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

• Since $\text{F}_2$ reacts with almost all the elements except a few rare gases, storage and transport of $\text{F}_2$ gas was also a challenge.
• Teflon is the preferred gasket material when working with fluorine gas.
• Equipments have to be kept dry as $\text{F}_2$ oxidizes water giving a mixture of $\text{O}_2$, $\text{O}_3$ 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


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.


Henri Moissan: poisoned, success, but shortened lifespan.
Henri Moissan prepared fluorine gas, F₂ 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 F₂ gas starting with KMnO₄ 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.

\[
2 \text{KMnO}_4 + 2 \text{KF} + 10 \text{HF} + 3 \text{H}_2\text{O}_2 \rightarrow 2 \text{K}_2\text{MnF}_6 + 8 \text{H}_2\text{O} + 3 \text{O}_2
\]

\[
2 \text{K}_2\text{MnF}_6 + 4 \text{SbF}_5 \rightarrow 2 \text{K}_2\text{SbF}_6 + 2 \text{MnF}_3 + \text{F}_2
\]

Also, weaker Lewis acids such as MnF₄ can be displaced from its salts by stronger Lewis acids such as SbF₅. MnF₄ is thermodynamically unstable and decompose to a lower fluoride MnF₃ with the elimination of fluorine gas. The formed F₂ gas has been ascertained by the formation of white solid HgF₂ 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 Stinkspat, Stinkfluss, Stinkstein, Stinkspar and fetid fluorite) first found in Wölsendorf, Bavaria, in 1841
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 $\beta$ and $\gamma$ 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.
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
Fluorine based neutral Interhalogen compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>Chemical Structure</th>
<th>Phase</th>
<th>Temperature</th>
</tr>
</thead>
<tbody>
<tr>
<td>ClF₃</td>
<td>ClF₃</td>
<td>b.p.</td>
<td>-100 °C</td>
</tr>
<tr>
<td>BrF₅</td>
<td>BrF₅</td>
<td>b.p.</td>
<td>20 °C</td>
</tr>
<tr>
<td>IF₃</td>
<td>IF₃</td>
<td>m.p.</td>
<td>-45 °C; -28 °C (dec)</td>
</tr>
</tbody>
</table>

Reactions:

\[ \text{ClF}_3 \rightarrow \text{ClF} + \text{F}_2 \]

\[ 2\text{BrF}_3 \leftrightarrow \text{BrF}_2^+ + \text{BrF}_4^- \]
Chlorine Trifluoride (ClF₃): The most reactive fluorinated compound

A ton of ClF₃ 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 ClF₃ cannot be put out as it does not require atmospheric oxygen and it burns down all fire fighting equipments and chemicals.

It was first reported in 1930 by Ruff and Krug

\[ 3F_2 + Cl_2 \xrightarrow{250-280 \, ^\circ C} 2ClF_3 \]

\[ ClF_3 + H_2O \rightarrow HF + HCl + OF_2 \]

\[ ClF_3 + 2H_2O \rightarrow 3HF + HCl + O_2 \]

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.”
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 problems that were precipitated by hypocalcaemia and consequent hyperkalemia.

Antidote for HF burn: calcium gluconate
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$_2$PO$_3$F.

\[
\text{Ca}_5(\text{PO}_4)_3\text{OH} (s) + \text{H}^+ (aq) \rightarrow \text{Ca}_5(\text{PO}_4)_3^+ (aq) + \text{H}_2\text{O} (l)
\]
hydroxyapatite

\[
\text{Ca}_5(\text{PO}_4)_3^+ (aq) + \text{F}^- (aq) \rightarrow \text{Ca}_5(\text{PO}_4)_3\text{F} (s)
\]
fluorapatite

- 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.
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 to 10.0 ppm
- Kerala: 0.2 to 5.40 ppm
- Bengal: 1.1 to 14.5 ppm

Tolerable level: 0.7 to 1.5 ppm
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.

\[
\begin{align*}
^{235}\text{U} \rightarrow ^{144}\text{Ba} + ^{89}\text{Kr} + 3^1\text{n}
\end{align*}
\]

\(t\) \(_{1/2}\) = 704 million years

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 \(^{235}\text{U}\) is separated from \(^{238}\text{U}\) 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 membrane.
**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.

![Diagram of Laser Isotope Separation](image_url)

- 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$_2$F$_2$) 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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>UO$_3$</th>
<th>UO$_2$</th>
<th>UO$_2$F$_2$</th>
<th>UF$_4$</th>
<th>UF$_6$</th>
<th>U$_3$O$_8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>M.P. (°C)</td>
<td>200-650</td>
<td>2865</td>
<td>300 (dec)</td>
<td>1036</td>
<td>57</td>
<td>1500</td>
</tr>
</tbody>
</table>

\[
\text{UF}_6 (g) + \text{H}_2\text{O} (\text{steam}) \rightarrow \text{UO}_2\text{F}_2 (s) + \text{HF}(g)
\]

\[
\text{UO}_2\text{F}_2 (s) + \text{H}_2(g) \rightarrow \text{UO}_2(s) + \text{HF}(g)
\]

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.
Fluorination: Primary reactions

Balz-Schiemann reaction

\[ \text{ArN}_2^+\text{BF}_4^- \xrightarrow{\Delta} \text{Ar-F} + \text{N}_2 + \text{BF}_3 \]

Swarts Reaction

\[
\begin{align*}
\text{CCl}_3 & \quad \text{SbF}_3 + \text{SbCl}_5 \text{ or } \text{Cl}_2 \\
\text{or HF} + (\text{SbCl}_3 + \text{SbCl}_5) & \quad \text{CFC}_3
\end{align*}
\]

Halex Process

\[
\begin{align*}
\text{X} & \quad \text{F}^- \\
\text{EWG} & \quad \text{CFC}\text{F} + \text{X}^-
\end{align*}
\]

Simons Process (Electrochemical Fluorination)

\[
\begin{align*}
\text{R}_3\text{CH} + \text{HF} \text{ (anhydrous)} & \xrightarrow{\text{electrolysis \ 5-6 \ V}} \text{R}_3\text{CF} + \text{H}_2 \\
\text{CH}_3\text{C(O)Cl} + 4 \text{HF} \text{ (anhydrous)} & \xrightarrow{\text{electrolysis \ 5-6 \ V}} \text{CF}_3\text{C(O)F} + 3 \text{H}_2 + \text{HCl} \\
\text{CF}_3\text{C(O)F} + \text{H}_2\text{O} & \xrightarrow{} \text{CF}_3\text{C(O)OH} + \text{HCl}
\end{align*}
\]
Fluorine in drugs

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

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

Ciprofloxacin
Broad spectrum antimicrobial

Levofoxacin
Broad spectrum antibiotic

Atorvastatin (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.
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). CF₃ 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 ¹⁹F 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 $\text{NAD(P)H}$

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

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

\[
\begin{align*}
R - H & \xrightarrow{[O]} R - OH & \text{Carbon oxidation} \\
RCH_2 - OH & \xrightarrow{[O]} RCH = O + H_2 O \\
RCH = O & \xrightarrow{[O]} RCOOH \\
R_2 N - H & \xrightarrow{[O]} R_2 N - OH & \text{Heteroatom oxidation} \\
R_3 N & \xrightarrow{[O]} R_3 N = O \\
R_2 S & \xrightarrow{[O]} R_2 S = O \\
RO - CH_2 R & \xrightarrow{[O]} ROH + O = CHR & \text{Dealkylation} \\
R_2 N - CH_2 R & \xrightarrow{[O]} R_2 NH + O = CHR \\
R - HC=CH - R & \xrightarrow{[O]} R - HC \overset{O}{\overset{\text{O}}{\text{\bigtriangleup}}} CH - R & \text{Epoxide formation}
\end{align*}
\]
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.

Oxidation by Cytochrome P 450 of drug molecules
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.
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

AMAZING NEW CONCEPT IN Cooking
NOTHING STICKS TO "HAPPY PAN"
A cast iron skillet sealed with DuPont TFELOM"
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.”


![Hydrogen Fluoride](image1)

Hydrogen Fluoride

\[ \text{[F\cdots H\cdots F]} \]

\~ 40 kcal/mol

![Organofluorine](image2)

Organofluorine

\[
\text{C–F\cdots H–X}
\]

\~ 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.”


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%).
<table>
<thead>
<tr>
<th>Property</th>
<th>PTFE</th>
<th>FEP</th>
<th>PVDF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Melting point</td>
<td>327 °C</td>
<td>265 °C</td>
<td>177 °C</td>
</tr>
<tr>
<td>Melt processability</td>
<td>Not melt processable</td>
<td>Melt processable</td>
<td>Melt processable</td>
</tr>
<tr>
<td>Melt viscosity</td>
<td>$10^{11}$ Poise</td>
<td>$10^5$ Poise</td>
<td>0.2-17 x $10^3$ Poise</td>
</tr>
<tr>
<td>Upper use temp.</td>
<td>260 °C</td>
<td>200 °C</td>
<td>150 °C</td>
</tr>
<tr>
<td>Tensile Strength</td>
<td>5000</td>
<td>3000</td>
<td>4500</td>
</tr>
<tr>
<td>Glass transition temp</td>
<td>115 °C</td>
<td>60 °C</td>
<td>-35 °C</td>
</tr>
<tr>
<td>Flexural modulus (MPa)</td>
<td>340-620</td>
<td>655</td>
<td>1140-2240</td>
</tr>
<tr>
<td>Opacity</td>
<td>opaque</td>
<td>translucent</td>
<td>Almost transparent</td>
</tr>
</tbody>
</table>
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 polarisability of organofluorine substituents (C-F bond) affects secondary intermolecular interactions.

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

<table>
<thead>
<tr>
<th>Product</th>
<th>Formula</th>
<th>Molecular Weight</th>
<th>Boiling Point</th>
</tr>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>°F</td>
</tr>
<tr>
<td>Freon 14</td>
<td>CF₄</td>
<td>88.0</td>
<td>-198.3</td>
</tr>
<tr>
<td>Freon 503</td>
<td>CHF₃/CCIF₃</td>
<td>87.3</td>
<td>-127.6</td>
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<tr>
<td>Freon 23</td>
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<tr>
<td>Freon 13</td>
<td>CCIF₃</td>
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<td>Freon 116</td>
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<td>138.0</td>
<td>-108.8</td>
</tr>
<tr>
<td>Freon 13B1</td>
<td>CBrF₃</td>
<td>148.9</td>
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</tr>
<tr>
<td>Freon 502</td>
<td>CHCIF₂/CCIF₂–CF₃</td>
<td>111.6</td>
<td>-49.8</td>
</tr>
<tr>
<td>Freon 22</td>
<td>CHCIF₂</td>
<td>86.5</td>
<td>-41.4</td>
</tr>
<tr>
<td>Freon 115</td>
<td>CCIF₃–CF₂</td>
<td>154.5</td>
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<tr>
<td>Freon 500</td>
<td>CCl₂F₂/CH₃CHF₂</td>
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<tr>
<td>Freon 12</td>
<td>CCl₂F₂</td>
<td>120.9</td>
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<td>Freon 114</td>
<td>CCl₂F₂–CCIF₂</td>
<td>170.9</td>
<td>38.8</td>
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<tr>
<td>Freon 21</td>
<td>CHClF₂</td>
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<td>Freon 11</td>
<td>CCl₃F</td>
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<td>CCl₂F–CCIF₂</td>
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<td>117.6</td>
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<tr>
<td>Freon 112</td>
<td>CCl₂F–CCl₂F</td>
<td>203.9</td>
<td>199.0</td>
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</tbody>
</table>

Freon Products

Freon 12 refrigerant
Freon 111 propellant
**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$_2$F$_2$: 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$_3$Br.

**HFC-134a**  
CF$_3$-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*
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.

UV-A (315-400 nm) not much harmful, Does not affect O₃
UV-B (280-315 nm) harmful, Affects O₃
UV-C (100-280 nm) lethal, Absorbed by O₃
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$_3$CF (CFC-11) being fixed at an ODP of 1.

<table>
<thead>
<tr>
<th>Compound</th>
<th>ODP</th>
<th>Compound</th>
<th>ODP</th>
<th>Compound</th>
<th>ODP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cl$_3$CF (freon 11)</td>
<td>1</td>
<td>HFC 134a (CF$_3$CFH$_2$)</td>
<td>0</td>
<td>HCFC113</td>
<td>0.8</td>
</tr>
<tr>
<td>CCl$_2$F$_2$ (freon 12)</td>
<td>1 (0.82)</td>
<td>HCFC225</td>
<td>0.033</td>
<td>CF$_3$I</td>
<td>0.013</td>
</tr>
<tr>
<td>1,1,2-Trichlorotrifluoroethane</td>
<td>0.8</td>
<td>HCFC123</td>
<td>0.02</td>
<td>CH$_3$I</td>
<td>0.016</td>
</tr>
<tr>
<td>HCFC22 (CF$_2$HCl)</td>
<td>0.055</td>
<td>CH$_3$Br</td>
<td>0.7</td>
<td>CF$_3$Br(halon1301)</td>
<td>10</td>
</tr>
</tbody>
</table>

Global Warming Potential is the relative measure of how much heat a greenhouse 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.

<table>
<thead>
<tr>
<th>Compound</th>
<th>GWP (100 year)</th>
<th>Lifetime* (years)</th>
<th>Compound</th>
<th>GWP (100 year)</th>
<th>Lifetime (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CO$_2$</td>
<td>1</td>
<td>Not specified. But taken as 35-200 years</td>
<td>N$_2$O</td>
<td>298</td>
<td>114</td>
</tr>
<tr>
<td>SF$_6$</td>
<td>22,800</td>
<td>3200</td>
<td>CH$_4$</td>
<td>25</td>
<td>12</td>
</tr>
<tr>
<td>HFC-23 (CHF$_3$)</td>
<td>14,800</td>
<td>270</td>
<td>CCl$_4$</td>
<td>1400</td>
<td>26</td>
</tr>
<tr>
<td>CFC-11 (CFCl$_3$)</td>
<td>5350</td>
<td>45</td>
<td>NH$_3$</td>
<td>0</td>
<td>&lt; 0.019</td>
</tr>
</tbody>
</table>
Fluorine in Refrigerants

1987 Montreal Protocol

1997 Kyoto Protocol

Rwanda HFC agreement 2016

Refrigerant Trends:
- 2010 HCFC Phase-Out [R-22]
- EPA Empowered to Regulate HFCs
- US Govt. Proposed Global HFC Phase-Down Amendment to Montreal Protocol
- Voluntary Initiatives, i.e. GreenChill

System Architecture:
- Reduced Charge
- Distributed & Secondary Loops Gaining Traction

Low GWP & Natural Alternatives:
- CO₂/Ammonia in Food Retail
- Propane in Food Service
- R-32 for China

Next Gen Refrigerant:
- DuPont R 32/ HFO Blends

HFC Production (GWP Weighted)

2012

2032

15%
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. (28th meeting of Montr. Protocol)

Maldives, Bangladesh 0.5 deg. gain global warming
<table>
<thead>
<tr>
<th>Code</th>
<th>CFC-12 (1987 banned)</th>
<th>HFC-134a (2017 banned)</th>
<th>HFO-1234yf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name of Refrigerant</td>
<td>Dichlorodifluoromethane</td>
<td>1,1,1,2-Tetrafluoroethane</td>
<td>2,3,3,3-Tetrafluoropropene</td>
</tr>
<tr>
<td>Formula</td>
<td>CCl₂F₂</td>
<td>CF₃-CFH₂</td>
<td>CH₂=CF-CF₃</td>
</tr>
<tr>
<td>Boiling Point</td>
<td>-29.8 °C</td>
<td>-26.3 °C</td>
<td>-30 °C</td>
</tr>
<tr>
<td>ODP</td>
<td>0.82</td>
<td>0.055</td>
<td>0.0</td>
</tr>
<tr>
<td>GWP (100 yrs)</td>
<td>10,900</td>
<td>1430</td>
<td>4</td>
</tr>
</tbody>
</table>

Synthesis of CFC-12

\[
\text{CCl}_4 + 2\text{HF} \rightarrow \text{CCl}_2\text{F}_2 + 2\text{HCl}
\]

Synthesis of HFC 134a

\[
\begin{align*}
\text{H}_2\text{C}≡\text{CH}_2 + \text{Cl}_2 & \rightarrow \text{ClCH}_2\text{CH}_2\text{Cl} \\
\text{Cl}_2\text{C}≡\text{CHCl} & \rightarrow \text{CF}_3\text{CH}_2\text{Cl}
\end{align*}
\]

\[
\begin{align*}
\text{Cl}_2\text{C}≡\text{CHCl} & \rightarrow 3\text{HF} \rightarrow \text{CF}_3\text{CH}_2\text{Cl} \\
\text{HF} & \rightarrow \text{SbF}_5 \rightarrow \text{CF}_3\text{CH}_2\text{F}
\end{align*}
\]

Synthesis of HFO 1234yf

\[
\begin{align*}
\text{CHCl}_3 + \text{HF} & \rightarrow \text{HCF}_2\text{Cl} \\
\text{HCF}_2\text{Cl} & \rightarrow \text{pyrolysis} \rightarrow \text{F}_2\text{C}≡\text{CF}_2 \\
\text{F}_2\text{C}≡\text{CF}_2 & \rightarrow \text{CH}_3\text{F} \rightarrow \text{SbF}_5 \rightarrow \text{H}_2\text{C}≡\text{CFCF}_3
\end{align*}
\]

World use in 2011 for HFCs was 79% for refrigeration and air-conditioning, 11% for foam making for packing cushions, 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
<table>
<thead>
<tr>
<th>Year of clinical use</th>
<th>Inhalation anesthetic</th>
<th>Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td>1846</td>
<td>Diethyl ether Et-O-Et</td>
<td>Flammable; have undesirable side effects, such as post-anesthetic nausea and vomiting.</td>
</tr>
<tr>
<td>1847</td>
<td>Chloroform CHCl₃</td>
<td>Severe cardiovascular depression, hepatic toxicity, many reports of sudden deaths; was in use till 1976.</td>
</tr>
<tr>
<td>1774</td>
<td>Nitrous oxide N₂O</td>
<td>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. <strong>Remains in use even today</strong></td>
</tr>
<tr>
<td>1923</td>
<td>Ethylene CH₂=CH₂</td>
<td>High concentrations required; is an explosive with O₂, unpleasant smell. flammable</td>
</tr>
<tr>
<td>1930</td>
<td>Divinyl ether CH₂=CHOCH=CH₂</td>
<td>Also called Vinethene; Flammable and explosive</td>
</tr>
<tr>
<td>1930</td>
<td>Trichloroethylene Cl₂C=CHCl</td>
<td>Non flammable alternative to ethylene. Decomposes to give phosgene when warmed in the presence of sodalime; human carcinogen and a non-carcinogenic health hazard.</td>
</tr>
<tr>
<td>1954</td>
<td>Fluroxene (CF₃)₂CH₂-O-CH=CH₂</td>
<td>First fluorinated anesthetic; Flammable, explosive mixtures with other gases, post operative liver and renal failure; withdrawn from the market in 1974</td>
</tr>
<tr>
<td>1956</td>
<td>Halothane CF₃CHClBr</td>
<td>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</td>
</tr>
<tr>
<td>1960</td>
<td>Methoxyflurane (CHCl₂)CF₂-O-CH₃</td>
<td>Biodegradation produces inorganic fluoride and dichloroacetic acid which are toxic for major organs of the human body; also nephrotoxicity</td>
</tr>
<tr>
<td>1963</td>
<td>Enflurane (CHFCl)CF₂-O-CHF₂</td>
<td>Nonflammable, non irritant, low toxic, high potency, rapid onset, Cardiovascular depressant and convulsing properties shows hepatic dysfunction, hypotension</td>
</tr>
<tr>
<td>1971</td>
<td>Isoflurane CF₃CHCl-O-CHF₂</td>
<td>Its pungency can irritate the respiratory system.</td>
</tr>
<tr>
<td>1992</td>
<td>Desflurane CF₃CHF-O-CHF₂</td>
<td>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.</td>
</tr>
<tr>
<td>1994</td>
<td>Sevoflurane (CF₃)₂CH-O-CH₂F</td>
<td>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: air solubility; minimal cardiovascular and respiratory side effects, minimal end-organ effects</td>
</tr>
</tbody>
</table>
### Table 1 – Inhalation anesthetic agents (Year available for clinical use).

<table>
<thead>
<tr>
<th>Agents in clinical use</th>
<th>New Agents</th>
<th>Agents of historical interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enflurane (1973)</td>
<td>Xenon (1997)</td>
<td>Diethyl ether (1846)</td>
</tr>
<tr>
<td>Methoxyflurane (1960)</td>
<td></td>
<td>Fluroxene (1951)</td>
</tr>
<tr>
<td>Nitrous Oxide (1844)</td>
<td></td>
<td>Trichlorethylene (1930)</td>
</tr>
</tbody>
</table>
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.

<table>
<thead>
<tr>
<th>Isoflurane</th>
<th>$\text{CF}_3\text{CHCl-O-CHF}_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>$\text{CF}_3\text{CHF-O-CHF}_2$</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>$(\text{CF}_3)_2\text{CH-O-CH}_2\text{F}$</td>
</tr>
</tbody>
</table>
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 F₂ gas which requires great care and special apparatus for handling and usage.
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 C₆F₅H, essential for the synthesis of pentafluorophenyl substituted compounds are difficult to prepare by direct fluorination and HDF is the best method to make them

\[
\begin{align*}
\text{Reagent / Catalyst conditions} & \quad \text{yield} \\
\text{A. } \text{Cp}_2\text{ZrCl}_2, \text{Mg, HgCl}_2 \text{ or PMe}_3, \text{THF, RT, 2h} & \quad 93\% \\
\text{B. } \text{Zn, H}_2\text{O, NH}_3 & \quad 71\% \\
\text{C. } \text{Ph}_3\text{SiH, TBAT, THF, 60 °C, 40h} & \quad 83\%
\end{align*}
\]

silyl hydrides, R₃SiH, exchange H for F as Si–F bonds are stronger than Si–H bonds.
According to Gillespie, protic acids stronger than 100% sulfuric acid can be considered superacids. Thus, perchloric acid (HClO₄), anhydrous hydrofluoric acid (HF), trifluoromethanesulfonic acid (CF₃SO₃H) and fluorosulfonic acid (HSO₃F) 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 ¹H-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.
<table>
<thead>
<tr>
<th>Acid</th>
<th>Formula</th>
<th>Hammett Acidity function (H₀)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sulfuric acid</td>
<td>H₂SO₄</td>
<td>−12</td>
</tr>
<tr>
<td>Fuming sulfuric acid (50 mol% SO₃)</td>
<td>H₂S₂O₇</td>
<td>−14.5</td>
</tr>
<tr>
<td>Chlorosulfonic acid</td>
<td>ClSO₃H</td>
<td>−13.8</td>
</tr>
<tr>
<td>Perchloric acid</td>
<td>HClO₄</td>
<td>−13.0</td>
</tr>
<tr>
<td>Triifluoromethylsulfonic acid (triflic acid)</td>
<td>CF₃SO₃H</td>
<td>−14.1</td>
</tr>
<tr>
<td>Fluorosulfonic acid</td>
<td>FSO₃H</td>
<td>−15.1</td>
</tr>
<tr>
<td>Hydrogen fluoride (anhydrous)</td>
<td>HF</td>
<td>−15.1</td>
</tr>
<tr>
<td>Magic acid</td>
<td>(FSO₃H–SbF₅) (90 mol% SbF₅)</td>
<td>−23</td>
</tr>
<tr>
<td>Fluoroantimonic acid</td>
<td>H₂F[SbF₆]</td>
<td>−28 to −31.3</td>
</tr>
</tbody>
</table>
Superacid

$\text{HF-SbF}_5$ or $\text{FSO}_3\text{H-SbF}_5$

$\text{RH}^+$

$\text{RSH}_2$

$\text{RSH}$

$\text{RCO}^+$

$\text{[RCO}_2\text{H}_2]^+$

$\text{H}_2\text{O}$

$\text{XeH}^+$

$\text{NO}_2^+ + \text{H}_3\text{O}^+$

$\text{[H}_2\text{NO}_3]^+$

$\text{X}^8$

$\text{H}_2$

$\text{H}_3^+$

$\text{R}_2\text{OH}^+ + \text{R}_3\text{O}^+$

$\text{R}_2\text{O}$

$\text{R}_2\text{X}^+$

$\text{2RX}$

$X = I, \text{Br, Cl}$

$\text{O}_3$

$\text{RCH=CH}_2$

$\text{R}_2\text{CO}$

$\text{[R}_2\text{C-OH}]^+$

$\text{RCHCH}_3$

$\text{+OOOH}$

$\text{ArH}$

$\text{ArH}_2^+$