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Fluorine-18: An untapped resource in inorganic chemistry

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Abstract

Advances in the field of fluorine chemistry have been applied extensively to the syntheses of ^{18}F -labelled organic compounds and radiopharmaceuticals. However, ^{18}F has sparsely been used as a tool to explore inorganic chemistry and can be viewed as a research area worthy of further development. This review highlights the application of ^{18}F in development of inorganic fluorinating agents, mechanistic studies and imaging tools.

Graphical Abstract

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Conflicts of interest

There are no conflicts to declare.

Introduction

The extensive chemistry of ^{19}F in organic molecules has paved the way for the use of biomolecules labelled with the radionuclide ^{18}F . Applications of fluorine-18 (β^+ , $t_{1/2} = 109.8$ min) in radiochemistry and medical imaging with positron emission tomography (PET) have expanded over recent years. The widespread clinical use of [^{18}F]2-fluoro-2-deoxy-D-glucose ([^{18}F]FDG) has resulted in an increased production of ^{18}F , which is commercially available in the form of ^{18}F -tracers or [^{18}F]fluoride ion in Curie quantities with high molar activity (A_m). The preparation and use of ^{18}F -labeled inorganic compounds was reviewed by Winfield in 1980, who concluded that this radionuclide had been underused in inorganic fluorine chemistry and attributed this to the specialized equipment and infrastructure required for its production.¹ Nowadays, [^{18}F]fluoride can be safely distributed in water or deposited on an ion exchange resin for further use in fundamental chemical studies.² From this, ^{18}F is available for radiochemists with minimal licensing and infrastructure, specifically without having to house a cyclotron or facilities to support high level radioactivity production or preclinical/clinical PET imaging infrastructure. Despite the broad dissemination of [^{18}F]fluoride, ^{18}F in inorganic fluorine chemistry is still largely under-utilized when compared to ^{18}F -labelling of organic molecules. It is noteworthy that there has been a growing focus on utilizing the inorganic interactions between B- ^{18}F , Si- ^{18}F and Al- ^{18}F , however, the focus of these applications is for labelling biomolecules.³ This review aims to survey: (i) the current status and use of inorganic ^{18}F -fluorinating reagents in radiochemistry; (ii) ^{18}F as an isotopic marker to provide fundamental reaction mechanistic insight; and lastly (iii) highlight some ^{18}F -labelled inorganic compounds which have found utility as a PET imaging agents, with the overall goal of inspiring new research directions and collaborative research in fundamental inorganic fluorine chemistry.

Fluorine-18 production

Fluorine-18 is typically produced in a cyclotron by proton-bombardment *via* the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ reaction. This reaction is applied to prepare [^{18}F]F $^-$ or [^{18}F]F $_2$ by irradiation of enriched [^{18}O]H $_2$ O or [^{18}O]O $_2$, respectively. [^{18}F]fluoride is commonly extracted from the target (no-carrier-added, n.c.a.) using helium gas, whereas [^{18}F]F $_2$ is extracted by use of carrier-added F $_2$. It is important to note that high A_m is often required in neuroreceptor imaging studies to avoid saturation of the receptor system by non-radioactive carrier molecules.⁴ Radiopharmaceuticals synthesised from [^{18}F]F $^-$ are normally obtained with higher A_m [^{18}F]F $^- \rightarrow A_m = 5.55 \times 10^3$ GBq/ μmol (1.50×10^5 Ci/mmol), [^{18}F]F $_2 \rightarrow A_m = 1.30$ GBq/ μmol (35 Ci/mmol).^{5, 6}

Improvement of the A_m of [^{18}F]F $_2$ can be obtained from CH $_3^{18}\text{F}$ (synthesized from n.c.a. $^{18}\text{F}^-$) and F $_2$ by atomization using electric discharge or ultraviolet irradiation.⁷ These “post-target” methods provide [^{18}F]F $_2$ with molar activities up to 55 GBq/ μmol . However, these methods have not gained broad adoption in the PET radiochemistry community due to its overall technical complexity in a radiopharmaceutical chemistry production facility.

Another method that has been used to produce ^{18}F , in the past, involves a Li $_2$ CO $_3$ target. ^6Li is irradiated with thermal neutrons yielding tritium, which in turn bombards ^{16}O to give ^{18}F .

⁸ Li₂CO₃ is an advantageous carrier-free target material and this two-step process for production of ¹⁸F is outlined in Scheme 1.^{9, 10}

Inorganic ¹⁸F-labelled reagents

Electrophilic Fluorination:

Fluorine-18 labelled perchlorylfluoride, [¹⁸F]ClO₃F, has been prepared by reaction of potassium chlorate and [¹⁸F]F₂ (eq. 1) in 23% radiochemical yield, with respect to [¹⁸F]F₂ (maximum theoretical radiochemical yield of 50%).¹¹ The [¹⁸F]ClO₃F was successfully used to prepare fluoroaromatics with lithiated precursors. The yields of the fluoroaromatics varied between 3 to 30%, with respect to [¹⁸F]ClO₃F. This electrophilic fluorinating agent was suggested for use in the preparation of ¹⁸F-labelled radiopharmaceuticals, however, the strongly oxidizing nature of ClO₃F, and the relatively low radiochemical yields have limited its use in radiopharmaceutical development.

Alternative [¹⁸F]F₂ sources have been avidly sought for nearly 40 years. Xenon difluoride is a versatile electrophilic fluorinating agent and has been used for selective fluorination of a wide variety of organic compounds.^{12, 13} There are several routes to produce [¹⁸F]XeF₂. Fluorine-18 labelled XeF₂ was first prepared by Schrobilgen, Chirakal, and co-workers, by treating SO₂ClF solutions of XeF₂ with [¹⁸F]HF, [¹⁸F]SiF₄ or [¹⁸F]AsF₅, where ¹⁸F was produced via the Li₂CO₃ production route (**Route 1**, Scheme 2).¹³ They observed a maximum radiochemical yield of 30% with this method, by labelling with [¹⁸F]HF or Lewis acids, [¹⁸F]SiF₄ or [¹⁸F]AsF₅. The exchanges are attributed to the Lewis acid properties of the labelled fluorides, which presumably act as weak acceptors towards XeF₂ and promote exchange according to the equilibria shown in equations 2 and 3.

Subsequently, the same group synthesized [¹⁸F]XeF₂ by the thermochemical reaction of carrier-added [¹⁸F]F₂ and excess xenon in a high pressure nickel vessel at 390°C for 40 min (**Route 2**, Scheme 2).¹⁶ With this method, a decay-corrected radiochemical yield of 68%, relative to [¹⁸F]F₂ was observed. It is noteworthy that the first stereospecific synthesis of the most commonly used PET radiopharmaceutical, [¹⁸F]FDG and regiospecific synthesis of the widely explored [¹⁸F]6-fluoro-L-DOPA ([¹⁸F]6-F-DOPA) (Scheme 3) were accomplished by use of [¹⁸F]XeF₂ as the fluorinating agent.^{15, 17, 18}

More recently, efforts have been devoted to produce $[^{18}\text{F}]\text{XeF}_2$ *via* isotope exchange with n.c.a. $[^{18}\text{F}]\text{F}^-$ (**Route 3**, Scheme 2).¹⁹⁻²¹ It has been postulated that XeF_2/F^- exchange occurs through the formation of the trifluoroxenate (II) anion, XeF_3^- , although the isolated anion is not known.^{21, 22} Previously, XeF_4 and XeF_6 were the only binary xenon fluorides known to form ionic salts with fluoride ion donors. Through experimentation, XeF_2 has not conclusively demonstrated to exhibit fluoride ion acceptor properties in solution or in solid state. However, the first evidence of XeF_3^- in solution was demonstrated *via* 2-D ^{19}F - ^{19}F EXSY and single-selective inversion ^{19}F -NMR spectroscopic studies which proved that fluoride ion exchanges with XeF_2 in CH_3CN solvent (Fig. 1).²¹ The syntheses of salts containing the XeF_3^- anion would provide useful insights for further applications of $[^{18}\text{F}]\text{XeF}_2$. The geometry of the XeF_3^- anion is also interesting because it would represent the first AX_3E_3 valence shell electron pair repulsion (VSEPR) arrangement.

Nucleophilic Fluorination:

It is still an ongoing goal to discover new methods for more efficient and more selective radiofluorination from nucleophilic $[^{18}\text{F}]\text{fluoride}$ sources. $[^{18}\text{F}]\text{fluoride}$ is produced with high yields and obtained as a water solution, resulting in an ion that is strongly hydrated and unreactive as a nucleophile.²³ F^- itself is a highly basic nucleophile, but the conjugate acid exhibits a $\text{pK}_a(\text{H}_2\text{O})$ of 3.2, this can be attributed to the formation of a strong hydrogen bond between F^- and $\text{H}-\text{OH}$, as well as the formation of a bifluoride (HF_2^-) in water.^{24, 25} The HF_2^- anion total bond dissociation energy is 182 kJ/mol.²⁶ This has been speculated to be one of the strongest hydrogen bonds known, and the formation of this species in water greatly contributes to the low basicity of F^- .²⁶ Recovery and activation of $[^{18}\text{F}]\text{F}^-$ is required for use in nucleophilic fluorination, often accomplished by adsorption onto an ion exchange resin, followed by elution with 2.2.2. cryptand and base. Azeotropic drying with CH_3CN is carried out and newer methodologies are under development to eliminate this step. Alternatively, $[^{18}\text{F}]\text{fluoride}$ can be recovered as $[^{18}\text{F}]\text{HF}$, a nucleophilic fluoride source, albeit is rarely used. A recently reported procedure to automate and simplify this reaction by acidification of the $[^{18}\text{O}]$ -enriched target water employed 98% H_2SO_4 because of its non-volatile nature and thermal stability. This methodology should enable widespread use of $[^{18}\text{F}]\text{HF}$.²⁷

Alkali Metal Fluorides and Isotopic Exchange Reactions

Fluorine-18 has been useful in studying fluorine exchange reactions. Early studies used ^{18}F to determine the efficiency of exchange between alkali metal fluorides and covalent fluorides.²⁸ It was observed that, by treating SiF_4 with ^{18}F -labelled KF , RbF , CsF and LiF , $[^{18}\text{F}]\text{LiF}$ was the most efficient reagent for labelling. It was noted that the other alkali metal fluorides formed stable $[^{18}\text{F}]\text{fluorosilicate}$ compounds (eq. 4) with silicon tetrafluoride.²⁹ The small size and strong polarizing power of the lithium ion, was attributed for avoiding the undesirable formation of $[^{18}\text{F}]\text{fluorosilicates}$.

Furthermore, Azeem and Gillespie prepared ^{18}F -labelled BF_3 , POF_3 , PF_5 , AsF_5 , SF_4 , SOF_2 and SeF_4 by an exchange reaction, which involved passing these volatile compounds over heated Li^{18}F .³⁰ This study claimed to have provided the first evidence for the POF_4^- anion, by the observation of fluorine exchange between POF_3 and Li^{18}F at 200°C . Subsequently, the POF_4^- anion was formed by reaction of $[\text{N}(\text{CH}_3)_4][\text{F}]$ and POF_3 in CHF_3 solvent at -140°C and was characterized by ^{19}F and ^{31}P NMR spectroscopy.³¹ The POF_4^- anion was shown to react with POF_3 between -140 to -100°C , forming the $\text{OF}_2\text{P-O-PF}_5^-$ anion (eq. 5), which, at higher temperatures, reacts with F^- anions to form the PO_2F_2^- and PF_6^- anions (eq. 6), providing a low activation energy barrier pathway for the highly exothermic dismutation reaction of the POF_4^- anion. The thermal instability of the POF_4^- anion at low temperatures implies that this anion is unlikely to be an exchange intermediate in the reaction of POF_3 and Li^{18}F at 200°C . $[\text{F}^{18}]\text{LiF}$ was prepared by the irradiation of Li_2CO_3 with thermal neutrons (*vide supra*). It may be necessary to

purify ^{18}F -labelled compounds produced by the Li_2CO_3 route to recover $[\text{F}^{18}\text{O}]\text{H}_2\text{O}$ and remove any undesired tritium. Previous methods have described initial dissolution of lithium carbonate to remove tritium produced during irradiation. Activity of tritium in purified product was seen to be as low as 0.21 mCi .³² As well, acid digestion of Li^{18}F product to remove tritium releases H^{18}F , and is followed by neutralization to form Cs^{18}F . The produced Cs^{18}F can be used to further synthesize a wide variety of labelled fluorides.⁸ CsF was treated with Lewis acid ^{18}F -labelled fluorides (AsF_5 , BF_3 , and SF_4); it was found that the order of reactivity of Lewis acids with CsF was $\text{AsF}_5 \gg \text{BF}_3 > \text{SF}_4$, which corresponds to the order of fluoride-ion affinities of these inorganic compounds.³³

Appelman and Jache showed that the reaction of F_2 with ice produced mixtures of $[\text{F}^{18}]\text{OF}_2$, $[\text{F}^{18}]\text{HOF}$, O_2 and H_2O_2 , in addition to the formation of $[\text{F}^{18}]\text{F-H-OH}$ and $[\text{F}^{18}]\text{HF}_2^-$.^{25, 34, 35} The authors used ^{18}F -labelling experiments to determine the reaction stoichiometry of $[\text{F}^{18}]\text{HOF}$ with F_2 , and they were able to conclude that the $[\text{F}^{18}]\text{OF}_2$ produced contained one fluorine atom from $[\text{F}^{18}]\text{HOF}$ and one from F_2 (eq. 7).

The kinetics of isotopic exchange, specifically ^{18}F exchange between HF and fluorine-18 labelled tetrafluoroboric acid, has been analyzed. It was determined that the isotopic exchange between $[\text{F}^{18}]\text{BF}_4^-$ and HF has a rate constant $k = 4.5 \times 10^4 e^{-24.7/\text{RT}}$. The mechanism of exchange was seen to match that of the mechanism of acid hydrolysis of the fluoroborate ion (Scheme 4), and that the two steps involved are the slow acid hydrolysis of HBF_4 and the fast isotopic exchange between BF_3OH^- .³⁶

Fluorine-18 labelling has also been used to deduce structural information. For example, the Lewis acid-base adduct $[^{18}\text{F}]\text{BF}_3 \cdot \text{SF}_4$ was shown to have two symmetrical sulfur-fluorine-boron bridges, by determination of the relative distribution of ^{18}F radioactivity in BF_3 (83%) and SF_4 (17%) after the decomposition of the ^{18}F -labelled $\text{BF}_3 \cdot \text{SF}_4$ adduct.³⁷ If the bridges were unsymmetrical, the bonds would be weaker than the symmetrical bonds, in this scenario the weak bonds would break and no fluorine transfer would be observed. Fluorine transfer was observed at -80°C and -100°C , indicating symmetrical bonds. Upon later elucidation of the crystal structure of the adduct, it was concluded that there are three S-F contacts, two of the same length (symmetrical) and one shorter (eq. 8).³⁸

(eq. 8)

^{18}F has been used as a radiotracer to probe inorganic reaction mechanisms in which postulated the existence of “hypervalent” species of nitrogen and chlorine as potential intermediates.^{39, 40} Experimental data indicated the existence of hypervalent carbon and boron, but convincing evidence for penta-coordinated nitrogen compounds had not been presented.^{41, 42} On the question of the possible existence of NF_5 , the reaction of $[^{18}\text{F}]\text{CsHF}_2$ with NF_4PF_6 was conducted at room temperature in HF to form $[^{18}\text{F}]\text{NF}_4\text{HF}_2$.³⁴ Upon thermal decomposition at 100°C , the ^{18}F -activity would be scrambled among NF_3 , HF and F_2 . There are two possible mechanisms which can lead to ^{18}F scrambling: (1) the nucleophilic attack of $[^{18}\text{F}]\text{F}^-$ on nitrogen, causing isotopic scrambling among the five fluorines, therefore 60% of the original ^{18}F -activity would be found as $[^{18}\text{F}]\text{NF}_3$ and 40% would be found as $[^{18}\text{F}]\text{F}_2$ (eq. 9), (2) if the $[^{18}\text{F}]\text{F}^-$ attacked a fluorine of NF_4^+ , then $[^{18}\text{F}]\text{NF}_3$ will not form and all of the radioactivity would be found as $[^{18}\text{F}]\text{F}_2$ (eq. 10). Following the decomposition of $[^{18}\text{F}]\text{NF}_4\text{HF}_2$, essentially no ^{18}F -activity was detected on NF_3 , providing conclusive evidence that the attack of

(eq. 9)

(eq. 10)

$[^{18}\text{F}]\text{HF}_2^-$ on NF_4^+ occurred exclusively on the fluorine, therefore NF_5 is not an intermediate in this reaction.

Although ^{18}F -labelling was used to show the non-existence of a hypervalent nitrogen species, the existence of a hypervalent chlorine species was conclusively revealed by use of ^{18}F -labelling experiments, in conjunction with ^{19}F NMR and vibrational spectroscopic studies.³⁷

This work considered the existence of ClF_7 by reaction of $\text{ClF}_6^+\text{AsF}_6^-$ with $[^{18}\text{F}]\text{NOF}$. Two modes of attack by F^- on ClF_6^+ were possible, at the central chlorine (eq. 11) and at a fluorine ligand (eq. 12).

The existence of ClF_7 as an intermediate could be indicated by the presence of $[^{18}\text{F}]\text{ClF}_5$ in the products. These experiments did reveal the presence of $[^{18}\text{F}]\text{ClF}_5$, but other exchange pathways that could transfer ^{18}F to ClF_5 could not be ruled out (eq. 13-15).⁴³ Another experiment conducted between ClF_5 and $[^{18}\text{F}]\text{NOF}$ showed complete randomization of ^{18}F -distribution between the two molecules. This reaction likely required the ClF_6^- anion as the intermediate (eq. 16).

Inorganic ^{18}F Imaging Agents

$^{18}\text{F}[\text{NaF}]$ was first introduced in 1962, and approved as a radiopharmaceutical by the United States Food and Drug Administration in 1972.^{44, 45} It is noteworthy that $^{18}\text{F}[\text{NaF}]$ has been synthesized via the selective fluorinating agent $^{18}\text{F}[\text{NOF}]$ (prepared via $^{20}\text{Ne}(\text{d}, \alpha)^{18}\text{F}$ reaction), but is now routinely and simply prepared via ^{18}F fluoride.⁴⁶ $^{18}\text{F}[\text{NaF}]$ is extensively used for skeletal system imaging via PET/computed tomography (CT) (Fig. 2). The labelled fluoride exchanges with hydroxyl groups of hydroxyapatite crystals, which exist at the sites of new bone formation.⁴⁷ From this, bone imaging of benign and malignant diseases are routinely conducted. $^{18}\text{F}[\text{NaF}]$ has been used for numerous applications, including for assessing bone fractures in suspected child abuse cases, as it was displayed to be more sensitive than the conventional skeletal survey in children under the age of 2.⁴⁸ $^{18}\text{F}[\text{NaF}]$ has been explored as a tracer for detecting bone metastases in metastatic prostate cancer with $^{18}\text{F}[\text{NaF}]$ PET/CT, and found to be promising with potentially higher imaging capabilities of smaller metastases, in comparison to conventional imaging techniques.⁴⁹ More recently, $^{18}\text{F}[\text{NaF}]$ is being applied in imaging heart disease, for imaging metabolically active calcific plaque.⁵⁰ $^{18}\text{F}[\text{NaF}]$ has been used to study patients who have had a coronary event, but applications in diagnosis are being explored to assess the risk of a patient before the event occurs, specifically for identifying coronary lesions.^{51, 52}

Recent studies have assessed the imaging characteristics, safety, biodistribution, A_m , and radiation dosimetry of novel ^{18}F -based inorganic PET radiotracers, such as $^{18}\text{F}[\text{NaBF}_4]$. The model study that has been consistently carried out involves imaging the sodium-iodide symporter (NIS) *in vivo* using mice, as well as the human form of sodium iodide symporter (hNIS) *in vitro* using human cell lines.⁵³ Historically, tracers such as $^{124}\text{I}^-$ and $^{99\text{m}}\text{TcO}_4^-$ have been used to image thyroid disease and the hNIS gene expression via gamma camera and (single photon emission computed tomography) SPECT, respectively. Due to increased interest in developing PET radiotracers for thyroid imaging, ^{18}F tetrafluoroborate has been analyzed for NIS imaging, improving sensitivity, resolution, quantification, and dynamic imaging, as well as showing selective uptake by the main NIS-expressing organs and tissues (thyroid, salivary glands, and stomach).⁵³ ^{18}F tetrafluoroborate production has been limited by previous methodologies of producing ^{18}F , which consisted of the Li_2CO_3 method, and other similar exchange reactions (e.g. reaction between ^{18}F fluoride and potassium tetrafluoroborate in acid) which would yield poor molar activities.^{54, 55} Newer methods have since been published, namely using isotopic exchange of BF_4^- with ^{18}F fluoride in hot HCl and purified using an alumina column.⁵⁶ ^{18}F tetrafluoroborate has been produced with molar activities of 1–8.8 GBq/ μmol .^{56–58} PET images revealed the appropriate uptake of the tracer *in vivo* using mice, as well as the difference in standardized uptake values (SUV) between ^{18}F tetrafluoroborate vs. $^{124}\text{I}^-$ (Fig. 3). ^{18}F tetrafluoroborate exhibited higher NIS-expressing tumour SUV values than $^{124}\text{I}^-$, as well as the commonly used tracer, ^{18}F FDG.⁵³ ^{18}F tetrafluoroborate offers lower absorbed doses of radiation than $^{124}\text{I}^-$, and meet adequate safety and biodistribution requirements in humans.⁵⁹

In efforts to make a ^{18}F -based radiotracer to image NIS-expressing tumours with a simpler radiosynthesis, resulting in more appreciable A_m , the synthesis of $^{18}\text{F}[\text{SO}_3\text{F}]^-$ has been

explored. Published radiosynthesis of $[^{18}\text{F}]\text{SO}_3\text{F}^-$ consists of the reaction between 2, 2, 2-cryptand/ ^{18}F -KF and SO_3 -pyridine complex (eq. 17).⁶⁰

(eq. 17)

Using a starting activity of about 750 MBq, a A_m of at least 48.5 ± 13.4 GBq/ μmol was obtained. The main advantage of using $[^{18}\text{F}]\text{SO}_3\text{F}^-$ is that there is only one fluorine atom, allowing for a n. c. a. synthesis, enhancing the molar activity. The tracer was imaged by PET to confirm uptake in the main NIS-expressing organs and tissues

^{18}F -labelled rare-earth nanoparticles (RENs)

RENs have been gaining attention for their use in magnetic resonance imaging and photoluminescence bioimaging due to their unique optical and magnetic properties. In order to expand their application, for example, to be used in PET imaging, current research focuses on radiolabelling certain RENs with ^{18}F . A quick and simple method for synthesizing ^{18}F -labelled RENs resulted in strong binding and efficient coupling between Y^{3+} and F^- , as demonstrated by XPS and TLC autoradiogram analysis, as well as high radiolabelling stability.⁶¹ As such, RENs such as Y_2O_3 and NaYF_4 have potential as novel PET imaging probes, with the ability to label NaYF_4 through a simple isotopic exchange reaction. To further the applications of these imaging probes, co-doping with lanthanide ions has resulted in multimodal bioimaging probes, allowing for molecular imaging that combines sensitivity, resolution, and depth. NaYF_4 co-doped with a mixture of $\text{Gd}^{3+}/\text{Yb}^{3+}/\text{Er}^{3+}$ displayed multimodal imaging, namely MRI, UCL (upconverting luminescence), and PET.⁶² The presence of Yb^{3+} and Er^{3+} improved UCL emission for luminescent imaging, the presence of Gd^{3+} improved MRI contrast by providing paramagnetic relaxivity, and the presence of ^{18}F , considering the aforementioned strong affinity of certain RENs for F^- , allowed for *in vivo* PET imaging. Another successful method for incorporating the ^{18}F radionuclide into nanoparticles involves direct proton irradiation of metal oxide nanoparticles.⁶³ High energy protons were used to irradiate purified and dried Al_2O_3 nanoparticles that were prepared using ^{18}O water. Through the $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$ nuclear reaction, ^{18}F -labelled nanoparticles were obtained, and proved to be efficient for *in vivo* biodistribution studies in rodents.

Conclusions

In conclusion, ^{18}F has a long history of applications in PET imaging studies and radiochemical experiments in the organic chemistry field but has been underutilized in inorganic synthesis. The limited use of ^{18}F in inorganic chemistry can still be attributed to the radionuclide's short half-life, which restricts the chemical techniques that can be employed in synthetic work and characterization. Structural characterization of ^{18}F -labeled inorganic fluorine compounds is often challenged by the lack chromophores thereby restricting use of UV detection, and relies on radiochemical analysis (primarily

radiochromatography and counting techniques), as well as “cold” characterization from carrier-added fluorinations that can take advantage of ^{19}F -NMR spectroscopy and mass spectrometry. However, the increased opportunities for inorganic fluorine chemistry groups to work in collaboration with a cyclotron or accelerator facility in close proximity needs to be taken advantage of for fundamental science. There are major opportunities to bridge inorganic chemists with fluorine chemists and radiochemists to lead to advances in basic science as well as applied reagents, methods and mechanistic insights relevant to PET radiopharmaceutical production.

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Fig. 1.

A) The 2-D ^{19}F - ^{19}F EXSY spectrum of an equimolar sample of XeF_2 and $[\text{N}(\text{CH}_3)_4][\text{F}]$ in CH_3CN solvent, acquired at 15°C using a mixing time of 400 ms. The asterisks (*) denote natural abundance ^{129}Xe satellites ($^1J(^{129}\text{Xe}-^{19}\text{F})$, 5657 Hz). **B)** ^{19}F NMR resonances of XeF_2 , $[\text{N}(\text{CH}_3)_4][\text{F}]$, and $[\text{N}(\text{CH}_3)_4][\text{HF}_2]$ in CH_3CN solvent (-15°C). The 1-D NMR spectrum of XeF_2 , its natural abundance ^{129}Xe satellites and F^- (top trace) and the full-observed relaxation under the combined influence of spin-lattice relaxation and chemical exchange that results in the selective inversion of F^- with respect to XeF_2 . **C)** Calculated gas-phase geometries (PBE1PBE/aVTZ) of the XeF_3^- anion (transition state, C_{2v} symmetry).

Fig. 2. ^{18}F PET/CT Images.

PET/(CT) images of human subjects following administration of [^{18}F]NaF (prepared in our laboratory). 260 MBq injected, 30 min uptake, 2 min /bed.

Fig. 3.

Comparing *in vivo* imaging of NIS-expressing tumour using (a) PET/CT with $[^{18}\text{F}]\text{BF}_4^-$ and (b) SPECT/CT with $[^{123}\text{I}]\text{iodide}$ after 12, 36, and 120 min. Abbreviations: bladder (B), heart (H), kidney (K), stomach (S), thyroid and salivary glands (Th + SG), and primary tumour (T). Reproduced without changes from G.E.D. Mullen & G.O. Fruhwirth, et al.⁵³ (<https://creativecommons.org/licenses/by/4.0/>)

Scheme 1.

Production of ^{18}F from ^6Li , in the form of Li_2CO_3 .

Scheme 2.

A summary of the three $[^{18}\text{F}]\text{XeF}_2$ production methods outlined in this review.

Scheme 3.

Stereospecific synthesis of $[^{18}\text{F}]\text{FDG}$ and regiospecific synthesis $[^{18}\text{F}]\text{6-F-L-DOPA}$ from $[^{18}\text{F}]\text{XeF}_2$.^{14, 15}

Scheme 4.

Kinetic mechanism of isotopic exchange between fluoroboric acid and hydrofluoric acid.