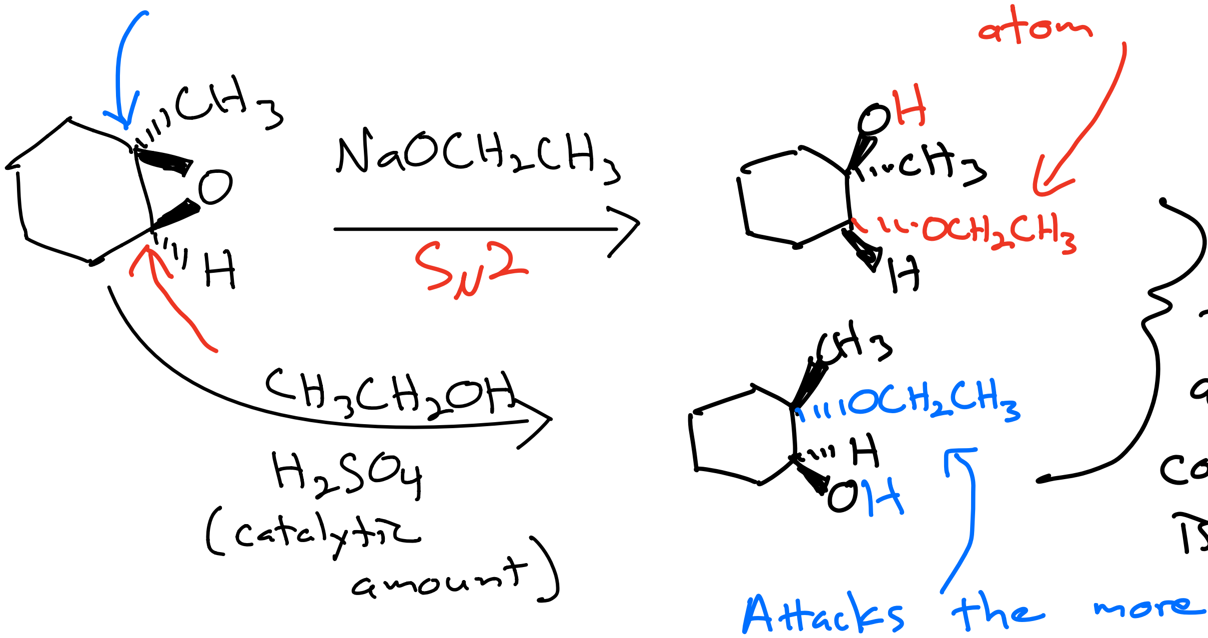
3rd Exam

Nomenclature	0%
Concepts	30%
Mechanisms	29%
Reactions	23%
Synthesis	18%

Works with alkoxides and alcohols as well

Attacks the less substituted carbon atom



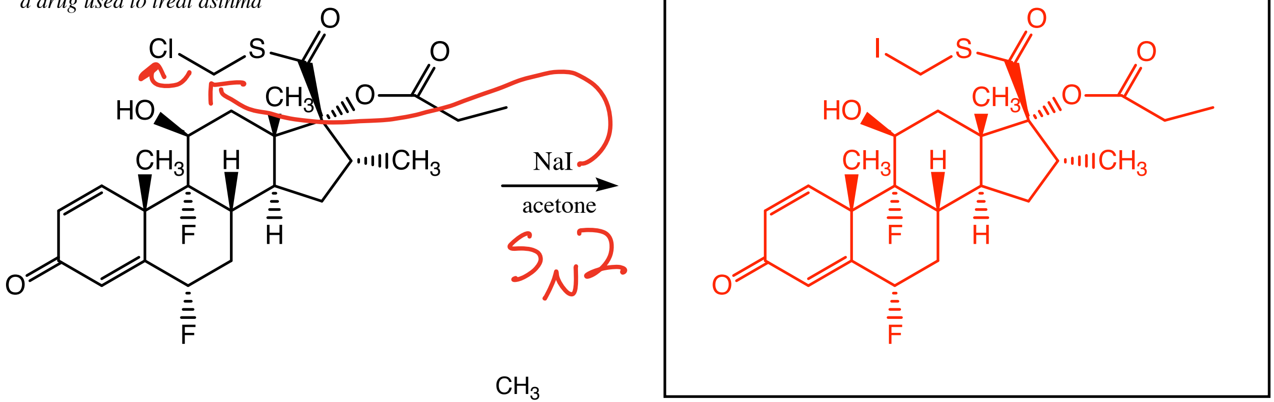
These are constitutional isomers!

Attacks the more substituted carbon atom!

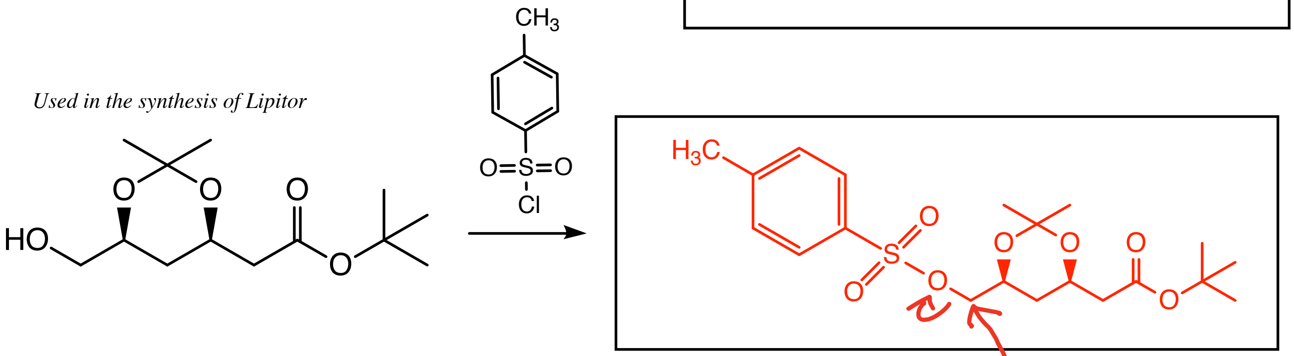
The key paradigm of organic chemistry: Functional groups react the same in complex molecules as they do in simpler ones.

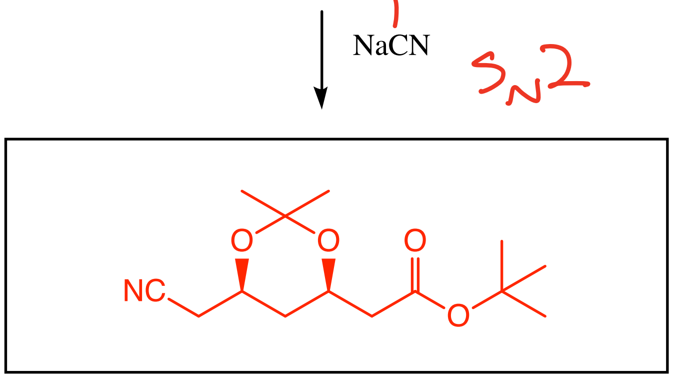
Reactions in the Context of Complex Molecules

Used in the synthesis of Fluticasone (Flonase), a drug used to treat asthma

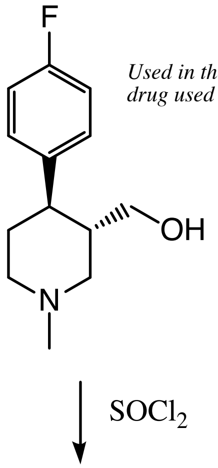


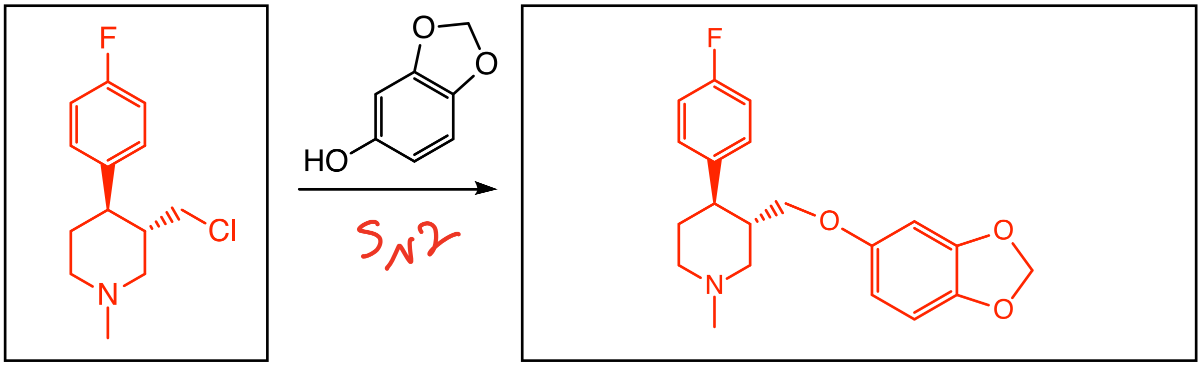
Used in the synthesis of Lipitor





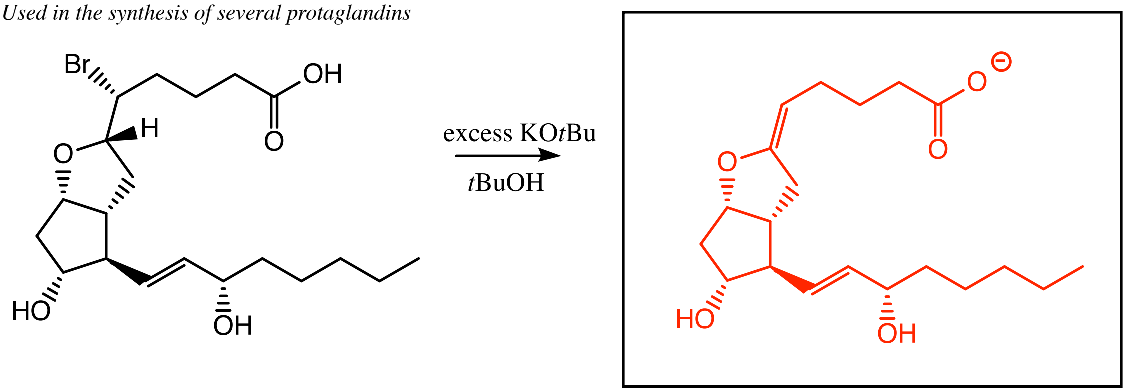
Used in the synthesis of Paxil, a drug used to treat depression



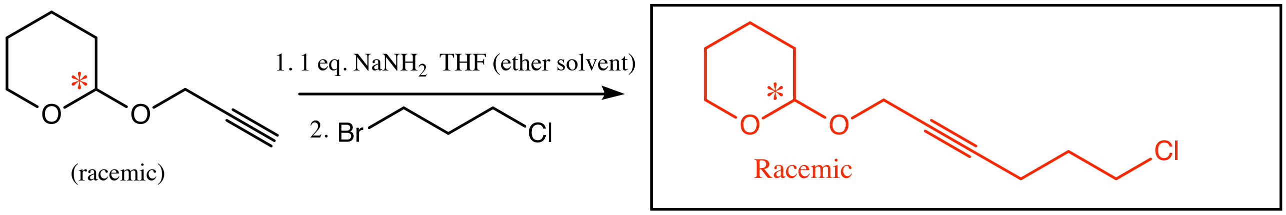


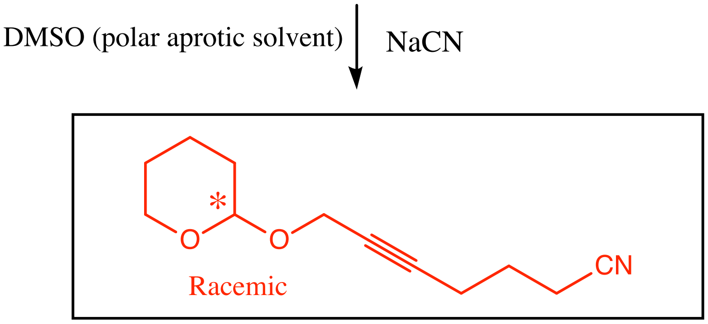
Reactions in the Context of Complex Molecules

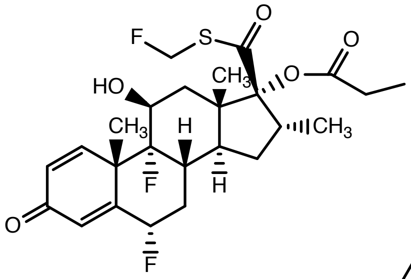
Used in the synthesis of several protaglandins



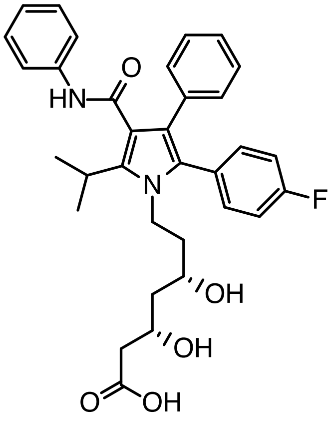
Used in the synthesis of protaglandin C_2

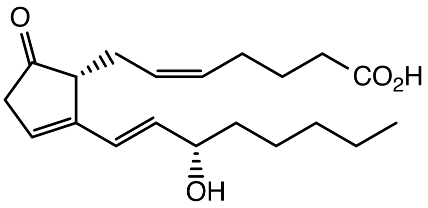




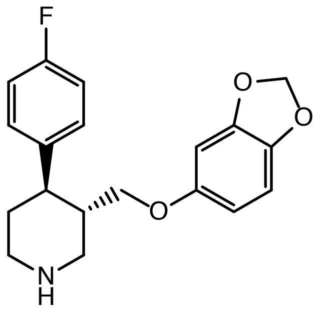


Fluticasone (Flonase)





Prostaglandin C_2

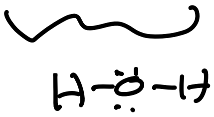


Paroxetine (Paxil)

Atorvastatin (Lipitor)

Here are some things I wish I had said when we were talking about substitution and elimination reactions:

Good leaving group → leaves to create a stable anion or molecule



Nucleophiles → not simple to explain what makes a good nucleophile → the Table for reference

Halogens → $Br^{\ominus}$, $I^{\ominus}$ are both good nucleophiles and good leaving groups

HOWEVER → not all nucleophiles are leaving groups!

Table of Nucleophiles

Strong Nucleophiles

Br^-, I^-, $R\text{-}S^-$, $H\text{-}S^-$, $N{\equiv}C^-$, N_3^-

Strong nucleophiles and good leaving groups

$Na^{\oplus}\,{}^{\ominus}CN$
NaCN
or
$K^{\oplus}\,{}^{\ominus}CN$
KCN
very useful!

$R\text{-}C{\equiv}C^-$, $R\text{-}O^-$, $H\text{-}O^-$ **Strong Bases**

Medium Nucleophiles

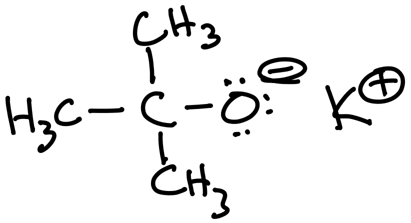
$R\text{-}CO_2^-$, $R\text{-}S\text{-}H$, R_2S,
NH_3, RNH_2, R_2NH, NR_3

Weak Nucleophiles

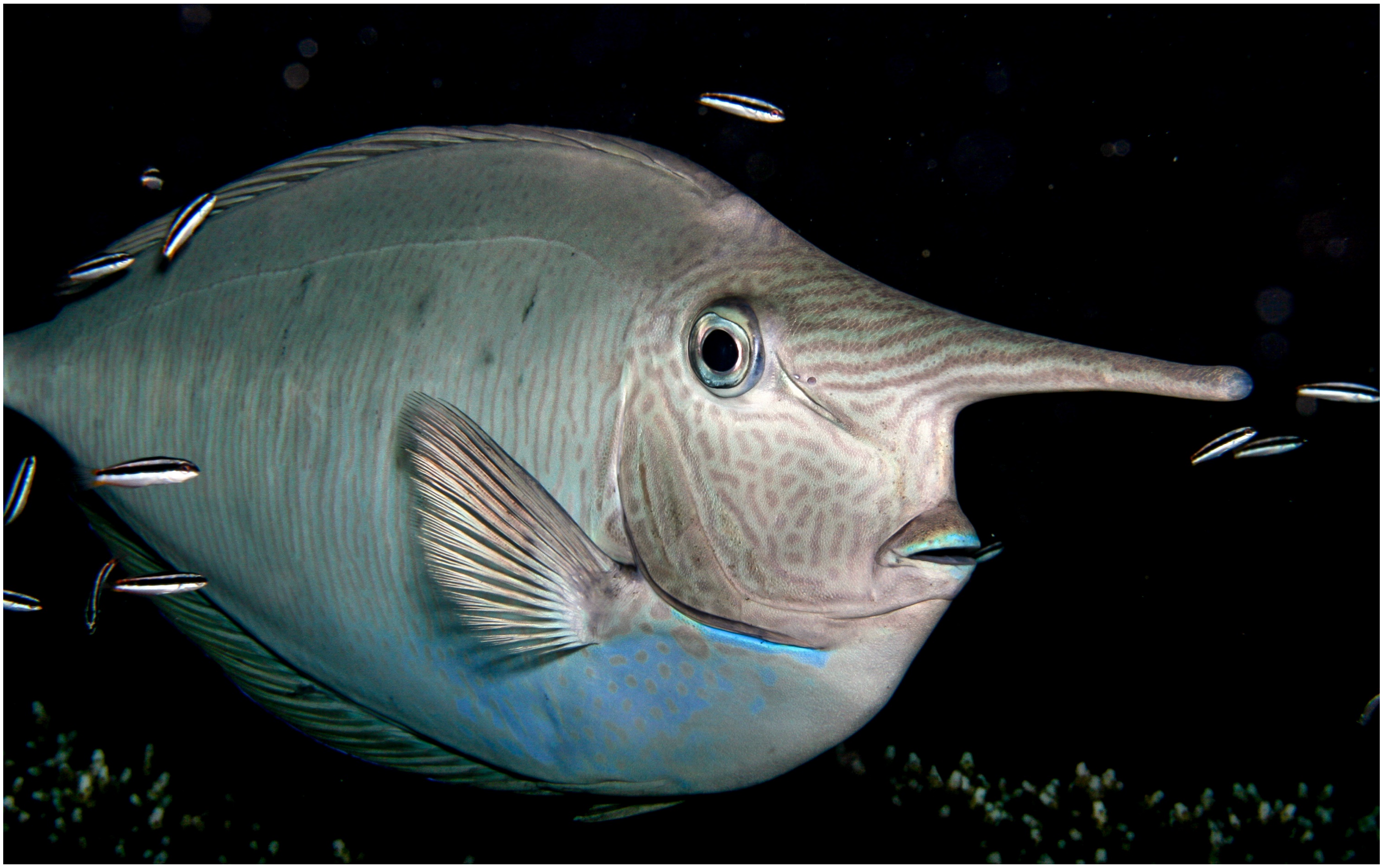
$R\text{-}CO_2H$, $R\text{-}O\text{-}H$, H_2O **Very Weak Bases**

Special Case

***Tert*-Butoxide ($tBuO^-$) is a strong base, but is not a nucleophile due to steric hindrance.**



"KOtBu"
or
"$tBuO^{\ominus}$"



To understand NMR you need to know the following:

A. Physics: Moving charge generates a magnetic field, and a moving magnetic field causes charges to move in a conductor.

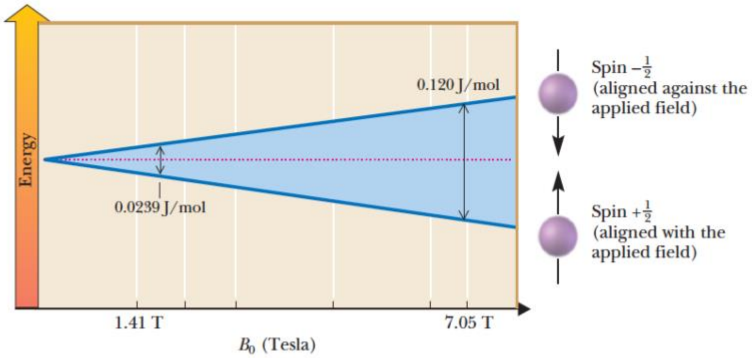
B. Atomic nuclei, like electrons, have a quantum mechanical property of "spin". Spin can be thought of as a small magnetic field around the nucleus created as if the positive charge of the nucleus were circulating.

C. NMR, nuclear magnetic resonance, is used to assign structures of organic molecules.

D. We care about the nuclei ^{1}H and ^{13}C since these are commonly found in organic molecules and they have spin quantum numbers of 1/2.

E. Nuclei with spin quantum number 1/2 are quantized in one of two orientations, "+1/2" (lower energy) or "-1/2"(higher energy) in the presence of an external magnetic field, that is, with and against the external field, respectively.

F. **The difference in energy between the +1/2 and -1/2 nuclear spin states is proportional to the strength of the magnetic field felt by the nucleus.**



G. Electron density is induced to circulate in a strong external magnetic field, which in turn produces a magnetic field that opposes the external magnetic field. This **shields** nuclei from the external magnetic field. The greater the electron density around a nucleus, the more shielded it is, and the lower the energy (frequency) of electromagnetic radiation required to flip its nuclear spin.

H. In the classic ^{1}H-NMR experiment, the molecule of interest is placed in solvent (the solvent has deuterium atoms in place of H atoms so the solvent molecules will not show up in the spectra, see R.) then is put in a spinning tube in a very strong magnetic field. The sample is exposed to radiofrequency irradiation and if it is of exactly the right frequency energy is absorbed and spins flip from +1/2 to -1/2 (come into resonance). The absorbed energy is plotted in the spectra.

I. All ^{1}H-NMR spectra are recorded as **chemical shift (∂, delta)** in the units of **ppm** (parts per million). Shielding magnetic field effects are around 1 millionth as large as the external magnetic field in which the sample is placed. Tetramethylsilane (TMS, $(CH_3)_4Si$)) is placed in the sample as a standard and assigned the value of 0.0 ppm. ***Warning the NMR scale is plotted "backwards", with higher values to the left!!***

Certain nuclei such as ^1H nuclei have a quantum mechanical property called spin that comes with an associated magnetic field.

^1H nuclei can exist in two different spin states, $+1/2$ and $-1/2$.

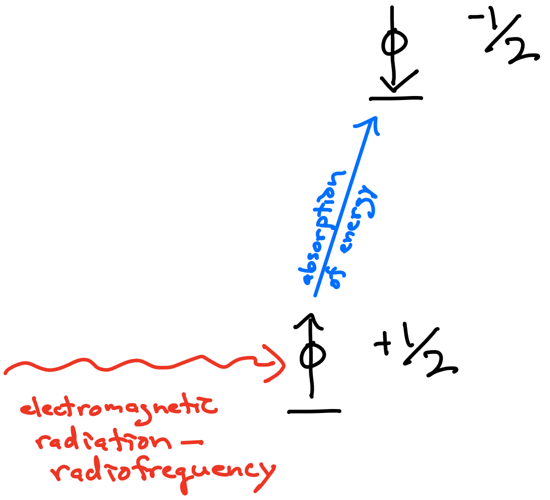
In a strong magnetic field, the nuclei with spin line up with $(+1/2)$ and against $(-1/2)$ the magnetic field.

Nuclei in the $+1/2$ spin state are of lower energy and nuclei in the $-1/2$ spin state are of higher energy in a magnetic field.

The difference in energy between the $+1/2$ and $-1/2$ spin states is directly proportional to the strength of the magnetic field experienced by the nuclei

Radiofrequency electromagnetic radiation of exactly the right energy (i.e. frequency) is absorbed by $+1/2$ spin state nuclei causing them to "flip" to the $-1/2$ spin state. ⇒ A process called "resonance"

NMR experiment → place sample of a molecule in a very very strong magnetic field



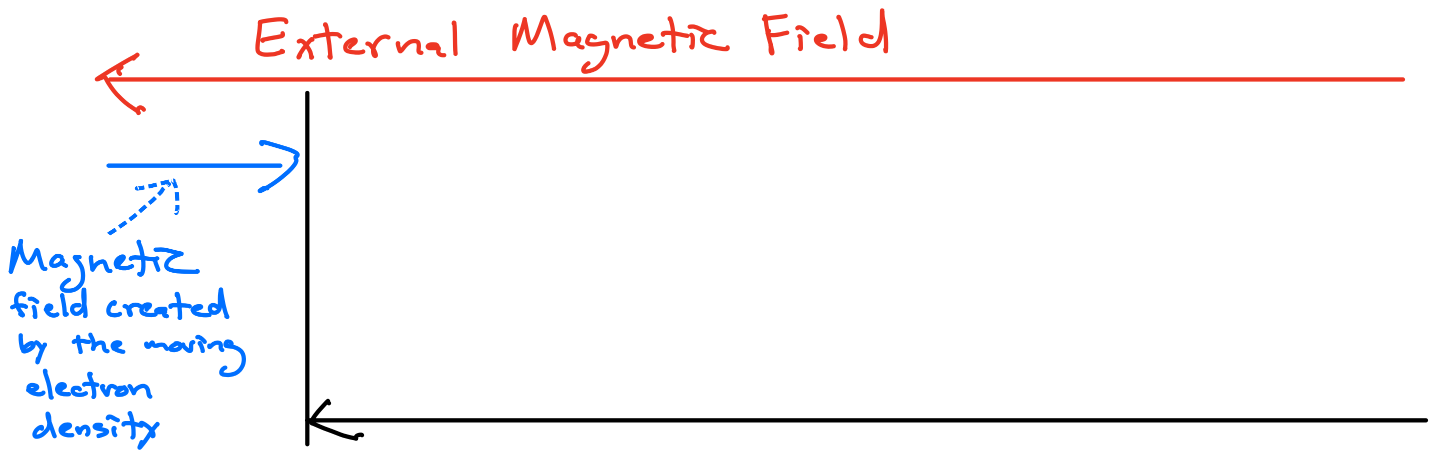
The energy absorption/nuclear spin flipping phenomenon is called "Resonance"

The ^1H nucleus of spin state $+1/2$ absorbs a quanta of energy of precisely the correct frequency and the nucleus is "excited" to the $-1/2$ spin state

Key Point → The energy of the of electromagnetic energy th is absorbed much match exactly the energy difference between the +½ and -½ nuclear spin states for resonance to happen

We monitor the energy that is absorbed by the nuclear spins as they flip

Shielding → explanation → The external magnetic field induces electron density to circulate, which creates its own magnetic field that always directly opposes the external magnetic field

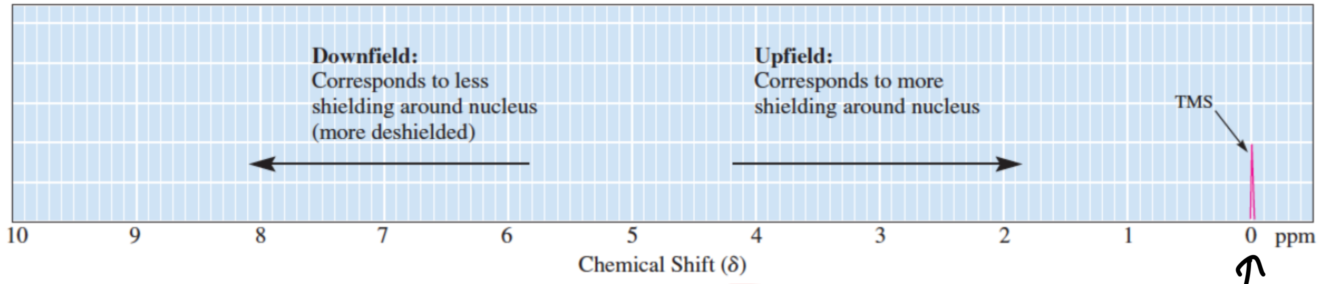


The magnitude of the magnetic field experienced by a nucleus under the electron density.

Shielding Bottom Line →

- ⇒ More electron density generates a larger opposing magnetic field so a nucleus under more electron density experiences a smaller magnetic field.
- ⇒ More electron density around a nucleus provides more shielding of the external magnetic field

Plot is backwards → larger values to the left!



Deshielding

Less electron density

Larger difference in energy between +½ and −½ nuclear spin states

Shielding

More electron density

Smaller difference in energy between +½ and −½ nuclear spin states

J. The hybridization state of carbon atoms attached to an H atom influences shielding in predictable ways by removing differing amounts of electron density around adjacent nuclei.

K. Electron density in pi bonds also has a large effect on H atom shielding because pi electrons are more free to circulate in an a magnetic field compared to electron density in sigma bonds. Geometry of the pi bond is important.

Table 13.3 The Effect of Hybridization on Chemical Shift

Type of Hydrogen (R = alkyl)	Name of Hydrogen	Chemical Shift (δ)
RCH_3, R_2CH_2, R_3CH	Alkyl	0.8–1.7
$R_2C{=}C(R)CHR_2$	Allylic	1.6–2.6
$RC{\equiv}CH$	Acetylenic	2.0–3.0
$R_2C{=}CHR$, $R_2C{=}CH_2$	Vinylic	4.6–5.7
$RCHO$	Aldehydic	9.5–10.1

Described by Maxwell's Equation

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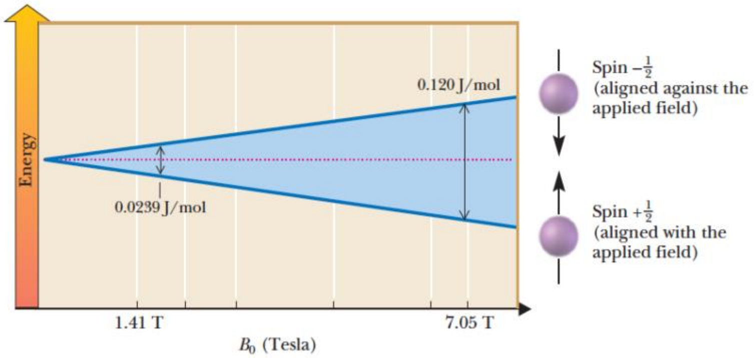

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