PET Radiochemistry

Lecture 1: Basics of radioactivity, isotope production
Lecture 2: Carbon-11 chemistry
Lecture 3: Carbon-11 chemistry (cont'd)
Lecture 4: Fluorine-18 chemistry
Lecture 5: Fluorine-18 chemistry (cont'd)

ATOMS & ISOTOPES

Bohr model of the atom:
The dense nucleus of neutrons and protons is surrounded by electrons at different energy levels (or shells) - innermost K, then L, M, N,...

In a **neutral atom** the number of protons equals the number of electrons.
The number of protons is the **atomic number** of the atom, ***Z***.
The number of neutrons is the **neutron number**, ***N***.
The number of neutrons plus protons is the **mass number**, ***A***.
Neutrons and protons are called **nucleons**.

Isotopes of an element E are designated ${}^{A}_{Z}\mathbf{E}_{N}$ (usually only *A* is written for a defined element) *e.g.* ^{123}I, ^{125}I, ^{131}I.

The term **nuclide** is used to describe a particular nuclear composition.
Nuclides with the same *Z* are called **isotopes**
with the same *N* are called **isotones**
with the same *A* are called **isobars.**

In a **stable atom** the electrons are fixed in their discrete shells.

THE ORIGINS OF RADIATION
A. From Extranuclear Processes

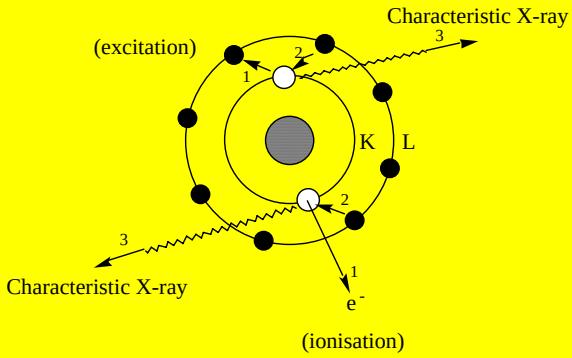
Electron removal from an atom is only possible by an input of energy.

e.g. from a photon or another electron.

Electrons may be moved to higher energy shells (**excitation**), or be completely removed from the atom (**ionization**).

The energy required to remove an electron is its **binding energy**.

1. Characteristic X-ray emission

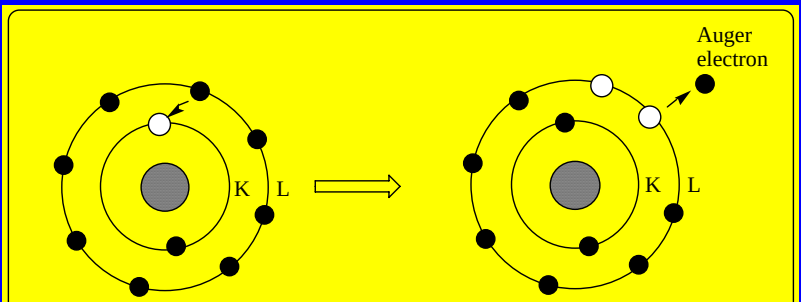


Characteristic X-ray emission following electron excitation or ionisation.
Solid circle = electron. Open circle = vacancy for electron.

When an electron is removed from an inner shell, an electron from an outer shell fills the vacancy,

- and energy is emitted in the form of a **characteristic X-ray**
- with an energy equal to the difference between the 2 shells,
- which will be characteristic for the particular element concerned.

2. Auger electron emission



Emission of an Auger electron.
This may be followed by other events such as characteristic X-ray emission.
Solid circle = electron. Open circle = vacancy for electron.

An alternative to characteristic X-ray emission is **Auger electron emission**. In this process the energy released by the outer shell electron is given to another electron, which then leaves the atom.

THE ORIGINS OF RADIATION

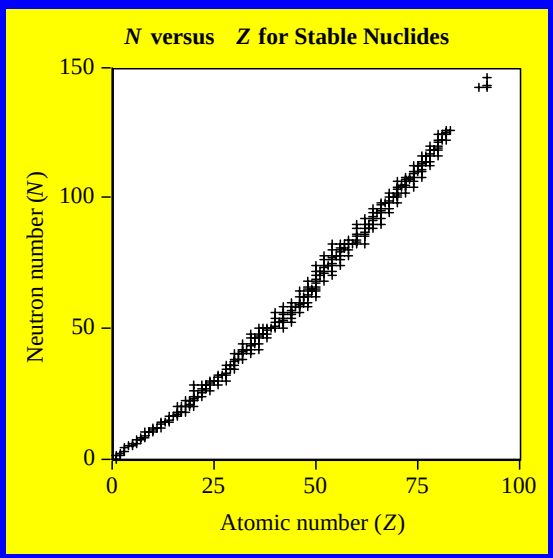
B. From Intranuclear Processes — Radioactivity

Stable and unstable nuclides

Certain combinations of neutrons and protons are stable, while others are unstable.

The most stable state of a nucleus is called the **ground state.**

The neutron-to-proton ratio in the nucleus determines its stability; the *N*/*Z* ratio for stability increases as *Z* increases:



Binding Energy

The mass of a nucleus is always smaller than the combined masses of the constituent nucleons; the **binding energy** of the nucleus accounts for the difference.

Thus, for example, for the ^{4}He nucleus:

^{12}C = 12 **a.m.u.** (atomic mass units) *by definition*

^{1}H = 1.007825 a.m.u. by mass spectrometry (MS)

^{1}n = 1.008665 a.m.u. by MS

^{4}He = 4.0026033 a.m.u. by MS

e^{-} = 0.0005486 a.m.u. by MS

Hence, the binding energy of ^{4}He nucleus
= (2x1.007825) + (2x1.008665) – 4.0026033 = 0.0303768 a.m.u., which by $E = mc^2$ equates to 28.296 MeV or ~ 7.1 MeV per nucleon. [1 a.m.u. = 931.5 MeV]

Unstable Nuclides

Unstable nuclides have a deficit or surplus of neutrons. All elements with A > 209 are unstable *e.g.* ^{238}U. Unstable nuclides tend to achieve greater stability by emitting radiation. This is the process of **radioactive decay**. The emitted radiation can be a mixture of 3 distinct types, α-particles, β-particles and γ-rays.

An **α-particle** is a ^{4}He nucleus (2 protons + 2 neutrons).

A **β-particle** is an electron (**negatron; β^-**) or **positron** (**β^+**).

A **γ-ray** is electromagnetic radiation (this differs only from an X-ray by being emitted *from the nucleus*).

Each type of radionuclide exhibits a set of characteristic properties:

- **half-life**
- **mode of decay** [type(s)of emission(s) and associated energies]

Half-life

Radionuclide decay is random. The probable rate of decay at any time is proportional to the number of atoms (**N**) of the radioisotope present. The decay process is characterized by a **decay constant**, **λ**, which is the fractional loss per unit time. By definition the radioactivity (disintegrations per unit time), **R**, is given by:

$$R = -\lambda N = dN/dt$$

where **N** is the number of radioactive atoms present,
from which it follows that the radioactivity at time **t** (R_t) is related to that at time zero (R_o) by: $R_t = R_o e^{-\lambda t}$
and that the time for half the radioactive atoms to decay, the **half-life** ($t_{1/2}$) is given by: $t_{1/2} = \ln 2/\lambda$
Half-lives of the radioisotopes vary over an *enormous* range.
The SI unit of radioactivity is the **Becquerel** (**Bq**).

1 Bq = 1 radionuclide disintegration per second

The older unit is the **Curie (Ci)** = 3.7 x 10^{10} Bq

N.B. 10^3 Bq = 1 kBq; 10^3 kBq = 1 MBq; 10^3 MBq = 1 GBq; 10^3 GBq = 1 TBq.

Estimation of Half-life from Decay Data

$$R_t = R_o e^{-\lambda t}$$

Therefore

$$\ln R_t = -\lambda t + \ln R_o$$

i) Plot $\ln R_t$ against **t**

ii) A straight line should be obtained with slope = **– λ,** the decay constant. (If a straight line is not obtained more than one radioisotope is present!).

iii) $t_{1/2} = \ln 2/\lambda$

Decay Correction

$\mathbf{R_t = R_o e^{-\lambda t}}$ or $\mathbf{R_o = R_t e^{\lambda t}}$

e.g. if a sample of carbon-11 has an activity of 250 mCi at 40.6 min after the end of production, what was the original activity?

Carbon-11; $t_{1/2}$ = 20.3 min
$\lambda = \ln 2/20.3\ \text{min}^{-1} = 0.6923/20.3 = 0.034145\text{min}^{-1}$

$\mathbf{R_o = R_t e^{\lambda t}} = 250 \times e^{(40.6 \times 0.034145)} = 250 \times 4 =$ **1000 mCi = 1 Ci**

Mechanisms of Radioactive Decay: α-Decay

α-Decay (ejection of a single α-particle) occurs in *neutron-rich* radioisotopes of *heavy elements* i.e. Z > 83:
The nuclear transformation may be represented as:

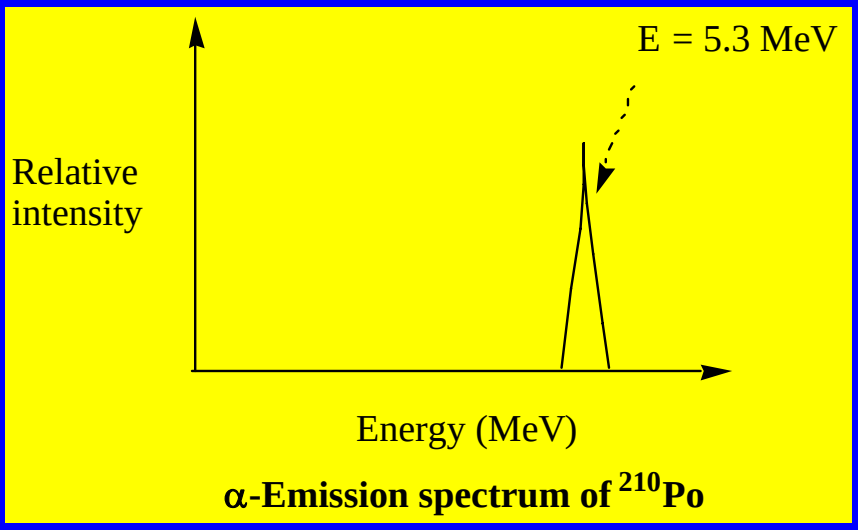
$$^{A}_{Z}X \rightarrow {}^{A-4}_{Z-2}Y$$

e.g. $^{238}_{92}U \rightarrow {}^{234}_{90}Th + \alpha + \text{energy}$

$^{210}_{84}Po \rightarrow {}^{206}_{82}Pb + \alpha + 5.4\ \text{MeV}$

α-Particles are generally produced with a low velocity (~ 10^7 m/s) but with a high discrete energy in the range 1.8 – 11.7 MeV. They are very highly ionizing and have only a short range in tissue. Hence, α-emission *cannot* be exploited for medical imaging.

α-Emission Spectra



α-Emission spectrum of ^{210}Po

Isomeric transition (γ-ray emission):

Nuclides with the same *A*, *Z* and *N* values are termed **isomers**. Most excited (unstable) nucleons reach the ground state by releasing energy *instantaneously*. However, if the nucleus remains in an excited state for a measurable time (*i.e.* > 1 s), it is regarded as a **metastable state** and as a separate nuclide. Examples of metastable states are:

^{81m}Kr ($t_{1/2}$ = 13 s) and
^{99m}Tc ($t_{1/2}$ = 6 h).

Metastable states may form by radioactive decay of other radionuclides (*e.g.* ^{99m}Tc from ^{99}Mo; $t_{1/2}$ = 67 h).
The process of de-excitation is called **isomeric transition (IT)** and results in **γ-ray emission**.

Internal conversion:

In **internal conversion** the radionuclide transfers its excess energy to an orbital electron which is ejected. Characteristic X-rays or Auger electrons follow internal conversion. No γ-ray is emitted.

$$^{A}_{Z}X^{*} \rightarrow {}^{A}_{Z}X + \text{IC electrons} + \text{X rays} = \text{Auger electrons}$$

Conversion electrons have *discrete* energies.

Spontaneous fission:

Some high mass radionuclides undergo spontaneous fission, with the emission of neutrons.

$$\textit{e.g.}\ \ ^{252}_{98}Cf \rightarrow {}^{140}Xe + {}^{108}Ru + 4n$$

A wide range of fission products is possible.

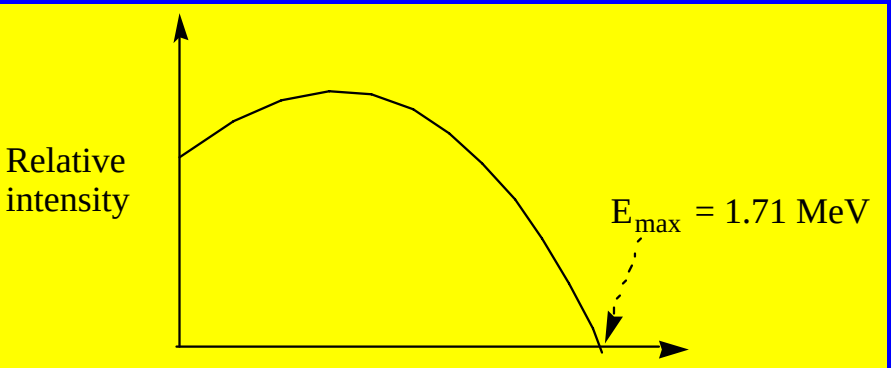
β^--(Negatron)-decay

β^--Decay occurs in *neutron-rich* nuclides
Emission of a β^--particle (plus a **neutrino**, υ) converts a neutron into a proton:

$$n \rightarrow p + \beta^- + \upsilon$$

The neutrino has no mass or charge. The released energy is shared between the emitted β^--particle and the neutrino.
Hence, the β^--particles emitted from a group of identical radionuclides present a continuous spectrum of energies (a **β^--emission spectrum**), ranging from zero to a maximum energy (E_{max}), characteristic of the type of radionuclide.
The average energy of the β^--particles is ~ $E_{max}/3$. Their velocities are high, about 10^8 m/s.

β^--Emission Spectrum



β^--Emission spectrum of ^{32}P

β⁻-(Negatron)-decay (Cont'd)

The nuclear transformation accompanying β⁻-decay may be represented in general by:

$$^{A}_{Z}X \rightarrow {}^{A}_{Z+1}Y$$

e.g. $^{90}_{39}Y \rightarrow {}^{90}_{40}Zr + \beta^{-} + \upsilon$

The β⁻-decay of some radionuclides results in an unstable nucleus, which goes on to decay by one or more other processes (*e.g.* **γ-emission**). E.g. ^{60}Co decays by either of 2 alternative β⁻-emission pathways, each to a corresponding excited state of ^{60}Ni. Each **metastable state** decays to the ground state by emission of its own characteristic γ-ray .

β⁻-(Negatron)-decay (Cont'd)

β⁻-Particles travel only a short range in tissue before being absorbed.
They are therefore useless for medical imaging.

Compounds labeled with β⁻-emitters are however useful for autoradiography of *post mortem* tissue (*e.g.* **^{3}H**),

or for radiotracer studies in animals (*e.g.* **^{14}C**) with *ex vivo* radioactivity measurement.

β^+ (Positron)-decay:

This occurs in *neutron-deficient* nuclei, when the potential decay energy exceeds 1.02 MeV (equivalent to 2 x the rest mass of an electron; $2m_ec^2$).

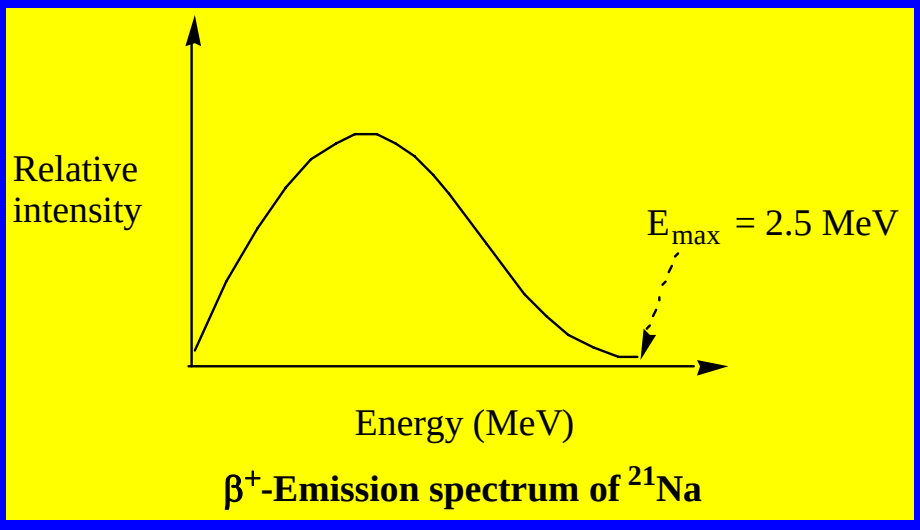
Emission of a β^+-particle (and a neutrino) converts a proton into a neutron:

$$p \rightarrow n + \beta^+ + \upsilon$$

The released energy is shared between the emitted β^+-particle and the neutrino.

Hence, there is a characteristic **β^+-emission spectrum** where the average energy ***E*** is ~ $\boldsymbol{E_{max}/3}$ *e.g.* for positron-emitting, ^{21}Na.

β^+- Emission Spectrum



β^+-Emission spectrum of ^{21}Na

β^+ (Positron)-decay (Cont'd)

The nuclear transformation accompanying β^+-decay may be represented in general by:

$$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y$$

e.g. $^{11}_{6}C \rightarrow {}^{11}_{5}B$

β^+-Decay may result in an unstable nucleus which may go on to decay by one or more other processes.

Note: Most low Z positron-emitters give stable daughter nuclides.

The Fate of Emitted Positrons: 511 keV γ-Emission

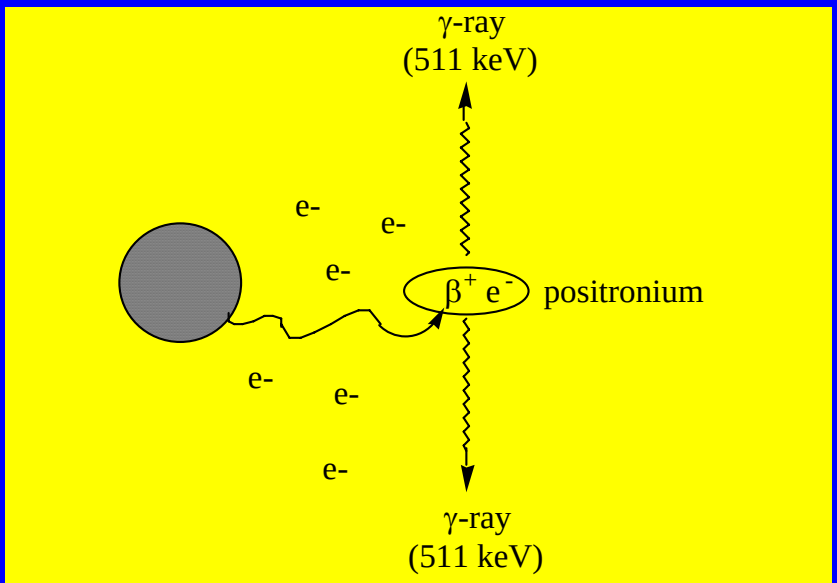
Positrons have only a short range in tissue, dependent on their initial kinetic energy and the tissue density. Once the kinetic energy is all but lost, the positron pairs with a nearby electron to form a merged species, **positronium**. This then rapidly annihilates to create 2 γ-rays of equal energy (**511 keV**, equivalent to the rest mass of an electron) that are propagated in almost exactly opposite directions (to conserve the almost zero momentum at the time of annihilation). This is called **annihilation radiation**.

The 2 γ-rays are capable of *penetrating tissue* and can therefore be exploited for medical imaging. The PET imaging technique exploits the special features of annihilation radiation to define the location of positron-emitters *in vivo*.

Important positron-emitters used with this technique are:

^{11}C, **^{13}N**, **^{15}O**, and **^{18}F**.

Schematic of Positron Emission



Events following radionuclide decay by positron-emission

Electron capture

If a neutron deficient nucleus lacks sufficient energy to decay by positron emission, the excess proton(s) may be reduced by capture of an extranuclear electron:

$$p + e^- \rightarrow n + \upsilon$$

In **electron capture (EC)**, the nuclear transformation is formally the same as for positron emission:

$$^{A}_{Z}X \rightarrow {}^{A}_{Z-1}Y$$

A particular type of radionuclide may decay by different processes, but in a fixed ratio. For example, in a sample of ^{18}F, 97% of the radionuclides will decay by positron emission and 3% by electron capture. The ratio of electron capture to positron emission tends to increase with *Z*.

Electron capture (cont'd)

Electron capture leaves a vacancy in one of the electron shells, usually the K shell, and so characteristic X-rays will be emitted. If the resultant nucleus has excess energy a γ-ray may also be emitted. The energies of the characteristic X-rays tend to increase with the *A* value of the radionuclide *e.g.* **^{51}Cr** decays to give a 5 keV X-ray.

Electron capture is the mode of decay of **^{123}I**, a very important radioisotope for medical imaging with SPECT. The principal emission is a 320 keV γ-ray. Some other radionuclides decaying by electron capture that are useful in medical imaging are **^{57}Co**, **^{67}Ga**, and **^{111}In.**

PRODUCTION OF RADIOISOTOPES — PRINCIPLES

<u>Via nuclear reactions</u>
1. Charged Particle Accelerators
2. Reactors

<u>Via radioactive decay</u>
1. Generators

Nuclear reactions

In a nuclear reaction, the incident particle is absorbed by the target nucleus to form a **compound nucleus [CN]**. The energy of the incident particle is rapidly shared by all the nucleons of the CN. In a second stage, the CN decays into a product nucleus, in a process independent of its formation.

A nuclear reaction may therefore be written as:

$$X + x \rightarrow [CN] \rightarrow Y + y$$

or in shorthand, as

X(x,y)Y

e.g. $^{10}B(\alpha,n)^{13}N$

The Energy of a Nuclear Reaction (Q)

Q is defined as the sum of the kinetic energies of the reaction products minus the sum of the kinetic energies of the target nucleus and the absorbed particle. Hence, a nuclear reaction may also be written as:

$$X + x \rightarrow Y + y + \mathbf{Q}$$

If **Q** is negative, reaction is **endothermic.**
If **Q** is positive, reaction is **exothermic.**

Threshold energy (T_{th})

If a nuclear reaction is **endothermic** the kinetic energy of the incident particle must exceed the **threshold energy (T_{th})**, which is always greater than the absolute value of **Q**, according to the following equation:

$$\mathbf{T_{th} = -Q(M_X + m_x)/M_X}$$

This is a consequence of the need to conserve momentum.

E.g. $^{14}N(\alpha,p)^{17}O$
Q = – 1.18 MeV (*i.e.* reaction is endothermic)
$M_X = 14$, $m_x = 4$
$T_{th} = -(-1.18)(18/14) = 1.52$ MeV

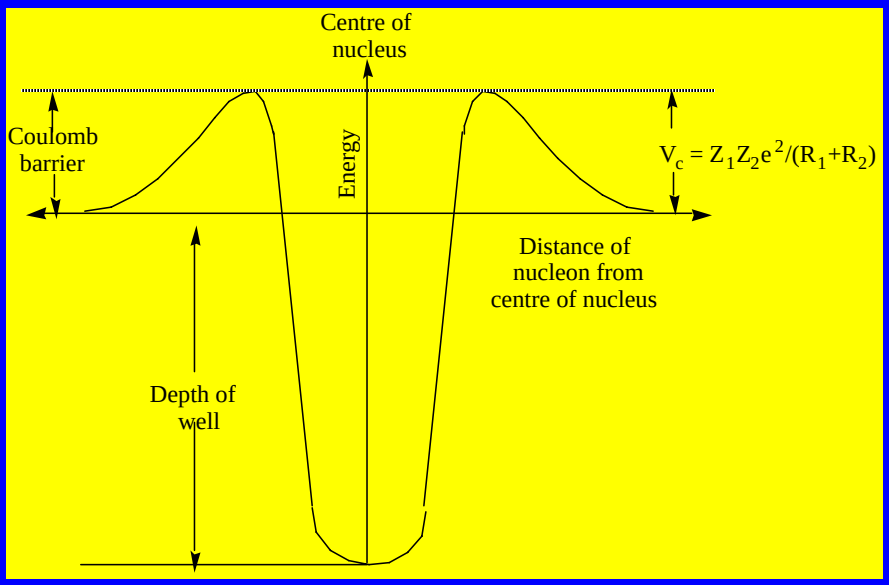
The Coulomb Barrier

For nuclear reactions involving positively charged projectiles (*e.g.* p, d, $^3He^{2+}$ or α –particle, the two positively charged nuclei must overcome their mutually repulsive force, the **Coulomb Barrier (CB)** before the **CN** can be formed**.**

This barrier, of magnitude $\mathbf{V_c}$, is related to the unit charge **e**, the number of protons, $\boldsymbol{Z_1}$ and $\boldsymbol{Z_2}$, and the atomic radii, $\mathbf{R_1}$ and $\mathbf{R_2}$, of the two interacting nuclei by the equation:

$$\mathbf{V_c = Z_1 Z_2 e^2/(R_1+R_2)}$$

Coulomb barrier (Cont'd)



Coulomb barrier (Cont'd)

The atomic radius, **R** cm, is empirically related to the atomic number (**A**) by the approximation:

$$\mathbf{R \sim 1.5 \times 10^{-15}\ A^{1/3}\ cm = 1.5\ A^{1/3}}\ \text{fm}$$

[if **R** is in Units of fm (*i.e.* femtometres), $\mathbf{V_c}$ is obtained in MeV]

For the $^{14}N(\alpha,p)^{17}O$ reaction $\mathbf{V_c}$ is 3.4 MeV.

Thus, the Coulomb barrier and not **Q** (– 1.18 MeV) determines the minimum practical threshold energy for the α-particle to induce this nuclear reaction.

To conserve the original momentum of the projectile, this energy must be

$$V_c(M_X + m_x)/M_X = 3.4 \times 18/14 = 4.4 \text{ MeV}$$

Reaction Cross Section

When a material (the **target**) is exposed to a beam of particles, the number of nuclei reacting per unit time (***R***) is proportional to the intensity of the beam (**I**) and the number of target atoms exposed to it (**N**) *i.e.*

$$R = \sigma I N = \sigma I n x$$

where:
I is the number of incident particles
n = number of target atoms per cm^3,
x = thickness of target in cm, and
σ is a proportionality constant, characteristic of the nuclear reaction considered.

σhas units of area, expressed as **barns** where

1 barn = 10^{-24} cm^2 (10^{-28} m^2).

Beam intensity (I)

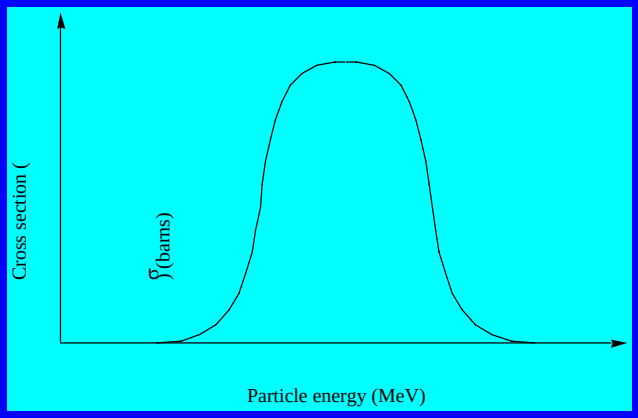
For a *thick target*, the incident beam will be attenuated in intensity as it passes through the target material. The attenuation of the beam intensity (***-dI***) over an infinitesimal distance (***dx***) is given by:

$$-dI = I n \sigma dx$$

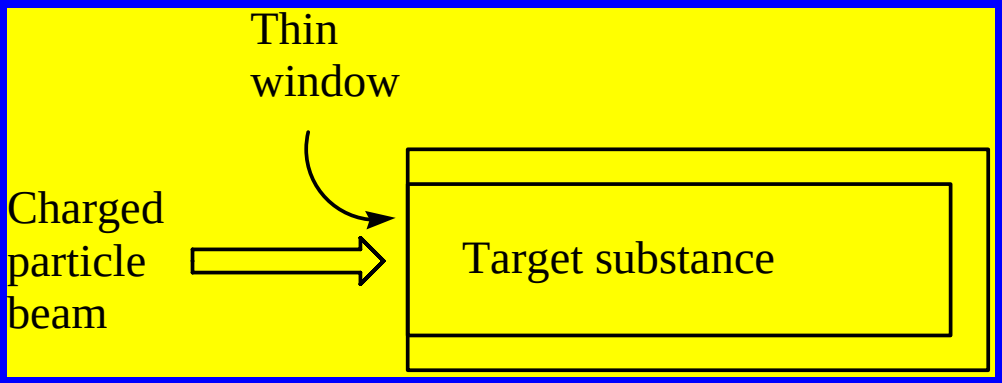
(assuming **σ** does not vary considerably with attenuated beam energy over the range considered - only truly valid for neutrons).

Excitation functions

Values of σ vary with the energy of the projectile, and this relationship is called the **excitation function** of the process.



Thick target (essentials)



Target substance may be a gas, a liquid or solid.
The window is typically a thin metal foil.
The target and window require cooling.

Thick target yield

The yield of radionuclides from a particular nuclear reaction in a thick target will therefore depend on a number of parameters *e.g.*

- Target thickness
- Concentration of target nuclide
- Intensity and energy of incident particle
- Irradiation time, and decay of product during this time.
- The integrated excitation function over the energy range of the particle in the target.

How long should an irradiation be?

$$A = A_{max} (1-e^{-\lambda t})$$

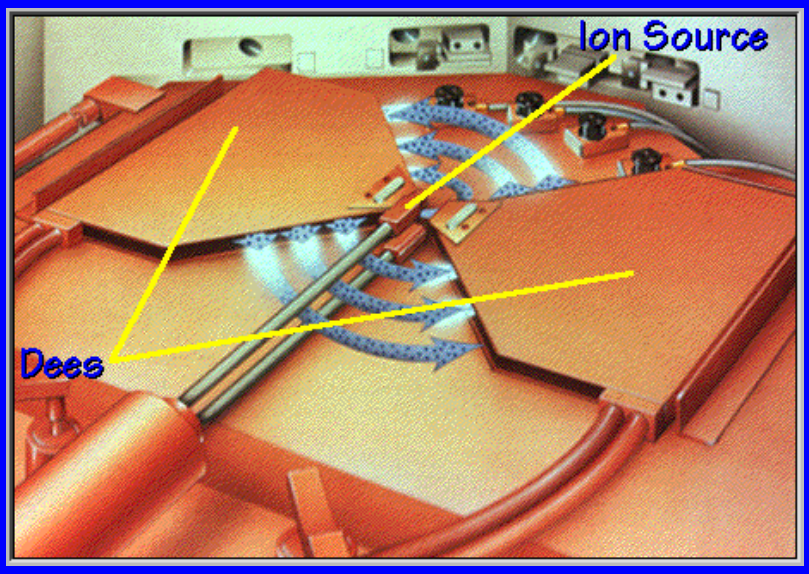
Half max activity is produced after 1 half-life
¾ max activity is produced after 2 half lives,
$^{7}/_{8}$ max activity is produced after 3 half lives, *etc*.

Charged Particle Accelerators as Sources of Radioisotopes

Charged particle-induced nuclear reactions are usually performed with cyclotrons. Modern cyclotrons are available for accelerating charged particles (generally protons, deuterons, helium-3 nuclei or α-particles) up to various maximal energies at beam currents up to 100 μA. The smaller machines are capable of accelerating single particles to low (*e.g.* E_d = 3.8 MeV; E_p = 10 MeV) or moderate energy (*e.g.* E_p = 16 MeV), while the larger machines accelerate a wider range of particles to higher energy ($E_{p,d}$ = 20 MeV: E_p = 40 MeV plus other particles).

Cyclotrons are especially useful for producing the main positron-emitters for application with PET.

Cyclotron - Principle



NIH Cyclotrons

	Cyclotron Beam Energies (MeV)		
	CS-30	JSW	GE PETtrace
p	26.53	17.5	16.5
d	14.8	9.8	8.4
$^{3}He^{2+}$	38.13		
$^{4}He^{2+}$	29.58		

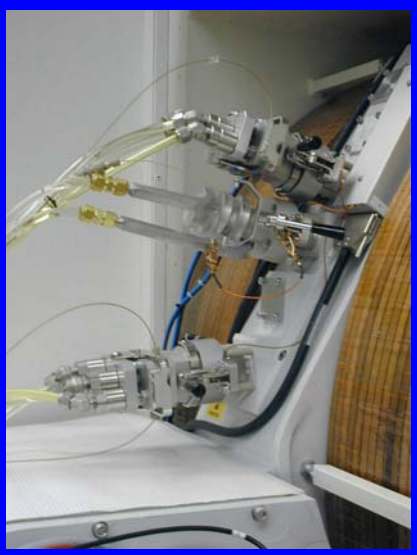
Cyclotron Targets

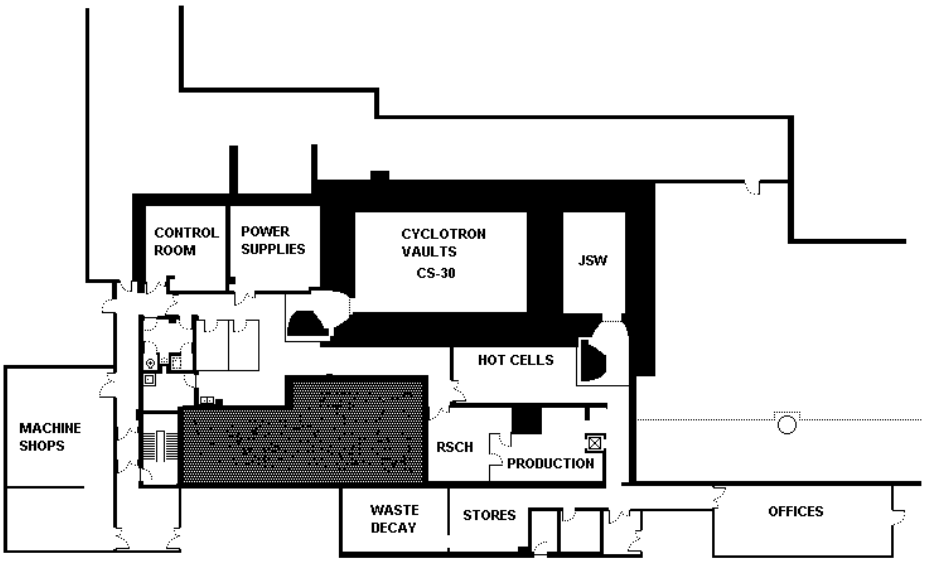
Target	CS-30	JSW	GE PETtrace
Internal	X		
Ext. Cup	X		
Ext. Foil	X		
O-15	X	X	
N-13sol		X	X
N_2-13		X	
C-11	X	X	X
HF-18	X	X	2X
F_2-18	X	X	

CS30 Cyclotron

JSW Cyclotron

GE PETrace





B-3 Level
Cyclotrons and Radiochemistry