

Fluorine chemistry at the millennium

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Abstract

In this “perspective” paper, some of the landmark discoveries and accomplishments of the past within the field of fluorine chemistry will be reviewed. Within this review, the dramatic changes (and growth in size and diversity) that the field has undergone, particularly over the last 50 years, will also be discussed. Then finally, where fluorine chemistry is and where it appears to be going will be briefly discussed. The future of fluorine chemistry indeed appears bright, with fluorine chemistry set to play a role, and usually a significant role in most important areas of technology of the 21st century. New perspectives will be required, but then, fluorine chemists have been providing such “new perspectives” to this ever-changing field for the last 75 years.

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1. Introduction

The field of fluorine chemistry may have been born in the latter part of the 19th century with Henri Moissan’s first isolation of elemental fluorine in 1886, but it was very slow in growing to become the field of great significance that characterizes it today. Fluorine chemistry has played a distinctive role in many significant and highly diverse technological developments over the last 80 years, beginning with the development of Freons for the purpose of refrigeration in the 1930s, evolving through its, again, singular role within the Manhattan Project and then blooming to a legitimate, multifarious field encompassing a broad spectrum of technologies, including, among others, the fields of fluoropolymers, pharmaceutical/agrochemical products, and material science. Because of the special synthetic challenges that it presents and because of the unique structure/reactivity relationships observed for fluorine-containing compounds, fluorine chemistry is also a field of great *fundamental* interest. Thus it is that the important scientific and technological advances in fluorine chemistry

have derived from an uncommon mix of academic and industrial scientists.

The singular nature of the fluorine atom, combined with the unique physical and chemical properties that the fluorine substituent imparts to compounds that contain it, is responsible for the importance of the field and for its constant “reinvention”. Thus, in spite of the immense contributions of fluorine chemistry to various technologies of the last century, the current period, i.e. the beginning of the 21st century, can authentically be considered a “renaissance” period for the field of fluorine chemistry, where renaissance, in particular, is defined as “a period characterized by vigorous activity along literary, artistic, or other lines” [1].

In this “perspective” paper, some of the landmark discoveries and accomplishments of the past within the field of fluorine chemistry will be reviewed, and because this is a personal perspective, these landmarks are seen largely from the eyes of an *organofluorine* chemist. Within this review, the dramatic changes (and growth in size and diversity) that the field has undergone, particularly over the last 50 years, will also be discussed. Then finally, where fluorine chemistry *is* and where it appears to be going will be briefly discussed. Indeed, the future is bright, with fluorine chemistry playing some role, and usually a significant role in

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most important areas of technology of the 21st century. In presenting this perspective, other, earlier published, historical and perspective “reviews” of the physical and chemical properties of organofluorine compounds, in particular, those of Smart [2], Chambers [3], Banks et al. [4–6], Hiyama [7], Kirsch [8] and a special issue of *Chemical Reviews* on Fluorine Chemistry in 1996 [9] will be drawn from freely. One last caveat bears mentioning. As much as I consider myself knowledgeable about the field of “Fluorine Chemistry”, based on the many years I have worked and studied the field, it did not take me very long, once starting to work on this “perspective”, to realize how *little* I actually know about this hugely diverse field. Thus let me offer my apologies right up front to all of my friends and colleagues whose wonderful science has not been adequately represented by this personal overview of the field of fluorine chemistry.

1.1. Landmark events in the history of fluorine chemistry

- 1886 Moissan’s isolation of elemental fluorine.
- 1892 Swarts’ discovery of the Cl/F exchange chemistry of SbF_3 .
- 1928 Midgley’s invention of “Freons[®]”.
- 1938 Plunkett’s discovery of “Teflon[®]” and birth of fluoropolymers.
- 1947 Fowler’s discovery of the CoF_3 method of perfluorination.
- 1949 Simons’ discovery of electrochemical fluorination.
- 1954 Fried’s initial pioneering work in “medicinal” fluorine chemistry.
- 1962 Bartlett’s discovery of noble gas chemistry (preparation of XePtF_6).
- 1974 Molina and Rowland’s model of ozone depletion by CFC’s published.
- 1979 Margraves’ “direct” perfluorination discoveries.
- 2003 O’Hagan’s isolation of the first fluorinating enzyme.

Although some of these landmark events actually resulted in Nobel Prizes, most of the others appear to me to have also been deserving of this honor.

Note the gap between singular events from 1979 to 2003. This does not mean that nothing great or significant was done in these years. It simply means that *so much* great and significant work was accomplished during this period, actually during the last 50 or so years, by so many people that it is almost impossible to make distinctions between the respective levels of greatness.

2. Discussion

2.1. Some properties of fluorine

As indicated above, the uniqueness of compounds containing fluorine can be attributed to the fact that (a)

fluorine is by a wide margin the most electronegative atom on the periodic table; (b) it is also the smallest substituent (other than hydrogen or hydrogen’s isotopes); and (c) F_2 is not only the most reactive halogen, but also arguably the most reactive *element* on the periodic table, combining with all other elements, except the lighter noble gases, He, Ne and Ar.

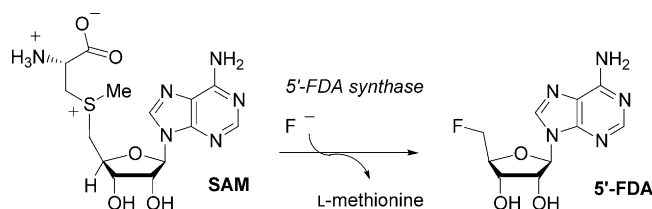
This high reactivity of F_2 can be attributed to a combination of the very weak (38 kcal or 159 kJ/mol) $\text{F}-\text{F}$ bond and the very strong bonds of fluorine to most other atoms. The mere presence of fluorine in an organic compound serves to strengthen the bonds between other proximate atoms in the molecule (i.e., C–C BDEs of CH_3CH_3 , CH_3CF_3 and CF_3CF_3 = 88.8 (372), 101.2 (423), and 98.7 (413) kcal(kJ)/mol, respectively), and unlike the effect of other atoms, the bond-strengthening effect of fluorine increases upon accumulation of additional fluorine substituents [i.e. CF_3-F , BDE = 130.5 (546) kcal(kJ)/mol versus 108.3 (453) kcal(kJ)/mol for CH_3-F]. The strength of C–H, C–C and C–F bonds in highly fluorinated compounds gives rise to the extraordinary thermal and oxidative stability that generally characterizes these compounds.

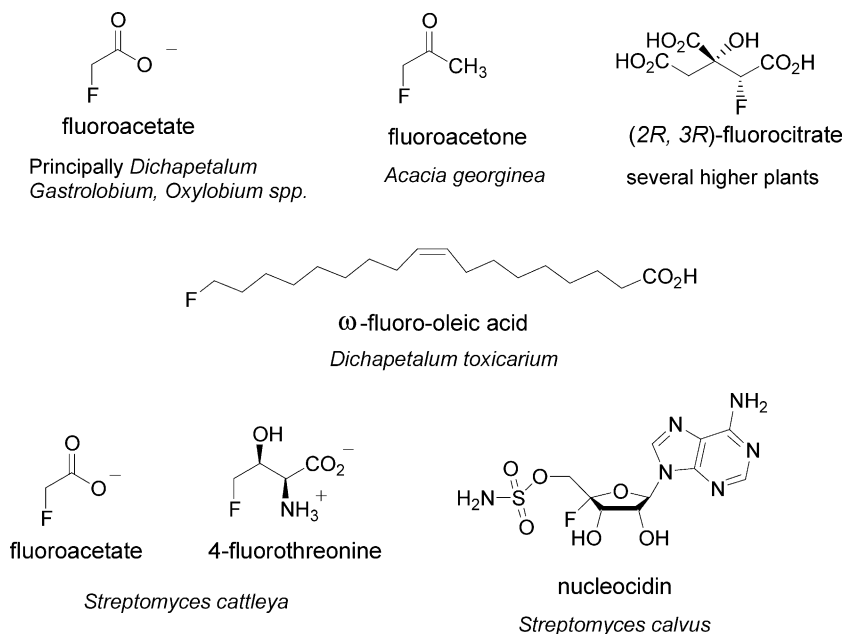
2.2. Few naturally occurring compounds containing fluorine

In spite of the strong bonds between carbon and fluorine, and in spite of the fact that fluorine is a very common element in the earth’s crust (13th most abundant), nature has generally found it difficult to incorporate fluorine into naturally occurring molecules, perhaps because of the very strong energy of solvation of fluoride ion in water. The known list of natural products containing fluorine is short indeed and it is presented in Scheme 1 [10].

2.3. The first fluorinating enzyme

The dearth of fluorine-containing natural products makes the isolation of the first enzyme known to incorporate fluorine into an organic compound all the more interesting and remarkable. Just a couple of years ago, O’Hagan et al., of the University of St. Andrews, reported the discovery [11], and more recently [12], the structural characterization of a bacterial fluorinating enzyme, 5'-fluoro-5'-deoxyadenosine synthase (5'-FDA synthase), which, as the name implies, provides the means to allow the reaction of fluoride ion with *S*-adenosyl-L-methionine (SAM) to form 5'-fluoro-5'-deoxyadenosine (5'-FDA).





Scheme 1. Natural occurring fluoroorganic compounds [10].

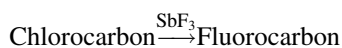
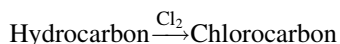
2.4. Organofluorine chemistry – basically a synthetic field

With so few naturally occurring fluorine-containing compounds (and *none* containing more than one fluorine atom), the field of organofluorine chemistry is necessarily a purely synthetic field, i.e. one where essentially all of the fluorine compounds in the world are man-made.

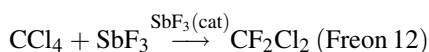
Elemental fluorine, F_2 , initially was found to be unsuitable (generally too reactive) for use in direct reaction with organic compounds. Nevertheless, beginning with work of Bigelow within the Manhattan Project [4,13], methodologies have been developed either using F_2 at low temperature in the gas phase [14,15], under specified conditions in the liquid phase [16], or indirectly, via electrochemical fluorination [17] to effect what is known as *perfluorination* (replacement of all hydrogens in a molecule by fluorines).

Synthetic organofluorine chemistry effectively had its beginning with the crucial discovery by Swarts of the SbF_3 -facilitated conversion of chlorocarbons to chlorofluorocarbons (CFCs) and fluorocarbons near the end of the 19th century [18].

The “Milestone” Swartz process:

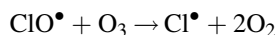
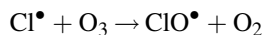
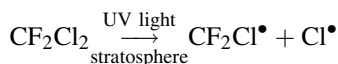


Of course, it was the discovery by Thomas Midgley of Frigidaire Corporation of the potential of chlorofluorocarbons as refrigerants that made organic fluorides anything



more than a scientific curiosity. The excellent, energy efficient refrigerant properties of Freon[®] 12 (CF_2Cl_2), along with its non-toxic and non-flammable properties, comprised a revolutionary scientific breakthrough that allowed the first widespread use of refrigerators and air conditioners. The use of CFCs as refrigerants constituted the *first commercial application* of organic fluorides. It certainly was not the last!

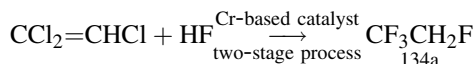
Anyone reading this paper is no doubt aware of Molina and Rowland’s ozone-depletion hypothesis, first expounded in 1974 [19], and immortalized by their Nobel prize in 1995. Their hypothesis, which has since been generally accepted as fact, claimed that the very stability of the Freons[®] that had led to their acceptance as “ideal” products for more than 40 years, was actually causing great environmental harm in the form of a depletion of the ozone layer in the stratosphere as a result of the chain reaction below induced by



ultraviolet-light-initiated decomposition of CF_2Cl_2 (and other chlorofluorocarbons) in the stratosphere. As a result of these findings, there have been enacted a number of worldwide measures (Montreal Protocol in 1987 and the U.S. Clean Air Act of 1990) to ban chlorofluorocarbons.

The fluorochemicals industry reacted (almost) immediately, initiating a search for alternatives to CFCs that has been amazingly successful both from an environmental and a commercial point of view. Replacement hydrofluorocarbons (short-term) and hydrofluorocarbons (longer-term) were identified and commercial processes quickly

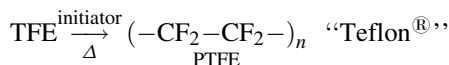
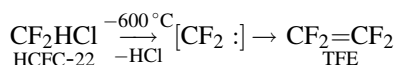
developed to manufacture them. The huge investment by industry in development of methods of making HFC 134a ($\text{CF}_3\text{CH}_2\text{F}$), a major replacement refrigerant, epitomizes this effort. This effort resulted in the important discovery (in a number of industrial laboratories almost simultaneously) that a “chromium-based” catalyst is particularly effective for carrying out gas-phase chlorine–fluorine exchange reactions [20,21]:



In 1988, the worldwide manufacture of CFCs reached a maximum of about 1 million metric tons, after which the quantities started dropping dramatically, reaching a, then, low of less than 50,000 metric tons per year in 1997. Meanwhile, the manufacture of replacement HCFCs and HFCs reached a high of only 300,000 metric tons that same year.

2.5. Fluoropolymers

Another landmark occurrence in the field of commercial organofluorine chemistry, also one that developed within the scope of early CFC development research, was the serendipitous discovery of polytetrafluoroethylene (PTFE), at DuPont by Roy Plunkett in 1938 [22], a discovery that, along with the almost simultaneous report of the preparation of polychlorotrifluoroethylene (PCTFE) [23], opened up what is probably presently the largest commercial application of organofluorine chemistry, the field of fluoropolymers.



Fluoropolymers have broad technological applications as thermoplastics, elastomers, coatings, fluids and membranes, as a result of their unique combination of properties. Such properties include high thermal and oxidative stability, low dielectric constant, low moisture absorption, low flammability, low surface energy, excellent biocompatibility, marked gas permeability and excellent resistance to most chemicals. See Section 2.8.2 for additional examples, and there are recent reviews on this subject [6,7], as well as excellent books available [24,25].

2.6. Fire extinguishants

It should not be surprising that the field of fire extinguishants was a beneficiary of the incomparable properties exhibited by halofluorocarbons. Their non-flammable and non-toxic properties, when combined with their relative high density gave them tremendous fire-extinguishing properties that led to the extensive use of Halons, most notably CF_3Br and CF_2ClBr , as exceptionally efficient and safe fire-extinguishing agents. These compounds exhibit exceptional fire-extinguishing properties,

being electrically nonconductive, dissipating quickly, leaving no residue and being remarkably safe for human exposure [26]. At a concentration of 30% in the air, these agents extinguished fires, but did not asphyxiate firefighters. With their banning (as ozone depleters and greenhouse gases) as of 2003, they are being replaced by other highly fluorinated materials, such as heptafluoropropane, $\text{CF}_3\text{CHF}_2\text{CF}_3$.

2.7. Anesthetics [27]

No area of application has been more greatly affected by the field of fluorine chemistry than anesthesiology. Indeed, no class of chemical compounds has contributed more toward the elimination of hospital trauma than anesthetics. Beginning with nitrous oxide and more importantly with the use of diethyl ether in the late 19th and early 20th centuries, various agents were used as anesthetics, with ether dominating up until the 1950s in spite of its odor, flammability and significant side effects. By this time, new methods of synthesizing organofluorine compounds had been developed which allowed larger numbers of fluorinated compounds to become commercially available. Early on, fluorine-containing compounds were being tested as possible anesthetics. Fluoroxene ($\text{CF}_3\text{CH}_2\text{OCH}=\text{CH}_2$) was the first fluorinated substance to be used as an anesthetic on people (1953), and its success led to the “*fluorine revolution*” within the field of anesthesiology.

Other fluorinated anesthetics followed, including halothane (CF_3CHClBr), methoxyflurane ($\text{CH}_3\text{OCF}_2\text{CHCl}_2$), enflurane ($\text{CHFClCF}_2\text{OCHF}_2$), isoflurane ($\text{CF}_3\text{CHClOC}(\text{HF}_2)$), sevoflurane ($(\text{CF}_3)_2\text{CHOCH}_2\text{F}$) and desflurane ($\text{CF}_3\text{CHFOCHF}_2$). The use of anesthetics such as sevoflurane and desflurane have indeed revolutionized the field of anesthesiology because of their low blood–gas partition coefficients and their minimal level of metabolism, which minimized side effects and thus shortened the recovery time of patients.

2.8. Modern age of fluorine chemistry

What can be called “the modern age of fluorine chemistry” ensued after World War II, with a period of rapid expansion of knowledge and technology regarding fluorine chemistry that continues to today. It was the beginning of the age of *designed synthesis* of partially fluorinated compounds [28–31].

Since the late 1940s, organic chemists who were interested in fluorine chemistry turned their talents to increasing the limited number of methods that were known for incorporating fluorine into organic compounds. Most of the synthetic methods that are used for putting other halogens into compounds are simply not appropriate for making fluorinated molecules.

The methods that were developed can be broken down into two classes of reactions, one involving fluorinating

reagents that can be used to put fluorine into molecules via functional group interconversion. The other one involves “building block” chemistry, i.e., using organic building blocks that already contain fluorine. Thus a multitude of methods have been developed for making alkylic, vinylic or aryl monofluoro compounds, alkylic and vinylic CF₂ compounds, and trifluoromethyl (CF₃)-containing aliphatic and aromatic compounds.

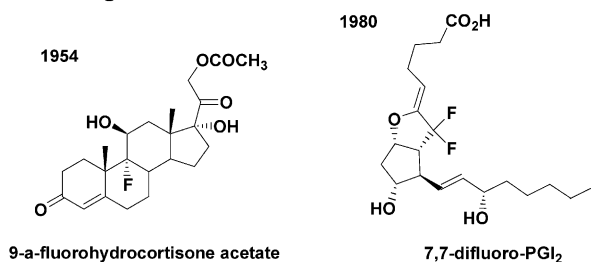
For the most part (but not always), when putting a *single* fluorine into a molecule, nucleophilic or electrophilic fluorinating reagents ultimately deriving from F[−], HF or F₂ are used. When putting a CF₂ group into a molecule, either fluorinating reagents or fluorinated building blocks can be used, and, lastly, when incorporating a CF₃ group, usually building block methods are used. Nevertheless, the ultimate source of fluorine for making any of these compounds is always either a metal fluoride (i.e., KF), HF or elemental F₂. Over the last 60 years, a large group of very creative synthetic organic chemists, too many to name, have directed their attention to developing new and often ingenious methods for making fluorinated organic compounds [28] and if the number of papers currently appearing on this subject is any indication, these efforts are continuing at an equal pace today. Everyone who is interested in the *applications* of fluorinated organics owes these 2–3 generations of synthetic fluoroorganic chemists much gratitude.

Nowhere was the impact of this explosion of synthetic activity greater than on the field of *biologically active fluorochemicals* [32,33].

2.8.1. Biologically active fluorochemicals

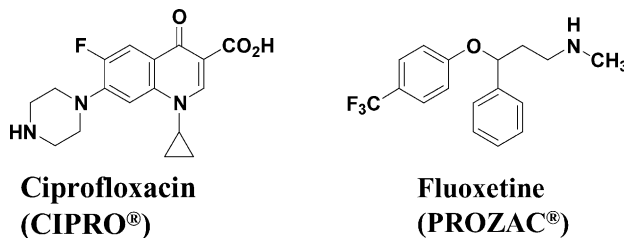
The application of fluorine-containing compounds to the fields of pharmaceuticals and agrochemicals has a very short history, beginning only about 35 years ago. Especially significant to these developments was the pioneering work of Fried, who, beginning in 1954 [34], demonstrated the potential importance of fluorine substituents in enhancing the efficacy of drugs through a number of noteworthy studies [35].

Pioneering Work of Fried



However, until the 1970s, fluorinated compounds were only rarely encountered in medicinal and agrochemicals, a situation that has changed dramatically since that time. Now, fluorine-containing drug and agrochemical candidates are routinely synthesized as a matter of course. At present, there are 128 fluorinated compounds with US trade names,

including 9 of 31 new drugs approved in 2002, according to the World Drug Index [36]. Two well-known examples of fluorine-containing drugs are given below:

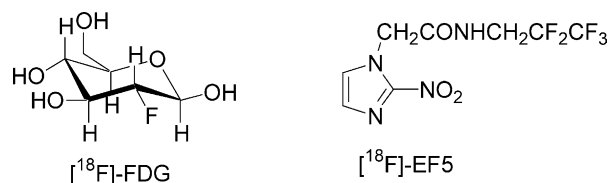


The small size of the fluorine substituent, combined with its high electronegativity and its impact upon bond strengths give rise to the observed distinctive effect of fluorine substituents upon biological activity of compounds. In the area of medicinal chemistry, incorporation of fluorine plays a significant role in the development of new anti-cancer and anti-viral agents, anti-inflammatory and anti-hypertensive agents, anti-fertility drugs and central nervous system drugs. In the area of modern crop protection, fluoro agrochemicals include herbicides, insecticides and fungicides [37]. Fluorine affects the biological activity of compounds in a number of important ways. The presence of fluorine at a particular position in a molecule can enhance its metabolic stability or modulate its physicochemical properties, such as its lipophilicity, acidity or basicity. Fluorination can increase a molecule's binding affinity to a target protein, and by a combination of factors interfere with specific enzyme action.

As a result, fluorine plays a huge role in the current areas of pharmaceutical chemistry and agrochemistry, with many of the most important new drugs and agents containing propitiously placed fluorine, trifluoromethyl, difluoromethyl or other fluorinated groups.

2.8.1.1. Use of ¹⁸F radioisotope in medicine. Ancillary to this field is the use of the ¹⁸F artificial radioisotope of fluorine in the increasingly important field of positron emission tomography (PET). Using appropriate molecules labeled with the short-lived (110 min half-life) ¹⁸F radioisotope, PET has been used to study biochemical transformations, drug pharmacokinetics, pharmacodynamics, and recently as a powerful and superior noninvasive, diagnostic scanning technique to survey living tissue in animals and humans [38].

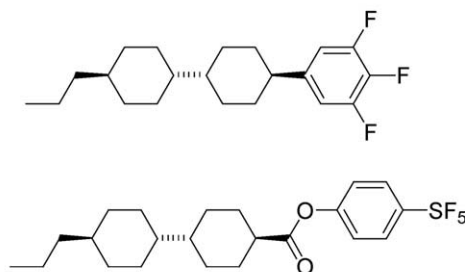
For example, PET imaging using [¹⁸F]fluoro-2-deoxyglucose (FDG, below) is significantly more effective in detecting many types of tumors than CT or MRI imaging procedures, whereas EF5 is excellent at pinpointing the location of hypoxic tissue [39,40].



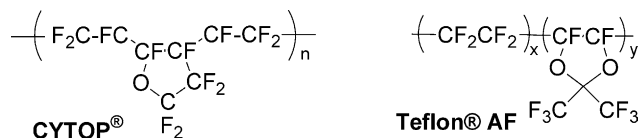
2.8.2. Fluorinated materials

Lastly, it needs to be mentioned that there is hardly a field involving the development of new materials today that does not involve *fluorinated* materials as an important component. Again, because of the hugely important properties of thermal and oxidative stability, fluorinated materials inevitably maintain an important, often dominant position in the various rapidly expanding areas of material science, including the fields of liquid crystals and, in particular, fluoropolymers.

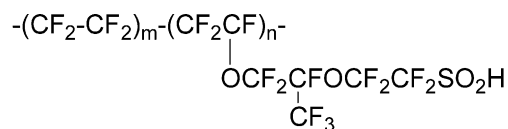
In recent years, liquid crystal displays (LCDs) have become an almost indispensable part of our daily life. Among the most rapidly growing applications are full-color, flat-screen displays capable of high-resolution graphics, as seen in computer monitors and “hang-on-the-wall” TV screens. Because of fluorine’s high electronegativity and thus strong electron-withdrawing effect, in relation to its small size, the presence of fluorine in a liquid crystal exerts a large influence on permittivity, while causing minimum change in molecular shape, and the “flat-screen” technology would not be possible without liquid crystals such as those shown below [39,41].



Recent developments in the field of fluoropolymers serve to illustrate the distinctive role of fluorine in material science. Thus, in the last decade or so, new amorphous fluorinated resins, such as CYTOP and Teflon® AF, have emerged to play a crucial role in the production of new materials for microchip manufacture, microlithography and fiber optics.

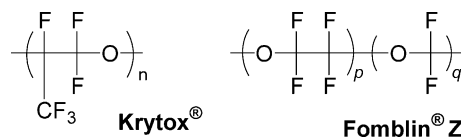


Ionomers, such as Nafion® are indispensable when serving as the ionic membranes for fuel cells [42], and perfluoropolyethers (PFPEs), such as Krytox® and



Nafion®: a perfluorosulfonic acid/PTFE copolymer

Fomblin® fluids have many important applications that take advantage of their unique performance properties, such as low vapor pressure, high thermal stability and low chemical reactivity [43].



Recent symposia [44,45] and a recent special issue of the *Journal of Fluorine Chemistry* [46] on “Fluorine in microlithography and microchip manufacture” bear witness to the importance of fluorine chemistry in these emerging fields of the early 21st century.

3. Conclusion – the future

As put so well by Smart in his editorial that introduced this special issue [47], in discussing the changing role for fluorine in industry, he stated that “. . . the future of fluorine rests with the products, processes and businesses that it uniquely enables . . .”. He claims that “this will require a new perspective . . .”. Of course, this is nothing new, since “new perspectives” are what fluorine chemists have been providing to the field of fluorine chemistry since its inception little more than 100 years ago.

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