Organofluorine Chemistry: Applications, sources and sustainability

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Abstract

Fluorine is an essential element for life in the developed world that impacts hugely on the general public because many pharmaceuticals, agrochemicals, anaesthetics, materials and air conditioning materials owe their important properties to the presence of fluorine atoms within their structures. All fluorine atoms used in organic chemistry are ultimately sourced from a mined raw material, fluorspar (CaF_2), but, given current usage and global reserve estimates, there is only sufficient fluorspar available for a further 100 years. New large scale raw material sources of fluorine are available but must be sufficiently developed for the benefits of fluorinated systems to continue in the long term.

1. Introduction

Since Moissan's isolation of fluorine gas by electrolysis of anhydrous hydrogen fluoride in 1886 and his largely unsuccessful attempts at the direct fluorination of organic systems [1], organofluorine chemistry has grown to be a field of research that impacts across the chemical, materials and life-science sectors. Swarts began his seminal studies on the synthesis of trifluoromethylated aromatic systems by halogen exchange processes in the 1920’s and the 1930’s saw the first syntheses of chlorofluorocarbons and perfluoropolymers which were quickly developed for use as refrigerants and heat and chemical resistant materials respectively [2]. Following further development of fluorination techniques and materials as part of the Manhattan project during the 1940’s, academic and industrial interest in these almost entirely man-made systems increase rapidly due to a combination of unusual chemical properties imparted by fluorinated groups on organic systems and some increasingly valuable commercial product streams. In 1954, a fluorinated corticosteroid was found to have increased biological activity over the non-fluorinated parent steroid [3] and this sparked the application of selectively fluorinated systems within the life science industries.

Apart from around a dozen naturally occurring fluorine containing organic systems largely based on fluoroacetate and present in a small number of plants located mainly in the southern hemisphere [4], organofluorine compounds do not occur in nature. Consequently, all fluorinated molecules used today for all commercially available applications are synthetic and require the construction of carbon-fluorine bonds as a key part of their synthesis ultimately using fluorine atoms derived from mineral sources.

In this short discussion paper, we provide an overview of the importance of organofluorine chemistry to modern life including the widespread application of fluorinated systems in key materials, energy, health and chemical sectors. Raw material sources of fluorine, an essential non-metallic element, for carbon-fluorine bond formation and the subsequent manufacture of fluorinated products and the long term sustainability of the field of organofluorine chemistry are discussed.

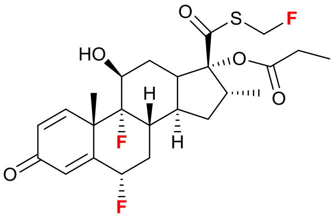
2. Applications of organofluorine chemistry

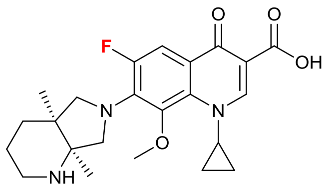
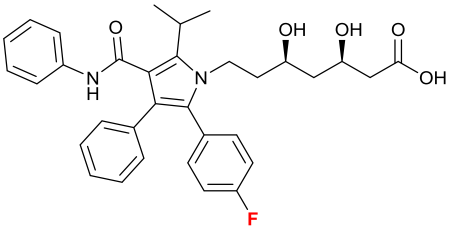
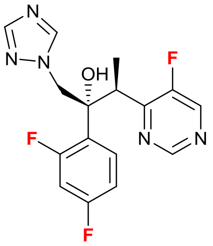
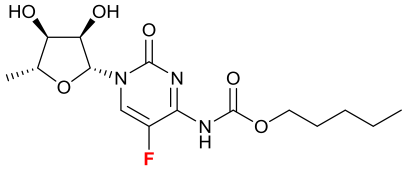
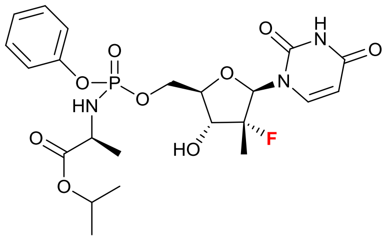
From unpromising beginnings [1], fluorine containing systems are now used by most people in the developed world on a daily basis although this is not widely appreciated even by the chemistry community. Indeed, it is fair to say, that organofluorine chemistry had a role to play in the majority of the spectacular technological achievements of the 20th century [5] and beyond and, here, we can provide only a brief indication of some of the uses of fluorinated systems in the modern world and the roles played in the ever important fields of human healthcare, food security, new materials and energy.

Healthcare

Since the FDA approval of the first fluorocorticosteroid drug in 1956, over 140 drugs have been introduced that contain at least one fluorine atom [6] and several blockbuster pharmaceuticals owe their biological activities to the presence of fluorine within their structures. Some examples of fluorine containing pharmaceuticals [7] are given in Table 1 demonstrating the range of therapeutic areas where fluorinated systems find useful application. Currently, approximately 20% of new pharmaceuticals entering the market bear fluorine atoms within their structures and the many roles played by fluorinated substituents to enhance drug efficacy by increasing metabolic stability, changing pK_a and/or enhancing lipohilicity [8] to the standards we now demand is sure to increase in future.

Table 1. Some fluorinated pharmaceuticals and anaesthetics

API structure	**API name**	**Brand name**	**Develope r**	**Therapeutic area**	**Annual sales (year)**
	Fluticasone propionate	Advair/Seretide (combination with salmeterol xinafoate)	GSK	Respiratory	5,274 £m (2013)[i]

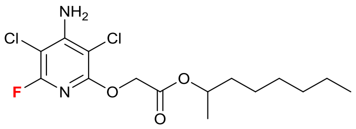
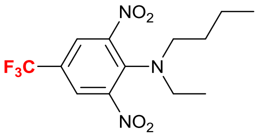
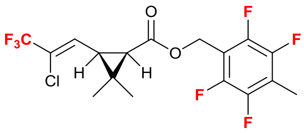
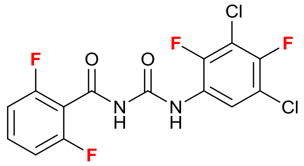
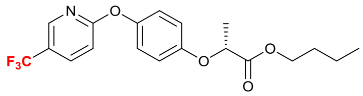
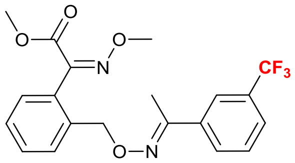
	Moxifloxacin	Avelox	Bayer	Antibiotic	426 €m (2013)[ii]
	Atorvastatin	Lipitor	Pfizer	Cardiovascular	2,315 $m (2013)[iii]
	Voriconazole	Vfend	Pfizer	Anti-fungal	775 $m (2013)[iii]
	Capecitabine	Xeloda	Roche	Anti-cancer	1,509 CHFm (2013)[iv]
	Sofosbuvir	Sovaldi	Gilead	Antiviral	5,754 $m (Jan-Jun 2014)[v]

Anaesthesia was revolutionised by the advent of volatile fluorinated gases such as halothane which have now been superceded by Desflurane and Sevoflurane and safe, global use of fluorinated anaesthetics in medical operations is now routine [9].

Food Security

The effect of fluorinated substituents on the biological activity of organic systems has been used for the development of many agrochemicals and a high percentage of herbicides, fungicides and insecticides (Table 2), contain fluorinated substituents possessing high activity with low dosage rates [10]. Of course, agrochemicals are required to ensure the food security of a growing global population that is currently just over 7 billion people and fluorine atoms play a key contribution in addressing this global problem.

Table 2. Fluorinated agrochemicals

Structure	Name	Brand name	Developer	Application
	Fluroxypyr methylheptyl	Starane®	Dow	Post emergence herbicide
	Benfluralin	Balan®, Team®	Dow	Herbicide
	Tefluthrin	Force®	Syngenta	Insecticide (seed treatment)
	Teflubenzuron	Nomolt®, Nomax®	BASF	Insecticide
	Fluazifop butyl	Fusilade®	Syngenta	Post-emergence herbicide
	Trifloxystrobin	Flint®	Bayer CropScience	Fungicide

Materials

Since the serendipitous discovery of polytetrafluoroethylene (PTFE) in the 1930's by scientists at the DuPont company [2] a range of fluorinated polymers have found applications in a wide number of technological fields [11], mainly due to the enhanced chemical and thermal stability of highly fluorinated polymers in various harsh operating conditions. PTFE is now widely used and well known by a number of trade names in areas as diverse as coated cookware (Teflon®, DuPont), protective clothing (Goretex®, WL Gore) and, increasingly, for medical applications. Perfluoropolyethers (Fomblin®, Solvay) are widely used as high performance lubricants that can withstand the extreme operating temperatures and pressures of air and space craft engines whilst perfluoroalkylated acid derivatives are the crucial components of high water and oil repellent textile treatments (Scotchgard®, 3M). Ethylene-tetrafluoroethylene (ETFE) copolymers (Asahi Glass) are relatively recent additions to the fluoropolymer range but these easily processed materials form the protective roofing materials for such iconic buildings as the Allianz Arena in Munich. Global demand for fluoropolymers was estimated in 2011 to be around $7.25 bn per annum reflecting the range and scale of fluoropolymer use [11].

Chlorofluorocarbons (CFCs) began to be manufactured in the 1950's on the large scale as refrigerants, replacing sulphur dioxide and ammonia which had been previously used. Following the discovery of CFC ozone depleting properties [12], a range of hydrofluorocarbons such as HFC-134a (CF_3-CFH_2) with much lower ODP became available and continue to be produced and used widely in air conditioning units worldwide [13].

Energy

The continuing supply of sufficient cheap energy for a growing, global population is perhaps the single most important problem of the 21st century and we can expect organofluorine chemistry to continue to play a role in energy generation. Uranium hexafluoride is produced using fluorine gas then separated and handled using various perfluoropolymer components as fuel for the atomic energy industry [14]. Renewable energy sources such as solar cells rely on fluoropolymer backing components and new generation fuel cells operate using perfluorinated sulfonic acid membranes (e.g. Flemion®, Asahi Glass) [15].

The above highly selective examples provide an indication of how fluorine atoms play a role within modern lifestyles in terms of comfort, health and technology, and serve to demonstrate how essential organofluorine chemistry is to developed populations. It would be difficult to imagine modern society wishing to return to the days of the 1930's with no realistic, safe air conditioning, ether as the anaesthetic in medical operations and no fluoropolymer materials or fluorinated drugs available.

3. Sources of fluorine atoms for organic chemistry

Given the importance of organofluorine chemistry discussed above, an economic and secure raw material source for fluorine atoms that can be used in low cost manufacturing plants is required for the long term. Since fluorine is the 13th most abundant element within the earth's crust (0.065% by mass), at first sight, we would not be too worried about future raw material supplies of fluorine atoms. However, while fluorine is present in many ores and minerals only three mineral classes, in principle, allow the useful economic extraction of fluorine sources for organic chemistry [16]. While cryolite (AlF_3, NaF) reserves are now exhausted, phosphate rock containing fluorapatite ($Ca_5(PO_4)_3F$) is abundant with the United States Geological Survey (USGS) estimating global reserves of more than 300 billion tonnes [17]. However, phosphate rock is currently barely used as a source of fluorine.

Indeed, all fluorine atoms used for organofluorine chemistry originate from fluorospar (CaF_2) which is mainly sourced by mining operations mainly in China and Mexico. The USGS estimates that current global use of fluorspar is 6.7 million tonnes with current global reserves of 500 million tonnes [18]. Around half of all fluorspar produced is used directly as a flux to reduce melting points and increase the viscosity of metals in iron and steel production [16]. All other fluorspar mined is used for the manufacture of anhydrous hydrogen fluoride (aHF) by reaction of 'acidspar' with aqueous sulfuric acid. aHF is the starting material for the synthesis of all fluorinated organic systems either directly as a fluorinating agent or, indirectly, when used to synthesise a fluorinating agent for subsequent reaction with an appropriate organic substrate.

The highest volume fluorination reactions currently carried out are processes involving reactions of anhydrous HF itself. Reaction of HF with small molecule chloroalkanes allows the synthesis of all important refrigerants (HFCs) and the small molecule hydrochlorofluorocarbon starting materials for all commercially successful fluoropolymers described above [11,13]. The most widely used selective fluorination reactions used for synthesis of life science products are Balz-Schiemann [19] and Swarts halogen exchange [20] processes for the manufacture of fluoroaromatic and trifluoromethylaromatic derivatives respectively. Both fluorination methods also use aHF as the fluorinating agent but, since aHF is very corrosive and superacidic in nature, there are a limited number of fluorination reactions that may be carried out effectively. Consequently, a range of fluorinating agents such as Selectfluor^{TM}, DAST and $Et_3N.3HF$, have been developed over the years [21] to meet the synthesis requirements of the life science industries. All fluorinating agents do however, originate from aHF and, consequently at the moment, mined fluorspar (Fig. 6).

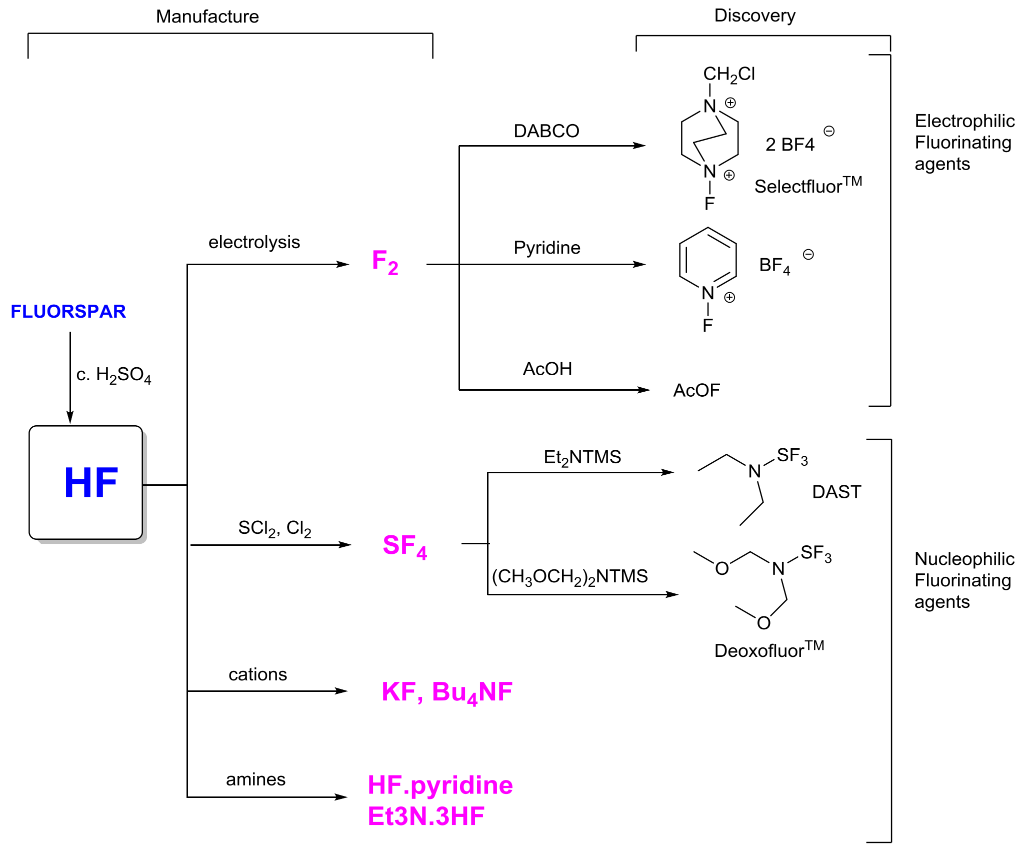


Figure 6. Most common sources of fluorine atoms for organofluorine chemistry

Currently, 6.7. million tonnes of fluorspar are used each year [18] for all applications including steel manufacture (51%) and chemical production, of which 27% is used for the preparation of inorganic fluorides and the remainder for fluorinated organic systems [16]. Since global reserves of fluorspar are estimated at around 500 million tonnes, by current estimates and usage patterns there is only sufficient fluorspar available to meet steel manufacture and fluorine chemistry requirements for a little under 100 years. Of course, new fluorspar deposits may be found but we can also expect higher consumption of fluorinated products from the developing world to more than take up any enhanced fluorspar production.

Limited reserves of fluorspar points, therefore, to a major problem for the long term sustainability of organofluorine chemistry and solutions are required to enable all the useful essential products used in modern life described above to continue to be widely available. So, what are the alternatives? Clearly recycling fluorine sources can be improved. At present fluorine atoms are either submitted to landfill either as heavy metal slag from iron smelting processes, as discarded fluoropolymers or lost to the atmosphere as volatile gases. Most HF waste from chemical processes is aqueous waste which is difficult to treat and recycle and, since most large scale fluorination manufacturing processes are very efficient and atom economic, it is difficult to see large reductions in overall fluorine atom usage. The many thousands of tonnes of depleted uranium hexafluoride generated by weapons and energy programmes that are currently stored indefinitely may offer a source of fluorine atoms and plasmachemical methods for the release of fluorine gas from UF_6 have been pilot tested [22]. However, all forms of recycling and efficiency gains will only make a limited contribution to the long term viability of aHF production.

Consequently, the most obvious source of fluorine atoms for smelting and chemical processes in the long term is the extraction of fluorine from the essentially unlimited reserves of phosphate rock 16.17]. Fluoroapatite, $Ca_5(PO_4)_3F$, is a component of phosphate rock (~30% P_2O_5) that is mined extensively with 224 million tonnes per annum extracted globally [17]. Production of phosphoric acid upon treatment with sulfuric acid from phosphate rock is a key part of the fertilizer industry and dilute fluorosilic acid (H_2SiF_6) solution is a side product of this ‘wet’ process. Currently, fluorosilic acid is not recovered by the fertilizer industry to any great extent although some technologies for the recovery of aHF from fluorosilic acid are available [16]. An estimated 76,000 tons of fluorosilicic acid, which is the fluorine equivalent of 134,000 tons of fluorspar, was recycled from phosphoric acid plants processing phosphate rock in 2013. Future research to develop processes for the recovery of fluorosilic acid and subsequent processing to aHF at the manufacturing scale are essential for the long term continuation of organofluorine chemistry.

4. Conclusion

The wide range of applications of organic systems bearing fluorine atoms by the general public including pharmaceuticals, anaesthetics, materials and air conditioning materials make the continuous long term supply of processable fluorine atom sources essential to modern life. Until now, organofluorine chemistry has relied on the mining of a finite geological source, fluorospar, for transformation into anhydrous hydrogen fluoride which is used to manufacture all downstream fluorinating reagents and fluoroorganic products. Given current usage and reserve estimates, there is only sufficient fluorspar resource available for less than 100 years and so new larger scale fluorine containing raw material sources must be developed for aHF production. Whilst recycling and more efficient smelting and organic chemistry processes may make a minor contribution to the longevity of fluorspar use, the recovery and transformation of fluorosilic acid, a by-product from the fertilizer industry and available in essentially unlimited quantities from large phosphate rock deposits, offers the most effective solution to long term organofluorine chemistry sustainability given appropriate development.

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