VU university medical center

Radiochemistry of fluorine-18 and iodine-123/124

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General aspects

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Cyclotron PET nuclides

Nuclide	Half life	E-max	Manufacture
Carbon-11	20 min	960 keV	$^{14}N(p,\alpha)^{11}C$
Nitrogen-13	10 min	1198 keV	$^{16}O(p,\alpha)^{13}N$
Oxygen-15	2 min	1735 keV	$^{14}N(d,n)^{15}O$
Fluor-18	110 min	634 keV	$^{18}O(p,n)^{18}F$
Zirconium-89	78.4 hr	909 keV	$^{89}Y(p,n)^{89}Zr$
Copper-64	12.7 hr	653 keV	$^{64}Ni(p,n)^{64}Cu$
Iodine-124	100 hr	1535, 2138 keV	$^{124}Te(p,n)^{124}I$

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Short half lives

- Create complicated logistics: chemistry, QC and transport
- On-site nuclide production required: cyclotrons
- Require fast methods: chemistry, purification and formulation
- Require high starting amounts of radioactivity: >30 GBq
- Cause strong safety regulations: radiation safety officers
- Operation in hotcels is a must: automation

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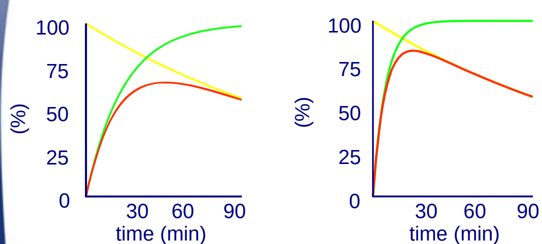
Reaction speed and yield



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Fluor-18 chemistry

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Why fluor-18

It has an good half life: not too short, not too long

Low positron energy: enables high resolution scanning

Can be produced in high amount as [^{18}F]fluoride

Can be obtained easily in high specific activity

Drawbacks:

Difficult chemistry

Limited application in bio-active compounds

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Transfer of [^{18}F]Fluoride

Transfer from cyclotron to hotcel at EOB

- the shorter the route the better
- via He overpressure or vacuum
- tubes of polypropylene, PTFE, TEFZEL, PEEK
- beware of 19F dilution from materials
- radiation damage: PEEK most suitable
- stainless steel: possible, not often applied.
- filter at end of line to catch particles
- store lines dry or wet?
- pre-flush of lines required?

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reactions

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^{18}F substitution reactions

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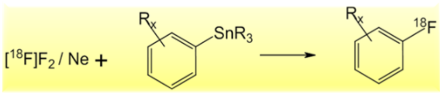
Nucleophilic:

$$^{18}F^- + R{-}L \xrightarrow[\text{solvent, heat, 5 - 30 min}]{\text{PTC}} R{-}^{18}F$$

Electrophilic:



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Most important: [^{18}F]FDG

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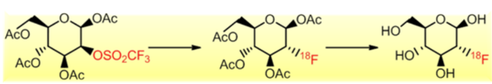

[^{18}F]FDG

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[^{18}F]FDG: distribution possible

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^{18}F nucleophilic substitution

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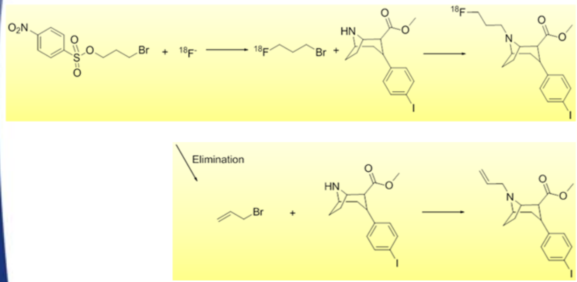
Aliphatic, primary



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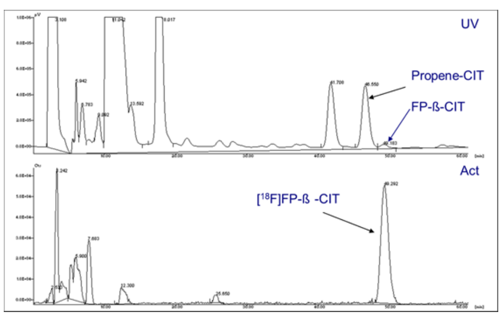

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^{18}F nucleophilic substitution

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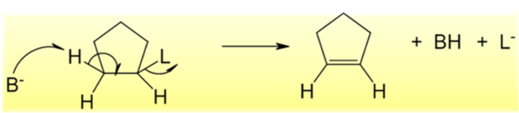
Aliphatic : secondary C atoms

Competing base catalyzed elimination reaction, high chance



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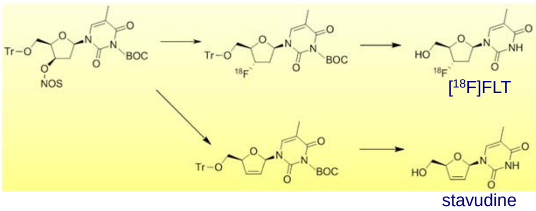
[18F]FLT synthesis



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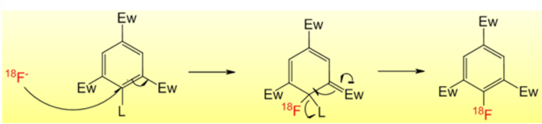
18F nucleophilic substitution

Aromatic :



Leaving group: Nitro, trimethylammonium
Ew : nitro, amide, nitril, aldehyde
(one at ortho or para position)

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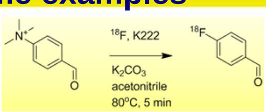
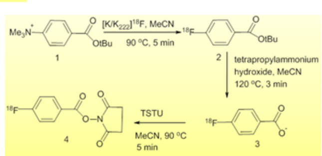
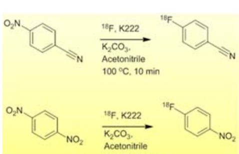
Some examples







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^{18}F Work up

Extract ^{18}F from $H_2{}^{18}O$

Anion exchange : Biorad AG1-X8 in CO_3^{2-} form

More practical Seppak QMA or MN PS-HCO_3^-

Elute ^{18}F from ion exchange column with CO_3^{2-} solution in water or mixture of CH_3CN/water with PTC and K_2CO_3

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^{18}F Work up

No fluorination in presence of water

Azeotropic distillation with Acetonitril

“naked” fluoride impossible in organic solvent :
Phase transfer catalyst, PTC, required

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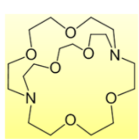
Typical reaction conditions

PTC : crown-ether or Ammoniumsalt

Crownether: Counter ion needed, K^+

Kryptofix[2.2.2] optimal :



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Typical reaction conditions

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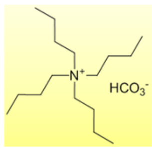
(n-Butyl)$_4$NHCO$_3$

made from (n-butyl)$_4$NOH and CO_2

Advantage : pH = 6-7



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Typical reaction conditions

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Solvents : aprotic and dry

Acetonitril, THF, DMSO, dioxane, (dichloro)benzene (DMF)

Temperatures : 80-180 °C

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[^{18}F]Fluorine specific activity

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Addition of F_2 is essential,
but decreases specific radioactivity

Typically : less then 1 GBq/μmol

Gives problems for receptor studies,
however for F-DOPA no problem

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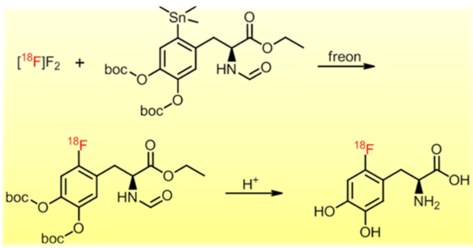
Electrophilic substitution

[^{18}F]F-DOPA



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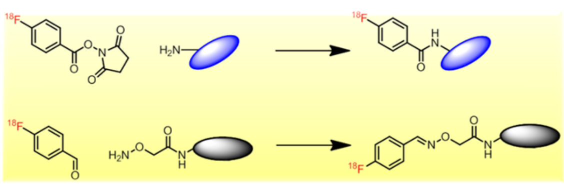
Peptide labeling with Fluorine-18

Many options,

[^{18}F]SFB mostly applied, several other alternatives possible.



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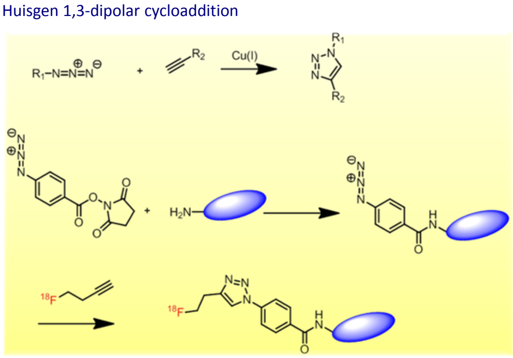
Click chemistry

Huisgen 1,3-dipolar cycloaddition



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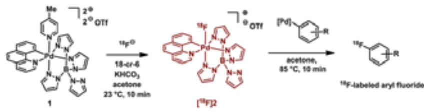
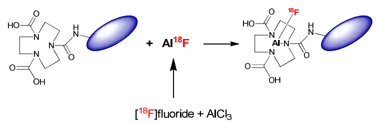
New developments

Recently: fluor-18 as fluoride, react with Pd complex after which fluor-18 reacts as electrophile



$[^{18}F]AlF$, ^{18}F labeled aluminum fluoride and NOTA for peptide labeling



Iodine-123 chemistry

Why Iodine

1. It has a lot of interesting nuclides

Radionuclide	$t_{1/2}$	Mode of decay (%)	E_{β}(max) keV	Main γ-rays [keV] (%)	Application
^{120}I	1.4 h	β^+ (56) EC (44)	4000	601 (58.0) 1523 (11.2)	PET
^{122}I	3.6 min	β^+ (77) EC (23)	3120	564 (18.0)	PET
^{123}I	13.2 h	EC (100)		159 (83.0)	SPECT
^{124}I	4.18 d	β^+ (22) EC (78)	2140	603 (61.0) 723 (10.0) 1691 (10.4)	PET; Therapy control
^{125}I	59.4 d	EC (100)	Auger electrons	35.5 (6.7)	RIA; Auger electron therapy
^{131}I	8.02 d	β^- (100)	606	284 (6.1) 364 (81.2) 637 (7.3)	Therapy

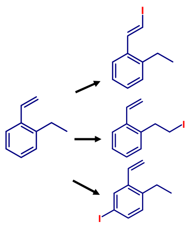
2. Radioiodide is no carrier added → Specific activity ≈ 1 TBq/μmol

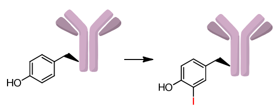
Iodine chemistry

Radioiodide is normally supplied in 0.01 N NaOH

- Under acidic conditions
- $2HI \rightarrow H_2 + I_2$
- Consequence: iodide is more easily oxidized to IO_x

Substitution reactions:





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Stability of C-I bond

R–I	$D(R^\bullet/I^\bullet)$kJ.mol^{-1}	$D(R^+/I^-)$ kJ.mol^{-1}
CH_3–I	234.72	889.52
C_2H_5–I	222.59	722.58
$(CH_3)_2CH$–I	222.17	638.48
$(CH_3)_3C$–I	210.87	562.33
CH_2=CHC H_2–I	184.51	671.95
HC≡CCH_2–I	206.27	748.10
$C_6H_5CH_2$–I	167.36	566.93
CH_2=CH–I	263.59	826.34
C_6H_5–I	269.45	790.36

Iodine substitute on SP2 Carbon is most stable.
Important for chemical stability (avoid de-iodination) and metabolic stability

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Influence of Iodine introduction

	H	F	Cl	Br	I	CH_3	CF_3
van der Waals radius (Å)	1.20	1.35	1.80	1.95	2.15	2.00	
Electronegativity	2.28	3.95	3.03	2.80	2.47	2.30	3.35

Introduction of an iodine atom also increases the lipophilicity

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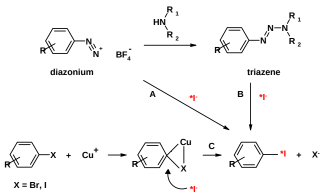
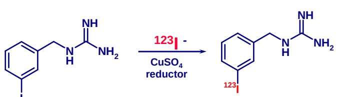
Nucleophilic substitution



Cu(I)-assisted labeling is the method of choice!!

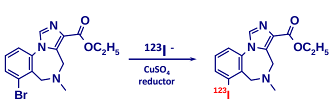
Nucleophilic substitution example



MIBG
(tumor detection)

Advantage: no HPLC separation necessary
Disadvantage: low specific activity (not useful for receptors)

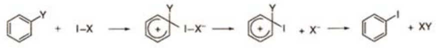
Nucleophilic substitution example



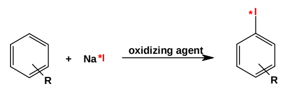
iomazenil

Advantage: high specific activity
Disadvantage: difficult purification by HPLC

Electrophilic substitution



Intermediate is stabilized by electron donating groups



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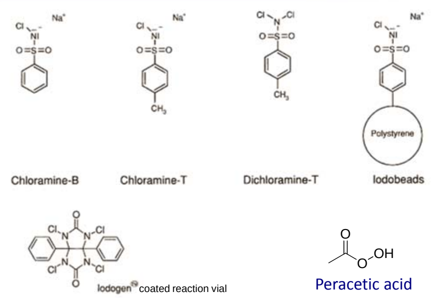
Oxydizing agents



Peracetic acid

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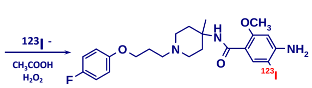
Electrophilic substitution example



only possible on electron rich aromatic compounds
chloramine T also gives corresponding chloro-compound

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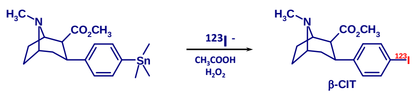
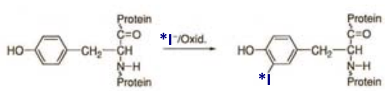
Electrophilic substitution example

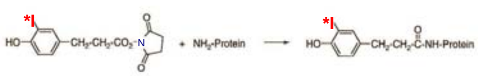


Instead of $Sn(Me)_3$ also possible with:
$Sn(Bu)_3$, $Tl(OCOCF_3)_2$, HgCl, $Si(Me)_3$, etc.

Electrophilic substitution example



Besides tyrosine also labelling of histidine residues possible



Bolton-Hunter reagent

Further reading

Molecular Imaging: radiopharmaceuticals for PET and SPECT
by Shankar Vallabhajosula

Chapter 10