



Chemistry and Radiochemistry: The Basics

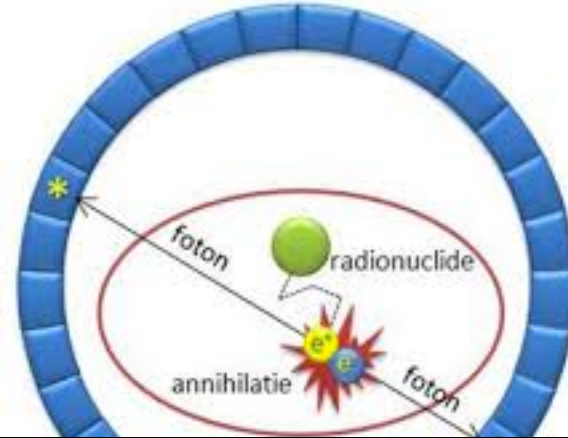
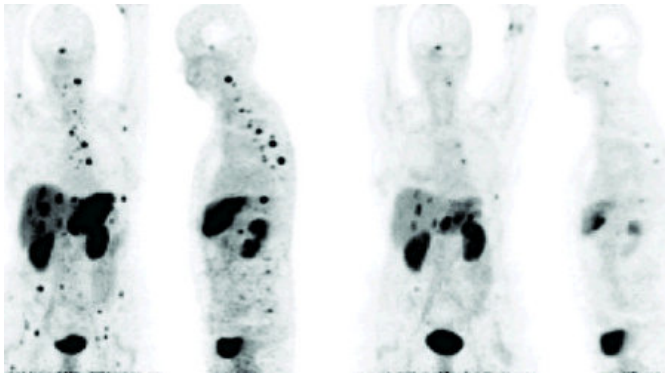
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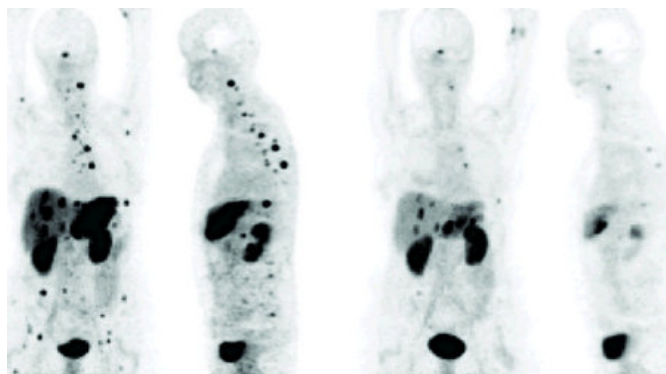
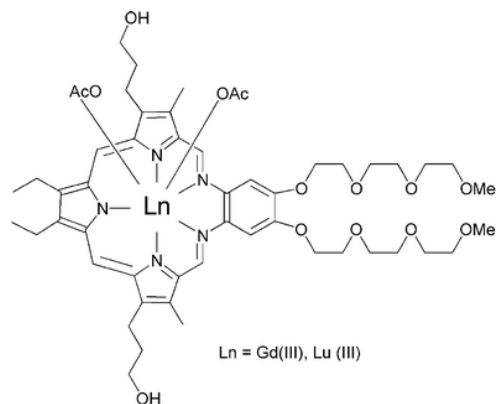
- Introduction:
 - Radiopharmaceuticals.
 - PET Tracers
 - Production
- Chemistry 101: The building blocks
 - Atomic structure
 - Essentials of Organic chemistry
 - Chelation Chemistry
- Radiochemistry:
 - Definitions
 - Specific Activity
 - Practical Radiochemistry

PET and Radiopharmaceuticals



Radiopharmaceuticals

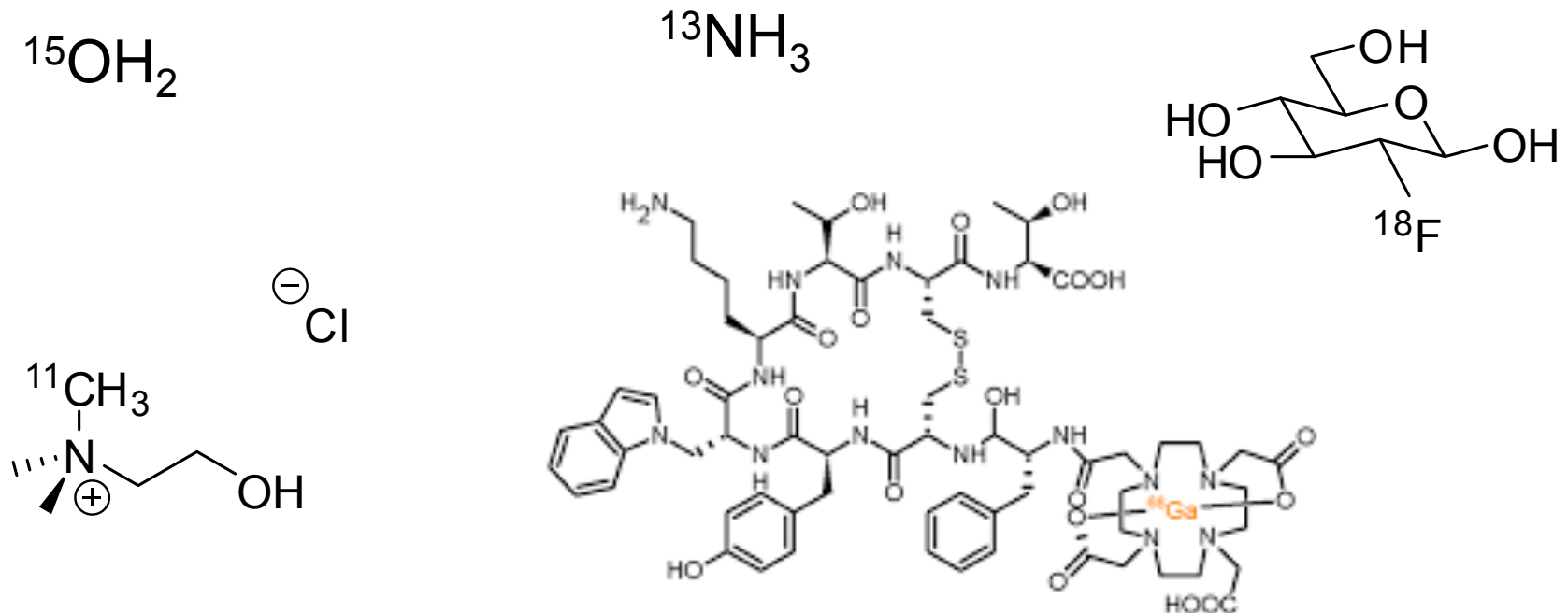
Radiopharmaceuticals are radioactive substances used to **diagnose**, **treat** or prevent **disease**. These compounds are made up of two components: a radioactive isotope that can be injected 'safely' into the body, and (typically) a carrier molecule which delivers the isotope to the area to be treated or examined.



Treatment with Bi-213

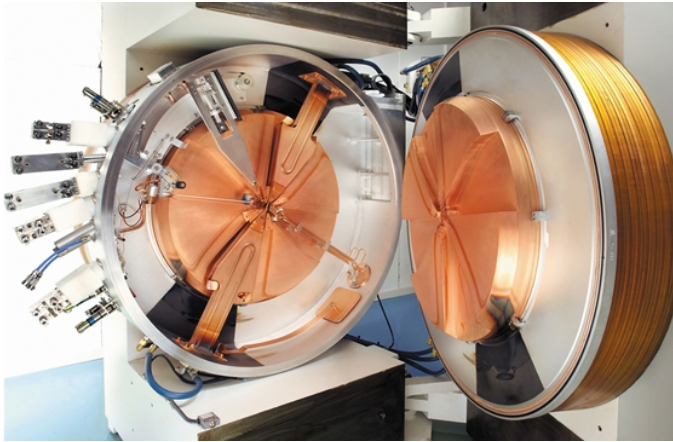


PET uses radioactively-labelled small molecules that are involved in biochemical processes, to elucidate/image tissue perfusion, metabolism, drug/receptor interactions, and gene expression *in vivo*.





Radionuclide Production



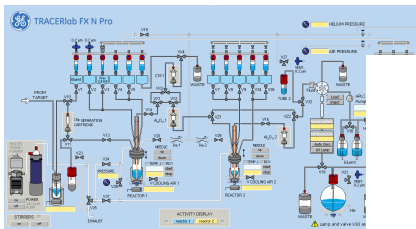
Cyclotron



Generator



Radionuclide isolation and preparation.



Computer controlled
Synthesis module

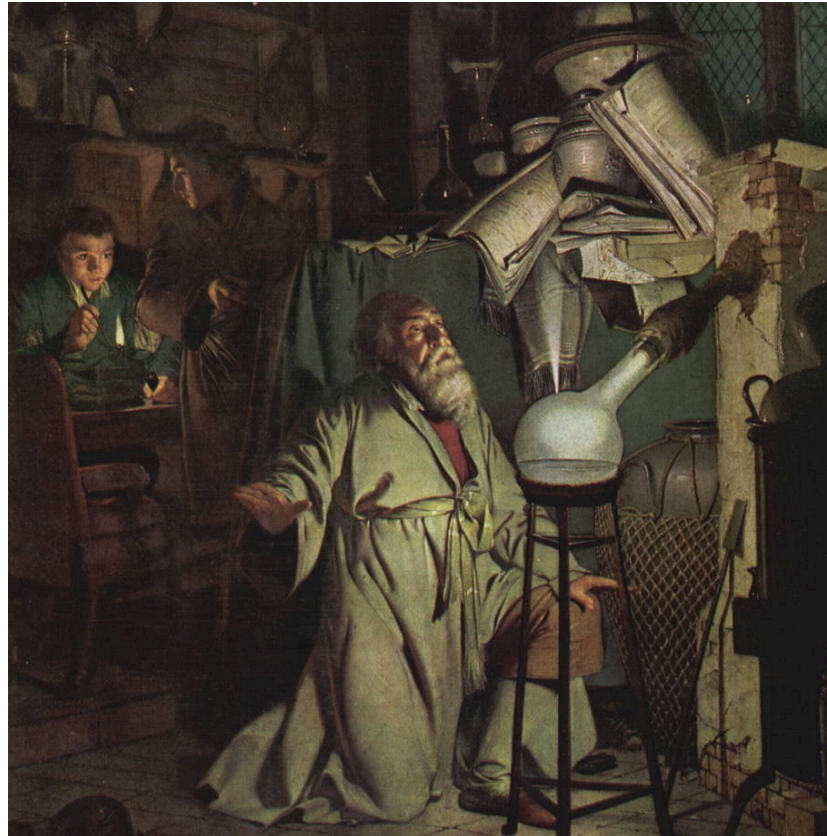


- Purification
- Dispensing
- Quality Control (QC)
- Lots of Paper Work!
- Delivery
- Patient!!





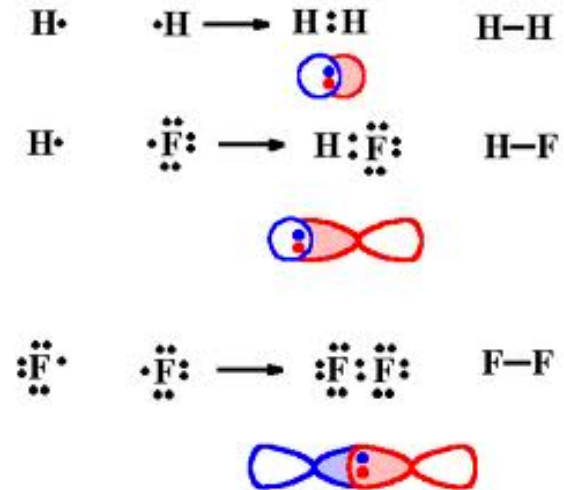
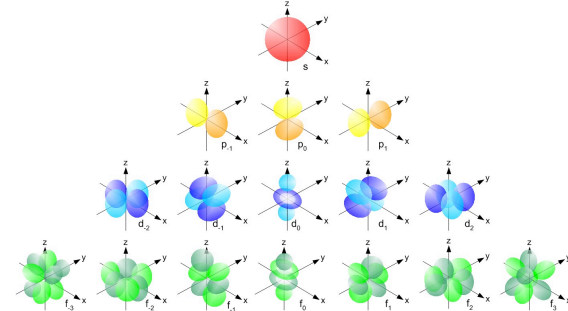
“**Chemistry** is the science of atomic matter, its properties, structure, composition and its changes during interactions and chemical reactions.”



Alchemy!!



- Atomic Structure
 - Nucleus (generally not directly involved in chemical transformations)
 - Electrons.
- Electrons
 - Orbit the nucleus in “clouds” known as orbitals.
 - Orbitals are: “quantum mechanically derived 3D probability distribution of where the electron has the highest chance of being found.”
 - The 4 main types are S,P,D and F orbitals.
 - The outer most electrons are called valence electrons.
- Valence electrons.
 - Can be shared between atoms to form “Bonds.”
 - This happens through a mixing of valence orbitals.
 - Bonds Always consist of **Two** shared electrons.
 - This is called “**covalent bonding.**”



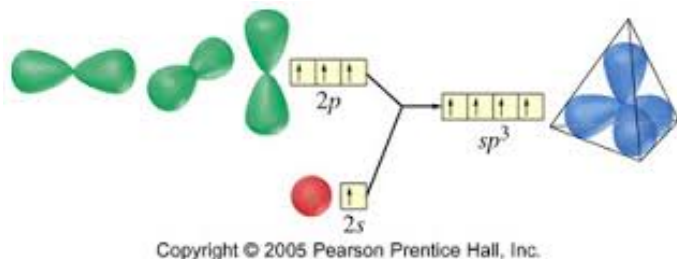


- A chemical bond describes the probability of the presence of two electrons within a certain space between two atoms.

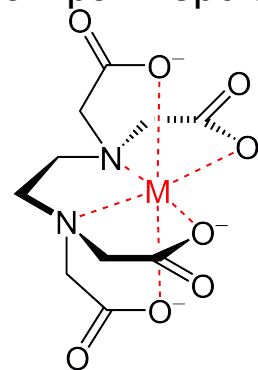
The Golden Rule: Most atoms in Org.Chem (C,N,O,F) want a FULL valence shell of $8e^-$. stable Electrons ALWAYS exist in pairs.

Therefore: These atoms can NEVER form more than 4 Bonds.
This is called the "**Octet Rule.**"

- By interaction of a nucleophile with an electrophile a new chemical bond will be created accompanied by a simultaneous break of an old bond.
- There are different theories which are applied to describe atomic or Molecular Orbitals, such as **Hybridization**, **VSEPR** (valence shell electron pair repulsion) or the **ligand field theorem**.



VSEPR Theory



Ligand Field Theorem



1. Nucleophiles:

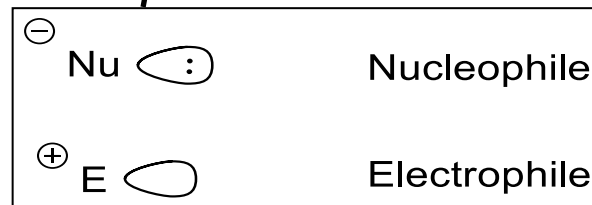
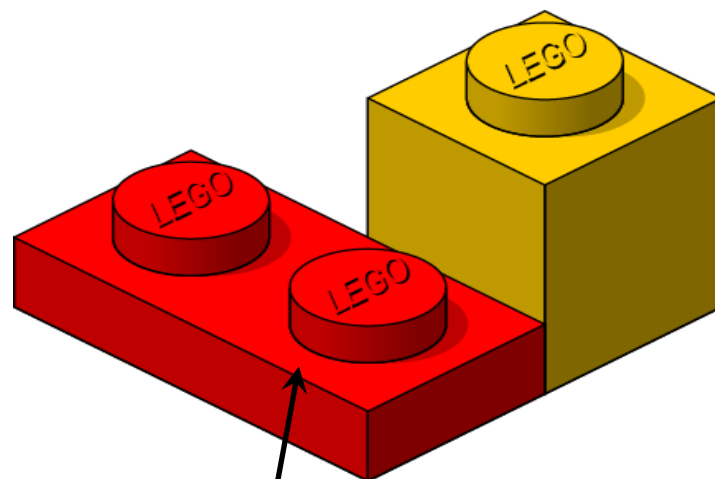
Electron rich. Looking for positive charge or partner to share electrons with

2. Electrophiles:

Electron deficient. Looking for electron rich, negatively charged partner.

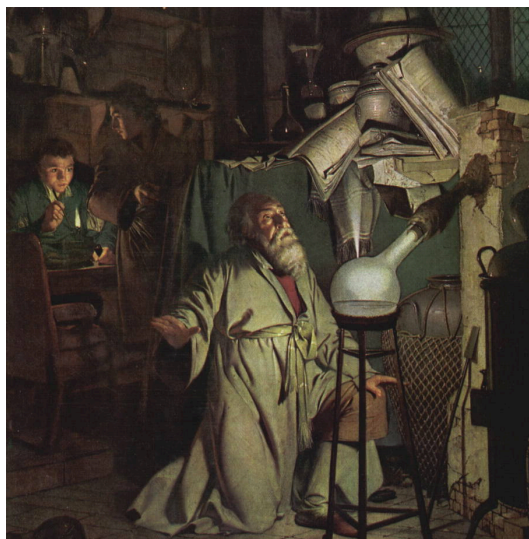
3. Leaving Group:

The group that is replaced.
Pretty stable on its own.





“**Chemistry** is the science of atomic matter, its properties, structure, composition and its changes during interactions and chemical reactions.”



Organic Chemistry is the study of compounds containing Carbon **and** Hydrogen and how they change and can be changed

“Organic chemistry is the study of carbon compounds

Biochemistry is the study of carbon compounds that crawl.” – Mike Adams



Organic Chemistry is principally divided in **four** classes:

1. Polar (or ionic) reactions:

Classical chemical reactions, chelating reactions.
e.g. methylation or fluorination reaction.

2. Pericyclic reactions:

Often thermal or (UV) light triggered.
electrons move together in cyclic system.
rearrangement reactions, “Click” chemistry.

3. Radical reaction:

Involve movements of single electrons.
Synthesis of Polymers (PE, PP, PET), Combustion of organic compounds.

4. Reduction / Oxidation reactions (redox)

Involve a transfer of electrons.
Production of iron from iron ore or production of aluminium.

Periodic Table

1A	2A	3B	4B	5B	6B	7B	8B	8B	8B	1B	2B	3A	4A	5A	6A	7A	8A
H																	He
Li	Be											B	C	N	O	F	Ne
Na	Mg											Al	Si	P	S	Cl	Ar
K	Ca	Sc	Ti	V	Cr	Mn	Fe	Co	Ni	Cu	Zn	Ga	Ge	As	Se	Br	Kr
Rb	Sr	Y	Zr	Nb	Mo	Tc	Ru	Rh	Pd	Ag	Cd	In	Sn	Sb	Te	I	Xe
Cs	Ba	57-71	Hf	Ta	W	Re	Os	Ir	Pt	Au	Hg	Tl	Pb	Bi	Po	At	Rn
Fr	Ra	89-103	Rf	Db	Sg	Bh	Hs	Mt	Ds	Rg	Cn	Uut	Fl	Uup	Lv	Uus	Uuo
Lanthanoids(57-71)																	
		La	Ce	Pr	Nd	Pm	Sm	Eu	Gd	Tb	Dy	Ho	Er	Tm	Yb	Lu	

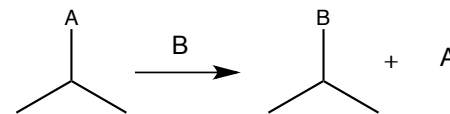


Polar reactions can be again divided into:

1. Nucleophilic/electrophilic **substitutions**:

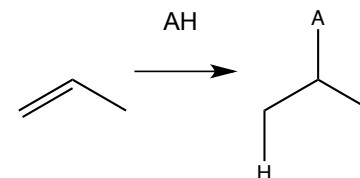
Switching one group for another.

^{11}C -methylations, ^{18}F -fluorinations, iodinations.



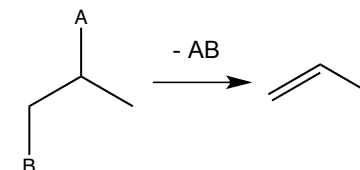
2. Nucleophilic/electrophilic **additions**:

Adding a new group to either a double or triple bond.



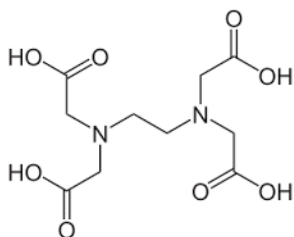
3. **Elimination** reactions:

Removing a group to form a double or triple bond.

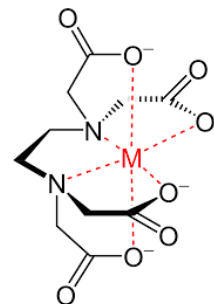


4. Chelating reactions / Complex chemistry / Coordination Chemistry:

Trapping a large metal ion in an organic “cage” known as a chelator to form a “Complex.”



+ Metal =



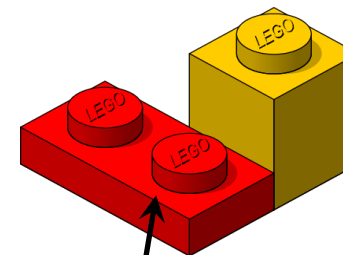
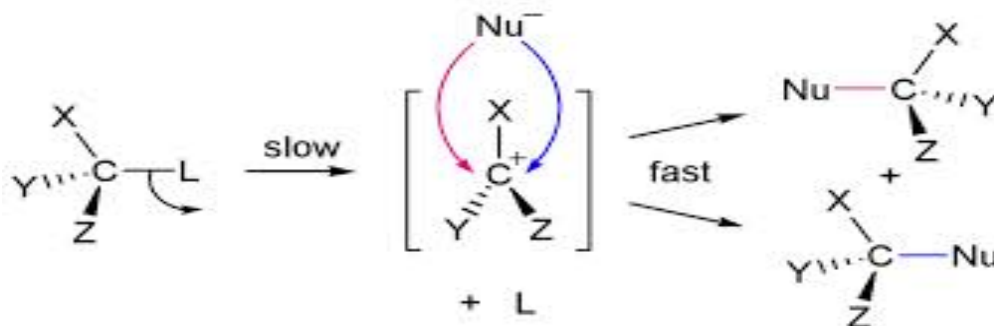


- Substitution reactions (The players):

- Electrophile
- Nucleophile.
- Leaving group.

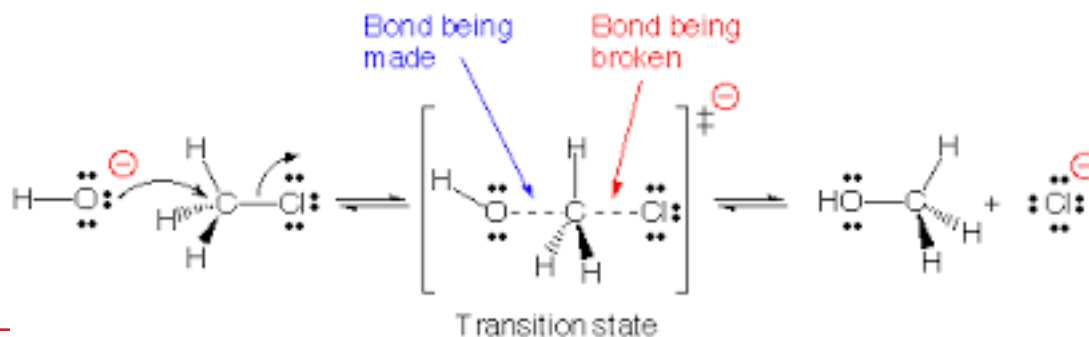
- Substitution reactions (The Mechanism):

- Three Types of substitution. S_N1 , S_N2 , S_NAr .
- S_N1 :



$\ominus$ Nu	Nucleophile
$\oplus$ E	Electrophile

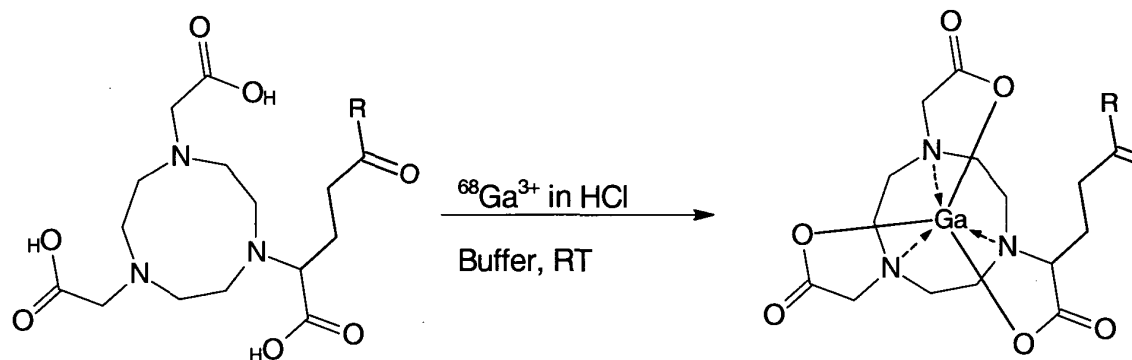
- S_N2 :



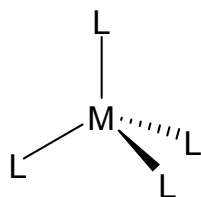
Inverted
3D
Shape!!!



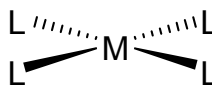
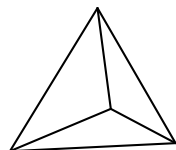
The term coordination compound describes stoichiometric compounds consisting of molecules and/or ions, which can exist also independent from each other.



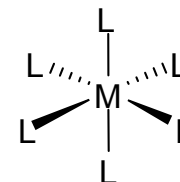
Through the formation of the complex, a compound is created which displays different properties than the individual compounds it is made of. Complexes are written with 'square brackets'. Within a complex unit there is the central atom (acceptor atom) and the ligands (donors).



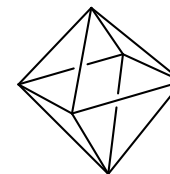
tetrahedral coordination



square-planar coordination



octahedral coordination

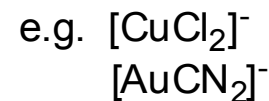
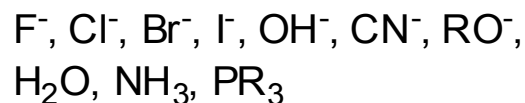


coordination number 4

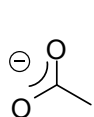
coordination number 6



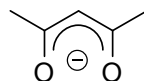
Monodentate ligands:



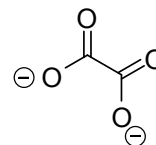
Bidentate ligands:



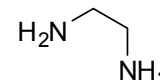
acetato



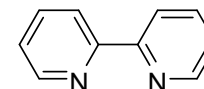
acetylacetonato



oxalato

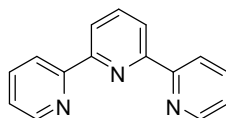


ethylenediamine
(en)

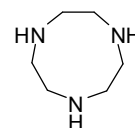


2,2'-Bipyridine

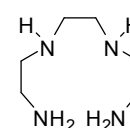
Tridentate ligands (tripod)
and higher order ligands



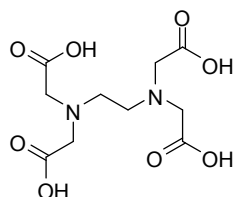
2,2',6',2''-Terpyridin
(terpy)



1,4,7-Triazacyclo-
nonane (9aneN₃)

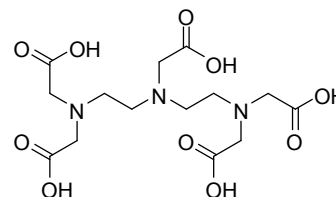


Triethyltetraamine
(trien)



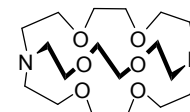
Ethylenediaminetetraacetic
acid (edta)

ideal for: Mn(II), Cu(II), Fe(II),
Pb(II), Co(III)



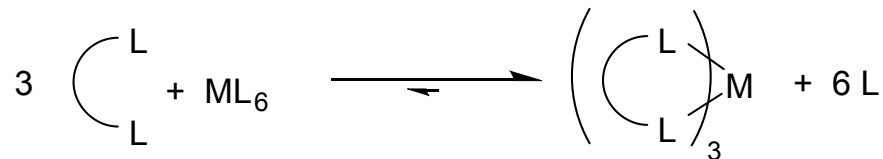
Diethylenetriaminepentaacetic acid
(dtpa)

ideal for: Fe(III), U(IV),
Th(IV), Ce(III/IV)



Kryptofix 2.2.2

Definition: If a monodentate and a multidentate ligand with the same donor atoms in an ideally identical chemical environment compete for the same metal center, empirical data indicates that the multidentate ligand replaces the respective number of monodentate ligands.



$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \quad \text{Gibb's free enthalpy}$$

$$\Delta G^\circ = -RT \ln \beta$$

$$\text{with } \beta = \frac{[\text{M(L-L)}_3] [\text{L}]^6}{[\text{ML}_6] [\text{L-L}]^3}$$

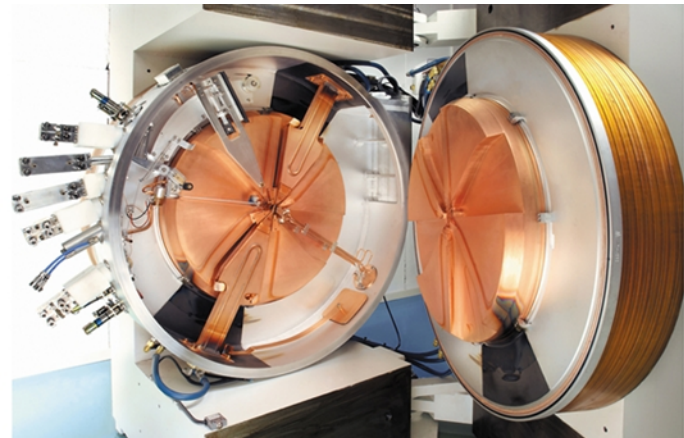
In general the formation of complexes between a metal and higher order ligands is thermodynamically and entropically favoured.

Chelators can be readily conjugated on to biomolecules and then “complexed” with radio-metals like ^{68}Ga and ^{64}Cu . A very effect strategy for labelling big biomolecules.





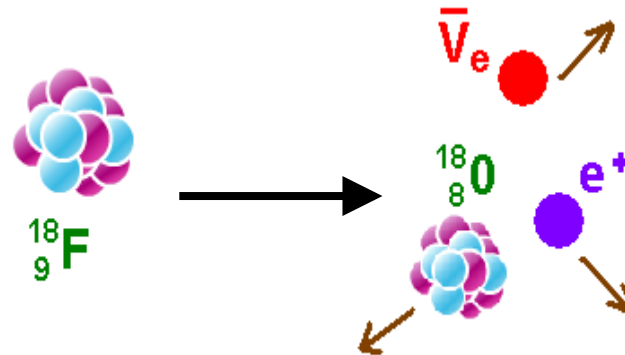
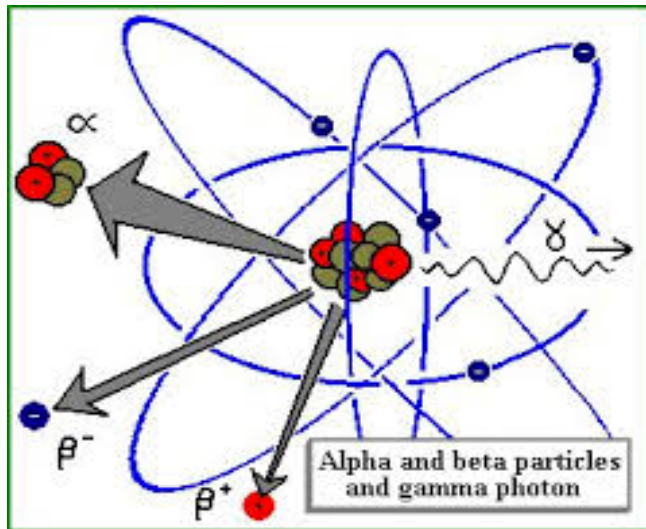
- Radiochemistry:
 - The chemistry of, and using radioactive isotopes. In the case of PET radiochemistry, especially isotopes such as ^{11}C , ^{13}N , ^{15}O , ^{18}F , ^{64}Cu , ^{68}Ga , ^{89}Zr and ^{124}I are applied for radiolabeling of molecules.





Radioactivity:

Radioactivity is a property of certain nuclides to spontaneously emit a particle or gamma photon from the nucleus or via emission of x-ray radiation after capture of a shell electron through the nucleus (electron capture EC). Through radioactive decay an unstable radioactive isotope undergoes a change into a finally more stable isotope.



β^{+} - decay

Radioactive decay:

- The radioactive decay is a statistical event. Each radioactive nucleus decays independently from its neighbouring nuclei with a certain probability. For a single atom of a radioactive nuclide, the moment of decay can not be predicted. Radioactive decay is measured in Becquerel's (Bq) (counts per second)

Half-life:

- The time it takes for half the radioactive sample to decay. A statistical constant of the decaying element. ^{18}F has a $T_{1/2} \approx 110\text{min}$, ^{11}C $T_{1/2} \approx 20\text{min}$, ^{64}Cu $T_{1/2} \approx 12\text{hrs}$.

- Radioactive decay: $N(t) = N_0 * e^{-\lambda t}$ $T_{1/2} = \frac{\ln 2}{\lambda}$ λ : decay constant $1/\text{s}$

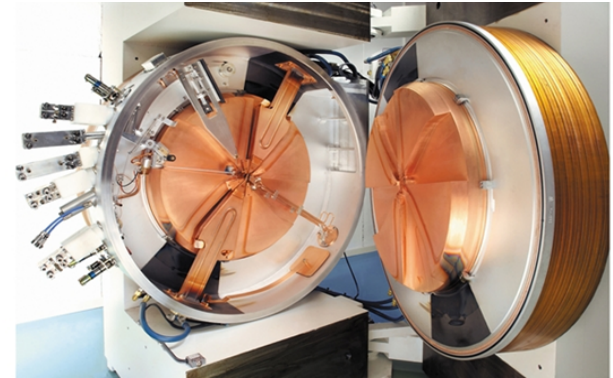
Specific activity: Defined as Bq/kg, but often given in GBq/ μmol .

- The specific (radio-)activity tells you how many decays per second take place in a certain amount of substance. A higher value means a higher ratio of the radioactive compound in comparison to the non radioactive compound.

Theoretical values by increasing $T_{1/2}$:

- ^{11}C 370 TBq / μmol ($8.4 \cdot 10^8$ Ci/g)
- ^{18}F 62 TBq / μmol ($9.3 \cdot 10^7$ Ci/g)
- ^{64}Cu 9 TBq / μmol ($3.8 \cdot 10^6$ Ci/g)
- ^{125}I 78 GBq / μmol ($1.7 \cdot 10^4$ Ci/g)
- ^{235}U 18 Bq / μmol ($2.1 \cdot 10^{-6}$ Ci/g)

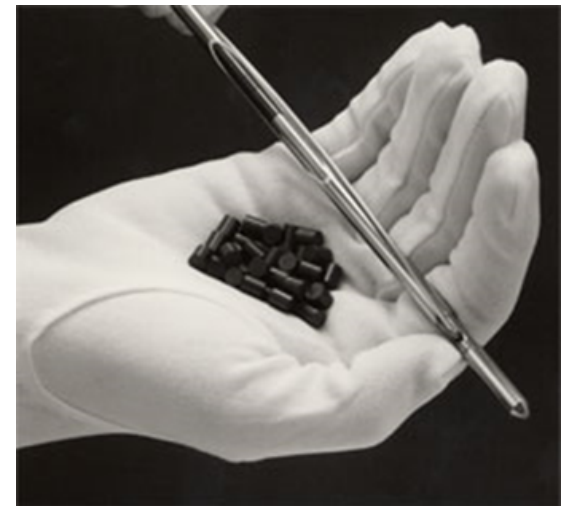
$$18 \text{ Bq} / 0.235 \text{ mg} \Rightarrow 18 \text{ kBq} / 0.235 \text{ g} \Rightarrow 76 \text{ MBq} / \text{kg}$$



In general, the higher a radionuclide's specific activity, the shorter its half-life (decay rate), and the more "radioactive" it is when compared to one with a lower specific activity.

Experimental results (Radiopharmacy Tübingen)

- ^{11}C 100 – 400 GBq / μmol
(after radiosynthesis)
- ^{18}F 50 – 100 GBq / μmol
- ^{64}Cu ~ 50 GBq / μmol



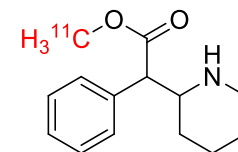


Various factors effect specific activity.

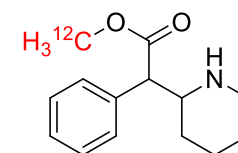
Carrier is the non-radioactive version of a radiopharmaceutical

Pseudo-carrier is a term used to describe material closely resembling the true carrier in some respect (e.g. biological activity, receptor binding affinity)

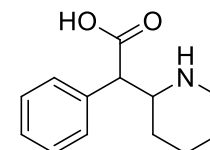
For synthetic radiotracers there is (often) a substantial dilution with a carrier. The carrier usually remains constant, while the radioactivity decays. So, specific radioactivity generally decreases according to the half-life of the radioisotope. Specific radioactivities for PET radiopharmaceuticals should be cited with respect to a particular time e.g. end of radionuclide production (EOB), end of synthesis (EOS) or time of injection (TOI).



^{11}C -Methylphenidat
(Ritalin)



Methylphenidat
(Ritalin)



Ritalinic acid

Carrier-free (CF)

A radiopharmaceutical is carrier-free (CF) when there is no accompanying carrier (more or less an ideal but non-reachable state).

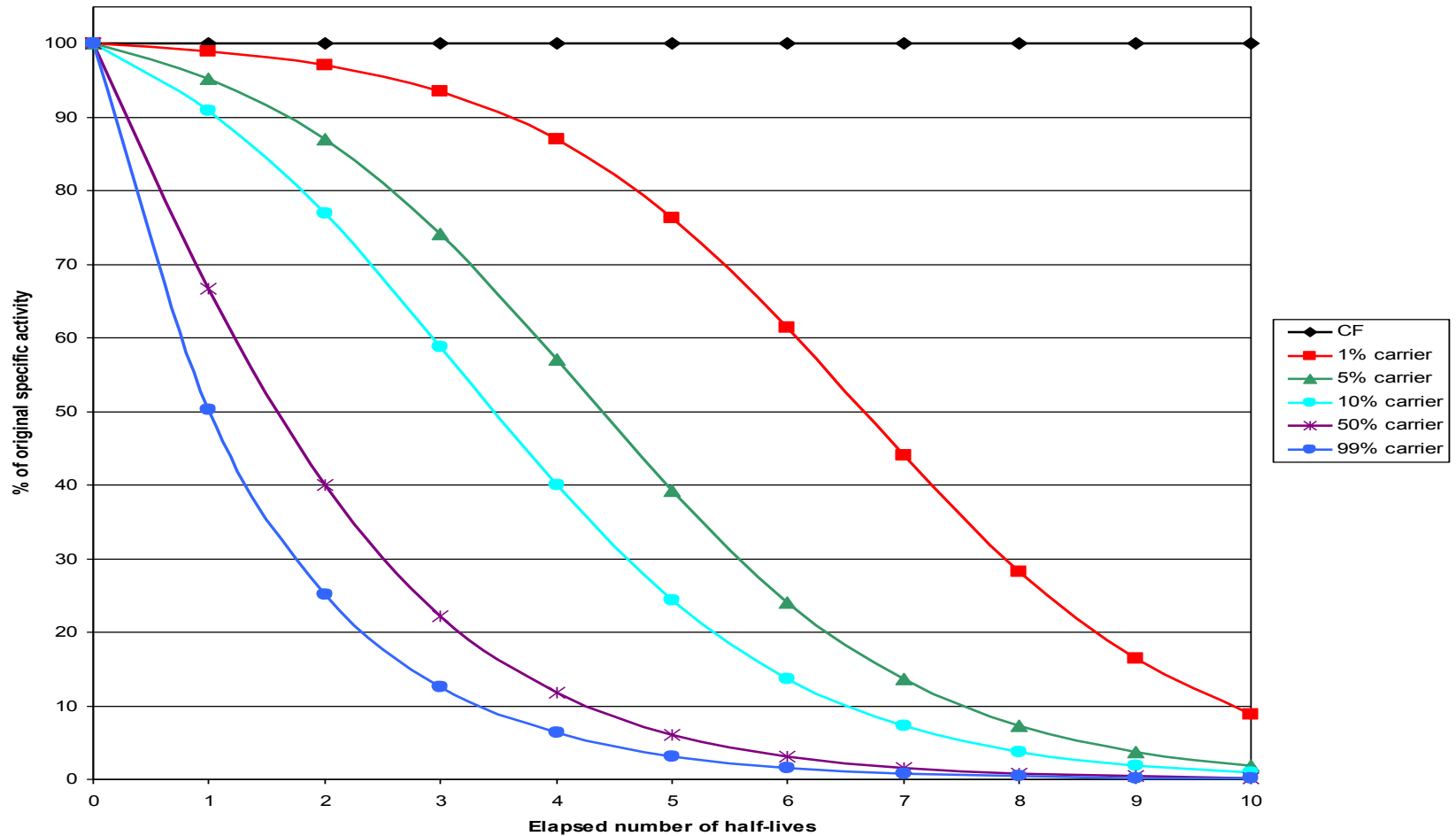
No-carrier added (NCA)

A radiopharmaceutical is no-carrier added (NCA) when no source of carrier has been added deliberately during its production, and when all reasonable precautions have been taken against the intrusion of sources of carrier.

Carrier-added (CA)

A radiopharmaceutical is carrier-added (CA) when a source of carrier has been added deliberately during its production.

Time-dependence of specific radioactivity on dilution with carrier



- Practical Factors effecting specific activity:

1. Ion contamination from the target.

- Ni^{64} contamination is a particular problem in ^{64}Cu production.

2. Contamination from materials.

- Radiolysis in Teflon tubing and components.
- Contamination from reagents.
- Contamination from QMA resins.

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

Teflon item	Surface (cm ²)	Time (min)	Mass (nmol)
1.5 mm Teflon tubing (790 cm)	252	1.25	72
Teflon resin holder	3.8	3	47
Teflon tube in reaction vessel	1.7	20	170
Rheodyne slider valve	2.3	1.25	6.3
Control-reagents only	0	0	25
Control-mock target water	0	0	23
All components	267	N/A	357

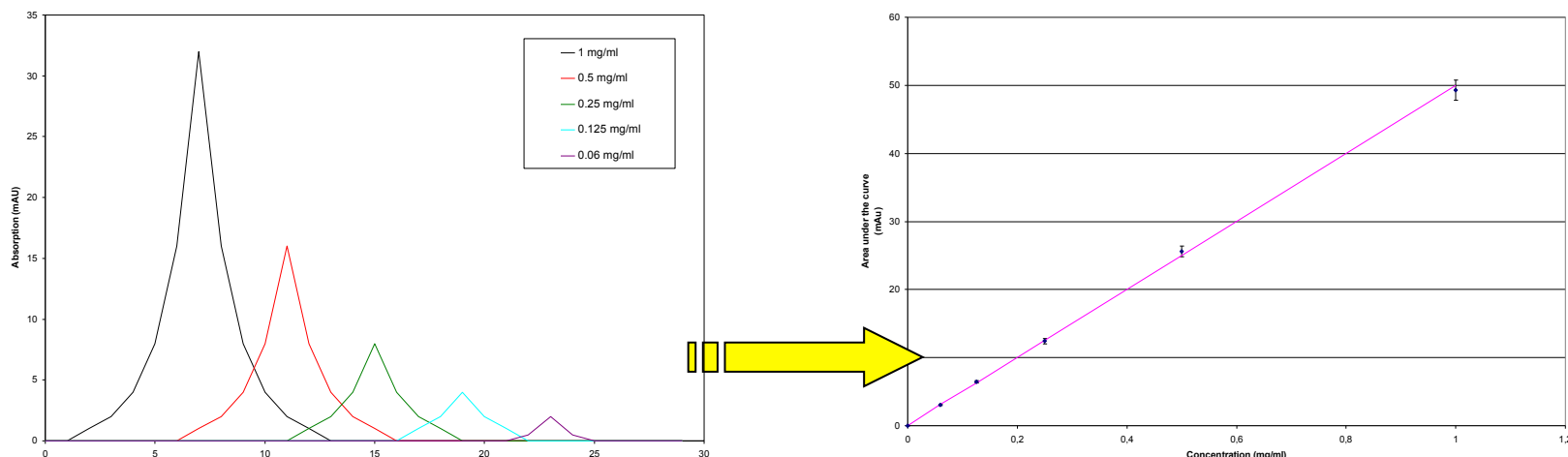
- Why is Specific activity so important??

- Cold tracer can block your targets.
- Can reduce your labelling efficiency.
- Contaminates are usually present in much greater amounts than your activity which is present only in ultra trace quantities (even for how amounts of radiation Bq))
- A large amount of effort goes into ensuring the max. SA possible!



Experimental determination of the specific activity

- Preparation of a serial dilution of the non-radioactive („cold“) standard and consecutive measurement with signal integration on a HPLC or GC system



- Perform a radiosynthesis and run a sample of defined volume of your reaction solution under the same conditions as the serial dilution => concentration of total amount (sum of hot and cold product).
- With the knowledge of the total volume of the reaction solution, the concentration of the reaction solution determined via HPLC or GC and the measured radioactivity, we can calculate the specific activity to the time of the HPLC/GC run

Practical radiochemistry



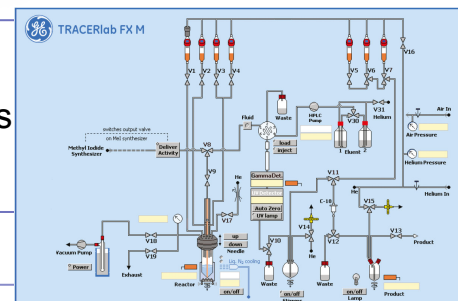
Setup Synthesiser

- Load reagents, chemicals, solvents, etc.



Run synthesis program

- Run a pre-made program based on a time list of scheduled events



Dispense Product

- Dispense and formulate product.
- Remove sample for QC.



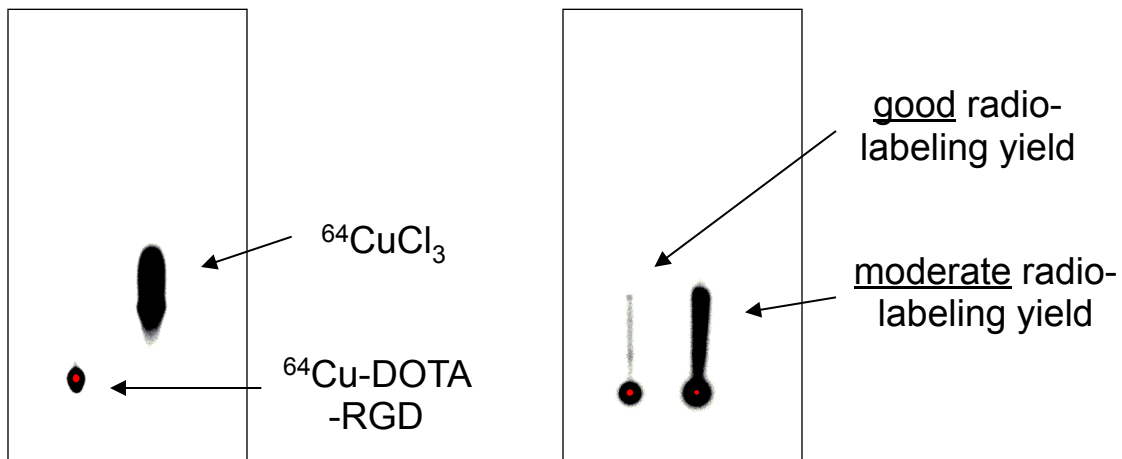
Quality Control

- HPLC (Chemical Identity)
- Radio TLC (Chemical purity)(RCY)
- PH
- Sterility

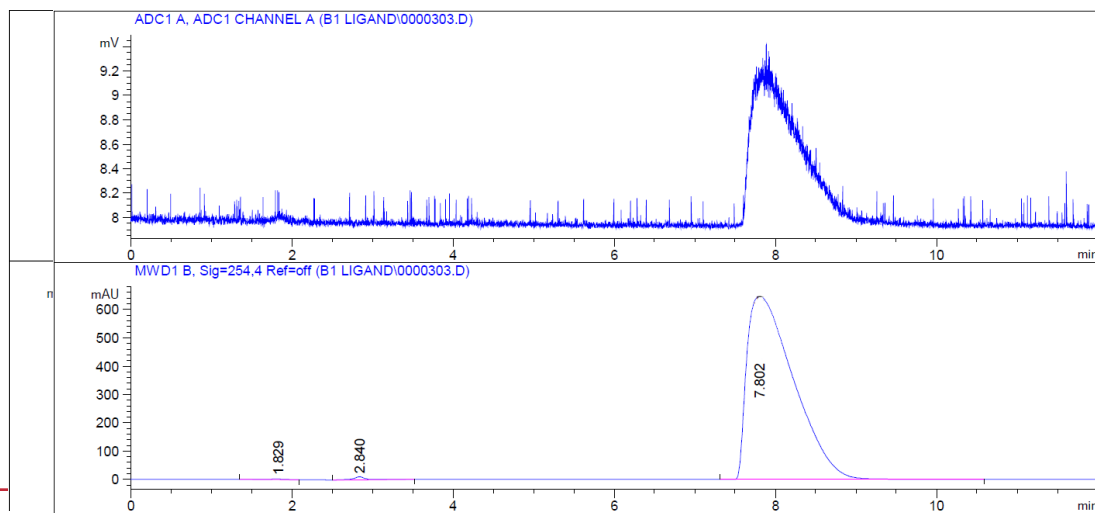




Radio-TLC



Radio-HPLC



- Basics of Chemical reactivity
- Basic principles of Radiochemistry.
- Up Next:
 - ^{18}F chemistry
 - ^{11}C chemistry

Questions???