Pharmacy 325

Nuclear Magnetic Resonance (NMR) Spectroscopy

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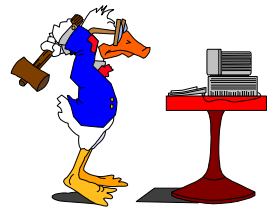
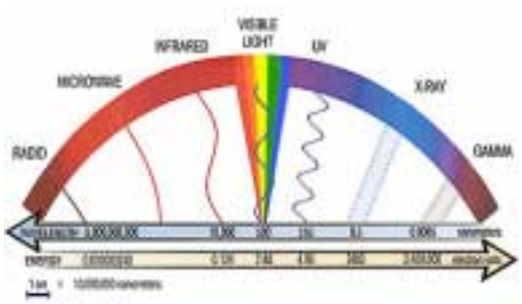
Hours: anytime after 4 pm

Lecture Notes Available At:

- http://redpoll.pharmacy.ualberta.ca
- http://www.pharmacy.ualberta.ca/pharm325/



Electromagnetic Spectrum



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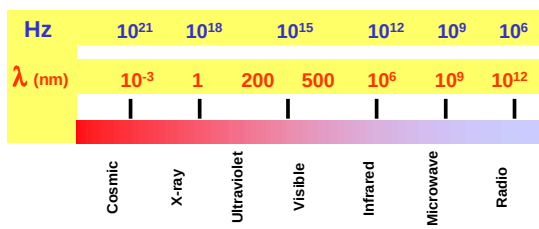
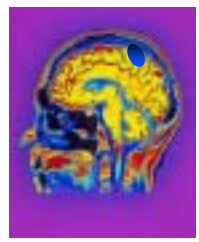


Different Types of NMR

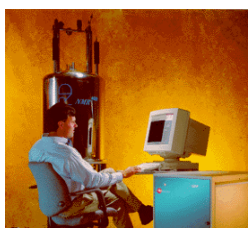
- **Electron Spin Resonance (ESR)**
  - 1-10 GHz (frequency) used in analyzing free radicals (unpaired electrons)
- **Magnetic Resonance Imaging (MRI)**
  - 50-300 MHz (frequency) for diagnostic imaging of soft tissues (water detection)
- **NMR Spectroscopy (MRS)**
  - 300-900 MHz (frequency) primarily used for compound ID and characterization

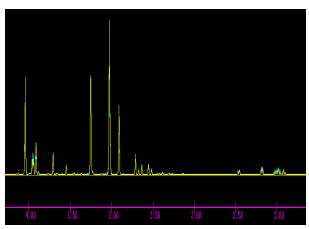
NMR in Everyday Life



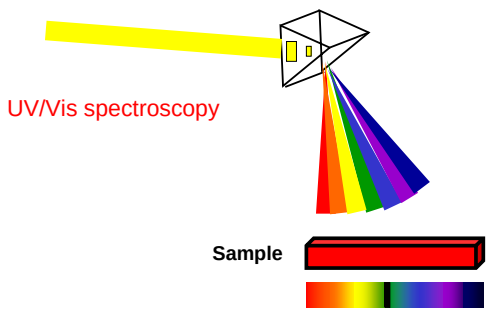
Magnetic Resonance Imaging

NMR Spectroscopy

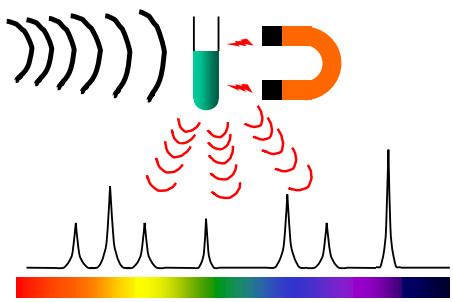




Explaining NMR



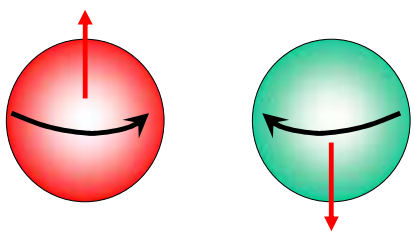
Explaining NMR



Principles of NMR

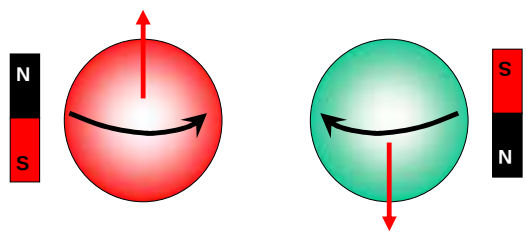
- Measures nuclear magnetism or changes
- NMR spectroscopy measures the
- NMR only occurs when a sample is in a
- Different nuclei absorb at different

Protons (and other



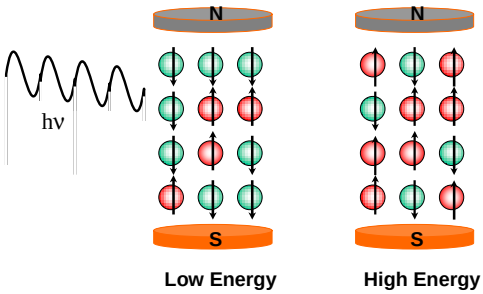
Spin up Spin down

Each Spinning Proton is



Spin up Spin down

Principles of NMR



Which Elements or

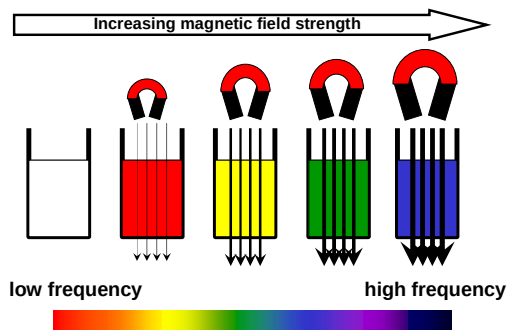
- Any atom or element with an odd
- Any molecule with NMR active atoms
- ^{1}H - 1 proton, no neutrons, AW = 1
- ^{13}C - 6 protons, 7 neutrons, AW =13
- ^{15}N - 7 protons, 8 neutrons, AW = 15
- ^{19}F = 9 protons, 10 neutrons, AW = 19

The NMR Equation

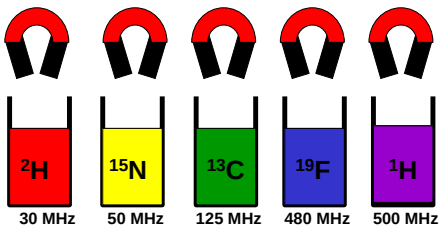
$$\nu = \gamma B/2\pi$$

- B = magnetic field strength in Tesla (1 Tesla = 10,000 Gauss = 1000 kitchen magnets)
- γ = magnetic ratio (characteristic of

Bigger Magnets are Better

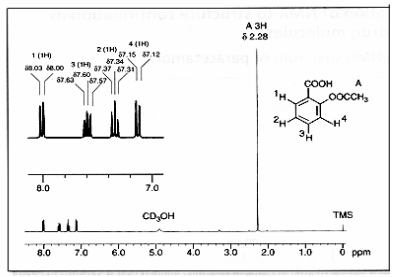


Different Isotopes Absorb at



low frequency — high frequency

Typical ^{1}H NMR Spectrum



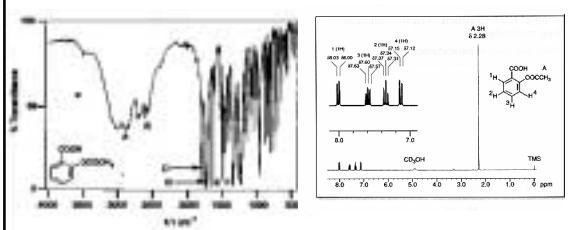
NMR Units of Measurement

- **Energies ~ 10^{-6} eV**
- **Wavelength ~ 30 cm - 100 cm**
- **Frequency ~ 10^{8} - 10^{9} Hz**
- **Parts per million (δ) 0 - 12 ppm (for ^{1}H)**

$$ppm = \frac{\nu_{obs} - \nu_{ref}}{\nu_{ref}} \times 10^{6}$$

ppm is proportional to frequency

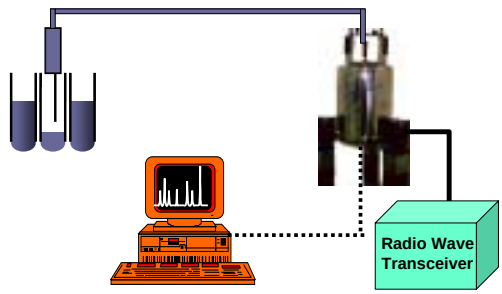
IR vs. NMR



NMR vs. IR

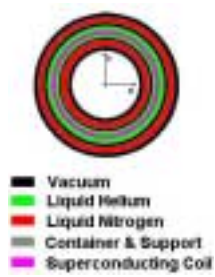
- NMR has narrower peaks relative to IR
- NMR yields far more information than IR
- NMR allows you to collect data on solids
- NMR is more quantitative than IR or UV
- NMR samples are easier to prepare
- NMR is much less sensitive than IR or UV
- NMR spectrometers are very expensive

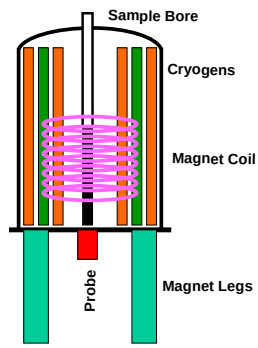
A Modern NMR Instrument



NMR Magnet

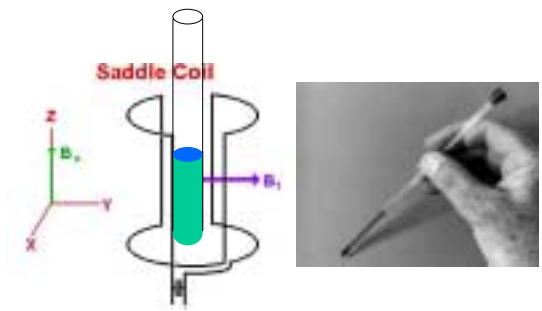
NMR Magnet Cross-Section



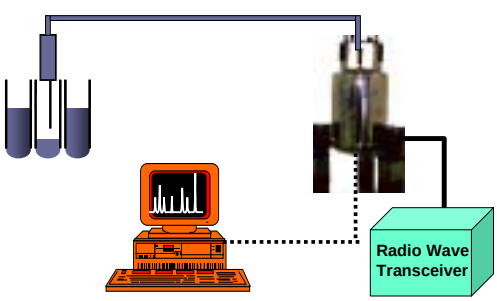


An NMR Probe

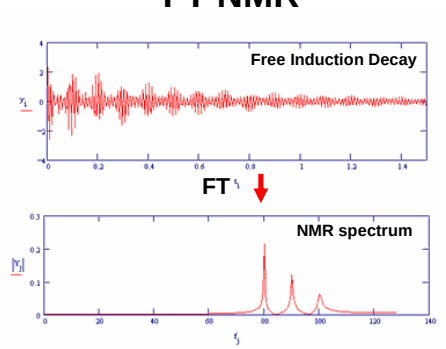
NMR Sample & Probe Coil



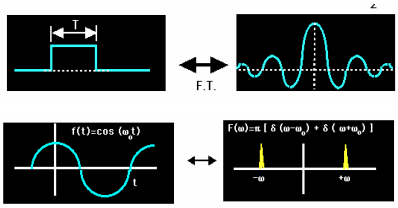
A Modern NMR Instrument



FT NMR



Fourier Transformation

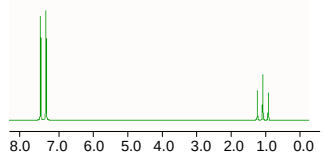


$$F(\omega) = \int f(t)e^{i\omega t}\,dt$$

Converts from units of time to units of frequency

^{1}H NMR Spectra Exhibit...

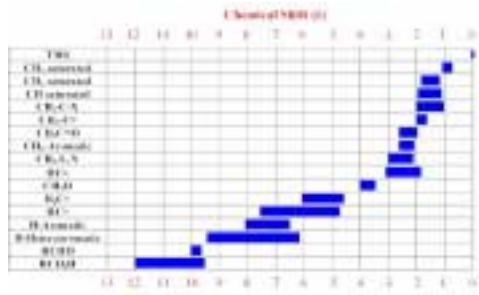
- Chemical Shifts (peaks at different frequencies or ppm values)
- Splitting Patterns (from spin coupling)
- Different Peak Intensities (# ^{1}H)



Chemical Shifts

- Key to the utility of NMR in chemistry
- Different ^{1}H in different molecules exhibit different absorption frequencies
- Arise from the electron cloud effects of nearby atoms or bonds, which act as little magnets to shift absorption ν up or down
- Mostly affected by electronegativity of neighbouring atoms or groups

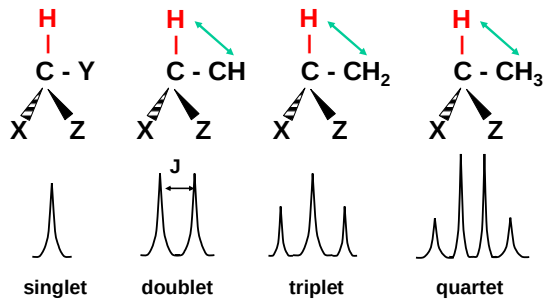
Characteristic Chemical Shifts



Spin-Spin Coupling

- Many ^{1}H NMR spectra exhibit peak splitting (doublets, triplets, quartets)
- This splitting arises from adjacent hydrogens (protons) which cause the absorption frequencies of the observed ^{1}H to jump to different levels
- These energy jumps are quantized and the number of levels or splittings = n + 1 where "n" is the number of nearby ^{1}H's

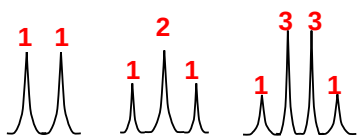
Spin-Spin Coupling



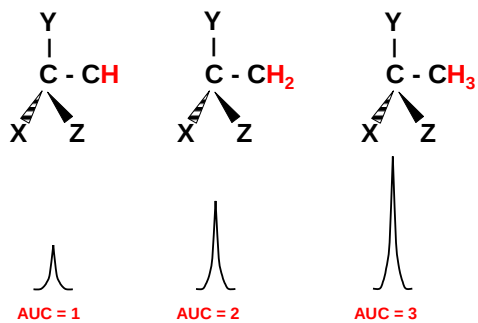
Spin Coupling Intensities

1
1 1
1 2 1
1 3 3 1
1 4 6 4 1
1 5 10 10 5 1

Pascal's Triangle



NMR Peak Intensities



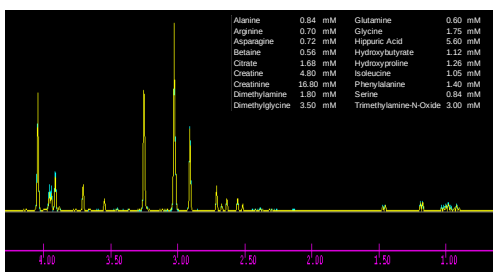
Applications

- Determination of exact structure of drugs and drug metabolites - MOST POWERFUL METHOD KNOWN
- Detection/quantitation of impurities
- Detection of enantiomers (shift reagents)
- High throughput drug screening
- Analysis/deconvolution of liquid mixtures
- Water content measurement

Metabonomics

- Analysis of blood, urine and other biofluid mixtures to quantify and identify metabolite changes
- Allows one to detect drug toxicity and even localize toxicity (for preclinical trials) in a non-invasive way
- Detection, identification and quantitation of primary and secondary drug metabolites

Metabonomics



Other Applications

- Clinical testing (detection of inborn errors of metabolism, cancer, diabetes, organic solvent poisoning, drugs of abuse, etc. etc.)
- Cholesterol and lipoprotein testing
- Chemical Shift Imaging (MRI + MRS)
- Pharmaceutical Biotechnology (proteins, protein drugs, SAR by NMR)