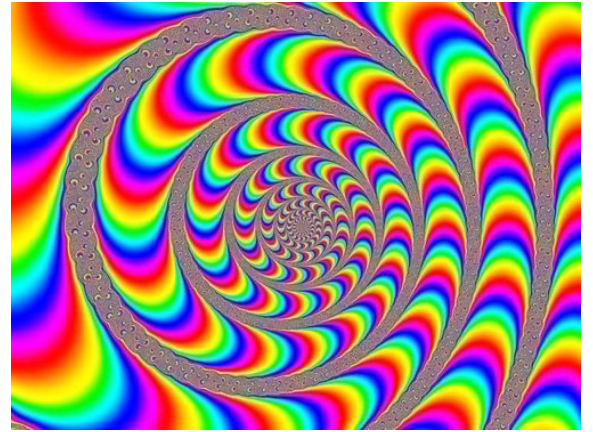
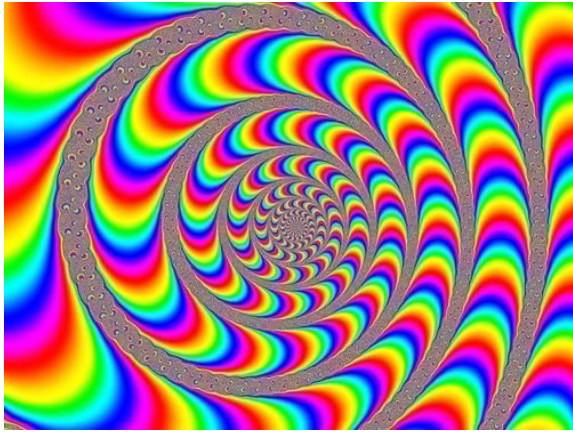


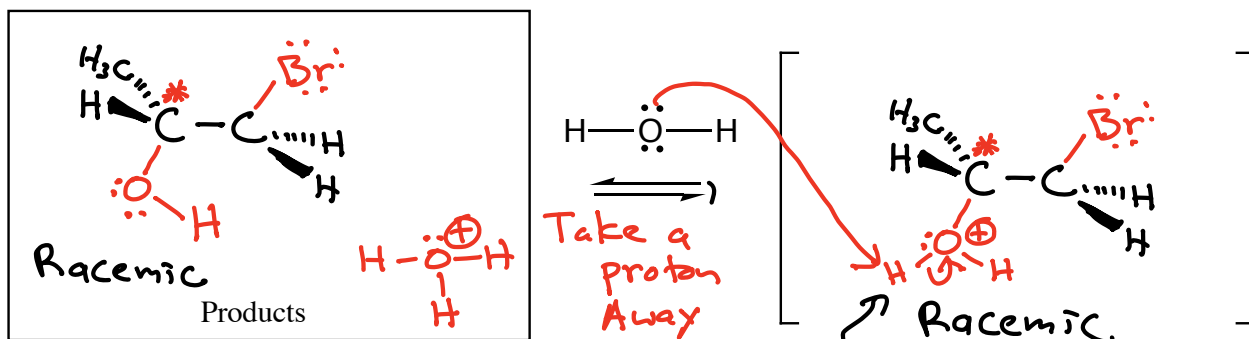
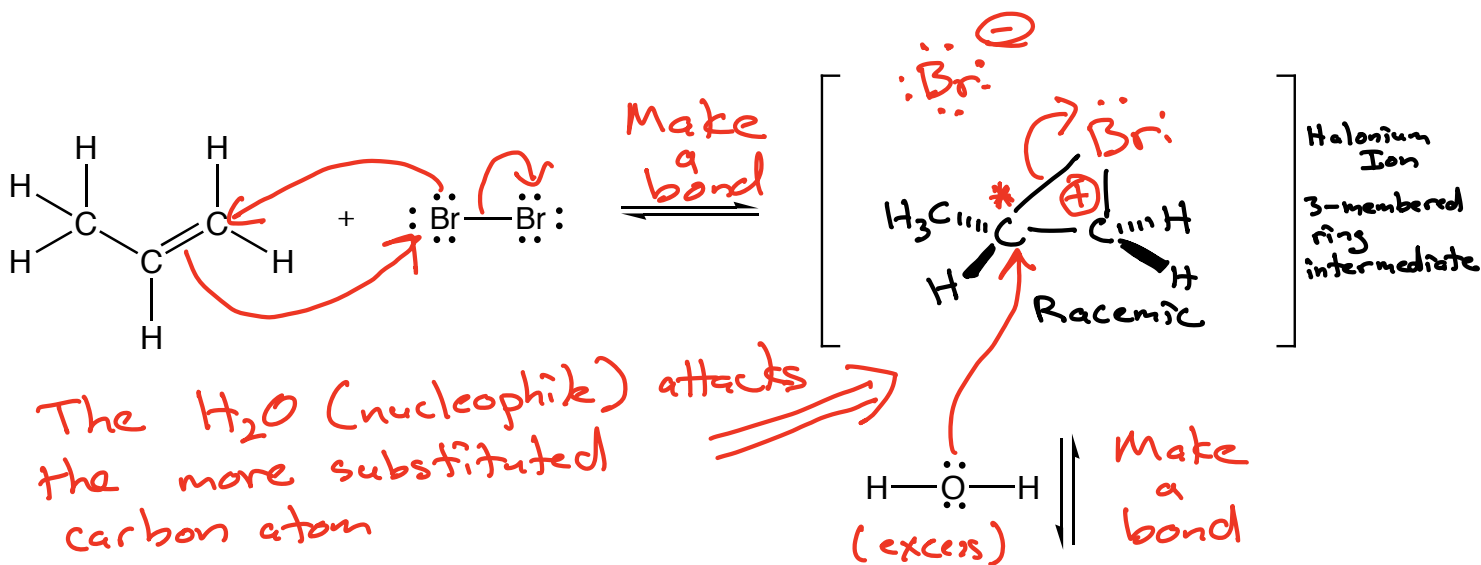




# Flashback!



# Alkene Hydrohalogenation



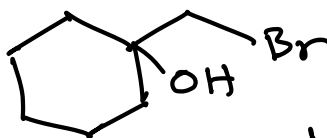
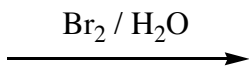
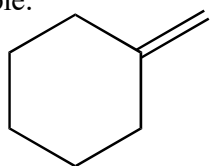
pH drops during the reaction!

Summary: Alkene reacts with  $\text{X}_2$  to give a 3-membered ring intermediate (halonium ion)  $\rightarrow$   $\text{H}_2\text{O}$  attacks the more substituted C atom and we take a proton away to give the halohydrin product.

Regiochemistry: Markovnikov (OH on more substituted C atom)

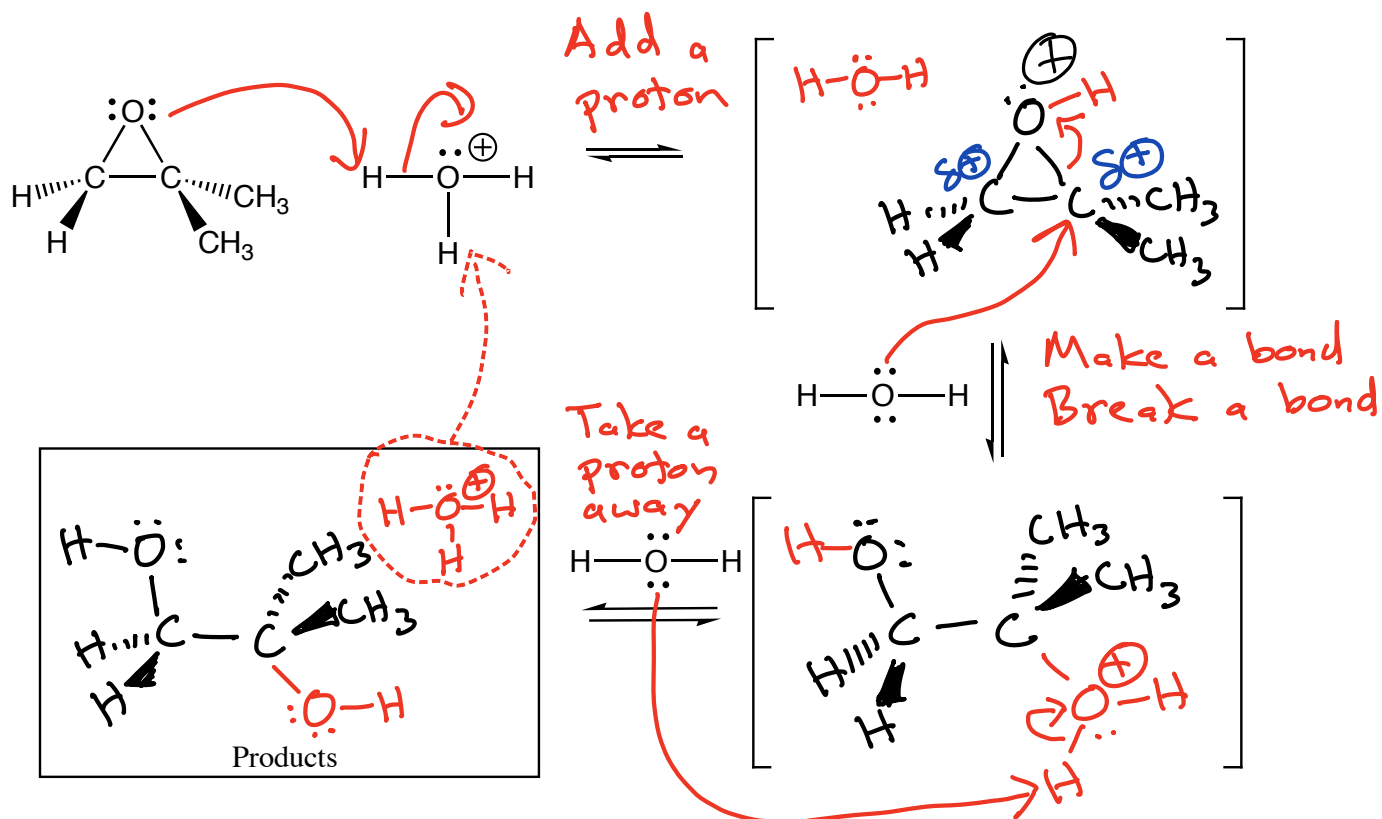
Stereochemistry: Anti

Example:



Not Chiral

## Acid-Catalyzed Epoxide Opening

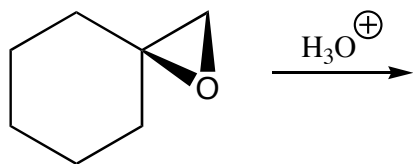


Summary: In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

Regiochemistry: "Markovnikov" Attack at more highly substituted carbon

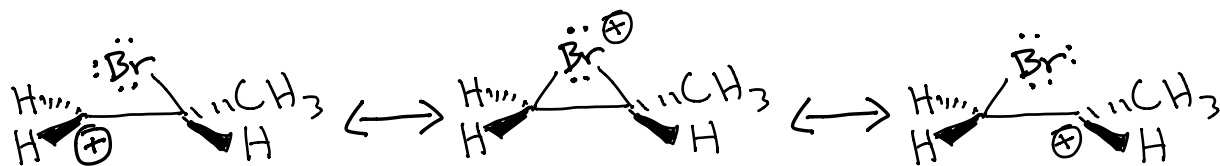
Stereochemistry: Anti

Example:





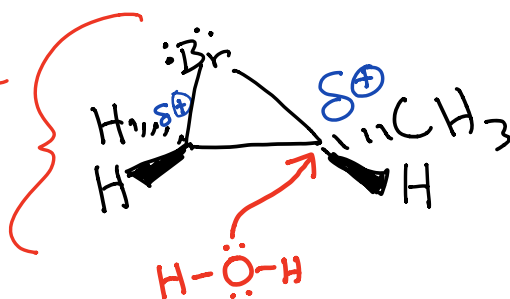
# Flashback → Halohydrin Mechanism



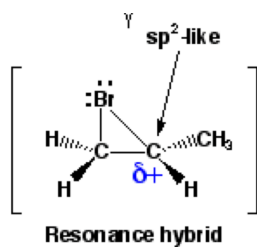
Minor Contributor

Major Contributor

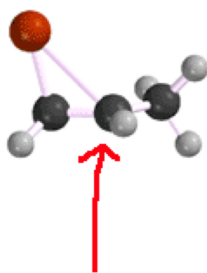
Resonance Hybrid



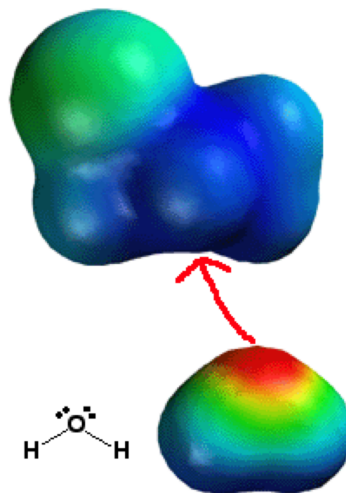
Water attacks the more substituted carbon atom because there is more partial  $\oplus$  charge



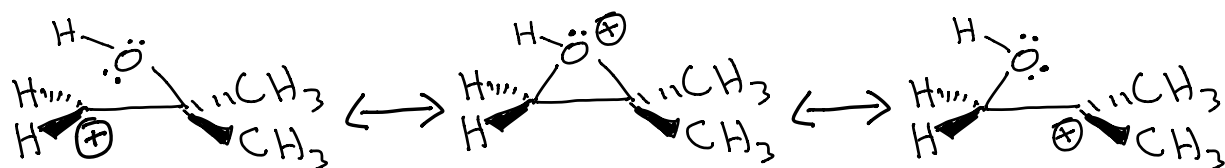
From "Pictures of the Day (POD)" 10-9-20



Nucleophiles Attack the More Positively-Charged Carbon Atom From This Face Leading to Markovnikov Regiochemistry and Trans Stereochemistry of Addition

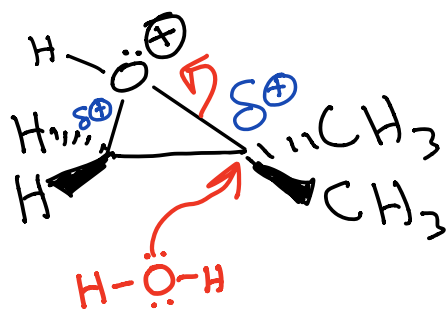


# Epoxide in acid

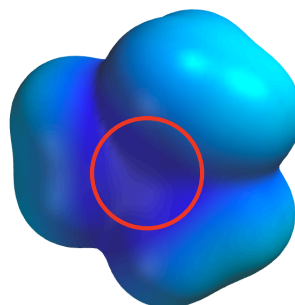
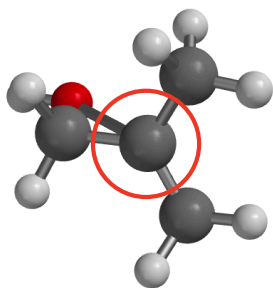
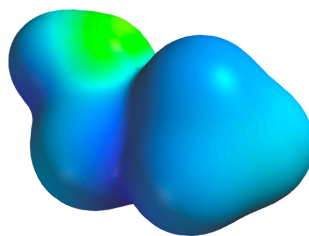
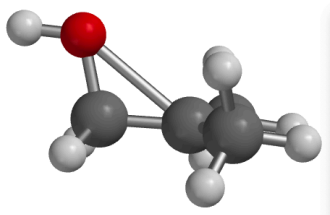


Minor Contributor

Major Contributor

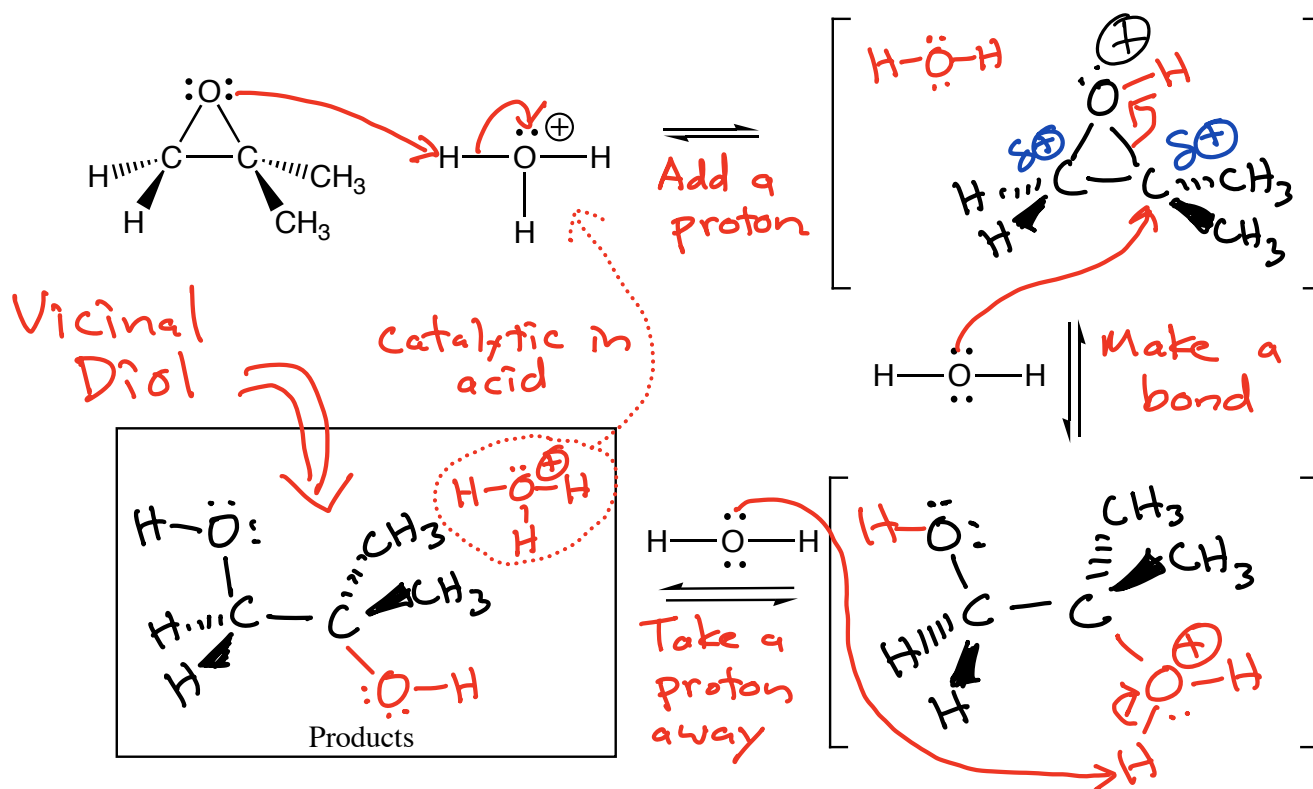


Side View





## Acid-Catalyzed Epoxide Opening

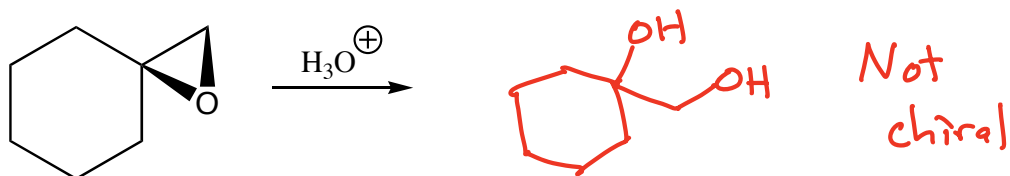


**Summary:** In acid, epoxides are protonated to give a highly reactive cation intermediate that reacts with nucleophiles at the more highly substituted carbon atom

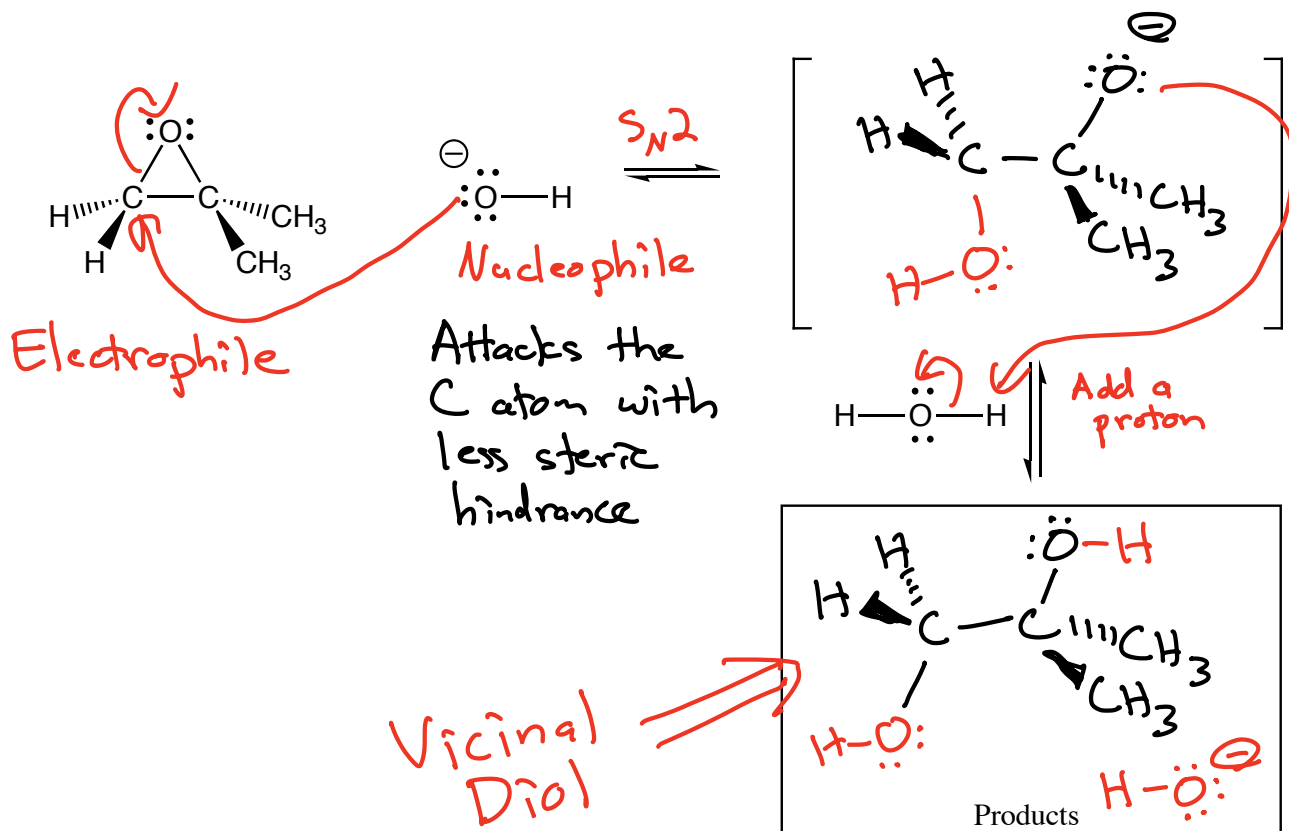
**Regiochemistry:** "Markovnikov" Attack at more highly substituted C atom

**Stereochemistry:** Anti ← !!!

**Example:**



# Nucleophilic ~~Base Promoted~~ Epoxide Opening

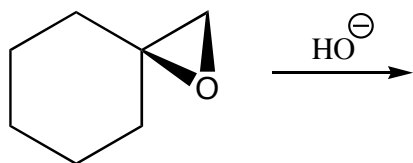


Summary: Epoxides add strong nucleophiles at the less hindered carbon atom

Regiochemistry: Less hindered (non-Markovnikov)

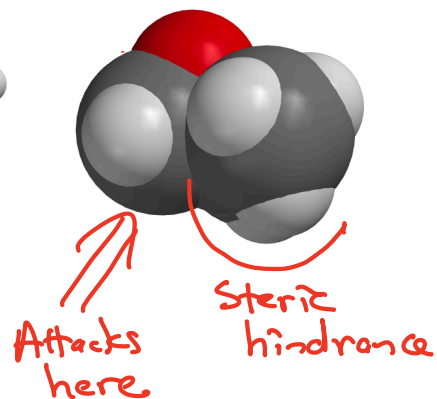
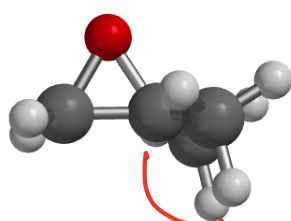
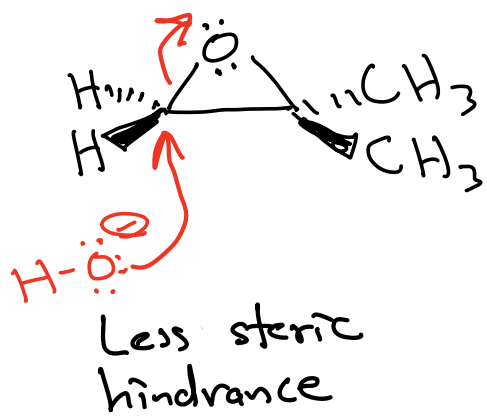
Stereochemistry: Anti addition

Example:



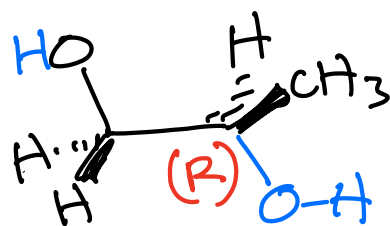
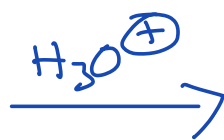
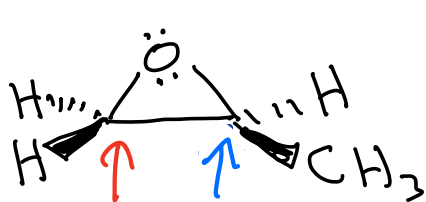


# Epoxide reacting with nucleophile

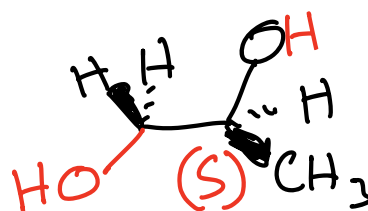


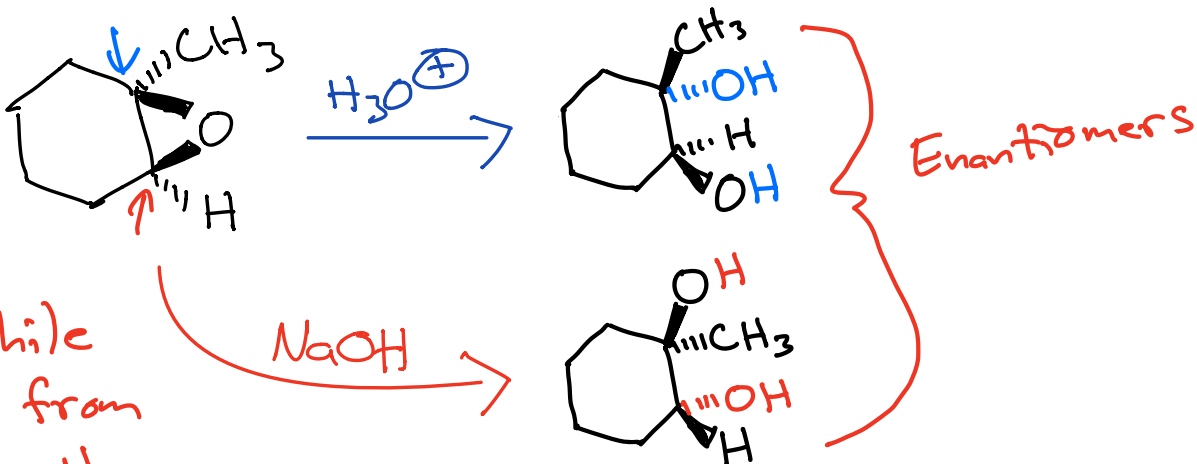
Watch out for the stereochemistry!

Single enantiomer



Anti products only!!

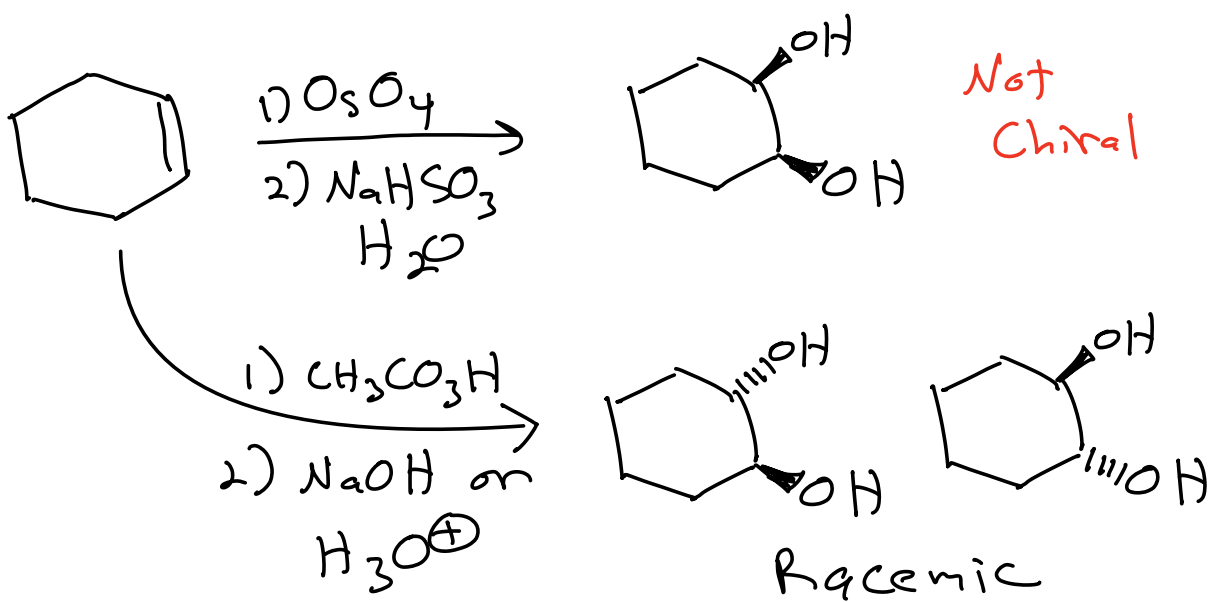




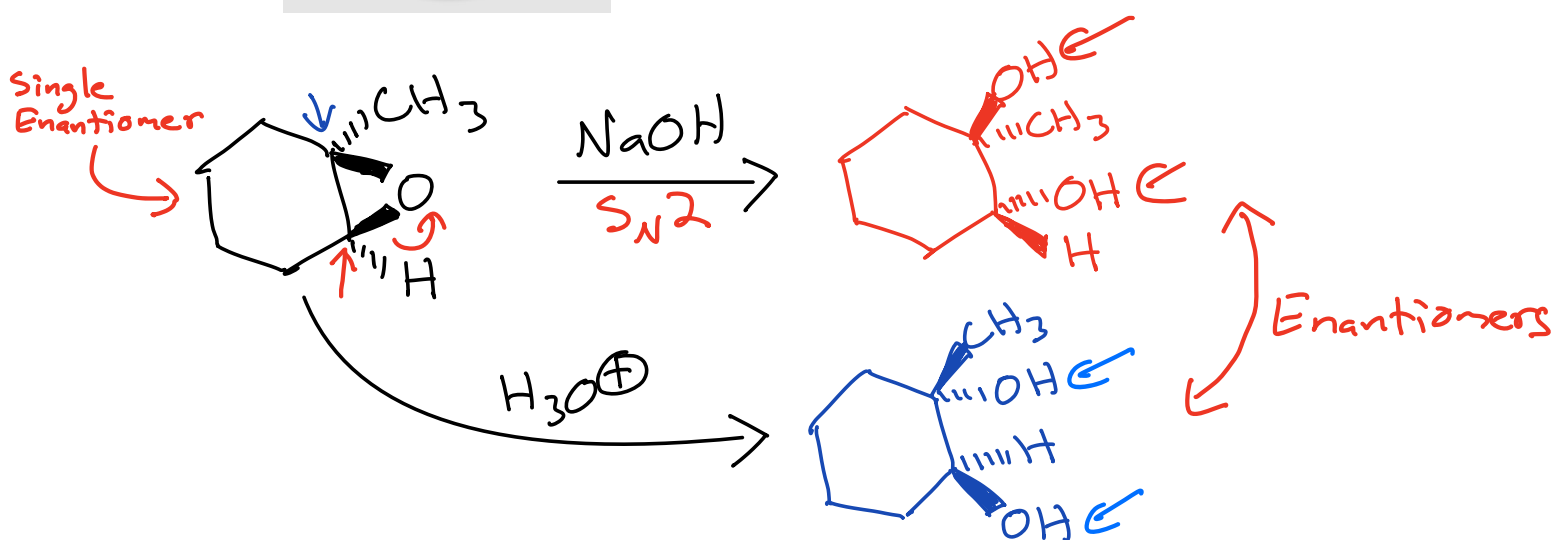
Nucleophile attacks from underneath

NaOH

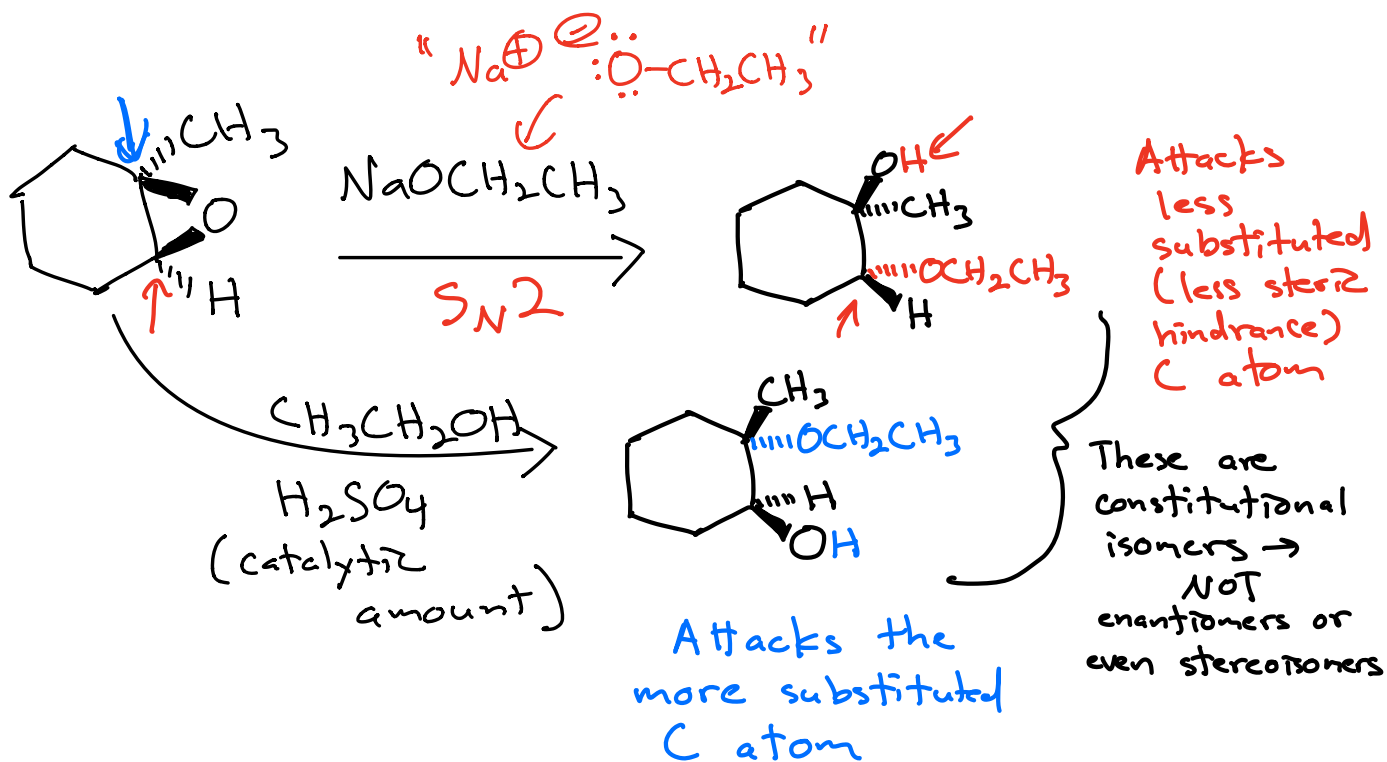




Watch out for the stereochemistry!



Works with alkoxides and alcohols as well)



Note: The attack always comes from behind the C-O bond of the epoxide



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

Good leaving group  $\rightarrow$  leaves to create a stable anion or molecule  
ex.  $\text{Br}^-$  ex.  $\text{H}_2\text{O}$

Nucleophiles  $\rightarrow$  not simple to explain what makes a good nucleophile  $\rightarrow$  the Table for reference

Halogens  $\rightarrow \text{Cl}^-, \text{Br}^-, \text{I}^- \rightarrow$  both good leaving groups and good nucleophiles

HOWEVER - not all nucleophiles are leaving groups

# Some things to notice

## Table of Nucleophiles

$Cl^-$

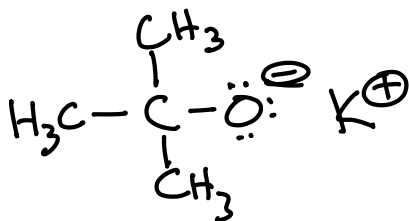
<b>Strong Nucleophiles</b> $Br^-$ , $I^-$ , $R-S^-$ , $H-S^-$ , $N\equiv C^-$ , $N_3^-$
$R-C\equiv C^-$ , $R-O^-$ , $H-O^-$ <b>Strong Bases</b>
<b>Medium Nucleophiles</b> $R-CO_2^-$ , $R-S-H$ , $R_2S$ , $NH_3$ , $RNH_2$ , $R_2NH$ , $NR_3$
<b>Weak Nucleophiles</b> $R-CO_2H$ , $R-O-H$ , $H_2O$ <b>Very Weak Bases</b>

Strong nucleophiles as well as being good leaving groups

$Na^+ \ominus CN$   
 $K^+ \ominus CN$   
or  
 $NaCN$   
 $KCN$   
 $\Downarrow$   
Very useful nucleophile

## Special Case

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



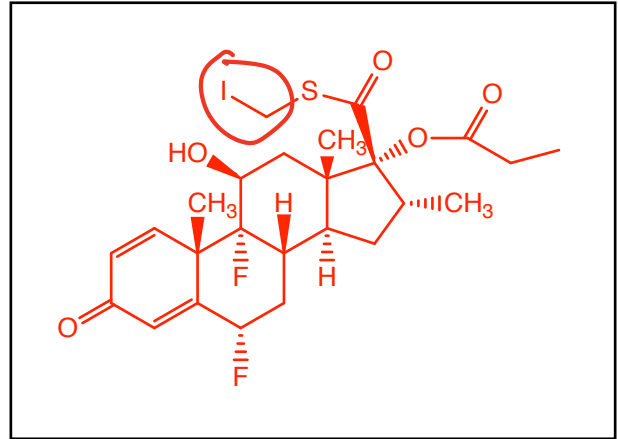
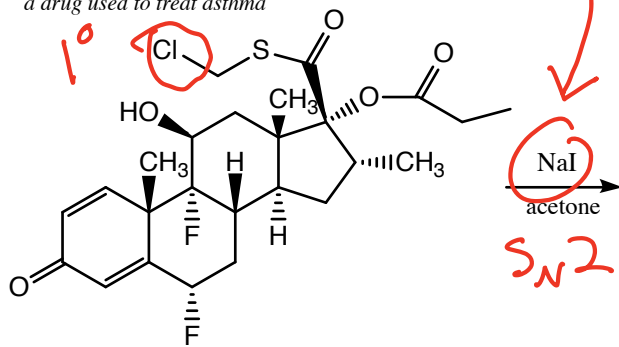
" $KOtBu$ "  
or  
" $tBuO^-$ "

# The Key Paradigm of Organic Chemistry

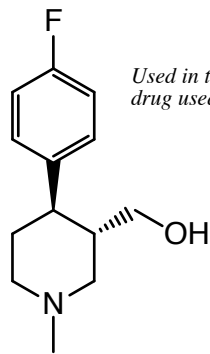
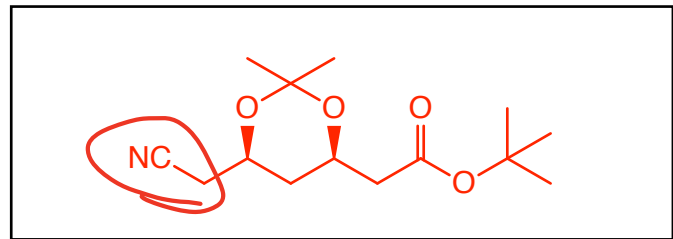
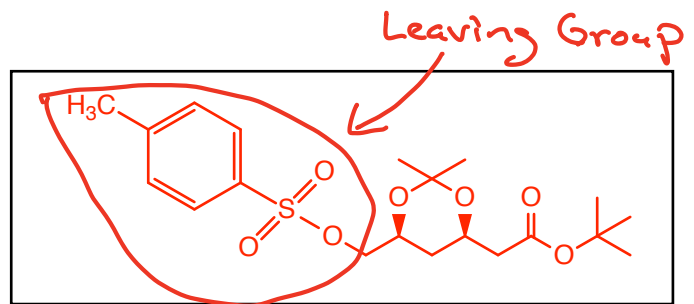
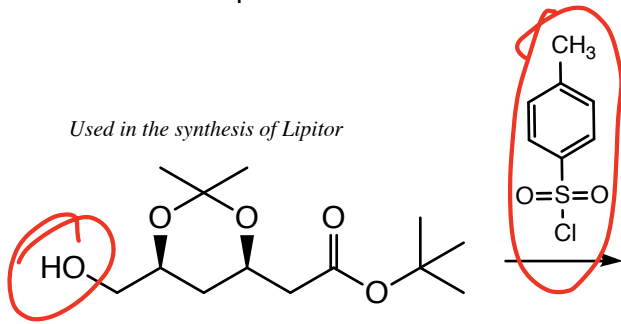
Functional groups react the same in complex molecules as they do in simple ones

## Reactions in the Context of Complex Molecules

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

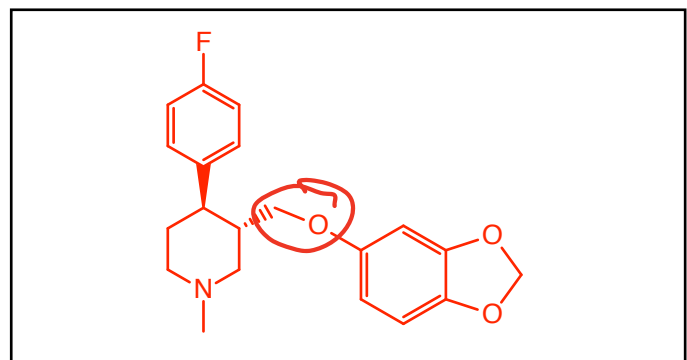
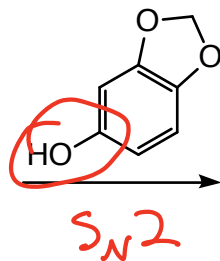
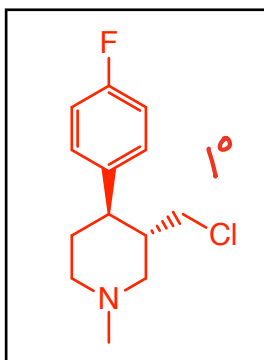


Used in the synthesis of Lipitor



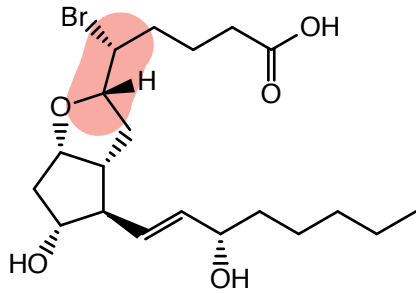
Used in the synthesis of Paxil, a  
drug used to treat depression

SOCl<sub>2</sub>

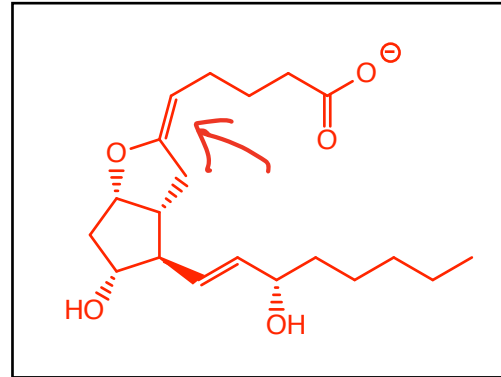


## Reactions in the Context of Complex Molecules

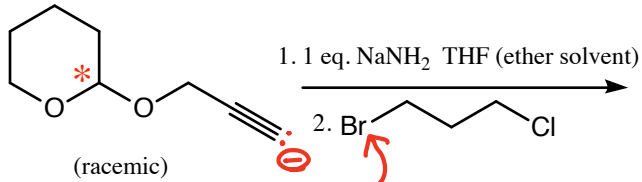
Used in the synthesis of several prostanoids



excess KOtBu  
tBuOH



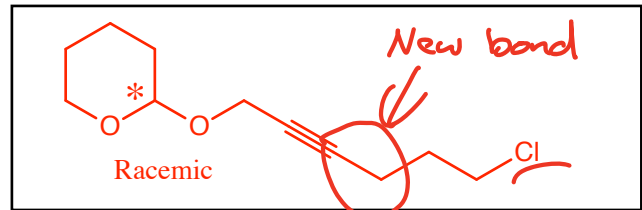
Used in the synthesis of prostaglandin C<sub>2</sub>



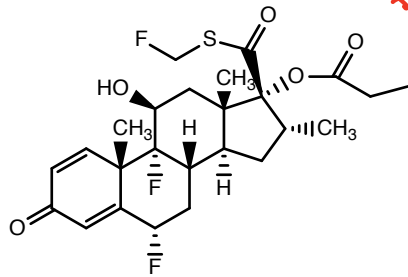
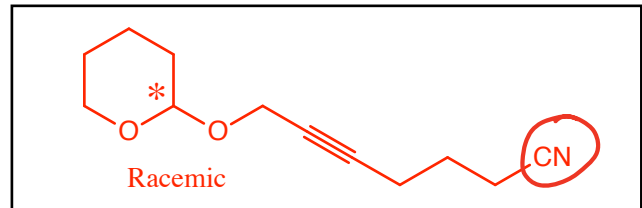
1. 1 eq. NaNH<sub>2</sub> THF (ether solvent)

2. Br-CH<sub>2</sub>-CH<sub>2</sub>-CH<sub>2</sub>-Cl

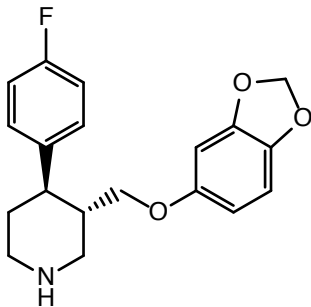
Better leaving group - reacts first



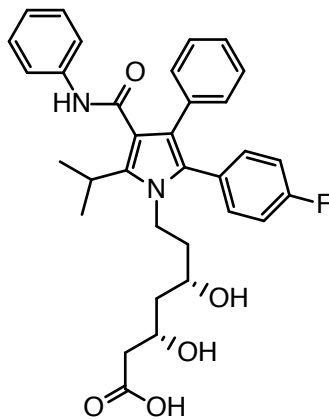
DMSO (polar aprotic solvent) NaCN S<sub>N</sub>2



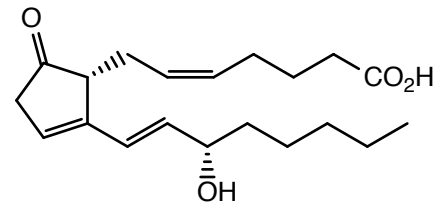
Fluticasone (Flonase)



Paroxetine (Paxil)



Atorvastatin (Lipitor)



Prostaglandin C<sub>2</sub>



**Organic Chemistry is the study of carbon-containing molecules.**

**This class has two points.**

***The first point of the class is to understand the organic chemistry of living systems. We will teach you how to think about and understand the most amazing things on the planet!!***

Water is essential for life, you will learn why water has such special properties. 8/28/24

You will learn the secret structural reason proteins, the most important molecular machines in our bodies, can support the chemistry of life. 9/11/24

You will learn why when you take Advil for pain, exactly half of what you take works, and the other half does nothing. 9/25/24

You will learn how toothpaste works. 10/7/24

You will learn how a single chlorofluorocarbon refrigerant molecule released into the atmosphere can destroy many, many ozone molecules, leading to an enlargement of the ozone hole. 10/30/24

You will learn how medicines like Benadryl, Seldane, and Lipitor work. 11/13/24

You will learn how Naloxone is an antidote for an opioid overdose.

You will learn why Magic Johnson is still alive, decades after contracting HIV.

You will learn how MRI scans work.

***The second point of organic chemistry is the synthesis of complex molecules from simpler ones by making and breaking specific bonds.***

You will learn how to understand movies of reaction mechanisms like alkene hydration. 10/9/24

You will learn reactions that once begun, will continue reacting such that each product molecule created starts a new reaction until all the starting material is used up. 10/30/24

You will learn reactions that can make antifreeze from vodka. 11/13/24

You will learn a reaction that can make nail polish remover from rubbing alcohol. 11/16/24

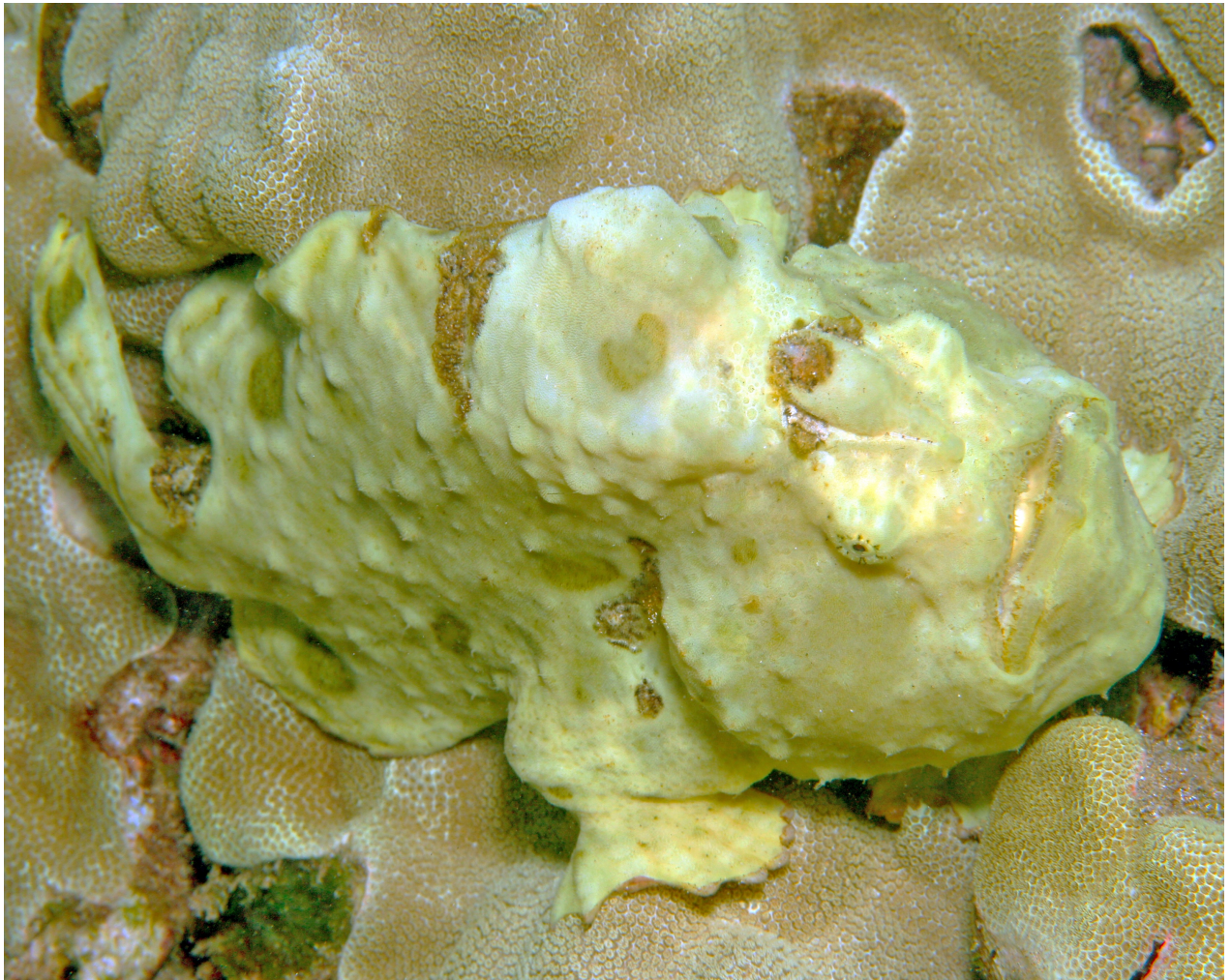
You will learn how to look at a molecule and accurately predict which atoms will react to make new bonds, and which bonds will break during reactions. 11/20/24

You will learn how to analyze a complex molecule's structure so that you can predict ways to make it via multiple reactions starting with less complex starting molecules. 11/20/24













Described by  
Maxwell's Equation

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.

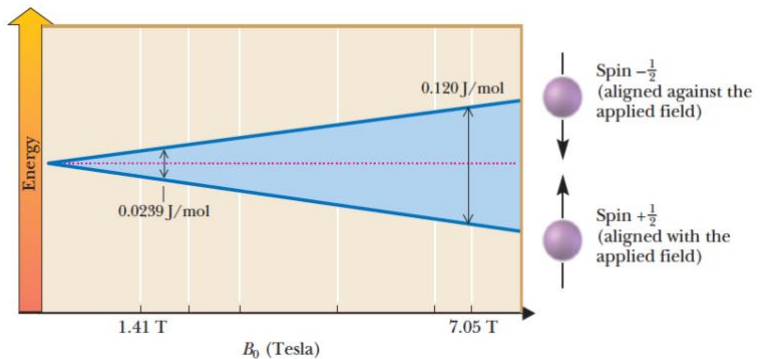
B. Atomic nuclei, like electrons, have a quantum mechanical property of "spin". Spin can be thought of as a small magnetic field around the nucleus created as if the positive charge of the nucleus were circulating.

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

D. We care about the nuclei  $^1\text{H}$  and  $^{13}\text{C}$  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.



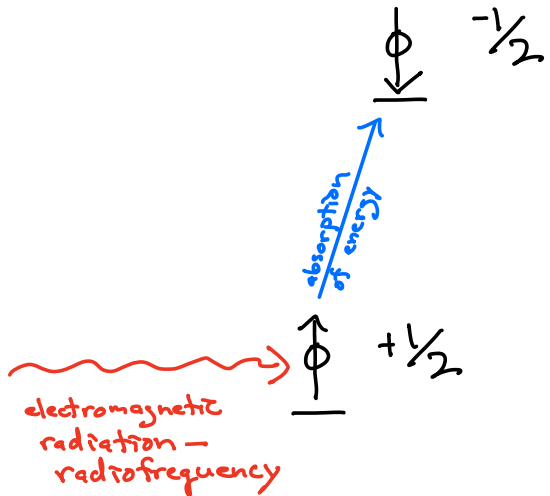
G. Electron density is induced to circulate in a strong external magnetic field, which in turn produces a magnetic field that opposes the external magnetic field. This **shields** nuclei from the external magnetic field. The greater the electron density around a nucleus, the more shielded it is, and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

H. In the classic  $^1\text{H}$ -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  $^1\text{H}$ -NMR spectra are recorded as **chemical shift ( $\delta$ , 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,  $(\text{CH}_3)_4\text{Si}$ ) 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!!**



NMR experiment  $\rightarrow$  place sample of a molecule in a very strong magnetic field



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

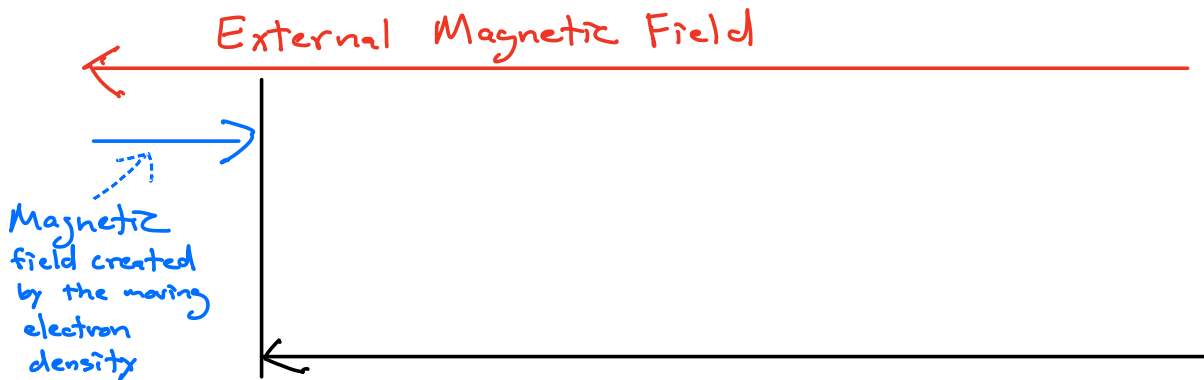
The  $^1\text{H}$  nucleus of spin state  $+\frac{1}{2}$  absorbs a quantum of energy of precisely the correct frequency and the nucleus is "excited" to the  $-\frac{1}{2}$  spin state.

Key Point → The energy of the of electromagnetic energy that is absorbed must match exactly the energy difference between the  $+\frac{1}{2}$  and  $-\frac{1}{2}$  nuclear spin states for resonance to happen

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

## Shielding $\rightarrow$ explanation

The external magnetic field induces electron density to circulate, which creates its own small magnetic field that will always directly oppose the external magnetic field.



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