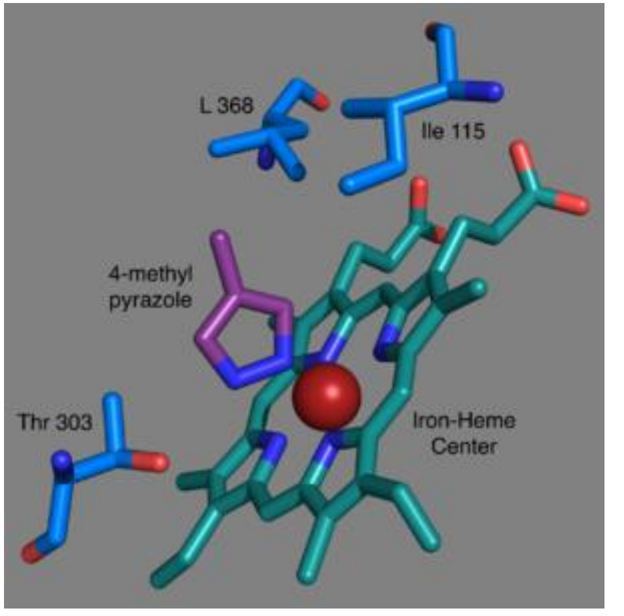
*C=O(CO_2) = 799

What happens when H is replaced by F in organic molecules?

1. Exchanging of H by F exerts a large electronic effect on neighboring carbon centers altering both dipole moment and pKa. In addition, the stability and reactivity of functional groups on the fluorinated molecule are also affected.
2. Size wise, fluorine and hydrogen mimic each other and the van der Waals radii of fluorine (1.35 Å) is close to that of hydrogen (1.10Å) which translates to the fact that only limited extra steric demands are present on the receptor sites by an exchange of H by F.
3. The C-F bond distance (1.26-1.41Å) is marginally higher than that of C-H bond (1.08-1.10Å). Therefore, there will be only a marginal change in bond distances when replacing H by F.
4. The presence of C-F bonds aids hydrophobic interactions.
5. Covalently bound fluorine also increases lipophilicity thus increasing its bioavailability (an important pharmacokinetic property of a drug defined ***as the fraction of the administered does of an unchanged drug that reaches the systemic blood circulation of the body). CF_3 group is one of the most lipophilic of all substituents***.
6. C-F bonds have high oxidation and thermal stability. In the body it has been found to be not susceptible to oxidation by cytochrome P-450.
7. The NMR activity of fluorine's sole natural isotope ^{19}F is convenient for characterization and also to obtain valuable information about active site interactions (-300 to +400 ppm)
8. The high electro-negativity and low polarisability of the C-F bond translates into very less secondary interactions (or intermolecular dispersion interactions) resulting in high volatility for small molecules having mostly fluorine substituents.

Introduction

- Cytochrome P450 (P450) → very large and diverse superfamily of hemoproteins
- range of proteins
- found in all domains of life
- P450 → use a plethora of both exogenous and endogenous compounds as substrates in enzymatic reactions
- The most common reaction catalysed by cytochrome P450 = a monooxygenase reaction
- insertion of one atom of oxygen into an organic substrate (RH) while the other oxygen atom is reduced to water



In this reaction, the two atoms of molecular oxygen(O_2) are reduced to one hydroxyl group and one water (H_2O) molecule by the concomitant oxidation of the cofactor NAD(P)H

$$RH + O_2 + NADPH + H^+ \rightarrow ROH + H_2O + NADP^+$$

P-450 is well known for hydroxylations of unactivated C–H bonds, epoxidations, dealkylations, and *N*- and *S*-oxidations as well as other less common reactions.

Resting state of P450s should be regarded as a mixture of Fe(III) and Fe(II) forms in both aerobic and oxygen-limited conditions.

$$R{-}H \xrightarrow{[O]} R{-}OH$$ Carbon oxidation

$$RCH_2{-}OH \xrightarrow{[O]} RCH{=}O + H_2O$$

$$RCH{=}O \xrightarrow{[O]} RCOOH$$

$$R_2N{-}H \xrightarrow{[O]} R_2N{-}OH$$ Heteroatom oxidation

$$R_3N \xrightarrow{[O]} R_3N{=}O$$

$$R_2S \xrightarrow{[O]} R_2S{=}O$$

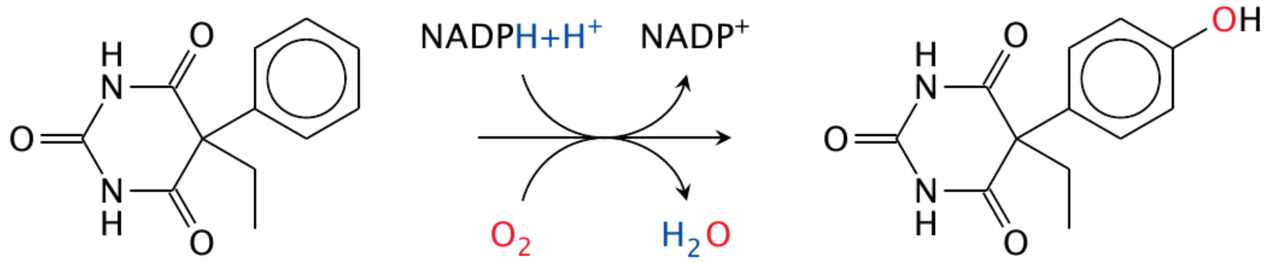
$$RO{-}CH_2R \xrightarrow{[O]} ROH + O{=}CHR$$ Dealkylation

$$R_2N{-}CH_2R \xrightarrow{[O]} R_2NH + O{=}CHR$$

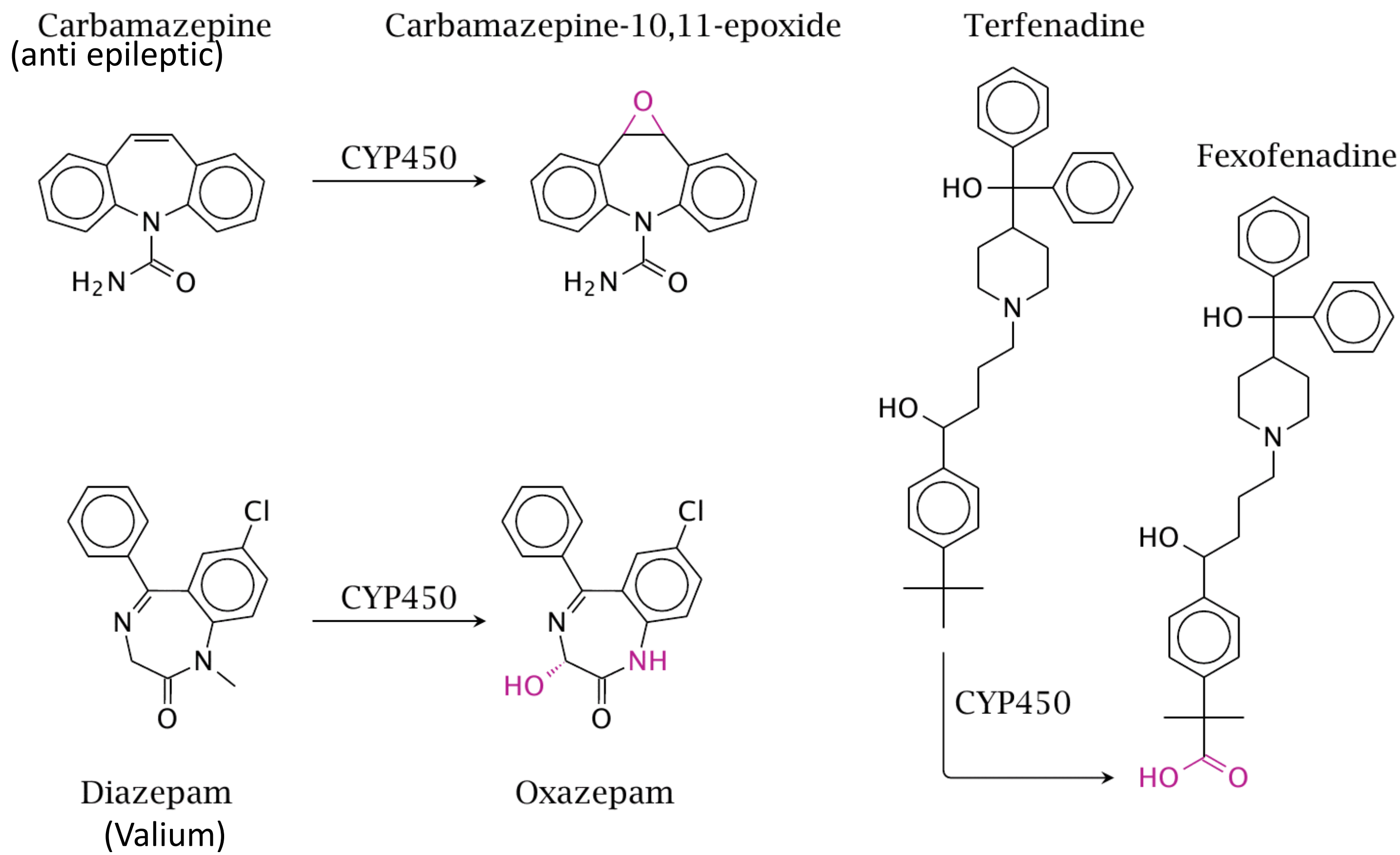
$$R{-}HC{=}CH{-}R \xrightarrow{[O]} R{-}HC\overset{O}{\triangle}CH{-}R$$ Epoxide formation

Cyt-P450 activity can result in reduced pharmacological effect, decomposition of drugs, drug toxicities and adverse drug reactions.

Oxidation by Cytochrome P 450 of drug molecules

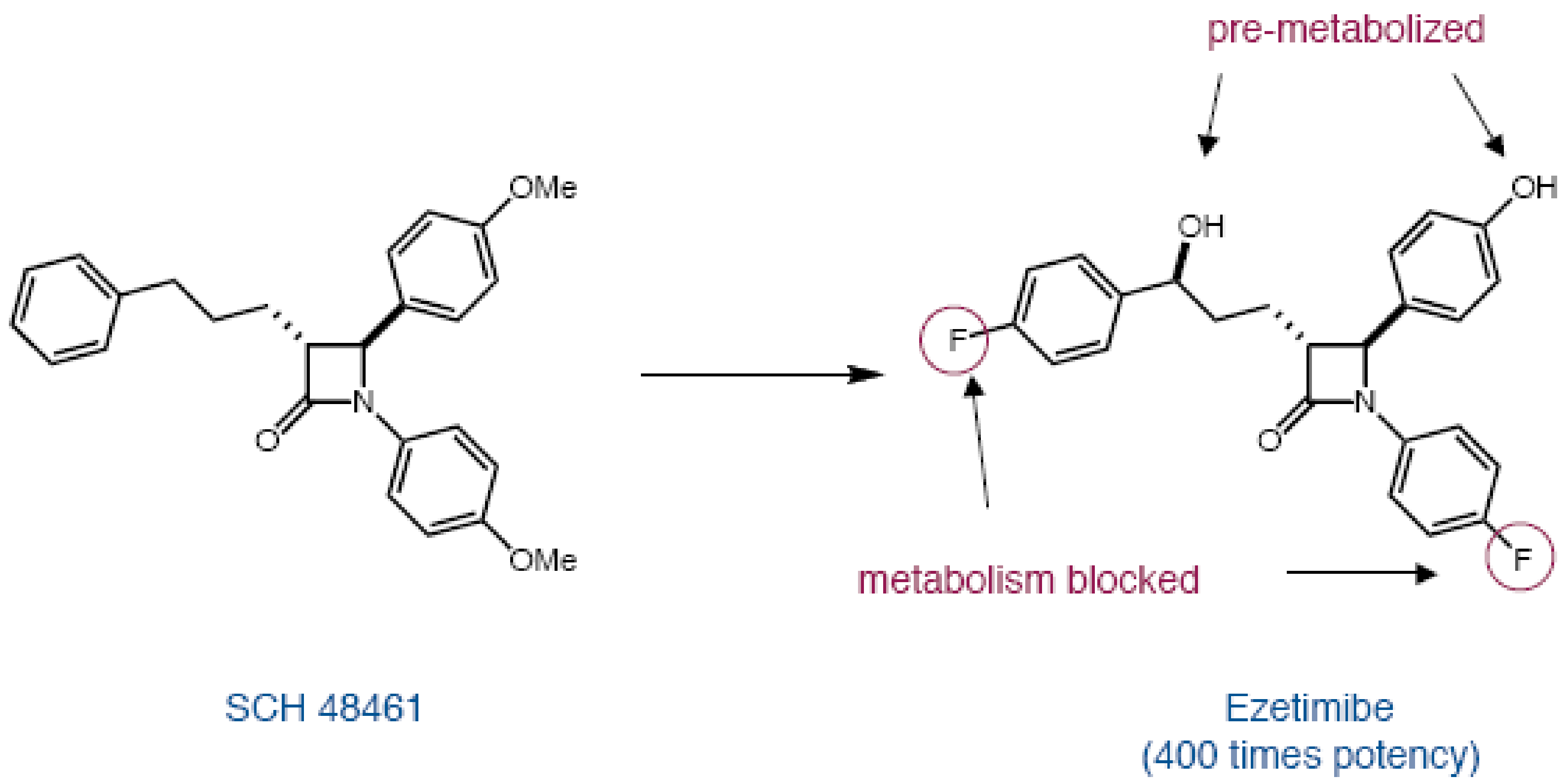


Phenobarbital, a barbituric acid derivative with both sleep-inducing and anti-epileptic activity, illustrates both the significance and the workings of **drug metabolism**. The drug molecule itself is quite hydrophobic. This causes the drug to distribute into fat tissue.



Increased Metabolic Stability of Organofluorine

Productive metabolism incorporated and non-productive blocked

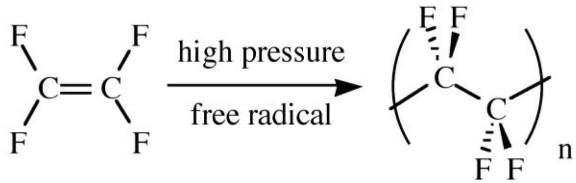


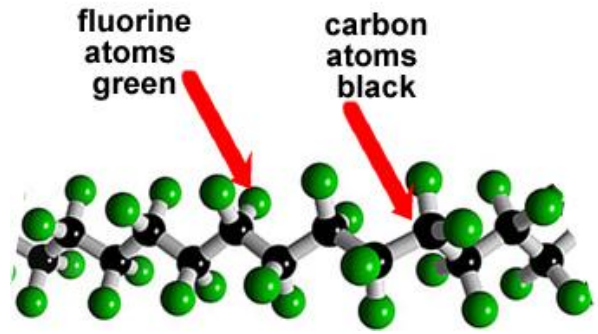
Ezetimibe is a drug that lowers plasma cholesterol levels. It acts by decreasing cholesterol absorption in the small intestine. It may be used alone , when other cholesterol-lowering medications are not tolerated, or together with statins

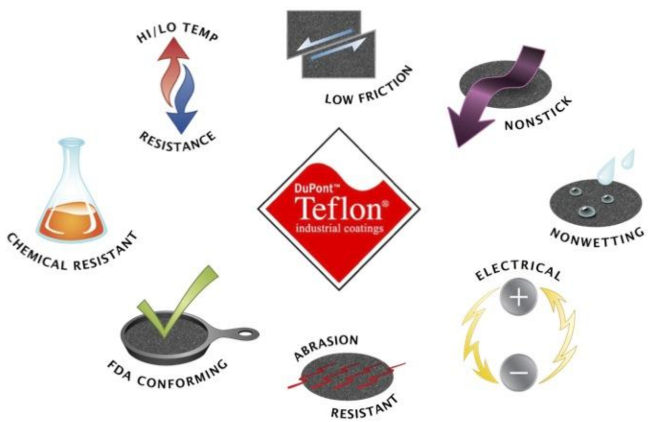
Bottom line: C-F bonds are not oxidized by Cytochrome P-450

Roy J. Plunkett

1938

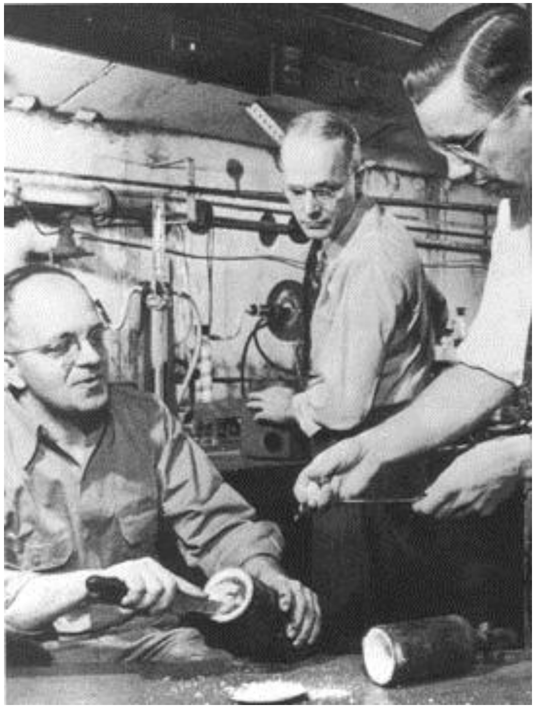






Poly tetrafluoroethylene (Teflon) accidentally discovered by **Roy J. Plunkett** of kinetic chemicals (A subsidiary of DuPont) while attempting to make a new CFC using tetrafluoroethylene.

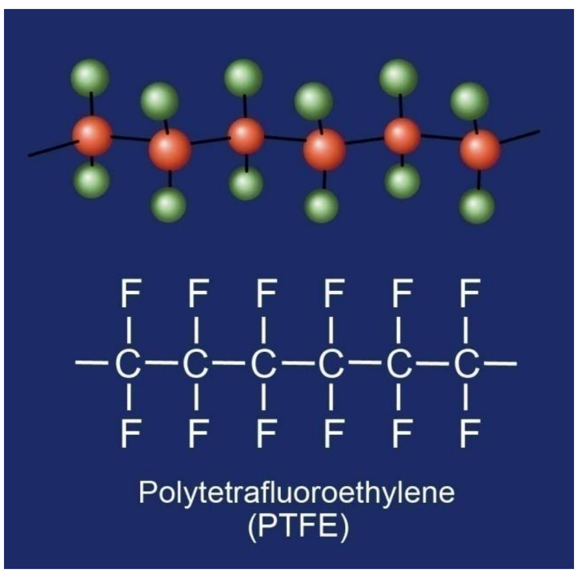
C-F bond isn't very polarisable. The electrons won't move sufficiently towards a hydrogen from water (or anything similar) in order for a hydrogen bond to form.

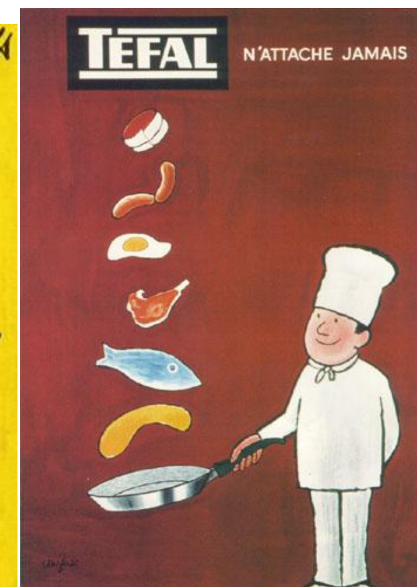


Roy Plunkett

Marc Gregoire

Collette

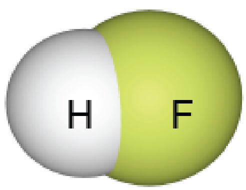




Hydrogen Bonding and the C–F Bond

"only the most electronegative atoms should form hydrogen bonds, and the strength of the bond should increase with increase in the electronegativity of the two bonded atoms… It is found empirically that fluorine forms very strong hydrogen bonds, oxygen weaker ones, and nitrogen still weaker ones."

- Linus Pauling, *The Nature of the Chemical Bond, 2nd Ed.*, **1939**

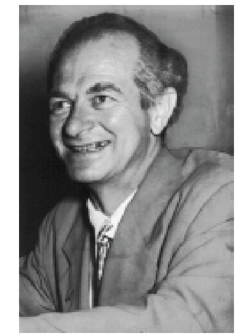


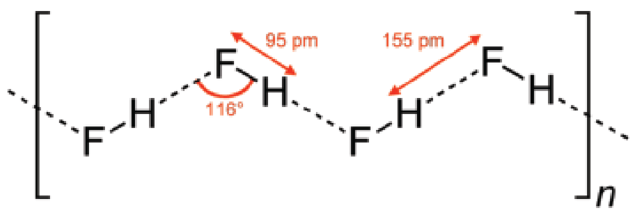
Hydrogen Fluoride

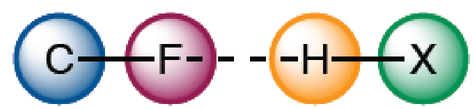
[F•••H•••F]
~ 40 kcal/mol

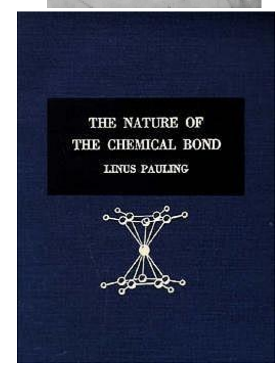
Organofluorine

C–F•••H–X
~ 1.5 – 2.4 kcal/mol







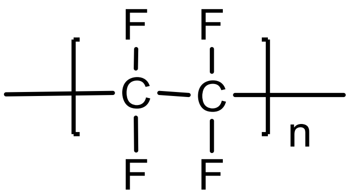


"It is interesting that in general fluorine atoms attached to carbon do not have significant power to act as proton acceptors in the formation of hydrogen bonds in the way that would be anticipated from the large difference in electronegativity of fluorine and carbon."

- Linus Pauling, *The Nature of the Chemical Bond, 3rd Ed.*, **1960**

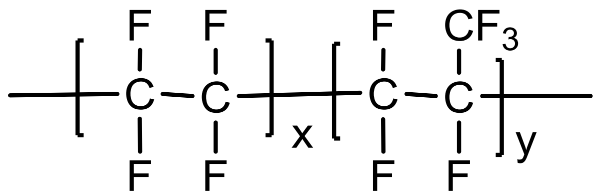
Dunitz, J. D. *ChemBioChem* **2004**, *5*, 614.

The largest application for PTFE is in **electrical insulation**. It is an excellent dielectric and very chemically stable. It is also used extensively in the chemical process industry where **corrosion resistance** is needed: in coating pipes, in tubing, and gaskets. Another major use is architectural fabric (PTFE-coated fiberglass cloth used for stadium roofs and such). The major consumer application is **non-stick cookware**. Other fluoropolymers tend to have similar properties to **PTFE—high chemical resistance** and **good dielectric properties**—which leads to use in the chemical process industry and electrical insulation. They are easier to work with (to form into complex shapes), but are more expensive than PTFE and have lower thermal stability. A study in 2102 indicated that three fluoropolymers constitute 85% of all fluoropolymers consumed across the world. These are PTFE (60%), PVDF(15%) and FEP (10%).



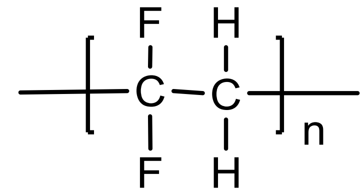
PTFE

Poly tetrafluoroethylene



FEP

Fluorinated ethylene propylene



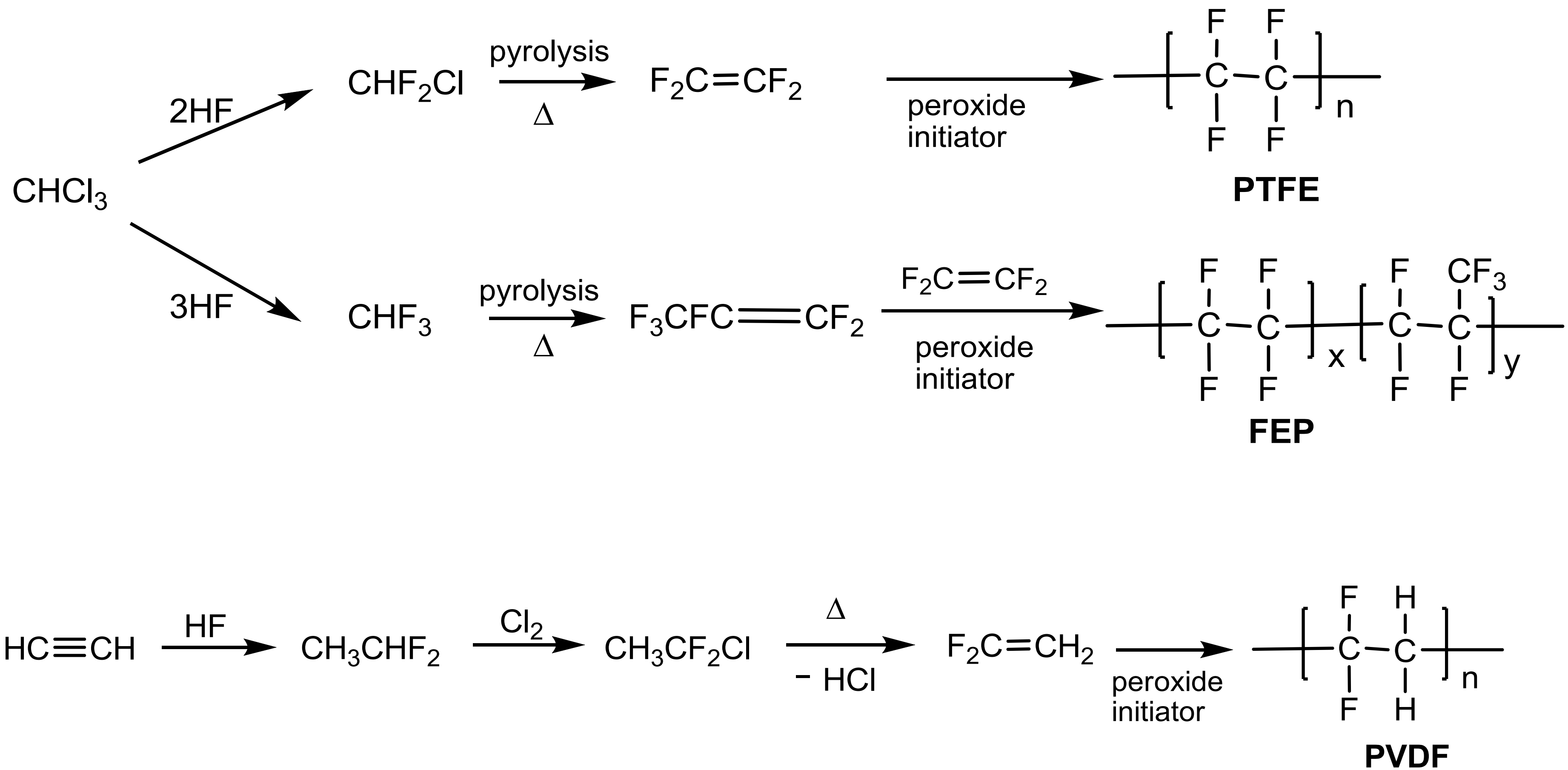
PVDF

Poly vinylidene difluoride

World Fluoropolymers

60% **10%** **15%**

Property	**PTFE**	**FEP**	**PVDF**
Melting point	327 °C	265 °C	177 °C
Melt processability	Not melt processable	Melt processable	Melt processable
Melt viscosity	10^{11} Poise	10^{5} Poise	0.2-17 x 10^{3} Poise
Upper use temp.	260 °C	200 °C	150 °C
Tensile Strength	5000	3000	4500
Glass transition temp	115 °C	60 °C	-35 °C
Flexural modulus (MPa)	340-620	655	1140-2240
Opacity	opaque	translucent	Almost transparent



2HF
CHF2Cl
pyrolysis
Δ
F2C=CF2
peroxide initiator
n
PTFE
CHCl3
3HF
CHF3
pyrolysis
Δ
F3CFC=CF2
F2C=CF2
peroxide initiator
CF3
x
y
FEP
HC≡CH
HF
CH3CHF2
Cl2
CH3CF2Cl
Δ
− HCl
F2C=CH2
peroxide initiator
n
PVDF

Fluorine based small molecules are much more volatile compared to other halogenated compounds; a consequence of small size and high electro negativity resulting **in very little secondary weak interactions**. The very low polarisabiliy of organofluorine substituents (C-F bond) affects secondary intermolecular interactions

Freon Unique Properties: Low toxicity, Low reactivity, Low Flammability, High Volatility,

Freon Products

Product	Formula	Molecular Weight	Boiling Point °F	Boiling Point °C
Freon 14	CF_4	88.0	–198.3	–128.0
Freon 503	$CHF_3/CClF_3$	87.3	–127.6	–88.7
Freon 23	CHF_3	70.0	–115.7	–82.0
Freon 13	$CClF_3$	104.5	–114.6	–81.4
Freon 116	$CF_3—CF_3$	138.0	–108.8	–78.2
Freon 13B1	$CBrF_3$	148.9	–72.0	–57.8
Freon 502	$CHClF_2/CClF_2—CF_3$	111.6	–49.8	–45.4
Freon 22	$CHClF_2$	86.5	–41.4	–40.8
Freon 115	$CClF_2—CF_3$	154.5	–37.7	–38.7
Freon 500	CCl_2F_2/CH_3CHF_2	99.3	–28.3	–33.5
Freon 12 refrigerant	CCl_2F_2	120.9	–21.6	–29.8
Freon 114	$CClF_2—CClF_2$	170.9	38.8	3.8
Freon 21	$CHCl_2F$	102.9	48.1	8.9
Freon 11 propellant	CCl_3F	137.4	74.9	23.8
Freon 113	$CCl_2F—CClF_2$	187.4	117.6	47.6
Freon 112	$CCl_2F–CCl_2F$	203.9	199.0	92.8

CFC and Halon Numbering scheme: *The industry adopted CFC and Halon numbering is obtained as follows: For CFC's consider the number consists of three digits a, b and c. The digit a will be number of carbon atoms minus 1, b will be the number of hydrogen atoms plus 1 and . If a is equal to zero it will not be displayed. For example for* CCl_2F_2*: a = 0, b= 1 and c=2 and it is termed CFC 12. To find the chemical formula if the CFC number is provided, add 90 to the abc number to obtain a three digit xyz number. Now x will be the number of carbon atoms, y will be the number of hydrogen atoms and z will be the number of fluorine atoms. Also 2x+2-y-z will be the number of chlorine atoms for the CFC. Eg. for CFC 11: 90+11 = 101; C=1, H=0,F=1 and Cl=2+2-0-1 = 3. Halons are fluorocarbons with at least one bromine atom and no hydrogen. Each halon has an abcd number where a = number of carbon atoms, b= number of fluorine atoms, c= number of chlorine atoms and d is the number of bromine atoms and if one of them is zero it is still mentioned. Eg. Halon 1301 is* CF_3Br*.*

HFC-134a $CF_3\text{-}CFH_2$

a will be number of carbon atoms minus 1

b will be the number of hydrogen atoms plus 1

c will be the number of fluorine atoms

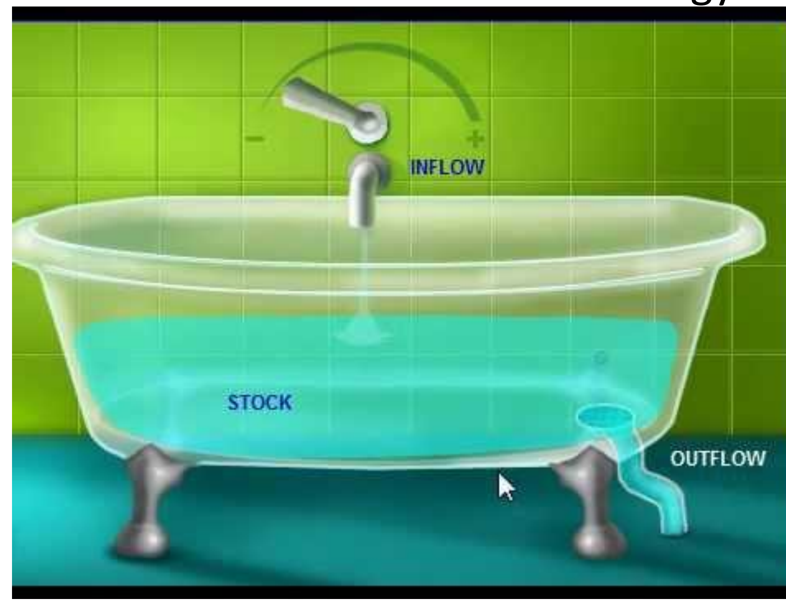
UV-A (315-400 nm) not much harmful, Does not affect O_3
UV-B (280-315 nm) harmful, Affects O_3
UV-C (100-280 nm) lethal, Absorbed by O_3

$$O_2 \xrightarrow[\text{240-160 nm}]{\text{UV}} O^{\bullet} + O^{\bullet}$$

$$O_2 + O \longrightarrow O_3$$

$$O_3 \xrightarrow[\text{290-230 nm}]{\text{UV}} O_2 + O$$

Bathtub analogy



$$CCl_2F_2 + h\nu \longrightarrow {}^{\bullet}CClF_2 + Cl^{\bullet}$$

$$\dot{Cl} + O_3 \longrightarrow ClO + O_2$$

$$ClO + O \longrightarrow {}^{\bullet}Cl + O_2$$

Since the chlorine free radical is regenerated after degrading a molecule of ozone, one Cl·, in principle, can destroy hundreds of thousands of ozone molecules if they are present in the vicinity.

Ozone Depletion Potential (ODP)

Ozone depletion potential is defined as the relative amount of degradation a compound causes to the ozone layer with trichlorofluoromethane, Cl_3CF (CFC-11) being fixed at an ODP of 1.

Compound	ODP	Compound	ODP	Compound	ODP
Cl_3CF (freon 11)	1	HFC 134a (CF_3CFH_2)	0	HCFC113	0.8
CCl_2F_2 (freon 12)	1 (0.82)	HCFC225	0.033	CF_3I	0.013
1,1,2-Trichlorotrifluoroethane	0.8	HCFC123	0.02	CH_3I	0.016
HCFC22 (CF_2HCl)	0.055	CH_3Br	0.7	CF_3Br(halon1301)	10

Global Warming Potential is the relative measure of how much heat a green house gas traps in the atmosphere. It compares the amount of heat trapped by a certain mass of a gas over a specific period of time interval (say 20, 100 or 500 years) to the amount of heat trapped by a similar mass of CO_2 in the same time interval.

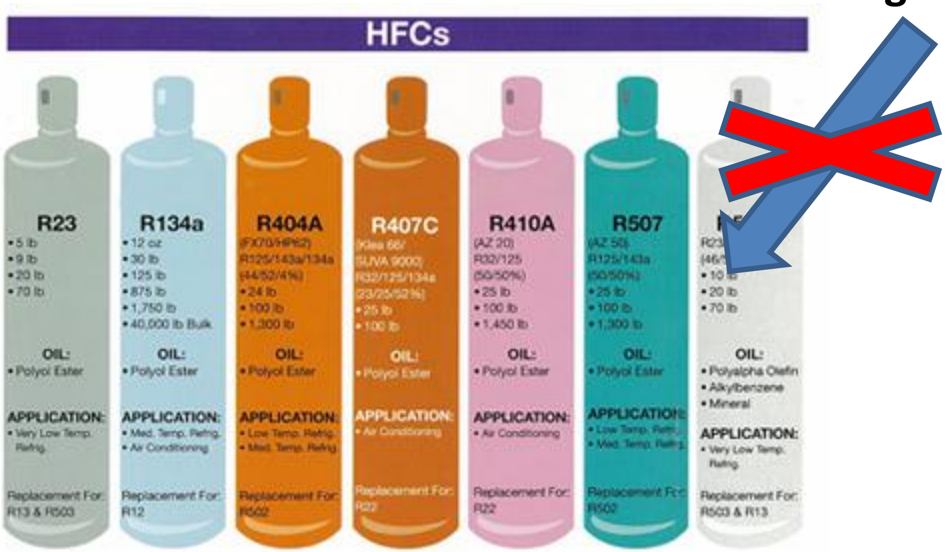
Compound	GWP (100 year)	Lifetime* (years)	Compound	GWP (100 year)	Lifetime (years)
CO_2	1	Not specified. But taken as 35-200 years	N_2O	298	114
SF_6	22,800	3200	CH_4	25	12
HFC-23 (CHF_3)	14,800	270	CCl_4	1400	26
CFC-11 ($CFCl_3$)	5350	45	NH_3	0	< 0.019

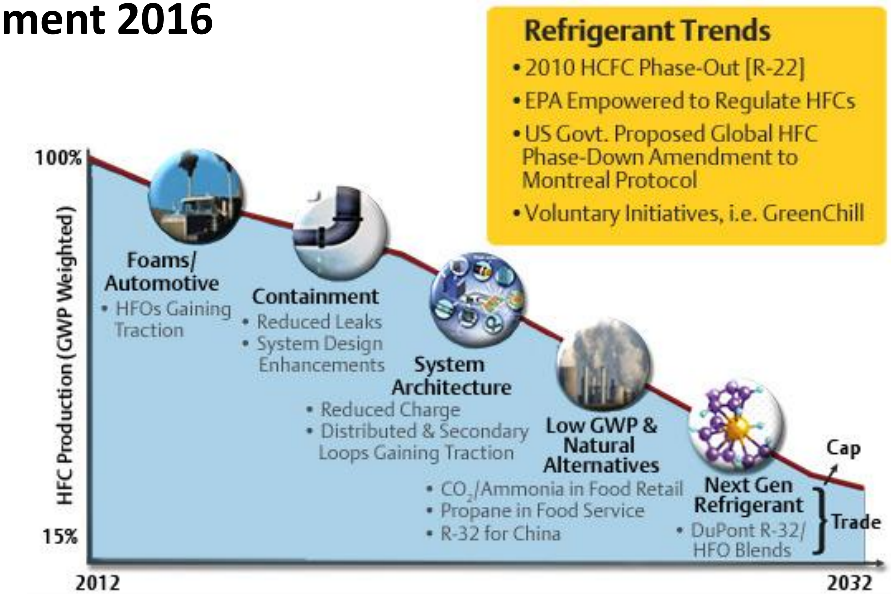
Fluorine in Refrigerants

1987 Montreal Protocol

1997 Kyoto Protocol

Rwanda HFC agreement 2016





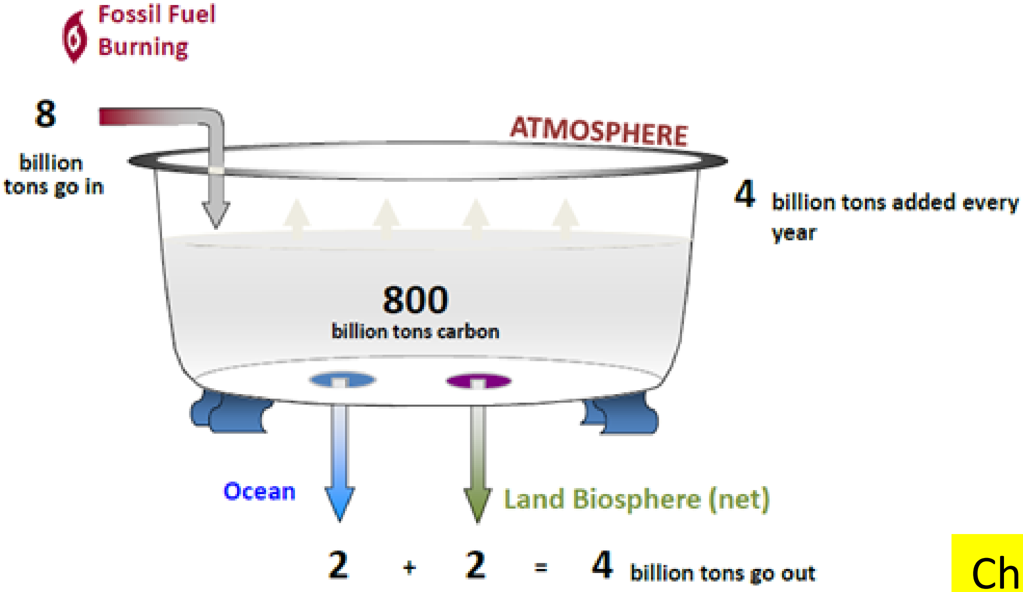


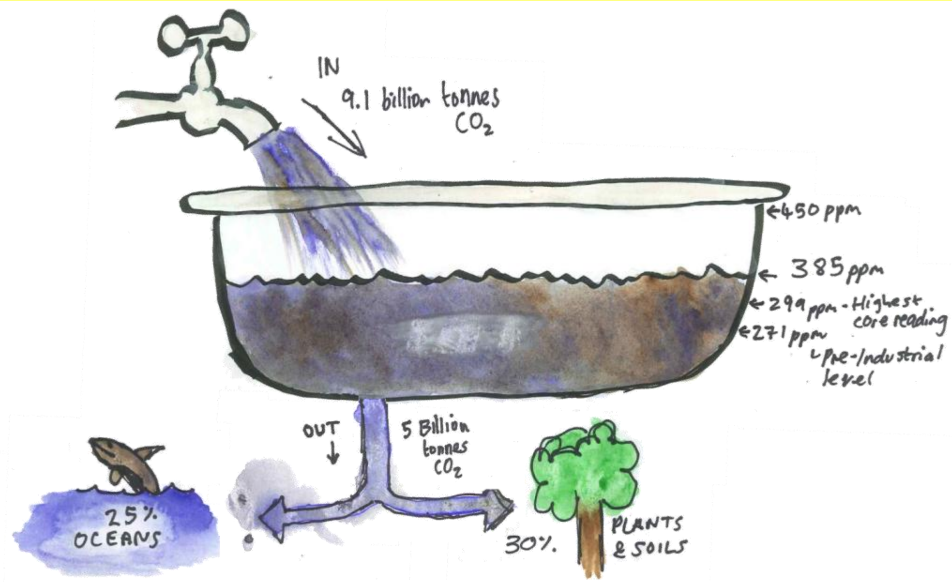
Figure 6. A simplified depiction of the atmospheric carbon mass balance (http://cmi.princeton.edu/wedges/pdfs/teachers_guide.pdf)

Global warming bathtub analogy

Montreal Protocol 1987 CFC Ozone

Kyoto Protocol 1997 Green house gases

Chemicals like HFC's which have higher GWP than CO2 need to be controlled faster



Rwanda HFC agreement 2016 oct

More than 190 countries, after a weeklong meeting in the Kigali capital of Rwanda, decided on Saturday to phase out the use of HFCs, short for hydrofluorocarbons, over the next 30 years. This single, relatively easy and painless intervention has the potential to prevent a rise of about 0.5 degrees Celsius in global temperatures by the end of the century. (28^{th} meeting of Montr. Protocol)

Maldives, Bangladesh 0.5 deg. gain global warming

Code	**CFC-12 (1987 banned)**	**HFC-134a (2017 banned)**	**HFO-1234yf**
Name of Refrigerant	Dichlorodifluoro methane	1,1,1,2-Tetrafluoro ethane	2,3,3,3-Tetrafluoro propene
Formula	CCl_2F_2	CF_3-CFH_2	CH_2=CF-CF_3
Boiling Point	-29.8 °C	-26.3 °C	-30 °C
ODP	0.82	0.055	0.0
GWP (100 yrs)	10,900	1430	4

Synthesis of CFC-12

$$CCl_4 + 2HF \longrightarrow \mathbf{CCl_2F_2} + 2HCl$$

Synthesis of HFC 134a

$$H_2C{=}CH_2 + Cl_2 \longrightarrow ClCH_2CH_2Cl \xrightarrow[400\ ^\circ C,\ Cl_2]{KCl,\ AlCl_3} Cl_2C{=}CHCl$$

$$Cl_2C{=}CHCl \xrightarrow{3\ HF} CF_3CH_2Cl \xrightarrow[SbF_5]{HF} \mathbf{CF_3CH_2F}$$

Synthesis of HFO 1234yf

$$CHCl_3 + HF \longrightarrow HCF_2Cl \xrightarrow[pyrolysis]{} F_2C{=}CF_2$$

$$F_2C{=}CF_2 + CH_3F \xrightarrow[SbF_5]{} \mathbf{H_2C{=}CFCF_3}$$

World use in 2011 for HFCs was 79% for refrigeration and air-conditioning, 11% for foam making for packing cusions, 5% for medicinal aerosprays and 5% for other uses such as degreasing solvents, fire extinguishers etc. European union has banned use of all HFCs having GWP > 150 in all new vehicles made after 2011 and any transport equipment after 2017

Fluorine in Inhalation anesthetics

History ?

- GA=absent mid-1800's
- Original discoverer
  - Crawford Long, Physician from Georgia: 1842, ether anesthesia
- Chloroform introduced
  - James Simpson: 1847
- Nitrous oxide
  - Horace Wells in 1845

Year of clinical use	Inhalation anesthetic	Properties
1846	Diethyl ether Et-O-Et	Flammable; have undesirable side effects, such as post-anesthetic nausea and vomiting.
1847	Chloroform $CHCl_3$	Severe cardiovascular depression, hepatptoxicity, many reports of sudden deaths; was in use till 1976.
1774	**Nitrous oxide** **N_2O**	Non ether; weak inhalation anesthetic ;commonly used in combination with other more potent inhalational anesthetics; suitable for dental applications. Can produce headache. Less potent and long acting compared to others. **Remains in use even today**
1923	Ethylene $CH_2=CH_2$	High concentrations required; is an explosive with O_2, unpleasant smell. flammable
1930	Divinyl ether $CH_2=CHOCH=CH_2$	Also called Vinethene; Flammable and explosive
1930	Trichloroethylene $Cl_2C=CHCl$	Non flammable alternative to ethylene. Decomposes to give phosgene when warmed in the presence of sodalime; human carcinogen and a non-carcinogenic health hazard.
1954	Fluroxene $(CF_3)_2CH_2$ -O-CH=CH_2	First fluorinated anesthetic; Flammable, explosive mixtures with other gases, post operative liver and renal failure;withdrawn from the market in 1974
1956	**Halothane** **$CF_3CHClBr$**	Non-ether compound; was in use for a long time; can cause nausea, flammable at high concentrations.rare case of hepatitis following anesthesia linked to halothane
1960	Methoxyflurane $(CHCl_2)CF_2$-O-CH_3	Biodegradation produces inorganic fluoride and dichloroacetic acid which are toxic for major organs of the human body; also nephrotoxicity
1963	Enflurane $(CHFCl)CF_2$-O-CHF_2	Nonflammable, non irritant, low toxic, high potency, rapid onset,Cardiovascular depressant and convulsing properties shows hepatic dysfunction, hypotension
1971	**Isoflurane** **CF_3CHCl-O-CHF_2**	Its pungency can irritate the respiratory system.
1992	**Desflurane** **CF_3CHF-O-CHF_2**	Pungent and irritable; has the most rapid onset and offset for any inhalation anesthetics; low blood solubility; high cost; low potency. It may cause tachycardia.
1994	**Sevoflurane** **$(CF_3)_2CH$-O-CH_2F**	After desflurane, it has the fastest onset and offset of anesthesia; inherently stable, low flammability, sweet smelling, lack of irritation to airway passages, low blood:gas solubility;minimal cardiovascular and respiratory side effects, minimal end-organ effects

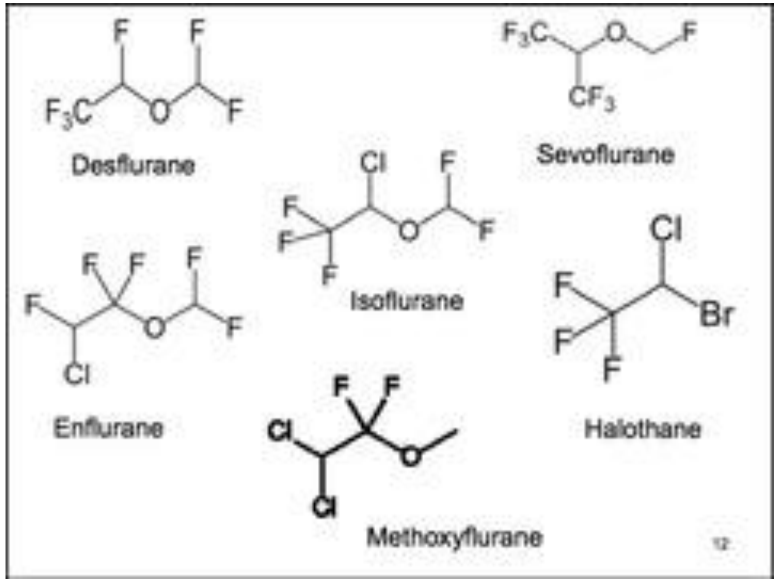


Table 1 – Inhalation anesthetic agents (Year available for clinical use).

Agents in clinical use	New Agents	Agents of historical interest
Halothane (1956)	Desflurane (1992)	Chloroform (1847)
Isoflurane (1981)	Sevoflurane (1994)	Cyclopropane (1925)
Enflurane (1973)	Xenon (1997)	Diethyl ether (1846)
Methoxyflurane (1960)		Fluroxene (1951)
Nitrous Oxide (1844)		Trichlorethylene (1930)

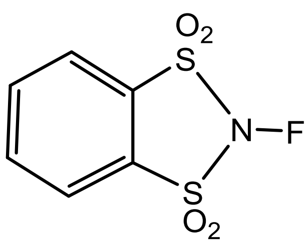
Isoflurane **$CF_3CHCl\text{-}O\text{-}CHF_2$**
Desflurane **$CF_3CHF\text{-}O\text{-}CHF_2$**
Sevoflurane **$(CF_3)_2CH\text{-}O\text{-}CH_2F$**

Characteristics of **fluorinated ethers** include

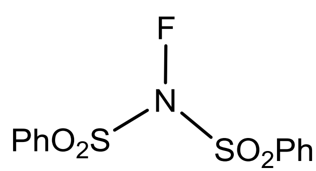
- inherent stability,
- low flammability,
- non-pungent odor,
- lack of irritation to airway passages,
- low blood:gas solubility allowing rapid induction of and emergence from anesthesia,
- minimal cardiovascular and respiratory side effects, minimal end-organ effects,
- minimal effect on cerebral blood flow,
- low reactivity with other drugs,
- and a vapor pressure and boiling point that enables delivery using standard vaporization techniques.

Electrophilic fluorination: selective conversion of C-H to C-F

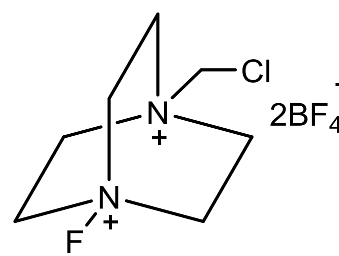
The development of crystalline, benchtop-stable fluorinating reagents with excellent selectivity such as N-fluorobis(phenyl)sulfonimide (NFSI), N-fluoropyridinium salts, *N*-fluoro-*o*-benzenedisulfonimide (NFOBS), Selectfluor I and Selectfluor II· have made electrophilic fluorination quite easy to perform. Although fluorinations employing N-F reagents do not use molecular fluorine directly, they are almost universally prepared from F_2gas which requires great care and special apparatus for handling and usage.



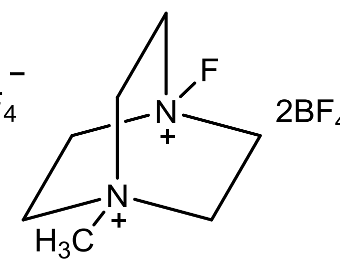
NFOBS



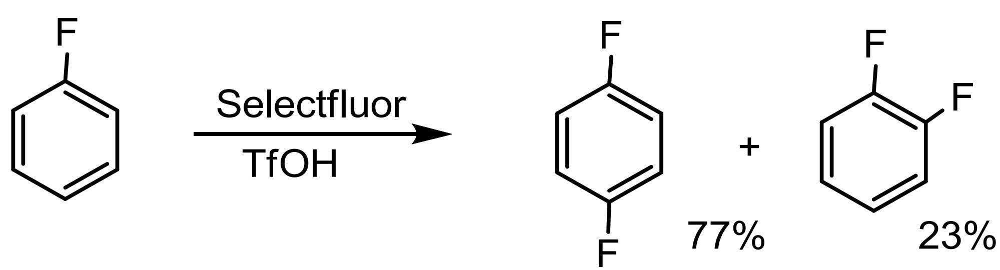
NFSI



Selectfluor

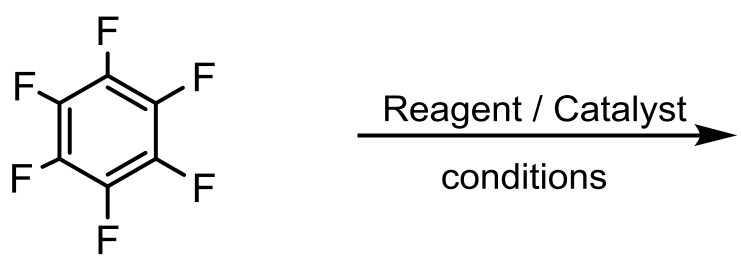


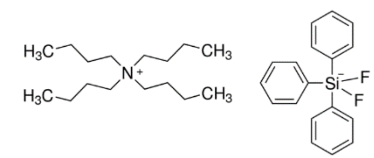
Selectfluor II



Hydrodefluorination reactions
Selective conversion of C-F to C-H

Selective conversion of C–F bonds to C–H bonds, commonly referred to as hydrodefluorination (HDF) is one of the most sought after reactions in the chemistry of organofluorine compounds. Fluorine is known to form the strongest σ bond to carbon. The C–F bond is significantly polar, is short, has a low polarisability and the σ* antibonding orbital is a low lying orbital. These features along with the fact that fluoride is a poor leaving group results in high thermodynamic stability and kinetic inertness for the C–F bond when compared to other carbon–halogen bonds. Partially fluorinated aromatics such as C_6F_5H, essential for the synthesis of pentafluorophenyl substituted compounds are difficult to prepare by direct fluorination and HDF is the best method to make them





A. Cp_2ZrCl_2, Mg, $HgCl_2$ or PMe_3, THF, RT, 2h — 93% yield
B. Zn, H_2O, NH_3 — 71% yield
C. Ph_3SiH, TBAT, THF, 60 °C, 40h — 83% yield

silyl hydrides, R_3SiH, exchange H for F as Si–F bonds are stronger than Si–H bonds

Fluorine in Superacids

According to Gillespie, protic acids stronger than 100% sulfuric acid can be considered superacids. Thus, perchloric acid ($HClO_4$), anhydrous hydrofluoric acid (HF), trifluoromethanesulfonic acid (CF_3SO_3H) and fluorosulfonic acid (HSO_3F) are all considered as superacids.

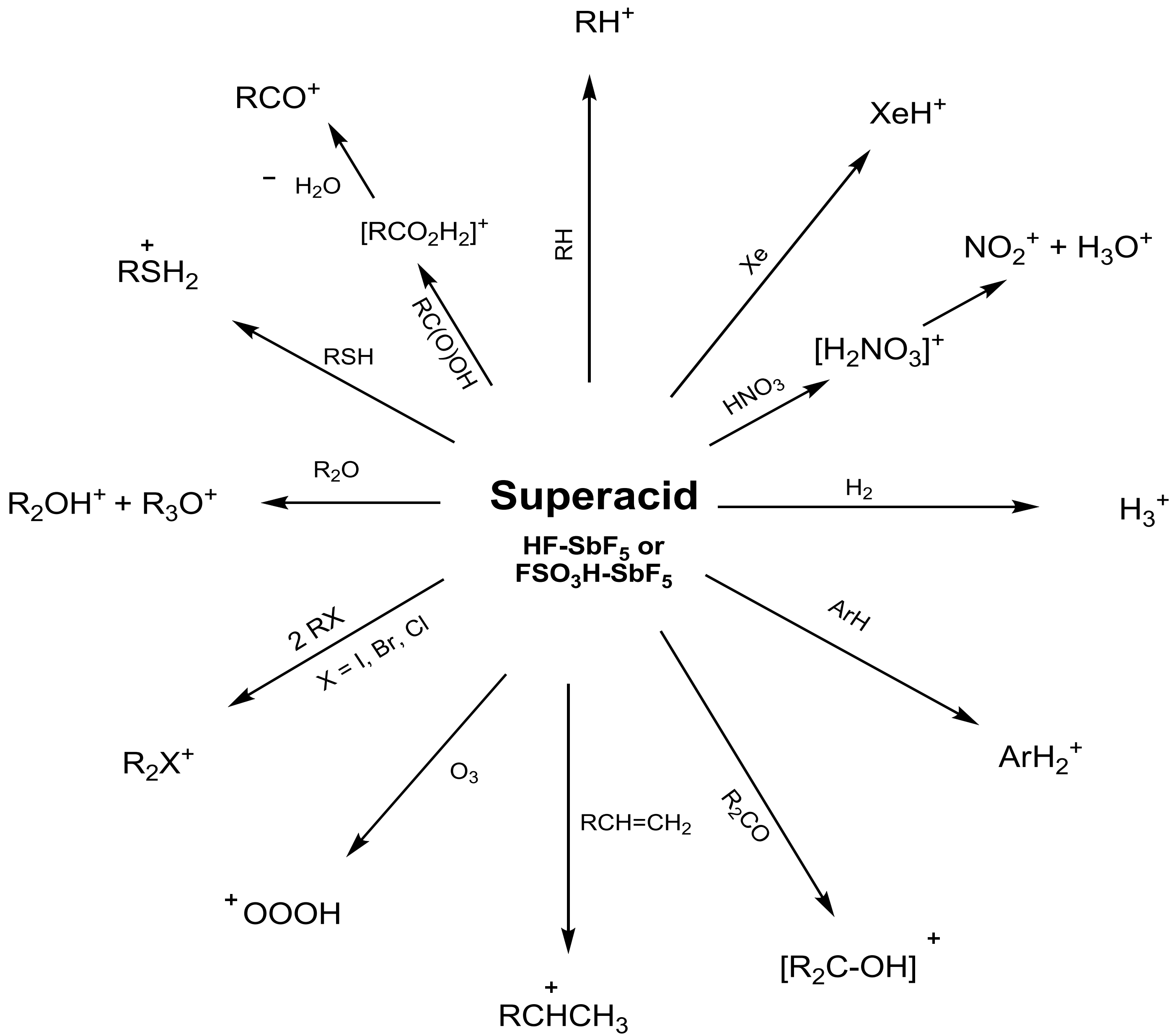
The usefulness of superacids was first shown by George Olah and coworkers, of the University of Southern California, from an accidental laboratory incident. During a Christmas party in his lab, one of his post doctoral associates dropped a candle accidentally in a solution kept in the lab. The candle dissolved but the solution was not a hydrocarbon but a mixture of fluorosulfonic acid and antimony pentafluoride. Analysis of the solution by ^{1}H-NMR indicated a single peak corresponding to the *t*-butyl cation.

The Hammett acidity function (H_0) is a measure of acidity that is used for superacids. While the pH scale is useful for dilute aqueous solutions, the H_0 scale is used to extend the measure of Brønsted–Lowry acidity beyond the dilute aqueous solutions. The Hammett acidity function, H_0, is defined using the following equation:

$$H_0 = pK_{BH^+} + \log \frac{[B]}{[BH^+]}$$

where pK_{BH^+} is −log(K) for the dissociation of BH^+, which is the conjugate acid of a very weak base B, with a very negative pK_{BH^+}. One can observe that it is as if the pH scale has been extended to very negative values.

Acid	Formula	Hammett Acidity function (H_0)
Sulfuric acid	H_2SO_4	–12
Fuming sulfuric acid (50 mol% SO_3)	$H_2S_2O_7$	–14.5
Chlorosulfonic acid	$ClSO_3H$	–13.8
Perchloric acid	$HClO_4$	–13.0
Triifluoromethylsulfonic acid (triflic acid)	CF_3SO_3H	–14.1
Fluorosulfonic acid	FSO_3H	–15.1
Hydrogen fluoride (anhydrous)	HF	–15.1
Magic acid	(FSO_3H–SbF_5) (90 mol% SbF_5)	–23
Fluoroantimonic acid	$H_2F[SbF_6]$	–28 to –31.3



RH+
RH
RCO+
- H2O
[RCO2H2]+
RC(O)OH
XeH+
Xe
NO2+ + H3O+
[H2NO3]+
HNO3
RSH2+
RSH
R2O
R2OH+ + R3O+
Superacid
HF-SbF5 or
FSO3H-SbF5
H2
H3+
2 RX
X = I, Br, Cl
R2X+
ArH
ArH2+
O3
+OOOH
RCH=CH2
RCHCH3+
R2CO
[R2C-OH]+