Fluorine-18 Radiochemistry

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Scholars Trained in Advanced Radiochemistry Technology
Outline

1. PET radioisotopes
2. Properties of fluorine
3. Basic principles in radiochemistry of short-lived isotopes
   i. Quantities
   ii. Specific activity
   iii. Radiolysis

4. Fluorine chemistry
   i. Source of Fluorine-18
   ii. Electrophilic and nucleophilic fluorine reagents

5. Electrophilic fluorination ("F⁺")
6. Nucleophilic fluorination ("F⁻")
   i. General workflow
   ii. Aromatic nucleophilic substitution (S_NAr)
   iii. Aliphatic nucleophilic substitution (S_N2)
      i. Mechanism
      ii. Solvents
      iii. Leaving groups, activating groups
PET Radioisotopes

1. Moderate half-lives
2. High specific activity

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Half-life</th>
<th>Decay</th>
<th>Maximum specific activity</th>
<th>mg GBq⁻¹</th>
<th>mg Ci⁻¹</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>20.4 min</td>
<td>β⁺ (99%)</td>
<td>3.4 × 10¹¹</td>
<td>3.5 × 10⁻⁸</td>
<td>1.2 × 10⁻⁶</td>
</tr>
<tr>
<td>N</td>
<td>9.96 min</td>
<td>β⁺ (99%)</td>
<td>6.9 × 10¹¹</td>
<td>2.0 × 10⁻⁸</td>
<td>6.9 × 0⁻⁷</td>
</tr>
<tr>
<td>O</td>
<td>2.07 min</td>
<td>β⁺ (99.9%)</td>
<td>3.4 × 10¹²</td>
<td>4.7 × 10⁻⁹</td>
<td>1.6 × 10⁻⁷</td>
</tr>
<tr>
<td>F</td>
<td>109.7 min</td>
<td>β⁺ (97%)</td>
<td>6.3 × 10¹⁰</td>
<td>3.0 × 10⁻⁷</td>
<td>1.0 × 10⁻⁵</td>
</tr>
<tr>
<td>H</td>
<td>12.3 years</td>
<td>β⁻ (100%)</td>
<td>1.1 × 10⁶</td>
<td>2.7 × 10⁻³</td>
<td>0.1</td>
</tr>
<tr>
<td>O</td>
<td>5730 years</td>
<td>β⁻ (100%)</td>
<td>2.3 × 10³</td>
<td>6.0</td>
<td>224</td>
</tr>
<tr>
<td>I</td>
<td>60 days</td>
<td>γ (EC)</td>
<td>8 × 10⁷</td>
<td>1.5 × 10⁻⁴</td>
<td>5.8 × 10⁻²</td>
</tr>
<tr>
<td>Tc</td>
<td>6 h</td>
<td>γ (IT)</td>
<td>1.9 × 10¹⁰</td>
<td>5.2 × 10⁻⁶</td>
<td>1.9 × 10⁻⁴</td>
</tr>
</tbody>
</table>

- EC: electron capture; IT: Isomeric Transition.
- Defined as the number of decay N per second and per mole.

3. Low positron energy- shortest diffusion ranges < 2.4 mm

<table>
<thead>
<tr>
<th>Radionuclide</th>
<th>Maximum energy (MeV)</th>
<th>Maximum linear range in H₂O (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>0.96</td>
<td>4.12</td>
</tr>
<tr>
<td>N</td>
<td>1.19</td>
<td>5.39</td>
</tr>
<tr>
<td>O</td>
<td>1.72</td>
<td>8.20</td>
</tr>
<tr>
<td>F</td>
<td>0.635</td>
<td>2.39</td>
</tr>
</tbody>
</table>
F18: Ideal Positron-Emitting Radionuclide

- Low positron energy and short range in tissue (high resolution)
- 97% $\beta^+$ decay
- High specific activity
- Can be produced in large amount in a cyclotron (>10 Ci)
- Can be labeled in high radiochemical yields for PET tracers
- Acceptable radiation dosimetry for multiple studies in a patient
- Allow transportation from production site to PET imaging centers ($T_{1/2} = 109.7$ min)
Properties of Fluorine

1. F bioisostere with O (size and electronegativity)
2. F most electronegative (highest number of protons in nucleus)

<table>
<thead>
<tr>
<th>Element (X)</th>
<th>van der Waals radius [Å]</th>
<th>Electronegativity (Pauling scale)</th>
<th>Bond length of C–X [Å]</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>1.20</td>
<td>2.20</td>
<td>1.09</td>
</tr>
<tr>
<td>O</td>
<td>1.52</td>
<td>3.44</td>
<td>1.43</td>
</tr>
<tr>
<td>F</td>
<td>1.47</td>
<td>3.98</td>
<td>1.35</td>
</tr>
</tbody>
</table>

M.-C. Lasne et al. Topics in Current Chemistry. 2002. 22

3. C-F bond is the strongest and is highly polarized

Hydration energy 507 kJ/moles

\[ \text{F}^- (\text{H}_2\text{O})_n \]

\[ \text{F}^- + \text{H}^\delta^+ \rightarrow \text{HF} \text{ (bonding)}: 565 \text{ kJ/moles} \]
Properties of Fluorine

Electron configuration → chemical reactivity (electrons!!)

1s2 2s2 2p5

(\(^{19}_9 F\) and \(^{18}_9 F\))

# Neutrons + Protons

1s2 2s2 2p6 → OCTET!

(“F\textsuperscript{+}”) F-F bond weakest (159 kJ/mole)

EXTREMELY REACTIVE

328 kJ/mole

(“F\textsuperscript{-}”) Donate a pair of electron (nucleophilic) or H acceptor (base)

1s2 2s2 2p6 → OCTET!
Where to Label? i.e.: PET probe design

Fluorine ~ H: size and valence e⁻ (isosteres)
~ O: electronegativity

Synthetic method consideration
(1) Chemoselectivity and (2) regioselectivity: which carbon?
(3) Stereoselectivity: spatial orientation of F relative to other functional groups?

![Chemical structures]

- Glucose
- 2-FDG
- 2-FDM

- L-DOPA
- 6-fluoro-L-DOPA

- Thymidine derivatives

38, [18F]FMAU
39, FdR
40, [18F]FAU
10, [18F]FUr
ONLY IN RADIOCHEMISTRY
Specific Activity

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield

\[
\text{Radioactivity (Ci)} \quad \frac{\text{Mass (\mu moles)}}{\text{Molecules of F-18}} \quad \text{Molecules of F-18 + F-19}
\]

Maximum theoretical SA of F-18 ion ~ 1710 Ci/\mu m mole

In reality, SA F-18 ions ([^{18}\text{F}]\text{F}^-/[^{18}\text{O}]\text{H}_2\text{O}] obtained from the cyclotron ~ 50-100 Ci/\mu m mole

SA of [^{18}\text{F}]\text{FDG} = 2-5 \text{ Ci/\mu mole}

How to measure specific activity of fluorine-18?: [^{18}\text{F}]\text{F}_2? [^{18}\text{F}]\text{F}^-?

Coenen et al. 1986, Appl Radiat Isot 37:1135
Syntheses and Specific Activity Determinations of No-Carrier-Added Fluorine-18-Labeled Neuroleptic Drugs

Chyng-Yann Shiue, Joanna S. Fowler, Alfred P. Wolf, Masazumi Watanabe, and Carroll D. Arnett

Chemistry Department, Brookhaven National Laboratory, Upton, New York


Scheme 1. i) irradiation; ii) Cs₂CO₃; iii) \( p \)-nitrobenzonitrile, DMSO, 140°C, 10 min; iv) cyclopropyllithium, Et₂O; v) HCl, MeOH, 110°C, 7 min; vi) \( R^1R^2\text{NH} \), KI, 100°C, DMF-THF
Why is SA important?

For imaging receptors (cell surface receptors, brains...etc)
- limited number
- irreversible binding

General rule of thumb:

~1000x F19 >> F18
What affects SA of F18 ion?

1. Radioactivity, bombardment time and dose

Dose vs Specific Act

![Graph showing specific activity vs dose](image)

Higher radioactivity, higher SA?

Table 1. Specific radioactivity of $^{18}$F, saturation activity and activity at EOB as functions of dose and dose rate for the nuclear reaction $^{18}$O(p, n)$^{18}$F (target system B, see also text)

<table>
<thead>
<tr>
<th>Dose (mC)</th>
<th>t_{ex} (min)</th>
<th>Dose rate (μA)</th>
<th>$A_{(EOB)}$ (mCi)</th>
<th>$A_{(EOSB)}$ (mCi/μA)</th>
<th>Sp. act. (Ci/μmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3</td>
<td>5</td>
<td>1</td>
<td>3.5</td>
<td>114</td>
<td>2.7</td>
</tr>
<tr>
<td>0.9</td>
<td>15</td>
<td>1</td>
<td>11.6</td>
<td>128</td>
<td>11</td>
</tr>
<tr>
<td>1.5</td>
<td>5</td>
<td>5</td>
<td>16.1</td>
<td>103</td>
<td>16</td>
</tr>
<tr>
<td>3.0</td>
<td>5</td>
<td>10</td>
<td>31.5</td>
<td>101</td>
<td>—</td>
</tr>
<tr>
<td>3.6</td>
<td>60</td>
<td>1</td>
<td>33.9</td>
<td>107</td>
<td>20</td>
</tr>
<tr>
<td>4.5</td>
<td>15</td>
<td>5</td>
<td>47.3</td>
<td>105</td>
<td>38</td>
</tr>
<tr>
<td>9.0</td>
<td>15</td>
<td>10</td>
<td>78.0</td>
<td>86</td>
<td>62</td>
</tr>
<tr>
<td>18.0</td>
<td>60</td>
<td>5</td>
<td>159.1</td>
<td>101</td>
<td>130</td>
</tr>
<tr>
<td>36.0</td>
<td>60</td>
<td>10</td>
<td>269.3</td>
<td>85</td>
<td>140</td>
</tr>
</tbody>
</table>

Solin O., Appl Radiat Isot. 1988, 39, 1065-1071
3. Contamination from materials

(a) Radiolysis in Teflon tubing and components
- Radioactivity levels
- Incubation time

(b) Contamination from reagents
- $K_2CO_3 \sim 10$ nmole of F19
- $K222 = \sim 30$ nmole of F19
- Precursor $\sim$ negligible

(c) Contamination from QMA resins
- SAX resin
- Resin vs no resin: 5000 vs 700 mCi/umole

Controlled experiments **without** Teflon tubing: 25-51 Ci/umole
**In the presence** of Teflon tubing average SA $\sim 0.6$ Ci/umole

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**Table 1.** Carrier mass from 11.1 GBq (300 mCi) exposure to system components

<table>
<thead>
<tr>
<th>Teflon item</th>
<th>Surface (cm²)</th>
<th>Time (min)</th>
<th>Mass (nmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 mm Teflon tubing (790 cm)</td>
<td>252</td>
<td>1.25</td>
<td>72</td>
</tr>
<tr>
<td>Teflon resin holder</td>
<td>3.8</td>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>Teflon tube in reaction vessel</td>
<td>1.7</td>
<td>20</td>
<td>170</td>
</tr>
<tr>
<td>Rheodyne slider valve</td>
<td>2.3</td>
<td>1.25</td>
<td>6.3</td>
</tr>
<tr>
<td>Control-reagents only</td>
<td>0</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>Control-mock target water</td>
<td>0</td>
<td>0</td>
<td>23</td>
</tr>
<tr>
<td>All components</td>
<td>267</td>
<td>N/A</td>
<td>357</td>
</tr>
</tbody>
</table>

Berridge M.S. et al., JLRC. **2009**, 52, 543-548
How to measure specific activity of labeled molecules?

1. Develop calibration curve
2. Commonly used detection techniques:
   - HPLC (UV detection for UV-active molecules)
   - Pulsed amperometric (carbohydrates, non-UV active molecules)

Measure cold mass after probes decay.

Berridge M.S. et al., JLRC. 2009, 52, 543-548
Only in radiochemistry

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield

Theoretical specific activity $1710 \text{ Ci}/\mu\text{mole}$

1 Ci radioactivity $\sim 60 \text{ nmoles fluoride ion}$

Typical reaction conditions

Precursors and reagent : 10-100 mmoles

Reaction rate of stoichiometry $S_N2 = [\text{Substrate}] \times [\text{nucleophiles}]$

Reaction rate of $S_N2$ in radiochemistry $= [\text{Substrate}]$

Increased in $[\text{Substrate}]$, increasing reaction rates

Detection? Rates? Concentrations?
Basic Radiochemistry

Transient Toxicity of 2-Deoxy-2-$[^{18}F]$fluoro-D-Glucose in Mammalian Cells:
Concise Communication


Harvard Medical School, Boston, Massachusetts, and Brookhaven National Laboratory, Upton, New York

The kinetics of uptake and toxicity of the positron emitter F-18 have been examined in a cultured cell line. 2-Deoxy-2-$[^{18}F]$fluoro-D-glucose (18FDG) concentrated rapidly within Chinese hamster V79 cells, and the uptake was linear with the extracellular radioactive concentrations. Whereas 18FDG synthesized 2 hr before the incubation did not appear to be toxic, that synthesized 5 hr previously was highly toxic. Toxicity was transient and independent of both the extracellular/intracellular radioactive concentration and the energy released from the decay of fluorine-18. Similarly synthesized nonradioactive FDG and Na18F were not toxic under comparable experimental conditions. We conclude that this transient toxicity is due to an unidentified chemical species that is cytotoxic following intracellular localization. These toxic levels are not likely to be achieved in the clinical use of 18FDG due to dilution factors that are orders of magnitude greater than those used in these in vitro studies.


Conclusion: Toxic, unstable side products form by the presence of the higher energy positron in a concentrated solution.
Only in Radiochemistry

1. Specific activity  
2. Amount  
3. Radiolysis  
4. Radiochemical yield

Each $^{18}$F decay ($T_{1/2}=109.8$ mins, $E_{max\beta} = 0.69$ MeV) releases positrons ($\beta^+$) particles of 0.23 MeV

Buriova E et al., J Radioanalytical and Nucl Chem. 2005, 264, 595-602
General requirements of synthesis of short-lived radioisotopes

1. Fast, fast and fast. Rule of thumb: 3 half-life. For F18 <6 hours.
2. Non-stoichiometry reactions. Large excess of reagents/precursors to increase the reaction rates

Organic Synthesis
Stoichiometric reaction

[18F]fluoride ~ nM

Radiosynthesis
Non-Stoichiometric reaction

[precursor] ~ mM

3. High temperatures to increase the reaction rates
4. Optimization of reaction conditions (time, temperature, solvents, concentrations)
Only in Radiochemistry

1. Specific activity
2. Amount
3. Radiolysis
4. Radiochemical yield (RCY)

Definition RCY:
(1) Fluorination efficiency (radio-TLC or radio-HPLC) ** THIS IS NOT RCY!
(2) RCY yield = Percentage of (purified product/starting radioactivity)
   • Decay corrected (corrected to (EOB, EOS)
   • Non decay corrected
   • Which one is more useful?
   • Eg: decay corrected RCY = 20% with a synthesis time of 90 mins → Non decay corrected RCY ~ 11%

(3) For reaction optimization/research and development
   • Crude RCY % = [Total radioactivity collected x (conversion by radio-TLC)]/(total starting radioactivity)
   • ** important – losses as volatile side radioactive products; reoptimize conditions.
F18 LABELING METHOD
Fluorine Chemistry

Fluorinating agents

- MF
- HF
- Diethylaminosulfur Trifluoride (DAST)
- XeF₂
- Fluorobenzenesulfonimide (NFSI)
- Pyridine hydrofluoride
- Selectfluor

Table 4. Currently used methods of \(^{18}\)F production

<table>
<thead>
<tr>
<th>Nuclear reaction</th>
<th>Target material</th>
<th>Beam energy (MeV)</th>
<th>Product</th>
<th>Specific radioactivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>(^{20})Ne(d, (\alpha))(^{18})F</td>
<td>0.1 % F(_2)/Ne</td>
<td>18 or 23</td>
<td>([^{18}\text{F}]\text{F}_2)</td>
<td>30 – 370 MBq (\mu\text{mol}^{-1})</td>
</tr>
<tr>
<td>(^{20})Ne(d, (\alpha))(^{18})F</td>
<td>15% H(_2)/Ne</td>
<td>14</td>
<td>([^{18}\text{F}]\text{HF})</td>
<td>0.1 – 1 TBq (\mu\text{mol}^{-1})</td>
</tr>
<tr>
<td>(^{18})O(p, n)(^{18})F</td>
<td>H(_2)(^{18})O</td>
<td>15</td>
<td>([^{18}\text{F}]\text{F}^-)</td>
<td>0.01 – 7 TBq (\mu\text{mol}^{21})</td>
</tr>
</tbody>
</table>
[\textsuperscript{18}F]F-Labeling Methods

1. Direct labeling
   (i) Electrophilic Substitution
   \[
   \text{"}[\textsuperscript{18}F]F^+\text{"} \quad \text{Substrates-EDG} \rightarrow \text{[\textsuperscript{18}F]F-Substrates-EDG}
   \]

   (ii) Nucleophilic Substitution
   \[
   \text{"}[\textsuperscript{18}F]F^-\text{"} \quad \text{Substrates-EWG} \rightarrow \text{[\textsuperscript{18}F]F-Substrates-EWG}
   \]

2. Via built-up procedures
   \[
   \text{EWG-}^{\text{18}F}\text{-phenyl} \rightarrow \text{EDG-}^{\text{18}F}\text{-phenyl} \quad \text{OR} \quad \text{phenyl-}^{\text{18}F}
   \]

3. Via prosthetic groups
   \[
   \text{[\textsuperscript{18}F]F-Substrates-coupling\, group} + \text{Peptide or protein} \rightarrow \text{[\textsuperscript{18}F]F-Labelled\, peptide or protein}
   \]
ELECTROPHILIC FLUORINATION
Mechanism Electrophilic Fluorination

- Very reactive
- Mechanism (?)
- Highly exothermic
- Electron rich substrate

\[ \Delta H = -104 \text{kcal/mol} \]

F-F, FClO\textsubscript{3}, XeF\textsubscript{2}, CF\textsubscript{3}OF and CsSO\textsubscript{4}F

\[ \Delta H = -31 \text{kcal/mol} \]
Electrophilic Fluorination

1. Non selective (F₂, XeF₂, CH₃COOF source)

\[
\begin{align*}
\text{R} & \quad \text{F} - \text{F} \quad \text{R} \\
\text{F} & \quad \text{COOH} \\
\text{HO} & \quad \text{HO} \\
\text{12\%} & \\
\end{align*}
\]

2. Selective precursor (HgOCOCF₃ or Sn(CH₃)₃)

\[
\begin{align*}
\text{COOEt} & \quad \text{NH₂} \\
\text{Sn(CH₃)₃} & \quad [^{18}\text{F}]\text{F₂} \\
\text{HBr} & \quad \text{HO} \\
\text{HO} & \quad \text{21\%} \\
\end{align*}
\]
Electrophilic fluorination

→ U of Pennsylvania, the 1st $[^{18}\text{F}]$FDG PET imaging of the brain
1978: Preclinical studies of $[^{18}\text{F}]$FDG for myocardial metabolism
1980: Preclinical studies of $[^{18}\text{F}]$FDG for tumor metabolism

$[^{18}\text{F}]$FDG synthesis

18F-18F

(1) Separation

(2) Hydrolysis

8%; 2 hrs

Reaction of fluorine gas with 3,4,6-tri-O-acetylglucal

Poor stereoselectivity → 2-FDM (3:1 ratio)
Poor RCY; only 25% (max) is labeled
Low specific activity - $[^{18}\text{F}]$F2 gas doped with F2
N-[^18\text{F}]F Radiofluorination

Electrophilic fluorination agent
Reactive, but more selective
Easier to handle – solid, liquid
Not as corrosive as F\textsubscript{2} gas.

Gouverneur, V. et al, Angew Chemie Int Ed. 2012, 51, 2-14
[\textsuperscript{18}F]Selectfluor bis(triflate)

Isotopic exchange with BF\textsubscript{4}⁻

Electrical discharge methodology: Higher SA of [\textsuperscript{18}F]F\textsubscript{2}

\[ \text{[\textsuperscript{18}F]F}^- \text{(aq)} \xrightarrow{\text{K}_2\text{CO}_3, \text{CH}_3\text{CN}} \text{Kryptofix-222} \xrightarrow{\text{CH}_3\text{I, CH}_3\text{CN}} [\textsuperscript{18}F]\text{CH}_3\text{F} \xrightarrow{\text{F}_2 \text{electric discharge}} [\textsuperscript{18}F]F\textsubscript{2} \]

Protocol II
- Target irradiation: 15 min
- Beam current: 40 μA
- F\textsubscript{2} carrier added: 1200 nmol

Protocol III
- Target irradiation: 60 min
- Beam current: 40 μA
- F\textsubscript{2} carrier added: 600 nmol

Synthesis of [\textsuperscript{18}F]fluoroveratrole

\[ \text{MeO} \begin{array}{c} \text{SnMe}_3 \end{array} \xrightarrow{\text{\textsuperscript{18}F} + 2 \text{OTf}^-} \text{MeO} \begin{array}{c} \text{MeO} \end{array} \xrightarrow{2 \text{equiv AgOTf}} \text{MeO} \begin{array}{c} \text{MeO} \end{array} \]

18% RCY

Gouverneur, V. et al. Angew Chem Int Ed. 2010, 49, 6821
**Summary Electrophilic Fluorination**

1. $[^{18}\text{F}]\text{F}_2$ gas:
   i. Gaseous, difficult to handle
   ii. Low specific activity, doped with $\text{F}_2$ gas
   iii. Need dedicated cyclotron and radiochemistry lab
2. Extremely reactive.
3. Aromatic substrates (electron rich substrates)
4. New, milder, and more selective N-$[^{18}\text{F}]$ fluorination agent
5. Improve specific activity of $[^{18}\text{F}]\text{F}_2$ by gas discharge method (SA)
NUCLEOPHILIC FLUORINATION
PET Probes from Nucleophilic Fluorination

Aliphatic

FDG

Aromatic

FMISO

Fallypride

FLT

FAC family

[\text{\text{[^{18}F]Altanserine}}]

FDDNP

FDOPA

SFB
[18F]F Nucleophilic Sources

Alkaline metal fluoride
(1) MF (M: K, Cs, Ag)

Common alkali metal fluorides

Increasing ionic strength
LiF < NaF < KF < CsF

Increasing nucleophilicity
Increasing solubility

Metal cations that render nucleophilicity
Al, In, Ni, Cu, Zn, Ca, Na

(2) HF

[18F]fluoride ion/[18O]H₂O

K₂₂₂₂/ K₂CO₃
or
TBAOH/TBAHCO₃

KF/Cryptand

Tetraalkylammonium fluoride

(1) Role of PTC?
(2) Role of base?
Phase Transfer Catalyst (PTC)

Role of Cryptand and tetraalkylammonium salt?

C$_8$H$_{17}$Cl $\xrightarrow{\text{Bu}_3\text{P}^+\text{(CH}_2\text{)}_{15}\text{CH}_3\text{Br}^- 1 \ (1.5 \text{ mol} \%)}$ C$_8$H$_{17}$CN

NaCN, H$_2$O, 105 °C, 1.8 h

94% (n.r. without 1)

R-X $\rightarrow$ R-F

Organic phase

Aqueous phase

Starks, C.M. J. Am. Chem. Soc. 1971, 93, 195
Which PTC or Base?

1. Solubility, (2) Stability, (4) Hygroscopic (likes water)

\[ [^{18}\text{F}]\text{fluoride ion}/[^{18}\text{O}]\text{H}_2\text{O} \]

- Kryptofix (K\text{2.2.2})
- K\text{2CO}_3
- Tetrabutylammonium carbonate or bicarbonate
- Cesium carbonate or bicarbonate

\[ \text{Tetraalkylammonium fluoride} \]
\[ R = \text{methyl, ethyl, butyl} \]

\[ \text{Thermal decomposition of TBAF} \]
Role of Base

Role of base

(1) Prevent formation of H[18F]F → volatile, lost radioactivity
(2) Counter ion for [18F]fluoride ion complexation– phase transfer
(3) Side reactions and decomposition of PTC
(4) Base hydrolysis of precursor (base sensitive)
(5) Base catalyzed side reactions

Molar ratio Kryptofix >base (K₂CO₃ and KHCO₃)- decomposition, and 2 K⁺

Choice of base

<table>
<thead>
<tr>
<th>Base</th>
<th>pKb</th>
</tr>
</thead>
<tbody>
<tr>
<td>K₂CO₃</td>
<td>3.8</td>
</tr>
<tr>
<td>KHCO₃</td>
<td>7.6</td>
</tr>
<tr>
<td>K⁺ oxalate</td>
<td>10</td>
</tr>
<tr>
<td>H₂O</td>
<td>14</td>
</tr>
</tbody>
</table>

Kryptofix/K/oxalate system **ALONE**- resulted in 30% loss of radioactivity as H[18F]F
Add 30-50 ug of K₂CO₃ to prevent radioactivity losses during drying
Literature example, the role of base

Radiochemical yield ~ 1%

Direct nucleophilic fluorination of butyrophenone neuroleptics

Typical workflow of F18 ion radiochemistry

1. [$^{18}$F]-Fluoride trapping on anion exchange resin

2. [$^{18}$F]-Fluoride released with phase transfer catalyst

3. Azeotropic distillation to form "naked" [$^{18}$F]-fluoride

4. Addition of precursor and radiolabeling reaction
Phase Transfer Catalysis and azeotropic distillation in Radiochemistry?
Nucleophilic Aliphatic Substitution

(1) $S_N2$ substitution mechanism $\rightarrow$ Radiolabelled product

Precursor

Product
Stereochemical Consequences

**Kinetic differences of cell uptake**

Probe different biological functions

34, \( \beta \)-glucose

35, \( \beta \)-mannose

36, 2-deoxy-\( \beta \)-glucose
2-deoxy-\( \beta \)-mannose

2-[\( ^{18} \text{F} \)]fluoro-2-deoxy-\( \beta \)-glucose
\( (23, \text{[}^{18} \text{F}]\text{FDG}) \)

2-[\( ^{18} \text{F} \)]fluoro-2-deoxy-\( \beta \)-mannose
\( (37, \text{[}^{18} \text{F}]\text{FDM}) \)

38, \( \text{[}^{18} \text{F} \text{]} \text{FMAU} \)

39, FTdR

40, \( \text{[}^{18} \text{F} \text{]} \text{FAU} \)

10, \( \text{[}^{18} \text{F} \text{]} \text{FUdR} \)
Nucleophilic Aliphatic Substitution

3. Solvents (Dielectric constant? acidic H? H-bonding?)

Polar Protic
- ethanol
- water
- propan-2-ol
- acetic acid

Polar aprotic
- acetonitrile
- Dimethylsulfoxide
- \(N,N\)-dimethylformamide
- tetrahydrofuran
- \(N,N\)-dimethylacetamide
- Acetone

Non-polar
- hexane
- toluene
- chloroform
- ethoxyethane

Choice: Solubility, boiling point, dielectric constant
Nucleophilic Aliphatic Substitution

2. Side reactions

(1) Undesirable reaction: E2 elimination mechanism → Side product

Antiperiplanar

\[
\begin{align*}
\text{R}_1 & \quad \text{H} \\
\text{R}_2 & \quad \text{R}_3 \\
& \quad \text{LG} \\
\text{R}_4 & \quad \text{H} \\
\end{align*}
\]

or other base (K\(_2\)CO\(_3\), Kryptofix, KHCO\(_3\), TBAHCO\(_3\)...etc)

i. Optimal ratio of phase transfer catalyst:base:precursor

ii. Choice of base eg: potassium oxalate

iii. Higher temperature → higher elimination byproducts

iv. Better leaving group are more sensitive to elimination side reaction, especially with increasing temperatures

v. Elimination rate in 2\(^\circ\) LG >> 1\(^\circ\) LG
F18-F19 exchange

Side reaction

Lowers RCY. Importance of leaving group. Less reactive LG (mesylate) $\rightarrow$ 0 yield

Roeda D. et al., Current Radiopharm. 2010, 3, 81-108
Side reaction with leaving group

[Chemical structures and reactions shown]
Nucleophilic Aliphatic Substitution

Example: Side reaction in $[^{18}\text{F}]\text{FLT}$

Roeda D. et al., Current Radiopharm. 2010, 3, 81-108
Nucleophilic Aliphatic Substitution

4. Precursor design: Leaving group

- Triflate (Tf) \( K_{rel} 1.4 \times 10^{8} \)
- Nosylate (Ns) \( K_{rel} 4.4 \times 10^{5} \)
- Tosylate (Ts) \( K_{rel} 3.7 \times 10^{4} \)
- Mesylate (Ms) \( K_{rel} 3.0 \times 10^{4} \)

I\(^-\) 91
Br\(^-\) 14
CF\(_3\)CO\(_2\)\(^-\) 2.1
Cl\(^-\) 1
F\(^-\) 9 \times 10^{-6}
p-nitrobenzoate 5.5 \times 10^{-6}
CH\(_3\)CO\(_2\)\(^-\) 1.4 \times 10^{-6}
Literature Survey: FLT synthesis

Leaving group, $R =$

Nosylate (Ns)

Tosylate (Ts)

Mesylate (Ms)

Fluorination yield

19.8

7.8

5.3

The n.c.a. $[^{18}\text{F}]$FDG synthesis

Efficient Stereospecific Synthesis of No-Carrier-Added 2-$[^{18}\text{F}]$-Fluoro-2-Deoxy-D-Glucose Using Aminopolyether Supported Nucleophilic Substitution

K. Hamacher, H. H. Coenen, and G. Stöcklin

_Institut für Chemie 1 (Nuklearchemie), Kernforschungsanlage Jülich GmbH, Jülich, FRG_

An aminopolyether mediated synthesis of fluorine-18 ($^{18}$F) 2-fluoro-2-deoxy-D-glucose (FDG) has been developed. The nucleophilic fluorination with accelerator-produced $[^{18}\text{F}]$fluoride works at the no-carrier-added level and gives epimerically pure 2-$^{18}$FDG with an uncorrected radiochemical yield of a maximum 50% in a synthesis time of ~ 50 min from EOB.


![Chemical reaction diagram](image)
NUCLEOPHILIC AROMATIC SUBSTITUTION
Precursor Requirements

(a) Activating effect: EWG: $3\text{-NO}_2 < 4\text{-CH}_3\text{CO} < 4\text{-CN} < 4\text{-NO}_2$

Effect of activating (X) and leaving groups (Y) on nucleophilic aromatic fluorination

<table>
<thead>
<tr>
<th>X</th>
<th>Y</th>
<th>$k_{rel}$ (80°C)</th>
<th>$k_{rel}$ (120°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\text{NO}_2$</td>
<td>NMe$_3$ClO$_4$</td>
<td>400</td>
<td>30000</td>
</tr>
<tr>
<td>$\text{NO}_2$</td>
<td>$\text{NO}_2$</td>
<td>40</td>
<td>420</td>
</tr>
<tr>
<td>$\text{CN}$</td>
<td>NMe$_3$ClO$_4$</td>
<td>16</td>
<td>100</td>
</tr>
<tr>
<td>$\text{COMe}$</td>
<td>NMe$_3$ClO$_4$</td>
<td>8</td>
<td>33</td>
</tr>
<tr>
<td>$\text{CN}$</td>
<td>$\text{NO}_2$</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Meisenheimer complex; delocalization electron onto EWG

(b) Leaving group: $I < \text{Br} < \text{Cl} < F < \text{NO}_2 < \text{N}^+\text{Me}_3$

(C-F bond making is RLS. Polar effects favors addition step)

(c) Solvent effect: DMSO > DMAc (N,N,-dimethylacetamide) > sulfolane >> acetonitrile
Side Reactions in $S_{\text{NAr}}$

**Side reactions**

Fluorobenzaldehyde $\rightarrow$ site specific peptide (Prosthetic group) conjugation; away from the binding sites

Amino-oxy functionalized peptide

Trimethylammonium triflate LG
Most reactive
Easy to separate (charged)

Nucleophilic Aromatic Substitution of substrate without EWG?

Balz-Shciemann reaction

* High temperature, harsh reagent, corrosive, explosive
Low yield
[18F]F-Nucleophilic Heteroaromatic Substitution

LUMO of pyridine at ortho and para position lower than benzene
No need activating group


Table 2. Temperature dependence of the radiochemical yields of 18F-(IV)

<table>
<thead>
<tr>
<th>Reaction temp. (°C)</th>
<th>Radiochemical yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>room temp</td>
<td>55-66</td>
</tr>
<tr>
<td>50-60</td>
<td>68-75</td>
</tr>
<tr>
<td>80-90</td>
<td>0.4-1.4</td>
</tr>
</tbody>
</table>

1 Yields from the reaction for 20 min of 15 µmol of (II) with the solubilized K18F (1.2 µmol) in DMF-CE solution before addition of (II).

Gouverneur, V. et al. Angew Chem Int Ed. 2012, 51, 2-14
Summary Nucleophilic Substitution

1. Preferred method
2. High specific activity of $[^{18}\text{F}]\text{F}^-$ vs $[^{18}\text{F}]\text{F}_2$ (1740 Ci/umole vs 0.1 Ci/umole)
3. Easy to handle (liquid vs gas)
4. $[^{18}\text{F}]\text{F}^-$ Can be transported and distributed to nearby imaging clinicic (Decentralized model of PET probe production)
5. $S_N^2$, leaving group, solvent, phase transfer catalyst and base
6. Side reactions, optimization
7. Activated substrate and good leaving group for $S_{\text{NAr}}$
INDIRECT F18-LABELING
Commonly used [18F]Prosthetic groups

Chemoselectivity
Site-specific conjugation

CHALLENGES IN F18 RADIOCHEMISTRY
Radiochemistry Requirements

- High-cost
- Low-throughput
- Bulky
- Complicated
- Need skillful personnel
- Limited flexibility

- Hot cells. Pb shielding
- Automation
- Robotic arms
- Expensive, bulky synthesizer
  1-synthesizer, 1-probe workflow
- Dedicated radiochemistry lab

Slide adapted from Clifton Shen M248
A Typical Workflow of PET imaging

Centralized PET probes production

- PET radiopharmacies
- PET/CT imaging clinics

Produce

- \([^{18}\text{F}]\text{fluoride}\)
- Tracer

Dispense doses

- \([^{18}\text{F}]\text{FDG}\)

Clinical PET imaging center

- \([^{18}\text{F}]\text{FDG}\)

Preclinical PET research center

- \([^{18}\text{F}]\text{FDG}\)
DeCentralized Production of PET Probes

Produce \(^{18}\text{F}\)fluoride
Dispense doses

\(^{18}\text{F}\)F\(^{-}\) ion

Clinical PET imaging center

Produce tracer
- \(^{18}\text{F}\)FDG
- \(^{18}\text{F}\)FLT
- \(^{18}\text{F}\)FDOPA

Preclinical PET research center

Produce tracer
- \(^{18}\text{F}\)FDG
- \(^{18}\text{F}\)FAC
- \(^{18}\text{F}\)SFB-Db

New technologies, simplified chemistry, higher kinetics, higher reaction selectivity
References


Roeda D. et al., Current Radiopharm. 2010, 3, 81-108

M.-C. Lasne et al. Topics in Current Chemistry. 2002. 22


Gouverneur, V. et al, Angew Chemie Int Ed. 2012, 51, 2-14