

REVIEW

PREPARATION AND USE OF 18-FLUORINE LABELLED INORGANIC COMPOUNDS

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## A. INTRODUCTION

The purpose of this review is to focus attention on the use which may be made of  $^{18}\text{F}$ -fluorine in inorganic fluorine chemistry. Although naturally occurring fluorine is monoisotopic, a number of radioactive isotopes have been prepared artificially. Of these  $^{18}\text{F}$  has a half life sufficiently long,  $109.72 \pm 0.06$  min [1], to be used as a radiotracer. Its production and the subsequent experimental work must be carried out within one working day, but its radioactivity, 0.51 MeV  $\gamma$  radiation from the annihilation of its 0.64 MeV  $\beta^+$  decay, is easily detected, for example using a NaI well scintillation counter. The isotope is therefore very useful for determining the labilities of element-fluorine bonds and for the identification of reaction intermediates. Much of the early work involving inorganic compounds was carried out at the Argonne National Laboratory; this and other  $^{18}\text{F}$  exchange studies published prior to mid-1965 have been reviewed elsewhere [2].

The short half-life and easy detection of  $^{18}\text{F}$ , coupled with the high C-F bond energy, make  $^{18}\text{F}$  labelled compounds attractive as radiopharmaceuticals [3], and because of this, syntheses of organic compounds labelled with  $^{18}\text{F}$ , particularly those of medical significance, have been well reviewed [4]. Organic syntheses involve labelled inorganic fluorinating agents, and the preparations of these compounds are included in the present review.

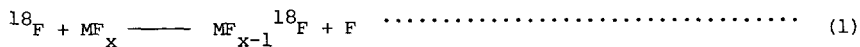
B. PREPARATION OF  $^{18}\text{F}$ -FLUORINE

$^{18}\text{F}$  can be prepared by a number of nuclear reactions, but in all cases a fast neutron source, accelerator, cyclotron, or nuclear reactor is required. In practice the reaction adopted will depend largely on access to suitable equipment and this will determine the subsequent labelling procedure. The methods available can be divided into two groups, those involving  $^{18}\text{F}$  atoms and those in which aqueous  $^{18}\text{F}$ -fluoride ion is involved at some stage.

(i) Methods involving  $^{18}\text{F}$  atoms

The reactions  $^{19}\text{F}(n^*, 2n)^{18}\text{F}$ ,  $n^*$  = fast neutron, and  $^{19}\text{F}(\gamma, n)^{18}\text{F}$  are well established methods [2,5] for labelling inorganic fluorides under anhydrous conditions. The chemistry of recoil  $^{18}\text{F}$  atoms so produced has

received considerable attention [6], and such species, moderated by multiple collisions with an inert gas to near thermal energies, are a powerful means of investigating F atom kinetics [7]. SF<sub>6</sub> is a very suitable target material and moderator for the recoil energy (>10<sup>5</sup> eV) which <sup>18</sup>F atoms possess initially. Multiple collisions produce 'hot' (30 - ~0.1 eV) and 'thermal' <sup>18</sup>F atoms (~0.03 eV) which differ in the behaviour. Experiments in which gaseous SF<sub>6</sub>, containing a small quantity of a covalent fluoride MF<sub>x</sub>, is bombarded to give a low <sup>18</sup>F activity (~1μCi) yield information on the reaction (equation 1).



Production identification is usually accomplished by radio gas chromatography, although hydrolysis can be a problem in some cases. By this means it has been shown that PF<sub>3</sub>, SbF<sub>3</sub>, SiF<sub>4</sub>, GeF<sub>4</sub>, SnF<sub>4</sub>, SOF<sub>2</sub>, SeF<sub>4</sub>, and IF<sub>5</sub> react with thermal <sup>18</sup>F atoms according to equation 1, whereas PF<sub>5</sub>, SbF<sub>5</sub>, SO<sub>2</sub>F<sub>2</sub>, SeF<sub>6</sub>, and TeF<sub>6</sub> do not [8]. The different behaviour has been correlated with the presence or absence of low lying vacant orbitals located on the central atom, but on this basis the lack of reaction observed for PF<sub>5</sub> and SbF<sub>5</sub> is surprising.

Complete retention of <sup>18</sup>F in neutron irradiated IF<sub>5</sub> and solid XeF<sub>2</sub> has been demonstrated and in solid XeF<sub>4</sub> retention is 89%; these experiments employed the pure compounds as targets [9]. Retention of <sup>18</sup>F has also been demonstrated in solid NaBF<sub>4</sub>, but not in its alkaline solution [10], in several MF<sub>6</sub><sup>2-</sup> complexes, M=Pt, Ir, Os, and Re [11], and in a number of Co<sup>III</sup> ammine complexes, for example [Co(NH<sub>3</sub>)<sub>5</sub>F][NO<sub>3</sub>]<sub>2</sub>H<sub>2</sub>O [12]. In the latter case the fraction of <sup>18</sup>F retained is small.

An alternative strategy for producing <sup>18</sup>F under anhydrous conditions is to generate <sup>18</sup>F from nuclear reactions involving Ne or O<sub>2</sub> targets. The compound to be labelled is added to the cyclotron target, if gaseous, or is placed at some point in the target chamber, if solid. High specific activities in the labelled compound are attainable by this means, particularly if the gaseous target is recirculated, and this makes the method attractive for nuclear medical work. Nuclear reactions involving bombardment of <sup>20</sup>Ne by deuteron, <sup>3</sup>He, or α particles [13,14] <sup>16</sup>O by <sup>3</sup>He or α particles [13], and <sup>18</sup>O by protons [15] all give <sup>18</sup>F. The <sup>20</sup>Ne(d,α)<sup>18</sup>F reaction is used most widely, but <sup>3</sup>He irradiation of <sup>20</sup>Ne produces less severe environmental radiation problems.

A recent account [14b] of the production of <sup>18</sup>FF, routinely 600 mCi, specific activity 10 Ci mmol<sup>-1</sup> [16], H<sup>18</sup>F, <sup>18</sup>FNO or Cl<sup>18</sup>F describes a

nickel target chamber passivated with  $F_2$  and connected to a Monel metal, Kel-F vacuum system. Ne gas to which small quantities of  $F_2$ ,  $H_2$ , NO, or  $Cl_2$  are added is the target material, the total gas pressure being in the range 2.5-4 At, and this is irradiated with a degraded 17.6 MeV deuteron beam. Relative recovery yields of  $^{18}FF$  depend on the quantity of  $F_2$  added; they vary from 100% for 7.5% added  $F_2$  to 7.65% when no  $F_2$  is added. Rather surprisingly deuteron irradiation of Ne containing added  $F_2CO$  leads to  $CF_3^{18}F$  rather than  $^{18}FFCO$  [14b]. Deuteron irradiation of Ne containing 1-10% added  $SF_4$  produces  $SF_3^{18}F$ , together with substantial quantities of  $SF_5^{18}F$ ,  $SOF^{18}F$ , and an unidentified species [17] (cf. ref 8). The  $SF_3^{18}F$  was used to prepare  $(C_2H_5)_2NSF_2^{18}F$ , currently popular as a fluorinating agent for organic compounds, by reaction with  $(CH_3)_3SiN(C_2H_5)_2$ . This compound can also be labelled by exchange with  $^{18}FF$  or  $H^{18}F$ ; the latter is the best of the three methods [17]. In this work  $H^{18}F$  and  $^{18}FF$  were both prepared via the  $^{20}Ne(d,\alpha)^{18}F$  reaction, but the preparation of carrier free  $H^{18}F$  by  $^3He$  bombardment of  $^{20}Ne$  has also been reported [18].

Labelling of solid fluorides can be accomplished by bombardment of Ne under pressure in a cooled, closed container whose inside walls are covered with a thin layer of the solid.  $KF$ ,  $SbF_3$ ,  $NaBF_4$ , and various aryl diazonium tetrafluoroborates have been labelled in this way [13]. Alternatively a recirculating target may be used in which the solid is adjacent to the target chamber. In this case Ne also acts as the carrier for the  $^{18}F$  produced. The target chamber, fabricated from aluminium with a borosilicate glass liner, is connected via P.T.F.E. tubing to a recirculating pump and a P.T.F.E. exchange vessel in which the solid fluoride (5-20 mg) is dispersed on a glass fibre filter paper [19]. As air is not rigorously excluded from the system, the labelling agent may be  $^{18}FNO_x$  or  $O_2^{18}F$  rather than  $^{18}F$ . An analogous preparation of very high specific activity  $Cs^{18}F$  employs deuteron bombardment of Ne containing 15% added  $H_2$  to give  $H^{18}F$  which is passed over a silver wool plug containing  $CsOH$  [20].

Recent doubts concerning the pharmacological inertness of chloro-fluorocarbons has prompted the preparation of  $^{18}F$  labelled  $CF_{4-n}Cl_n$  molecules in order to investigate their pharmacodynamics in animals and in man. The compounds can be prepared by a number of methods (Table 1) and their preparations illustrate the approaches described above.

#### (ii) Methods involving aqueous $^{18}F^-$ ion

These require the use of either a cyclotron or a nuclear reactor.

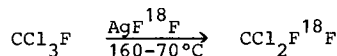
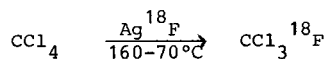
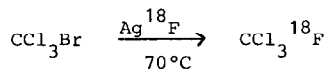
Cyclotron methods involve the bombardment of an  $H_2O$  target with  $^3He$  [25]

TABLE 1

Preparation of [ $^{18}\text{F}$ ] chlorofluoromethanes

Reaction	Target	Products	Ref.
$^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$	Ne/ $\text{CCl}_4$ (1.86%)	$\text{CCl}_3^{18}\text{F}$ (95%)	[21]
	Ne/ $\text{CCl}_3\text{F}$ or $\text{CCl}_2\text{F}_2$ (1%)	$\text{CCl}_2\text{F}^{18}\text{F}$ (60-70%)	
	Ne/ $\text{CClF}_3$ (1%)	$\text{CCl}_2\text{F}^{18}\text{F}$ (20-30%) $\text{CClF}_2^{18}\text{F}$ (35-50%) $\text{CF}_3^{18}\text{F}$ (30%)	
	Ne/ $\text{CF}_4$ (0.3-1%)	$\text{CF}_3^{18}\text{F}$ (80-90%)	
$^{19}\text{F}(\gamma,n)^{18}\text{F}$	$\text{CCl}_3\text{F}$ or $\text{CCl}_2\text{F}_2$	$\text{CCl}_3^{18}\text{F}$ , $\text{CCl}_2\text{F}^{18}\text{F}$ $\text{CClF}_2^{18}\text{F}$	[22]
$^{19}\text{F}(\text{p},\text{pn})^{18}\text{F}$	$\text{CCl}_3\text{F}$	$\text{CF}_3^{18}\text{F}$ , $\text{CClF}_2^{18}\text{F}$ $\text{CCl}_2\text{F}^{18}\text{F}$	[23]
$^{20}\text{Ne}(\text{d},\alpha)^{18}\text{F}$	Ne/ $\text{AgF}$ or $\text{AgF}_2$	$\text{Ag}^{18}\text{F}$ or $\text{AgF}^{18}\text{F}$	[24]

then



Yields up to 90%. Radiochemical yields up to 40%

or  $\alpha$  particles [26]. Another possibility is the  $^{18}\text{O}(\text{p},\text{n})^{18}\text{F}$  reaction using an  $\text{H}_2^{18}\text{O}$  target [15].  $^{18}\text{F}$  is produced as aqueous  $^{18}\text{F}^-$  ion and can be collected in situ by incorporating an anion exchange column in a recirculating  $\text{H}_2\text{O}$  target [26]. Hydrogen peroxide is formed during the irradiations [27], and allowance must be made in the target design for other  $\text{H}_2\text{O}$  radiolysis products.

Irradiation of a lithium-oxygen target by thermal neutrons in a reactor has proved to be a very popular method of producing  $^{18}\text{F}$ , not least because of the relative accessibility of research reactors. The sequence

of reactions  ${}^6\text{Li}(n,\alpha){}^3\text{H}$ ,  ${}^{16}\text{O}(t,n){}^{18}\text{F}$  requires  ${}^6\text{Li}$  and  ${}^{16}\text{O}$  to be intimately mixed; this is normally accomplished by using  $\text{Li}_2\text{CO}_3$  as the target material although  $\text{Li}_2\text{O}$  and other  $\text{Li}^+$  oxoacid salts have been used. It has been shown by paper chromatography that when the irradiated  $\text{Li}_2\text{CO}_3$  is dissolved in  $\text{H}_2\text{O}$ , >99% of the  ${}^{18}\text{F}$  activity is present as aqueous  ${}^{18}\text{F}^-$  ion [28]. High yields of  ${}^{18}\text{F}$  can be obtained if  ${}^6\text{Li}_2\text{CO}_3$  is used (the natural abundance of  ${}^6\text{Li}$  is 7.5%), for example 65-75 mCi of usable carrier free  ${}^{18}\text{F}$  have been obtained from a 3h irradiation using a neutron flux of  $4.2 \times 10^{13} \text{ n cm}^{-2} \text{ s}^{-1}$  [29].

A major, practical consideration is the post-irradiation 'work-up' procedure as the time for this needs to be kept to a minimum. Several techniques have been described, all of which have their devotees. All result in a solution containing  ${}^{18}\text{F}^-$  ion or a complex [ ${}^{18}\text{F}$ ] fluoroanion.

#### (a) Cation exchange

An aqueous solution of the irradiated target material is passed through a cation exchange column on which  $\text{Li}^+$  is retained [30]. In a non aqueous version the target is dissolved in glacial acetic acid, diluted with acetone/ethanol, and  $\text{Li}^+$  is retained by a cellulose column [31]. This variant is applicable if organic synthesis is contemplated subsequently.

#### (b) Distillation

The irradiated target is dissolved in fairly concentrated  $\text{H}_2\text{SO}_4$ .  $\text{H}^{18}\text{F}$  is distilled from the mixture, either by gentle warming or with the aid of an air current, and collected in aqueous alkali [32]. Precipitation with  $\text{Ca}(\text{OH})_2$  prior to acidification has also been recommended [33]. Distillation has the great merit of simplicity, but a disadvantage of the method is that the distillate is liable to be seriously contaminated by tritium, mainly as  ${}^3\text{H}_2\text{O}$  but also as [ ${}^3\text{H}$ ]-acetate and -formate [34]. See reference [35] for conflicting evidence regarding  ${}^3\text{H}$  levels. Serious contamination is obviously highly undesirable on medical grounds, but if a solid fluoride is to be isolated, normally the case for inorganic tracer studies, it may not be serious chemically.

#### (c) Chromatography using metal oxides and related materials

Several different compounds (Table 2) have been used to adsorb  ${}^{18}\text{F}$  from acidic solutions of target materials.

TABLE 2

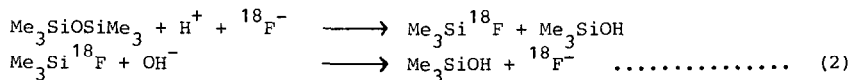
Chromatographic materials for aqueous  $^{18}\text{F}^-$  ion

Material	Ref
$\text{Al}_2\text{O}_3$	[36]
hydr. $\text{ZrO}_2$	[37]
$\text{HfO}_2$	[38]
hydr. $\text{SnO}_2$	[39]

Elution is achieved by aqueous  $\text{NaOH}$  or  $\text{NH}_4\text{OH}$ ; advantages of the method are the short time required and the low tritium content of the product.  $^{18}\text{F}$  eluted from  $\text{Al}_2\text{O}_3$  may be present in solution as  $\text{Al}^{\text{III}}\text{-}^{18}\text{F}$  complex anions as well as  $^{18}\text{F}^-$  anion [36b, 40] but  $^{18}\text{F}^-$  anion is the sole product using  $\text{ZrO}_2$  [40]. Isolation of  $^{18}\text{F}$  in the presence of  $\text{Al}^{\text{III}}$  (pH 8-9), can be accomplished by using a  $\text{Pb}_7\text{Sr}_3(\text{PO}_4)_6(\text{OH})_2$  column at  $100^\circ\text{C}$  [41].

#### (d) Solvent extraction

Tributyl phosphate [42],  $\text{Ph}_4\text{SbBr}$  in  $\text{CCl}_4$  [43], and  $\text{Ph}_3\text{SbCl}_2$  in  $\text{CCl}_4$  [44] have been used to extract  $^{18}\text{F}$  from acidified target solutions. The latter two reagents are useful when the ratio of  $^{18}\text{F}$  to target material is small, and in one report [44] extraction in the presence of  $\text{Al}^{\text{III}}$  is described. A variation of this approach involves the hexamethyldisiloxane assisted diffusion of  $^{18}\text{F}$  from an acidic solution to an alkaline trapping solution, represented schematically (equation 2) by



Recovery is reasonably good, but the main advantage of the method is that it can be used during transport of the isotope from the reactor to the laboratory where it is to be used [45].

If a  $\text{Li}_2\text{CO}_3$ ,  $\text{H}_2\text{O}$  slurry or paste is irradiated, >90% of the  $^{18}\text{F}$  activity is found in the  $\text{H}_2\text{O}$  component and 70% of this can be recovered in a very short time by a single extraction with aqueous  $\text{NaOH}$ . The method is claimed to be particularly useful if enriched  $^6\text{Li}_2\text{CO}_3$  is used, as unchanged target recovery is quantitative [46].

C. ADSORPTION OF  $^{18}\text{F}$ -FLUORINE

Yields of  $^{18}\text{F}$  from nuclear reactions may be seriously reduced by adsorption, for example at the walls of the target chamber. Despite its importance, adsorption of  $^{18}\text{F}$  has not been studied systematically, however several relevant observations have been made.  $^{18}\text{F}$  is rapidly removed from the gas phase by aluminium [19], indeed aluminium and stainless steel surfaces are stable deposition environments for  $^{18}\text{F}$  atoms at low pressures [47]. Removal of  $^{18}\text{F}$  from the gas phase by nylon, perspex, brass, and glass occur slowly, and  $^{18}\text{F}$  is apparently inert towards P.T.F.E. and silver, all in the temperature range 30-90°C [19]. Not surprisingly,  $\text{H}^{18}\text{F}$  is rapidly trapped by glass [19] and  $^{18}\text{FF}$  appears not to react with  $\text{NiF}_2$  [14]. Aqueous solutions of  $^{18}\text{F}$  interact with polyethylene, glass, aluminium, and titanium surfaces. Adsorption on Al increases linearly with time, and is substantially higher than for other surfaces. Adsorption maxima are observed for both Ti and glass. The behaviour can be explained qualitatively in terms of complex ion formation [48].

## D. PREPARATION OF LABELLED ALKALI METAL FLUORIDES AND RELATED COMPOUNDS

Alkali metal [ $^{18}\text{F}$ ] fluorides are key compounds in  $^{18}\text{F}$  tracer work as they can be used to label covalent, inorganic fluorides by straightforward Lewis acid-base reactions. If direct methods for preparing anhydrous  $\text{M}^{+18}\text{F}^{-}$  compounds (Section B(i)) are not available, they must be obtained from aqueous solution. Neutron irradiated  $\text{Li}_2\text{CO}_3$  has been used directly to label  $\text{BF}_3$  by flowing the gas over the solid at 200°C [49], but more usually a metal fluoride is isolated from solutions obtained using the procedures described above (Section B(ii)).  $\text{Li}^{18}\text{F}$  has been prepared by precipitation [49],  $\text{K}^{18}\text{F}$  and  $(\text{C}_2\text{H}_5)_4\text{N}^{18}\text{F} \cdot 2\text{H}_2\text{O}$  by evaporation of solutions, previously treated with a cation exchange resin and to which carrier fluoride has been added [50], and  $\text{Cs}^{18}\text{F}$  by distillation of  $\text{H}^{18}\text{F}$  into aqueous  $\text{CsOH}$ , neutralisation with  $\text{HF}$ , and evaporation of the solution [51]. In all cases additional drying, for example by heating in vacuo, is required.

$\text{K}^{18}\text{F}$  or  $(\text{C}_2\text{H}_5)_4\text{N}^{18}\text{F}$ , usually dissolved in dipolar, organic or crown ether solvents, are widely used nucleophiles for synthesis of  $^{18}\text{F}$  labelled organic compounds [31,52] and might be applied to inorganic synthesis. An interesting alternative is an anhydrous [ $^{18}\text{F}$ ] anion exchange resin which has been used for several organic syntheses, often at elevated



temperatures [53]. An anion exchange resin in the acetate or fluoride form is rinsed with carrier free  $^{18}\text{F}^-$  ion solution and dried before use. Fluoride ion capacities of a resin determined by radiometric and conventional analysis are in good agreement, but the use of P.T.F.E. for all equipment is recommended to avoid contamination by  $\text{SiF}_6^{2-}$  anion [54].

#### E. $^{18}\text{F}$ -FLUORINE EXCHANGE REACTIONS

Exchange reactions have been carried out either to label an inorganic fluoride of interest, or to probe some aspect of a compound's physico-chemical behaviour. Experimental results are normally expressed in terms of the fraction of  $^{18}\text{F}$  activity exchanged ( $f$ ) where  $f$  is defined by equation 3.

$$f = \frac{\text{fraction of activity in the initially unlabelled compound}}{\text{fraction of fluorine (g.atom) in the initially unlabelled compound}}$$

Obviously  $f = 1$  corresponds to a random distribution of  $^{18}\text{F}$  activity between the two compounds, and is the situation corresponding to complete exchange. Counting considerations and the short half life of  $^{18}\text{F}$  dictate that the working specific activities should be in the range  $10^3$ - $10^4$  counts  $\text{s}^{-1} \text{mmol}^{-1}$ , therefore the rate and extent of an exchange reaction will determine the  $^{18}\text{F}$  activity required initially. In practice many reactions can be investigated very adequately using an initial  $^{18}\text{F}$  activity, for example as  $\text{Cs}^{18}\text{F}$ , of ca. 0.1 mCi.

##### (i) Labelling studies

Many covalent fluorides can be labelled efficiently by heterogeneous reaction with an alkali metal [ $^{18}\text{F}$ ] fluoride at moderate temperatures under flow [55,49] or static [51,56,57] conditions. Although complex fluoro-anions are logical transition states for the exchange reactions,  $^{18}\text{F}$  exchange between  $\text{M}^{18}\text{F}$  and  $\text{SiF}_4$  occurs under conditions where formation of  $\text{M}_2\text{SiF}_6$  is not observed [55], and this situation is commonly observed in other systems.

Halogen fluorides were one of the first groups of compounds to be studied in detail [2], and more recently  $^{18}\text{F}$  exchange between  $\text{CsBrF}_5$   $^{18}\text{F}$  and  $\text{BrF}_5$  has been demonstrated [58]. The transition state is suggested to be  $[\text{F}_5\text{Br}^{18}\text{FBrF}_5]^-$  rather than one involving  $\text{BrF}_5$  self ionisation.  $^{18}\text{F}$  exchange between  $\text{XeOF}_3$   $^{18}\text{F}$  and  $\text{XeO}_2\text{F}_2$  at  $0^\circ\text{C}$  is complete within 1h indicating an exchange half life  $< 7$  min [59]; no  $^{19}\text{F}$  exchange was detectable by n.m.r. spectroscopy. Exchange between  $\text{XeF}_2$  and  $\text{H}^{18}\text{F}$  or  $^{18}\text{F}^-$  ion in  $\text{H}_2\text{O}$  at  $0^\circ\text{C}$

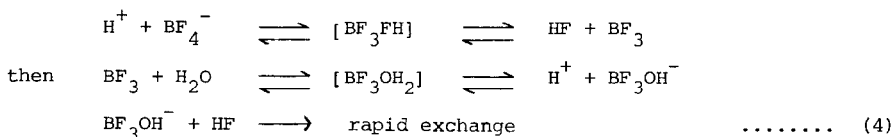
is very slow; these observations, together with the results of conductivity studies, rule out equilibria involving  $\text{XeF}_2$  and  $\text{XeF}(\text{OH})$ ,  $\text{XeF}^+$ , or  $\text{XeF}_4^{2-}$  [60].

Rapid exchange occurs between  $\text{WF}_5^{18}\text{F}$  and  $\text{WF}_7^-$  and between  $\text{UF}_5^{18}\text{F}$  and  $\text{UF}_6^-$  or  $\text{UF}_7^-$  at room temperature in  $\text{CH}_3\text{CN}$ . In all cases exchange is complete within 1h, and presumably F-bridged dinuclear transition states are involved [61].

### (ii) Kinetic studies

The rate of an isotopic exchange reaction occurring under homogeneous conditions can be obtained by studying the variation of  $f$  with time, the McKay equation [62]. A first order exchange law will apply irrespective of the exchange mechanism, as no stoichiometric change occurs during the reaction providing the concentrations of labelled species are small. The reaction order must be determined by conducting separate series of experiments, in which different reactant concentrations are used. This can be a laborious procedure when  $^{18}\text{F}$  is involved, and such studies are rare. Useful information can be obtained however by comparing exchange rates determined for different reactions at equivalent concentrations.

One of the few detailed kinetic studies that have been reported deals with  $^{18}\text{F}$  exchange between HF and tetrafluoroboric acid in aqueous solution [63]. The  $^{18}\text{F}$  exchange rate law is very similar to that of the acid hydrolysis of  $\text{BF}_4^-$ , also determined using  $^{18}\text{F}$ , and a common mechanism (equation 4) is postulated



The non-acidic hydrolysis of  $\text{BF}_4^-$  proceeds via a dissociative mechanism. This work is very relevant to the preparation of [ $^{18}\text{F}$ ] fluoro-aryl derivatives which are often prepared by thermal decomposition of aryl diazonium  $\text{BF}_3^{18}\text{F}^-$  salts, the Balz-Schiemann reaction [64]. Although high  $^{18}\text{F}$  specific activities are attainable by this reaction, the method is inefficient radiochemically as only 25% of the activity in  $\text{BF}_3^{18}\text{F}^-$  is available. Routes based on piperidyl or aryl triazenes and  $\text{CsF}$  or  $\text{HF}$ -pyridine may be more satisfactory in this respect [20a,65].

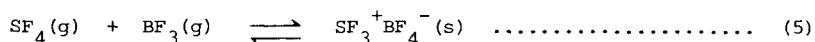
$(\text{CH}_3)_3\text{Si}^{18}\text{F}$  and  $(\text{CH}_3)_2\text{SiF}^{18}\text{F}$  have been used to probe element-fluorine bond lability in various methoxide, fluorides [57]. Linear McKay plots

were obtained with  $WF_{6-n}(OCH_3)_n$  ( $n = 1-3$ ), and  $IF_4OCH_3$  therefore the non equivalent F atoms within each molecule undergo exchange at identical rates within experimental error. Exchange between  $(CH_3)_3Si^{18}F$  and  $WF_5OCH_3$  is second order in the latter and first order in the former, which is consistent with an associative mechanism but not with a simple four-centre transition state. Sequences of exchange rates are  $WF_6 < WF_5OCH_3 > cis-WF_4(OCH_3)_2 > mer$  and  $fac-WF_3(OCH_3)_3 > cis-WF_2(OCH_3)_4$ ;  $MoF_6 \gg MoF_{6-n}(OCH_3)_n$  ( $m = 4$  or  $5$ );  $IF_4OCH_3 > IF_5$ .  $^{18}F$  exchange with  $Te^{VI}$  fluorides was too slow to measure. The  $^{18}F$  exchange behaviour parallels the reactions of these compounds with  $(CH_3)_3SiOCH_3$  and  $(CH_3)_2Si(OCH_3)_2$ , and both steric and electronic properties of the  $CH_3O-$  ligand affect the M-F bond lability.

### (iii) Characterisation of compounds

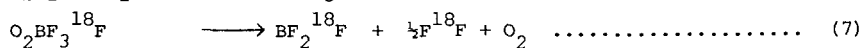
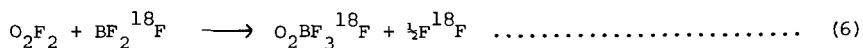
An  $^{18}F$  exchange study played an important part in the investigation of the system  $NaF, UF_6$ , as it provided the first, definitive evidence for the existence of  $Na_2UF_8$  rather than  $Na_3UF_9$  [5]. This was confirmed in subsequent synthetic work [66].  $^{18}F$  has also played a part in the characterisation of three complex cation, fluoroanion salts. In these cases the results obtained are useful rather than definitive.

$^{18}F$  exchange between  $SF_4$  and  $BF_3$  at  $25^\circ C$  is complete within 20 min and occurs via the equilibrium (equation 5)



Limited exchange occurs at lower temperatures, and this has been interpreted in terms of an ionic structure for the adduct in which the rotational motions of  $SF_3^+$  and  $BF_4^-$  are hindered [67]. This seems plausible, although the structural models used to interpret the low temperature exchange results are significantly different from the structure determined subsequently [68] by X-ray crystallography.

Tracer studies of the formation (equation 6) and decomposition (equation 7) of  $O_2BF_4$  indicate that the compound should be formulated as a dioxygenyl salt rather than an  $FO_2 \rightarrow BF_3$  complex [69]



It is suggested that  $O_2F$  is an intermediate in both processes.

Interest in the properties of  $\text{NF}_4^+$  salts, particularly the possibility of  $\text{NF}_5$  being a decomposition intermediate, has prompted a study of several isotopic exchange reactions involving  $\text{NF}_4^+\text{AsF}_6^-$  [70]. Complete exchange between  $\text{NF}_4^+\text{AsF}_6^-$  and  $^{76}\text{AsF}_5$  and between  $\text{AsF}_6^-$  and  $\text{AsF}_5^{18}\text{F}$  was observed, but no exchange was observed with  $^{18}\text{F}$  or  $^{15}\text{NF}_3$ . There is no evidence for the involvement of  $\text{NF}_5$  therefore, and the inertness of  $\text{NF}_4^+$  towards exchange agrees with the conclusions drawn from  $^{19}\text{F}$  n.m.r. investigations [71]. Surprisingly, limited exchange was observed between  $\text{NF}_4^+\text{AsF}_6^-$  and  $\text{NF}_2^{18}\text{F}$ , and this is difficult to rationalise. The foregoing exchange work was carried out at room temperature, and the exchange mechanisms appear to differ from that recently suggested for the formation and decomposition of  $\text{NF}_4^+$  salts [72].

#### (iv) Catalysis by fluoride ion

Alkali metal fluorides are widely used catalysts in fluorine chemistry, representative reactions being (equations 8 and 9)



( $\text{R}_\text{F} = \text{F}, \text{CF}_3$  etc.)



Both reactions proceed at ambient temperature or below, in the presence of  $\text{CsF}$  as a catalyst [73]. Mechanisms for these and related reactions are usually considered to involve intermediates related to complex fluoroanions [73,74],  $\text{R}_\text{F}\text{CF}_2\text{O}^-$  and  $\text{SF}_5^-$  in the examples above, and if this is the case, a correlation is to be expected between an ionic, metal fluoride's catalytic ability, and its ability to undergo  $^{18}\text{F}$  exchange with the appropriate substrate. Experimental work involving alkali metal fluorides supports this postulate. Exchange between  $\text{CF}_3\text{C}(\text{O})^{18}\text{F}$ ,  $\text{F}^{18}\text{FCO}$ , or  $\text{SF}_3^{18}\text{F}$  and alkali metal fluorides varies in the order  $\text{Cs} > \text{Rb} > \text{K} > \text{Na} \geq \text{Li}$  [51,56].  $\text{CsF}$  is the best catalyst while  $\text{NaF}$  and  $\text{LiF}$  have little or no catalytic activity [74,75].  $^{18}\text{F}$  exchange between  $\text{F}^{18}\text{FCO}$  and alkali metal fluorides is enhanced by organic solvents which have good solvating properties for cations, for example diglyme, or a high dielectric constant, for example  $\text{CH}_3\text{CN}$ . The former has a particularly marked effect on  $\text{LiF}$  and  $\text{NaF}$  [56]. In both types of solvent the formation of  $\text{CF}_3\text{O}^-$  will be favoured. Additional support for an ionic  $^{18}\text{F}$  exchange mechanism comes from the observations that in  $\text{F}_2^{18}\text{FCO}^{18}\text{F}$  prepared from  $\text{F}_2\text{CO}$  and  $\text{F}^{18}\text{F}$  in the presence of  $\text{Cs}^{18}\text{F}$ , approximately one third of the  $^{18}\text{F}$  activity is found in the  $-\text{OF}$  group [76],

and that while  $^{18}\text{F}$  labelled  $\text{F}_2\text{CO}$  and  $\text{CF}_3\text{C}(\text{O})\text{F}$  are readily obtained by reaction with  $\text{Cs}^{18}\text{F}$ ,  $(\text{CF}_3)_2\text{CO}$  is not labelled under similar conditions [51,56].

The correlation between  $^{18}\text{F}$  exchange and catalytic ability breaks down for ionic fluorides other than those of the alkali metals, for example  $\text{TlF}$ ,  $\text{Hg}_2\text{F}_2$ ,  $\text{HgF}_2$ , and  $\text{LaF}_3$  readily undergo  $^{18}\text{F}$  exchange with  $\text{SF}_3^{18}\text{F}$  but are not catalysts for the chlorofluorination of  $\text{SF}_4$  [75]. Common intermediates for the two processes are not necessarily involved therefore, and metal fluoride pretreatment, which can increase its surface area, is particularly important for  $\text{CsF}$  [77].

#### F. CONCLUSION

$^{18}\text{F}$ -Fluorine has been underused in inorganic fluorine chemistry to date, no doubt because of the specialised equipment required for its production, but its increasing use in medical work should make facilities for its production more widely available. Certainly many fields in which tracer studies could be fruitful remain to be explored.

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