



# CHEM 233 FINAL EXAM PREP

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# FREE PREVIEW

## 01 Lecture Video: Hydrogenation

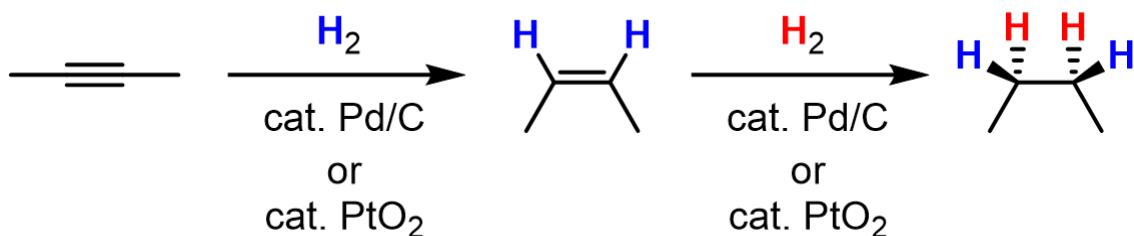
### Hydrogenation

**Key Reactions (3):** 1. Metal-catalyzed Hydrogenation; 2. Lindlar Catalyst; 3. Metal/Liquid Ammonia

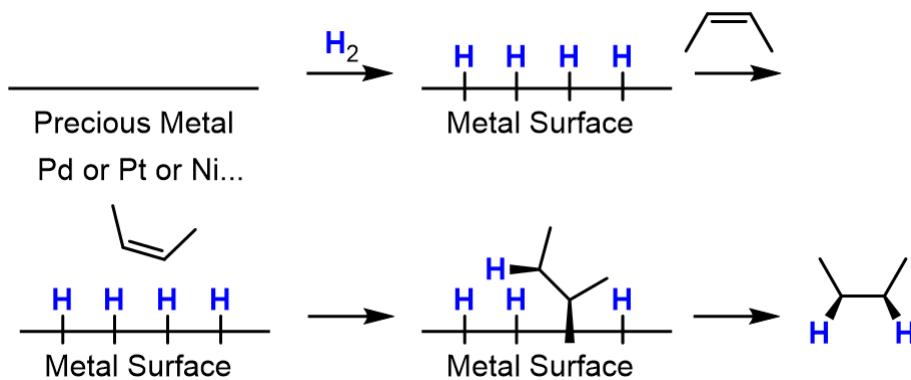
Hydrogenation refers to a type of reduction reaction where two hydrogen atoms are added across a multiple bond. In this case it refers to the reduction of alkenes and alkynes, but other functional groups (e.g. imines, ketones) can be reduced.

#### 1. Metal-catalyzed Hydrogenation

The most general type of hydrogenation involves hydrogen gas ( $H_2$ ) and a metal catalyst (most commonly Pd, Pt, Ni), see below. Due to the reaction conditions the reaction can't be stopped (if starting with an alkyne), everything is reduced to an alkane.

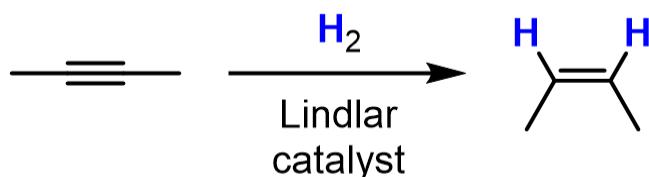


Metal-catalyzed hydrogenation is an example of **heterogeneous catalysis** (a process involving substances in different phases). In this case, **gaseous  $H_2$**  reacts with the metal surface to create **metal hydrides** that react with alkenes/alkynes. Due to the mechanism, the hydrogen atoms are delivered ***syn***.

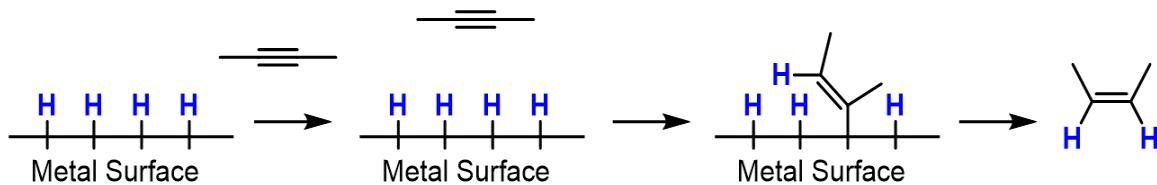


## 2. Lindlar Catalyst

There are scenarios when you will want to reduce alkynes to alkenes. Simple metal-catalyzed hydrogenation won't work since the reaction can't stop at an alkene! The **Lindlar catalyst**, a poisoned catalyst, was developed to stop the reduction at the *cis*-alkene. [Lindlar catalyst = Pd-CaCO<sub>3</sub>, Pb(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, Quinoline].

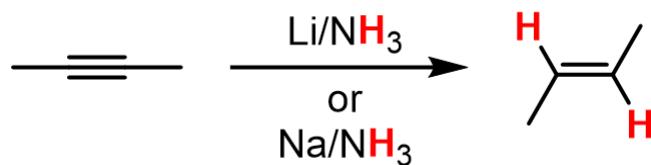


The reaction is still technically follows the same mechanism as metal-catalyzed hydrogenation (see below), but the catalyst design stops the reaction after the alkene is produced. The result is a *cis*-alkene.



## 3. Metal/Liquid Ammonia

What about trans-alkenes? These can be synthesized from alkynes using a reduction reaction with Lithium (Li) or Sodium (Na) metal in liquid Ammonia (NH<sub>3</sub>).

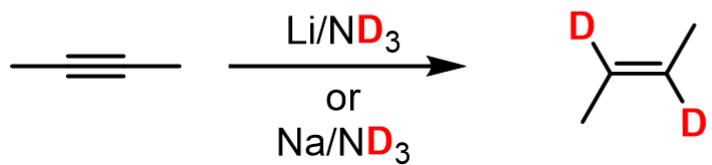
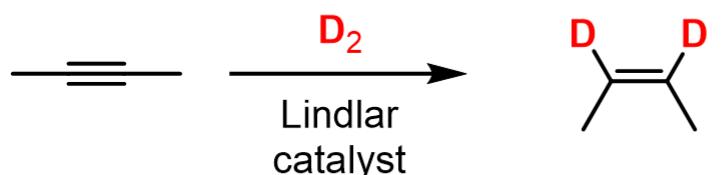
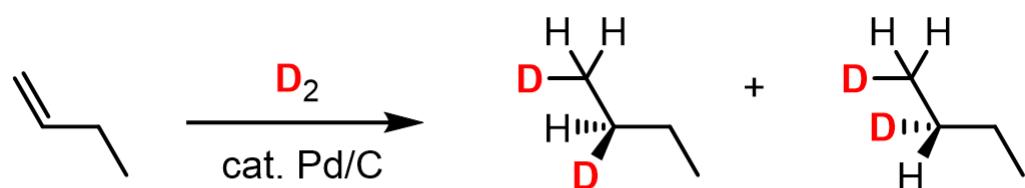


It's important to recognize the difference between sodium amide (NaNH<sub>2</sub>) and sodium/ammonia (Na/NH<sub>3</sub>). They both have applications in alkyne chemistry, but have completely different reactivities:



### Deuterium atoms in Hydrogenation Reactions

Deuterium, a heavier isotope of hydrogen (abbreviated <sup>2</sup>H or D), reacts in the same way as the hydrogen atom. Sometimes deuterium atoms will appear in exam questions to **check your understanding** of certain reactions. Deuterium is different from hydrogen, so it can create **chiral centres** (top example)!



## 02

## Section Quiz: Acid/Base Equilibria

# Wize Quiz

## Acid/Base Quiz (5 Qu.)

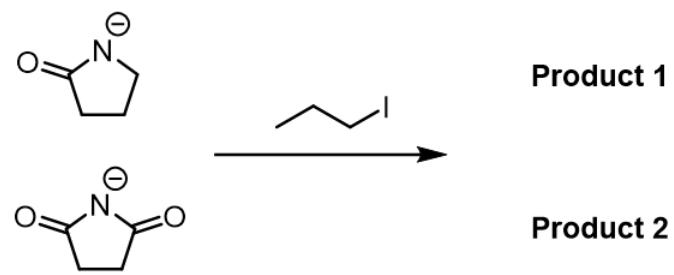
Find the full exam-like practice quiz  
with step-by-step solutions on  
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03 —————

### Concept Clarifier: Substitution Question

#### CONCEPT CLARIFIER

Draw the structures of product 1 and product 2. Which product forms faster?  
Justify your answer using pictures!!





**04** — **Practice Exam Questions**

## Wize Quiz

### Practice Exam 1 (6 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
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# FUNDAMENTALS

## 01 Lewis Structures and Formal Charges

### Lewis Structures and Formal Charges

#### Lewis Structures

Lewis structures, or Lewis dot diagrams, allow us to see how electrons are arranged around an atom by showing bonding pairs of electrons (BPe<sup>-</sup>s) and lone pairs of electrons (LPe<sup>-</sup>s). This lets us determine the molecular shape and geometry.

#### Representative Question

Provide Lewis Structures for the following compounds: NO<sub>3</sub><sup>-</sup>, N<sub>3</sub><sup>-</sup>, I<sub>3</sub><sup>+</sup>

#### Formal Charges

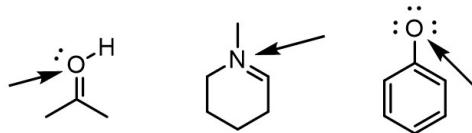
Formal charges allow us to see the charge on an atom (either neutral, positive, or negative) in a **Lewis structure**. Each atom will have a charge, usually neutral, that will be dictated by the number of bonds or lone pairs.

Formal charge is calculated using the following equation

$$\text{FC(atom)} = \# \text{ valence e}^- - (\text{lone pair e}^- + \text{number of bonds})$$

#### Representative Question

What is the formal charge on the indicated atom?



### WIZE's Rules for Drawing Lewis Structures

1. Position most electropositive atom in the middle, with more electronegative atoms around it
2. Add valence electrons (be aware of overall molecule charge) and form bonds between the central and terminal atoms (1 bond = 2 electrons)
3. Complete the octets of the terminal atoms by moving electrons out from the central atom
4. Calculate formal charges and add double bonds if necessary
5. Check to make sure all atoms have complete octets, and that if they don't it is allowed\*

*Carbon and Nitrogen can ONLY form 4 bonds!!!*

\* The octet rule exists because in organic chemistry many of the atoms we are dealing with are in the 2<sup>nd</sup> row of the p-block, and therefore can hold a maximum of 8 electrons. This is because the valence shell holds s-orbitals and p-orbitals (2 e<sup>-</sup> in s, and 2e<sup>-</sup> x 3 in p = 8e<sup>-</sup>). Often, only the heavier atoms S and P are discussed so extended valence structures are possible (more than 4 bonds).

**Draw the Lewis Structure for CO<sub>3</sub><sup>2-</sup>**

### CONCEPT CLARIFIER

Provide Lewis Structures for the following compounds:  $\text{NO}_3^-$ ,  $\text{N}_3^-$ ,  $\text{I}_3^+$ . Include formal charges on atoms as necessary

02

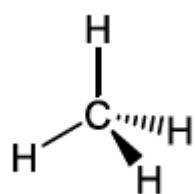
## Valence Bond Theory, Hybridization, MO Theory, and Resonance

### Valence Bond Theory and Hybridization

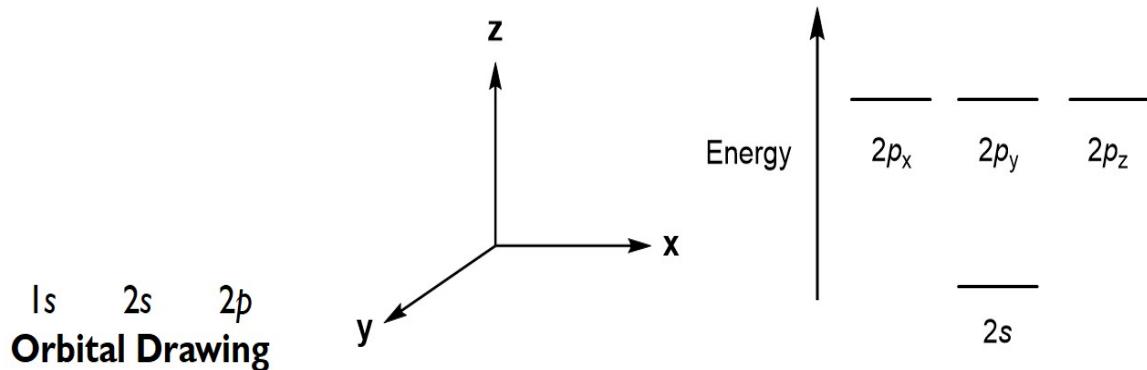
#### Valence Bond Theory

Defines the orbitals involved in bonding for each atom in a compound.

Let's take the simplest example of an organic molecule we can imagine – methane  $\text{CH}_4$ .



Here we see carbon make **4 bonds**, each with a hydrogen atom. If we examine the orbitals on the carbon atom and the available electrons we notice a problem:



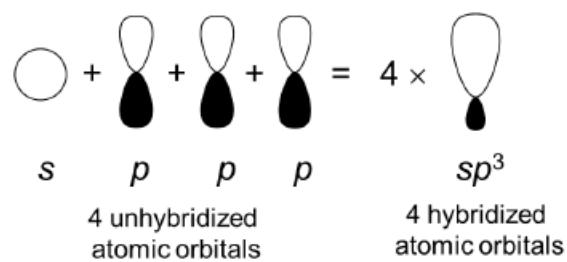
### Hybridization

The combination of atomic orbitals (usually s and p orbitals) to form **bonding** orbitals

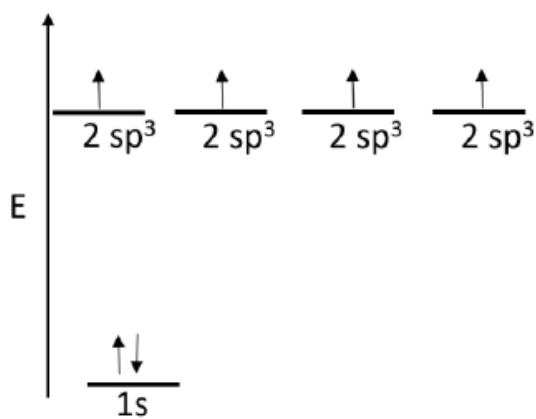
Based on VB theory carbon can only make 2 bonds. We know this is untrue! Hybridization helps explain how more bonds are formed.

**s and p orbitals hybridize for every "sigma" ( $\sigma$ ) bond (AKA single bond)**

The appropriate number of valence orbitals will hybridize (mix) to achieve a common energy. In this case we need 4  $\sigma$ -bonding orbitals around the carbon atom. Therefore, we must 'hybridize' four of the existing atomic orbitals starting at the lowest available energy orbital (2s) and working up to the 2p orbitals.

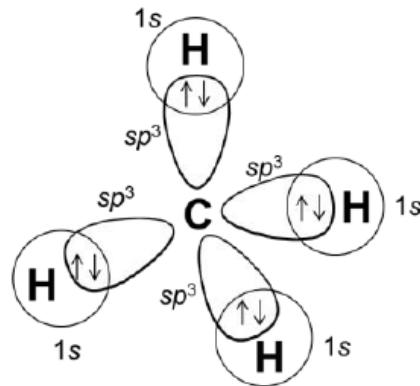


Now when we examine the valence shell atomic orbital energy diagrams we see:



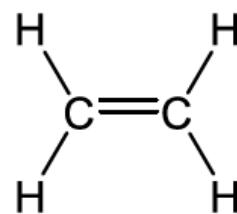
The energy level of the  $sp^3$  hybridized bonding orbitals has changed and now each orbital has the **same energy**. Each  $sp^3$  orbital is capable of forming a  $\sigma$ -bond.

These newly formed bonding orbitals allow us to explain the type of bond that is formed. In the example of methane, each bond is between a  $sp^3$  hybridized orbital on carbon, and a  $1s$  orbital on hydrogen:

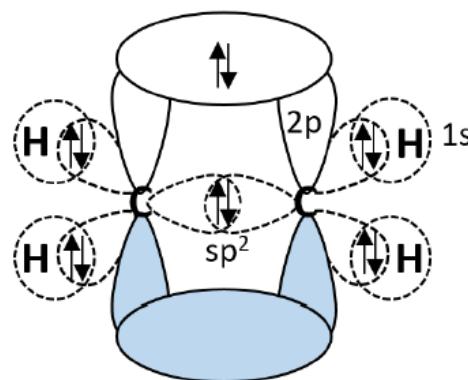
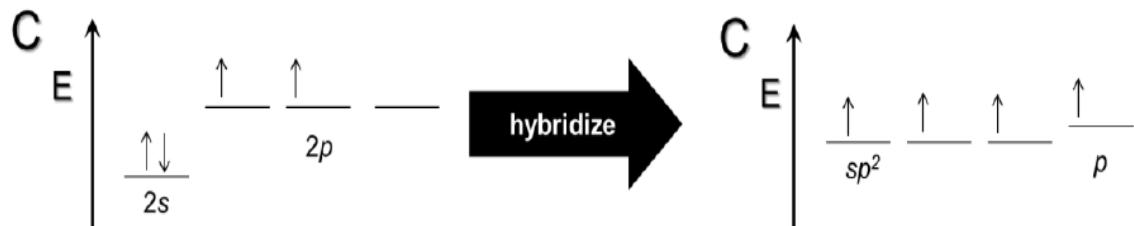
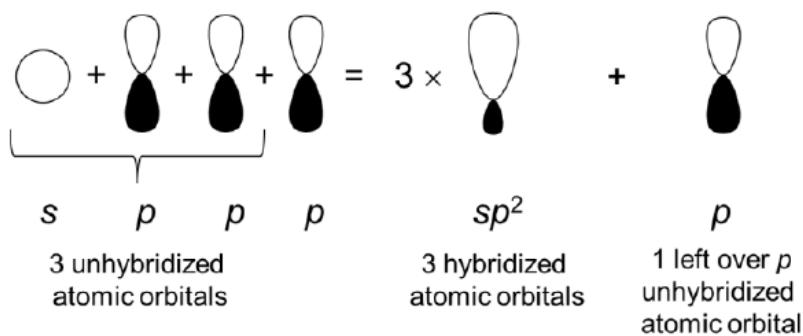


Sigma bonds are the strongest bonds because they have the most orbital overlap.

Let's apply the same concept to a molecule containing a C=C double bond. Consider ethene (C<sub>2</sub>H<sub>4</sub>):



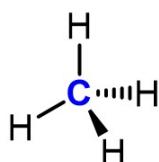
In this case we have **3 atoms** around each carbon and we will hybridize the appropriate number of atomic orbitals to make our  $\sigma$ -bonds:



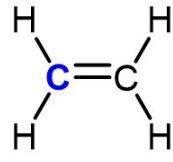
Here we see a bond formed between the  $2p$  orbitals of each carbon. These bonds are known as  $\pi$ -bonds (pi-bonds). These have lesser overlap than  $\sigma$ -

bonds, so they are not as stable. However!!  $\pi$ -bonds shorten the bondlength compared to analogous single bound compounds.

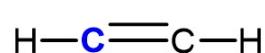
### What are the relative C-H bond lengths?



$4 \times Csp^3-H1s \sigma\text{-bond}$



$2 \times Csp^2-H1s \sigma\text{-bond}$   
 $1 \times Csp^2-Csp^2 \sigma\text{-bond}$   
 $C2p-C2p \pi\text{-bond}$



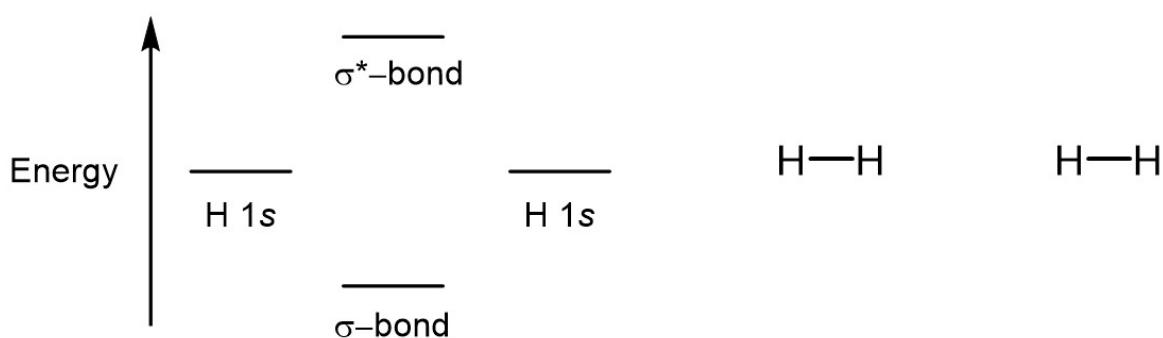
$1 \times Csp-H1s \sigma\text{-bond}$   
 $1 \times Csp-Csp \sigma\text{-bond}$   
 $2 \times C2p-C2p \pi\text{-bond}$

## MO Theory

### Molecular Orbital Theory

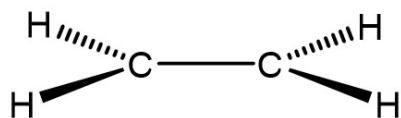
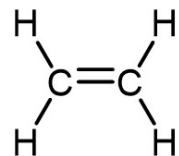
How the (usually *hybridized*) atomic orbitals combine to form bonds.

Let's look at the bonding in a molecule of hydrogen ( $H_2$ ). Hydrogen is each because each H atom only has **one electron** in a  **$1s$  orbital** available for bonding. Those two orbitals combine to form a new  $\sigma$ -bond and  $\sigma^*$ -bond (*antibond*). We can depict that visually:

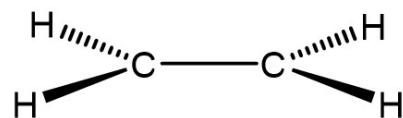




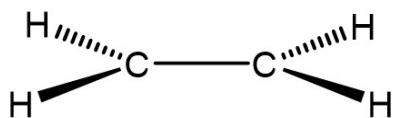
Let's look at orbital overlap in the sigma and pi bonds of ethene ( $C_2H_4$ ). Carbon is hybridized and has  $3\ sp^2$  orbitals and  $1\ p$  orbitals to form  $3\ \sigma$ -bonds and  $1\ \pi$ -bond. Again, we can depict this visually:



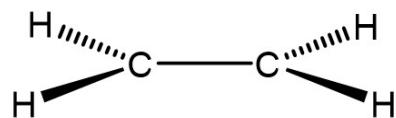
C-C  $\sigma$ -bond



C-C  $\sigma^*$ -bond



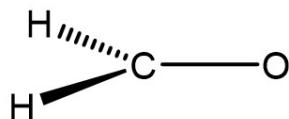
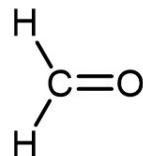
C-C  $\pi$ -bond



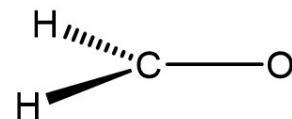
C-C  $\pi^*$ -bond

Finally, let's look at orbital overlap in the pi bond of formaldehyde ( $\text{H}_2\text{CO}$ ).

Carbon and oxygen are each hybridized and have  $3 \text{ } sp^2$  orbitals and  $1 \text{ } p$  orbitals. A  $\text{C}_p\text{-O}_p$   $\pi$ -bond is formed, but oxygen is more electronegative. Again, we can depict this visually:



C-O  $\pi$ -bond

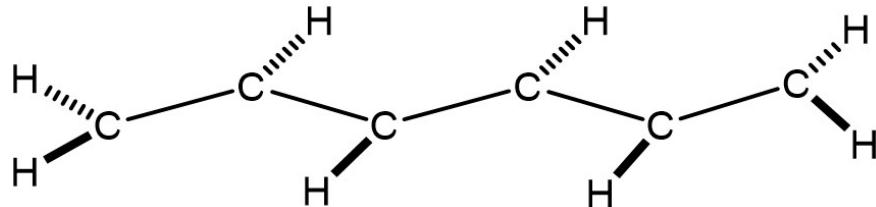


C-O  $\pi^*$ -bond

**To break a bond, donate electron density into the antibonding orbital**

## Bonding in Delocalized Systems

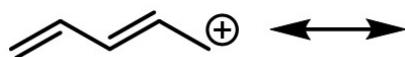
Let's look at the  $\pi$ -bonding in hexatriene ( $\text{C}_6\text{H}_8$ ) shown below. The optimum geometry and orbital overlap has all the  $p$  orbitals aligned. We can depict this visually:



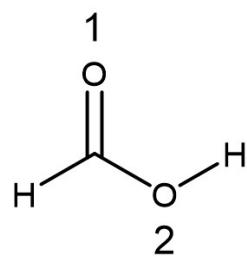
### Resonance

The state attributed to certain molecules of having a structure that cannot adequately be represented by a single structural formula but is a composite of two or more structures of higher energy.

Let's look at the  $\pi$ -bonding in a pentadienyl cation ( $C_5H_7^+$ ) shown below. Again, the optimum geometry and orbital overlap has all the  $p$  orbitals aligned. This orbital alignment is vital for **resonance** stabilization of the cation. Draw the reasonable contributing resonance structures of a pentadienyl cation:



Finally, think about the bonding in formic acid ( $CH_2O_2$ ):



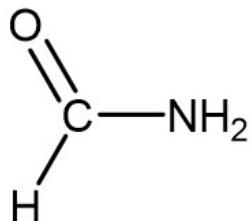
What is the hybridization of:

O1 \_\_\_\_\_

O2 \_\_\_\_\_

### CONCEPT CLARIFIER

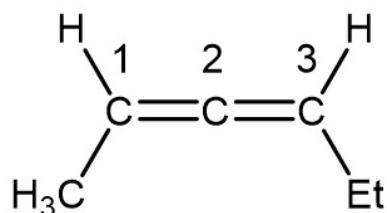
Draw the complete orbital overlap for formamide (shown below). List all the bonds and draw any contributing resonance structures.



## CONCEPT CLARIFIER

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An organic compound possessing an allene is shown below.



Draw the orbital overlap for C1, C2, and C3.

What is the hybridization of: C1, C2, and C3

Is the correct 3D depiction of the compound shown above?

Can the above compound be chiral?

## 03 — Drawing Organic Compounds

### 2D Notation

#### Chemical Formula

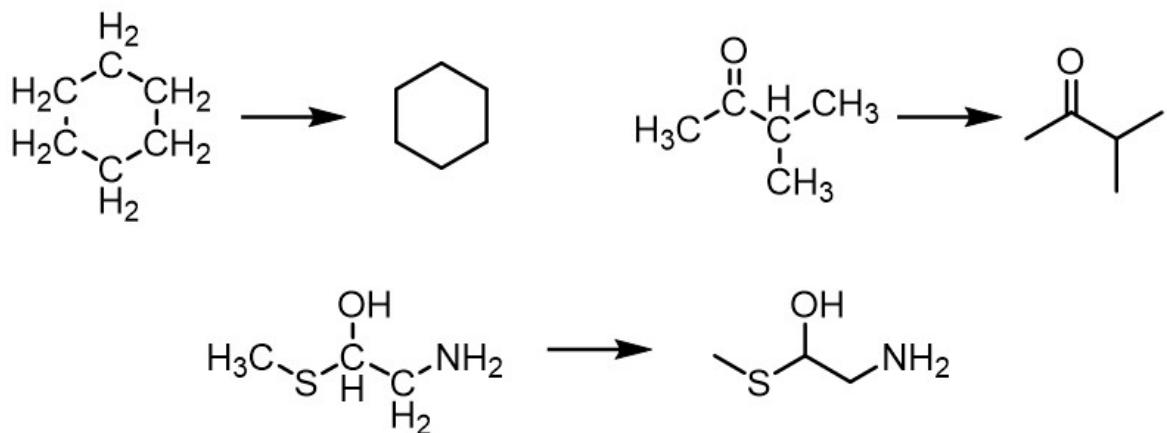
States the number of each element in a given compound. Example: Ethanol has a chemical formula  $C_2H_6O$ .

#### Condensed Structure

A more descriptive version of the chemical formula. This notation gives some structural information by showing which atoms are beside each other. Example: Ethanol has a condensed structure  $CH_3CH_2OH$

#### Line Drawing

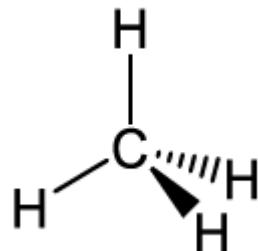
In organic chemistry, there's often a number of carbon and hydrogen atoms. Line drawings simplify this by replacing any nonessential carbons and hydrogens with lines:



## 3D Projections

### Wedge/Dash Notation

This notation uses solid wedge bonds and dashed bonds to specify whether a bond is going into the page, or out of the page:



Bonds coming out of the page are shown as a wedge bond



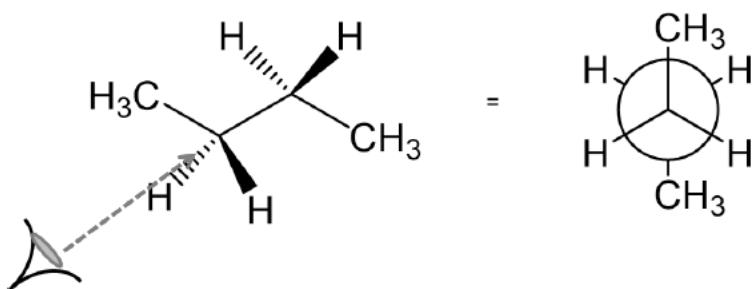
Bonds going into the page are shown as a dashed bond



### Newman Projections

Newman projections allow us to visualize **conformational changes** by looking "down" a C-C bond. By doing this, we observe a front carbon and its substituents and a back carbon with its substituents. This is very useful for looking at single bonds and rotation about them.

Example:

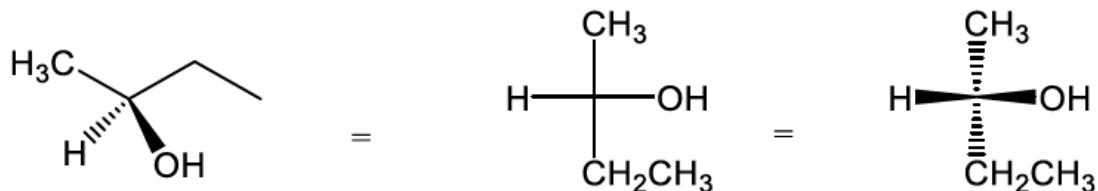


The **front carbon** is represented by the meeting of the 3 groups at the centre (looking like it forms 3 pie pieces). The **back carbon** is represented by the large circle, with its 3 groups also attached.

### Fischer Projections

Fischer projections use horizontal and vertical lines in order to depict whether atoms are going into the page or out of the page.

Example:

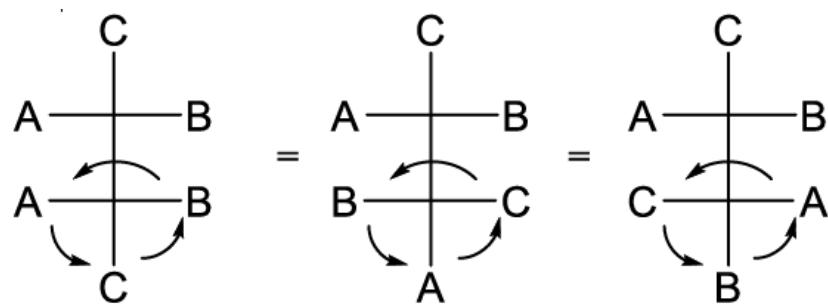


In a Fischer Projection the horizontal lines depict atoms coming out of the page, while the vertical lines depict atoms going into the page.

**Remember that horizontal lines mean going out of the page... like the compound is giving you a hug.**

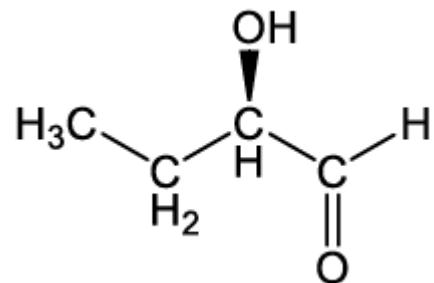
This notation is commonly used in determining stereochemistry, particularly in compounds with more than one. Also, acyclic carbohydrates/sugars are most commonly depicted as Fischer Projections.

**Note: The substituents can be easily moved around to compare stereochemistry:**

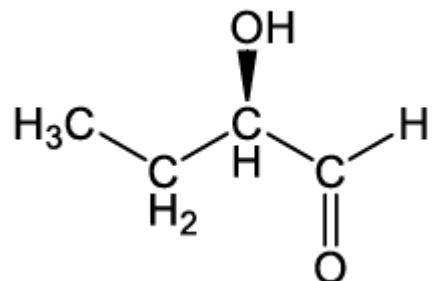


### CONCEPT CLARIFIER

Draw the following compound as Fischer Projection



Draw the following compound as Newman Projection along the CH<sub>2</sub>-CH bond

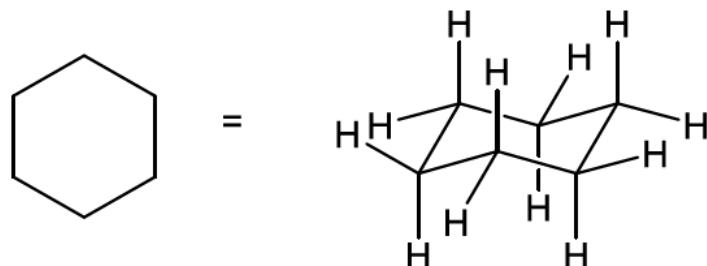


## Chair Conformations

### Cyclic Chair Representations

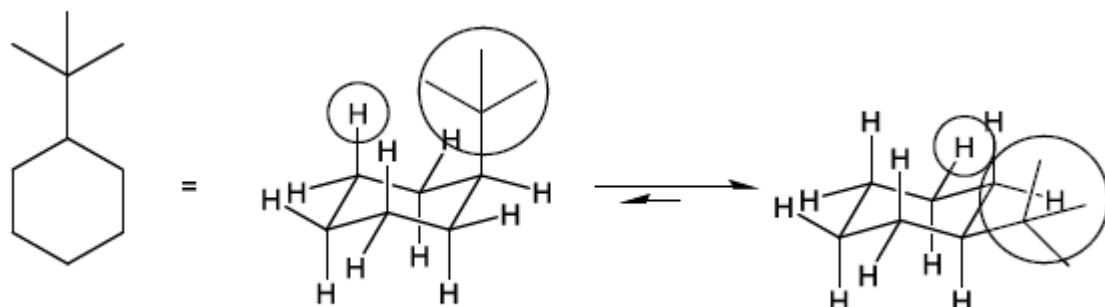
Often 6-membered rings containing only single bonds (cyclohexane rings) are represented in their 'chair' conformation. As these molecules only have single

bonds, they are free to rotate... but only so far. In the case of 6-membered rings, the most stable of these conformations is the 'chair'.



### Steric Factors in Cyclohexanes

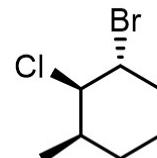
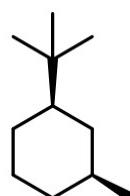
It is also important to note that if there are any bulky substituents on the ring, they will prefer to be in the equatorial position. This is because there is less steric interactions when the large substituents is in the equatorial position.



1,3 steric interactions are greater for the axial position

### CONCEPT CLARIFIER

Draw each of the following molecules in two different chair conformations. Circle the most stable.





## Wize Quiz

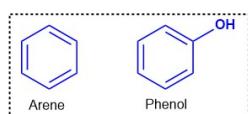
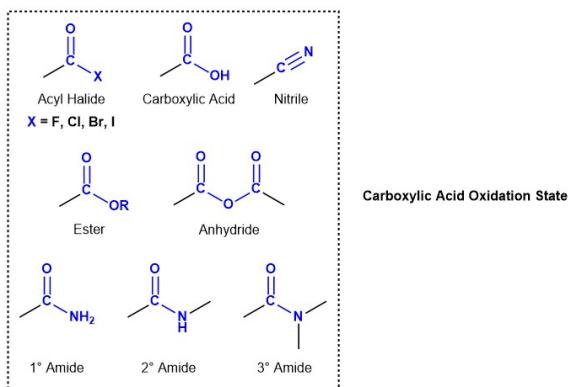
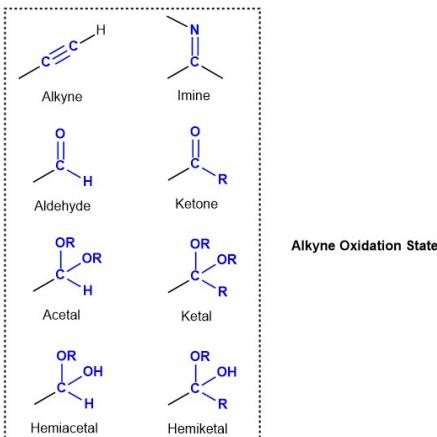
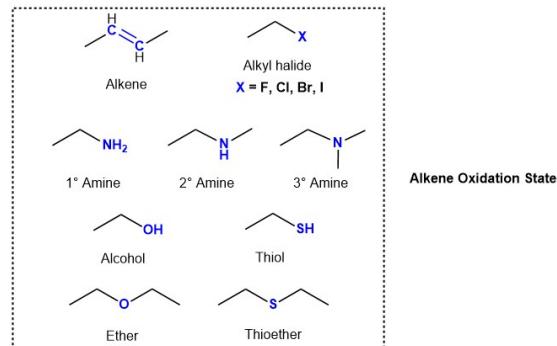
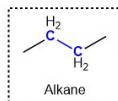
### Converting Structures - Drawing compounds (5 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

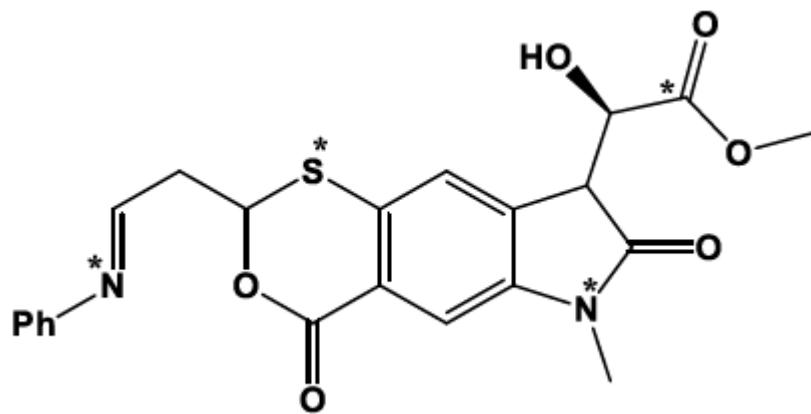
04 —————

## Common Organic Functional Groups

### Table of Important Functional Groups



Identify the functional group(s) in the organic molecule below. What is the hybridization of each starred atom?

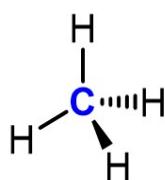


## 05 — VSEPR Theory

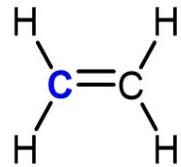
### VSEPR Theory

### Valence-Shell Electron-Pair Repulsion (VSEPR)

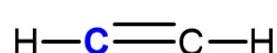
The geometry and shape of a molecule is dictated by the atom's hybridization (number of  $\sigma$ -bonds and  $\pi$ -bonds). It is important to consider lone pairs, they also occupy space! Let's look at the different hybridized



$\angle \text{H}-\text{C}-\text{H}$ : 109.5 °

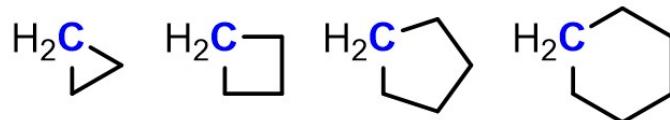


$\angle \text{H}-\text{C}-\text{C}$ : 120 °



$\angle \text{H}-\text{C}-\text{C}$ : 180 °

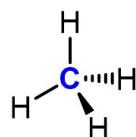
Sometimes atoms are forced to adopt a less-than-ideal geometry (due to the presence of a ring). This helps explain why five- and six-membered rings are more stable than their smaller and larger atom analogues.



$\angle \text{C}-\text{C}-\text{C}$ : 60 °    90 °     $\sim$ 109.5 °    109.5 °

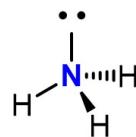
Bond angle at Carbon

As mentioned above, lone pairs occupy space similar to atoms. In fact, the repulsion of lone pairs is greater than other electron pairs.



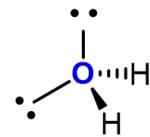
$\angle H-C-H: 109.5^\circ$

$CH_4$



$\angle H-N-H: 108^\circ$

$NH_3$



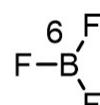
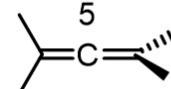
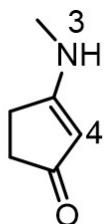
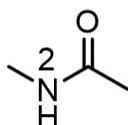
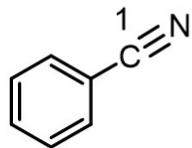
$\angle H-O-H: 104.5^\circ$

$H_2O$

In organic chemistry the magic numbers are  $109.5^\circ$  (around  $sp^3$  atoms),  $120^\circ$  (around  $sp^2$  atoms) and  $180^\circ$  (around  $sp$  atoms).

### CONCEPT CLARIFIER

What are the approximate bondangles at the following atoms:



## 06 — Polar Bonds

## Polar Bonds

For a molecule to be overall polar (posses a net dipole) it needs:

1. A Polar Covalent Bond
2. Appropriate Geometry

### Electronegativity

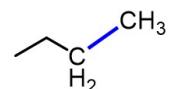
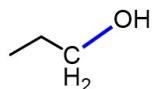
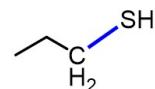
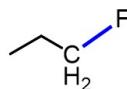
Tendency of an atom to bring electrons close, in a bond

A polar covalent bond (AKA polar bond) occurs between two different atoms with an electronegativity difference ( $\Delta E_{\text{neg}}$ ) greater than 0.4.

Pauling Electronegativity Values

5 B	6 C	7 N	8 O	9 F
2.04	2.55	3.04	3.44	3.98
13 Al	14 Si	15 P	16 S	17 Cl
1.61	1.90	2.19	2.58	3.16
31 Ga	32 Ge	33 As	34 Se	35 Br
1.81	2.01	2.18	2.55	2.96
49 In	50 Sn	51 Sb	52 Te	53 I
1.78	1.96	2.05	2.1	2.66

Which of the following bonds are polar covalent?



We can denote electronegativity by showing *partial positive character* ( $\delta+$ ) and *partial negative character* ( $\delta-$ ) on the appropriate atoms. This does not mean either atom has a formal charge!

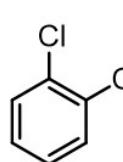
We can also show it with a **special arrow**. This arrow represents a **dipole**.

Having a difference in electronegativity (dipole) is not the only factor to consider when assigning a molecule as polar or non-polar. We must also consider molecular shape or geometry (VSEPR).

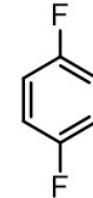
### CONCEPT CLARIFIER

Which of the following compounds are polar (posses an overall dipole)?

- (1)  $\text{BF}_3$  (2)  $\text{N}(\text{CH}_3)_3$  (3)



- (4)



## 07 Intermolecular Forces

### Intermolecular Forces

	Examples		
Ionic Forces	$\text{Na}^+ \text{Cl}^-$ $\text{K}^+ \text{Br}^-$ $\text{Cs}^+ \text{F}^-$		
Hydrogen Bonding	$\text{H}-\text{O}-\text{H}$ $\text{H}-\text{N}-\text{CH}_3$ $\text{H}-\text{O}-\text{C}-\text{CH}_3$		
Bond Strength	Dipole-Dipole Interactions		
	Van der Waals Forces		
	Present in <b>all</b> molecules – but <b>bigger is better!</b>		

### Van der Waals (London Dispersion) Forces

Weak, short-range electrostatic attractive forces between uncharged molecules, arising from the interaction of permanent or transient electric dipole moments. Present in all molecules but **larger molecules or bigger atoms (in the same group)** have larger VDFs!

### Dipole-Dipole Interactions

Only observed between molecules with a permanent dipole (i.e. **polar molecules**). Alignment of these dipoles cause an attractive force. Unlike Van der Waals, these dipoles are **permanent** so the attraction between these molecules are stronger.

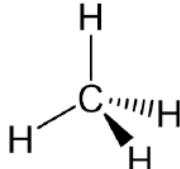
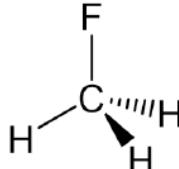
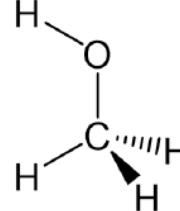
### Hydrogen Bonding

An **extreme case of Dipole-Dipole forces** involving functional groups that have an electronegative atom bound to a hydrogen (alcohols, amines, carboxylic acids, amides...). Hydrogen bond **acceptors** are any electronegative atom with a partial negative charge. These will then bind to the hydrogen (**bond donor**) to form a **strong** intermolecular force.

### Melting/Boiling Point Comparisons

We can use the intermolecular forces between molecules to predict the relative boiling and melting points of a set of compounds. In order to achieve a phase transformation, we must put energy in and ***break the molecules apart from one another***. So, the more forces holding the molecules together, the higher its melting/boiling point will be.

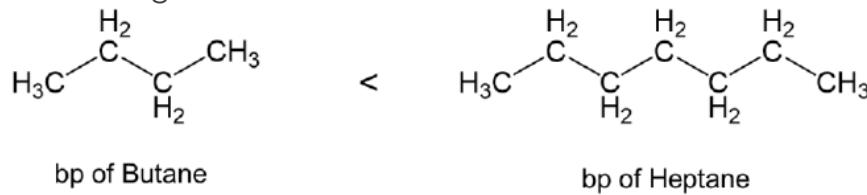
Take the following example:

	<		<	
mp(°)	90K	131 K	176 K	
bp(°)	109-113K	195 K	338 K	
Polar?	Non-polar	Polar	Polar	
Forces?	LDF	LDF, Dip-Dip	LDF, Dip-Dip HB	

How do you determine the relative boiling point if two molecules are similar?

### 1. Count the number of electrons

Imagine the following situation:



In this case, both molecules are non-polar and therefore both only have LDF, but the boiling point of heptane is higher than that of butane.

The ***larger size*** of the heptane molecule (more electrons) allows it to be ***more polarizable*** and it will have ***more Van der Waals forces*** holding the molecules together.

## 2. Consider the Molecular Shape

Imagine the following situation:

Melting point:

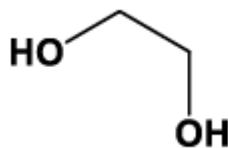


In this example, both have the same molecular formula,  $C_5H_{12}$ . Therefore we must look at the molecular shape. Notice how isopentane is branched while pentane is a straight chain. Because pentane is a straight chain, it can line up better with other pentane molecules, and therefore have a *greater area of polarized contact*. This increases the attraction observed between the molecules, and therefore increases its melting point.

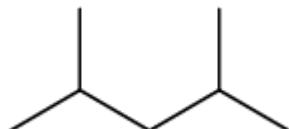
### CONCEPT CLARIFIER

List the following molecules in order of increasing boiling point.

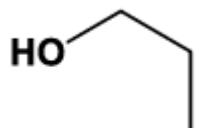
Molecule 1:



Molecule 2:



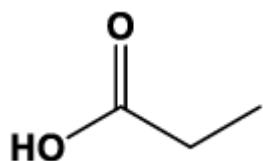
Molecule 3:



Molecule 4:

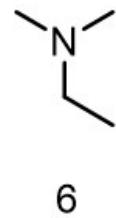
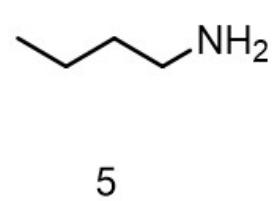
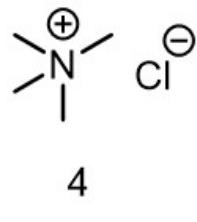
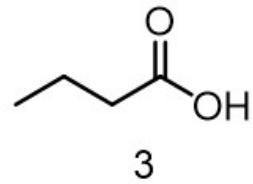
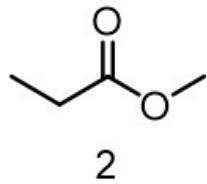
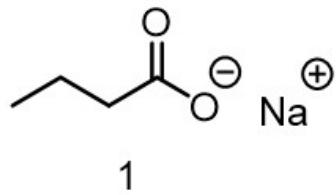


Molecule 5:



**PRACTICE QUESTION #1**

Label the important intermolecular forces in the following compounds. Rank 1-3 and 4-6 in order of boiling point.



### PRACTICE QUESTION #2

Rationalize the following observations:

- (1) H<sub>2</sub>O has a higher boiling point than MeOH
- (2) H<sub>2</sub>O has a higher boiling point than NH<sub>3</sub>

## Wize Quiz

### Practice Problems 1 – Boiling Point Comparisons (6 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

08 —————

## Section Quiz

# Wize Quiz

## Bonding (8 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

## 09 ————— Aromaticity

### Aromaticity

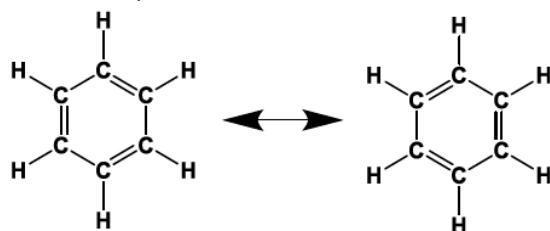
#### Criteria for Aromatic Compounds

1. The compound must obey Hückel's Rule (# of  $\pi$ -electrons =  $4n + 2$ )
  2. The compound must contain a 'concentric ring of aligned  $p$  orbitals.'
- Resonance!
3. The compound must be planar (big rings are not planar)

### Hückel's Rule

For a compound to be aromatic, the number of  $\pi$ -electrons in the overlapping  $p$  orbitals must be  $4n+2$ . What is he talking about?

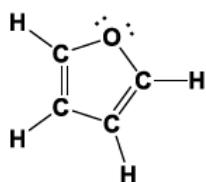
Let's take benzene as an example:



Benzene is concentric ring and all the atoms can be linked by resonance. How many  $\pi$ -electrons does benzene have?

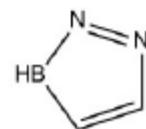
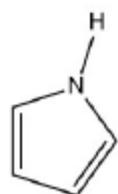
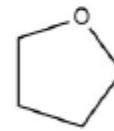
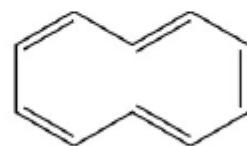
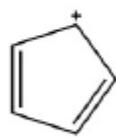
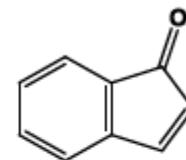
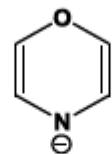
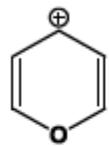
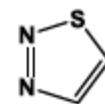
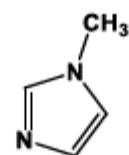
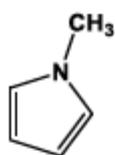
### Aromaticity and Lone Pairs

Let's examine the following compound, furan ( $C_4H_4O$ ). In which orbitals do the lone pairs on oxygen lie?



### CONCEPT CLARIFIER

Which of the following are molecules aromatic?

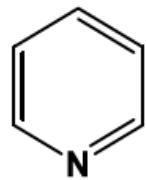


Solution

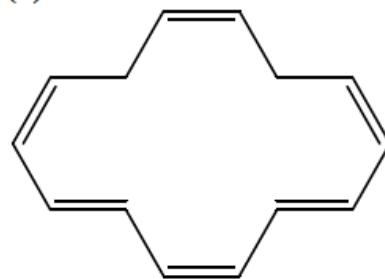
### PRACTICE QUESTION #1

Determine whether the following molecules are Aromatic or Anti-aromatic.

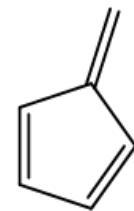
(a)



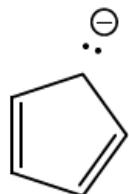
(d)



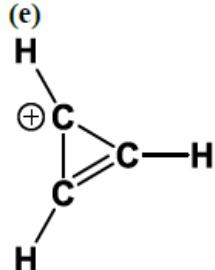
(g)



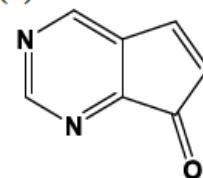
(b)



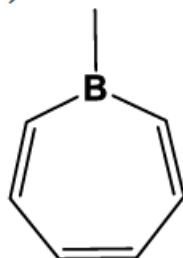
(e)



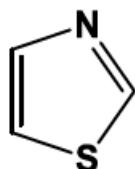
(h)



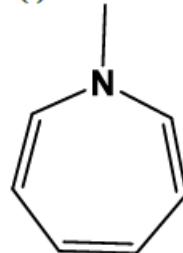
(c)



(f)

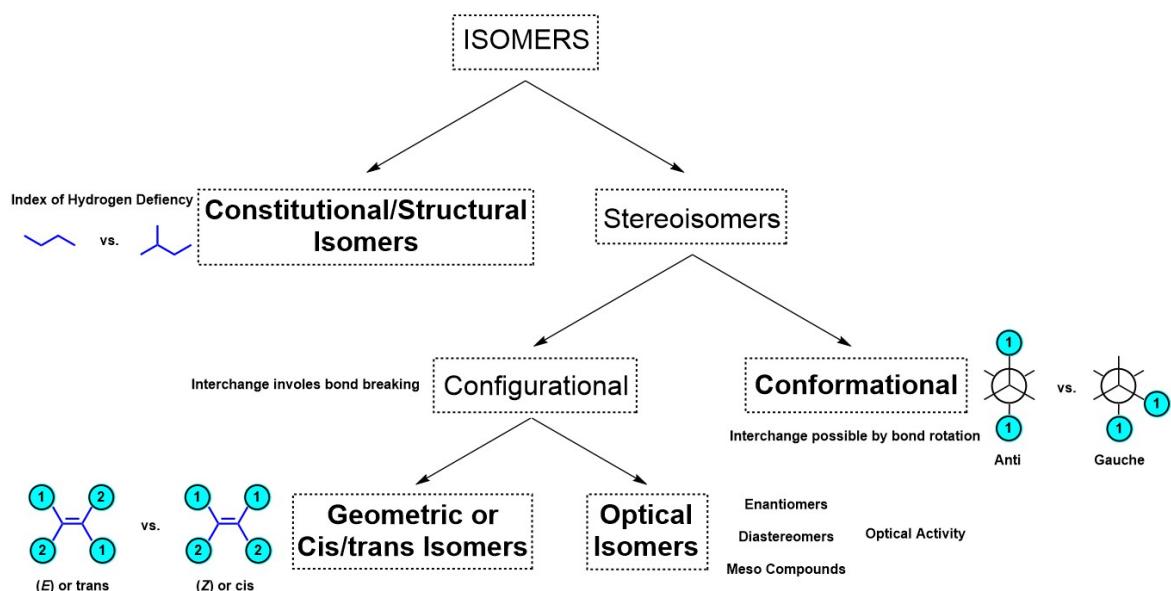


(i)



# STEREOCHEMISTRY

## 01 Isomers

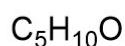
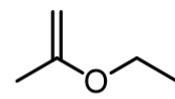
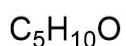
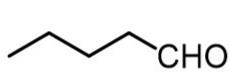
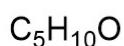
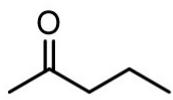
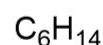
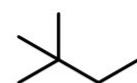
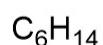
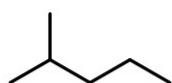
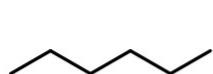


## Constitutional Isomers

### Constitutional or Structural Isomers

A form of isomerism in which molecules with the same molecular formula have different bonding patterns and atomic organization, as opposed to stereoisomerism, in which molecular bonds are always in the same order and only spatial arrangement differs.

Take for example hexane ( $C_6H_{14}$ , shown below). A number of branched structural isomers can exist for hexane, such as 2-methylpentane and 2,2-dimethylbutane which have the same chemical formula but completely different connectivity and physical properties.

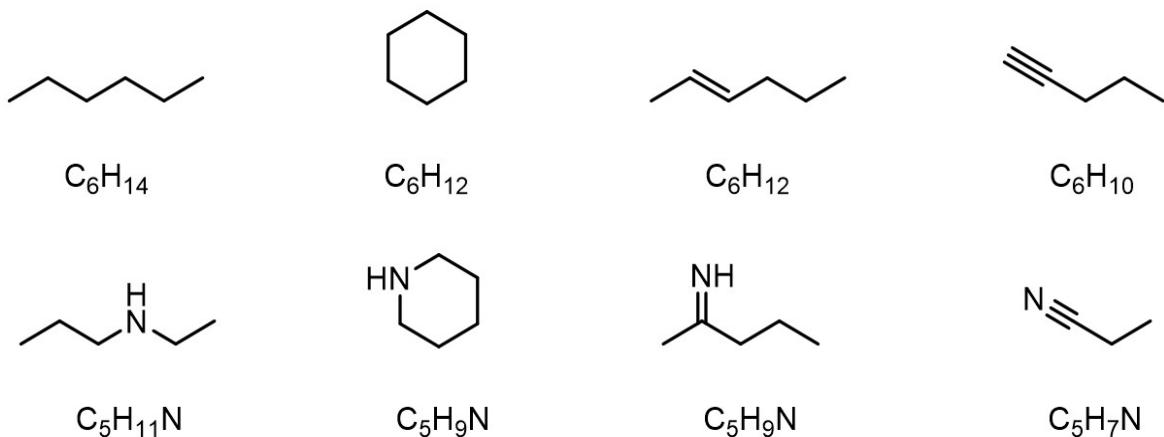


Heteroatom-containing compounds are no different. For example the atoms of 2-pentanone ( $C_5H_{10}O$ , shown above) can be rearranged to draw pentanal or 2-ethoxypropene.

### Index of Hydrogen Deficiency (IHD)

A calculation that determines the total number of rings and pi-bonds. Also referred to **units of unsaturation** and given as an integer value. Each ring or pi-bond decreases the number of hydrogen atoms. For every 2 hydrogen atoms the IHD increases by 1.

$$\text{Saturated Alkane} = \text{C}_n\text{H}_{2n+2}$$



$$IHD = \frac{(2x + 2 - y)}{2}$$

(where x and y = # of C and H respectively)

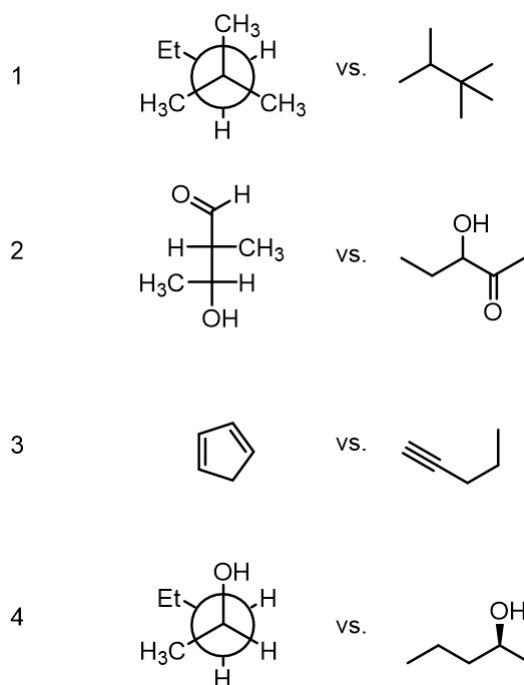
#### When drawing multiple isomers of carbon chain compounds:

1. Assess the IHD (determine if you need a ring or multiple bond)
2. Draw all the possible chain lengths and then look at branching sites

Example: Draw all the possible constitutional isomers for  $\text{C}_4\text{H}_8$

#### CONCEPT CLARIFIER

Which of the following pairs are constitutional isomers?



## Geometric or Cis/Trans Isomers

### Geometric Isomers

Arises when you have restricted rotation around a C-C bond (usually due to a pi-bond) and have two distinct possible orientations of the substituents on the carbon atoms. Commonly referred to as cis / (Z) (same) and trans / (E) (opposite) isomers.

**Cis isomer = (*Z*)-isomer**

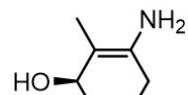
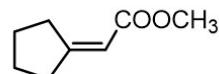
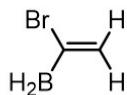
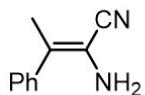
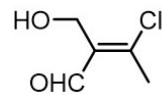
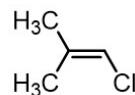
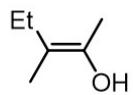
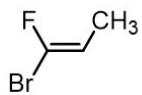
**Trans isomer = (*E*)-isomer**

Take for example cis/trans 2-butene ( $C_4H_8$ , shown below). Although they have the same molecular formula and connectivity (they are **not** constitutional isomers), they have different physical properties (boiling point etc.). The trans or (*E*)-isomer of 2-butene is favoured due to decreased steric interactions.



The priorities of the substituents on the carbon atoms, akin to assigning chiral centres, are based on molecular weight. If the two highest priority groups are on the **same** side of a double bond, this is a **cis** or (*Z*)-isomer

With the aid of a periodic table, label the following alkenes as **cis**, **trans**, or **neither**.

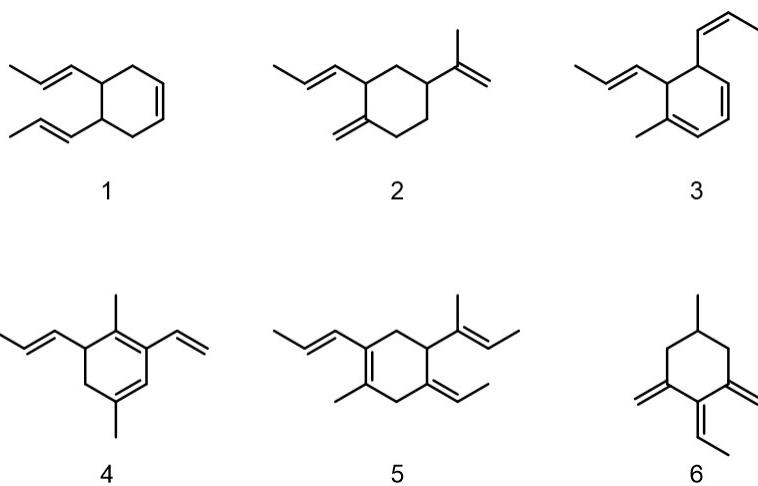


### CONCEPT CLARIFIER

Draw the cis/trans isomers for 1,3-dimethylcyclohexane and 1,2-dichlorocyclohexane.

### CONCEPT CLARIFIER

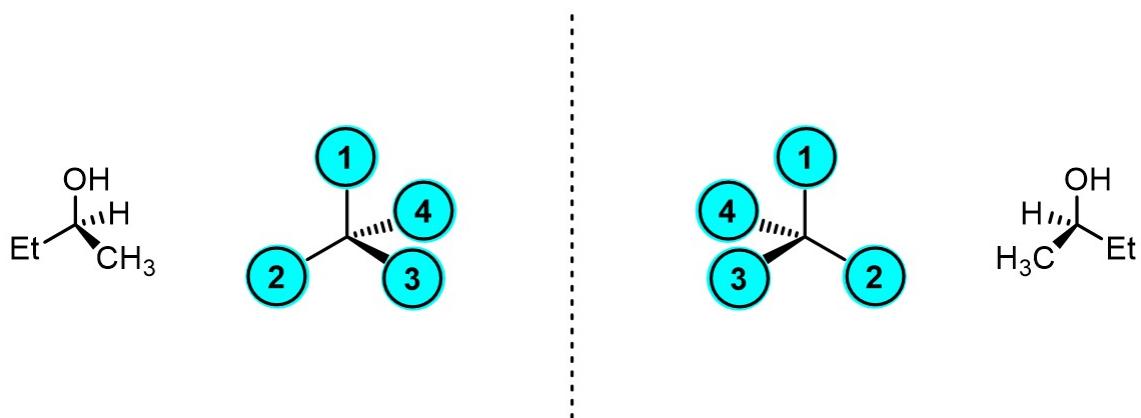
Which compound has the most possible cis/trans isomers?



## Chiral Molecules - Assigning R and S Stereocentres

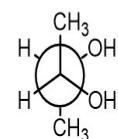
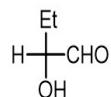
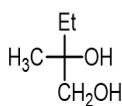
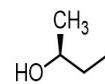
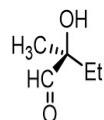
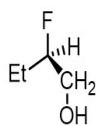
### Chiral Molecules

Asymmetric in such a way that the structure and its mirror image are not superimposable. Chiral compounds are typically optically active; large organic molecules often have one or more **chiral centres** where four different groups are attached to a carbon atom. Each chiral centre is denoted as either (R) or (S).



Assign the following stereocentres as either R or S:

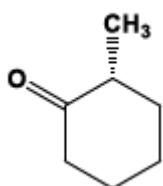
6 C	7 N	8 O	9 F
14 Si	15 P	16 S	17 Cl
32 Ge	33 As	34 Se	35 Br
50 Sn	51 Sb	52 Te	53 I



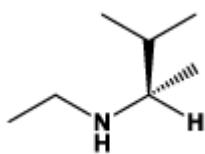
### CONCEPT CLARIFIER

Assign R/S for any asymmetric carbons in the following examples.

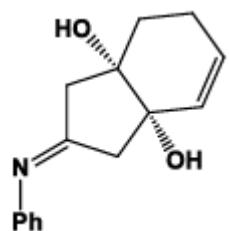
Molecule 1:



Molecule 2:

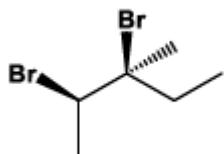


Molecule 3:

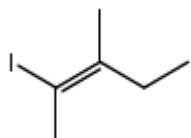




Name the following compound.



Name the following compound.



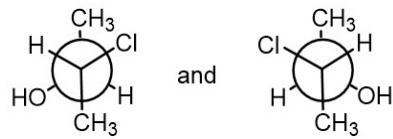
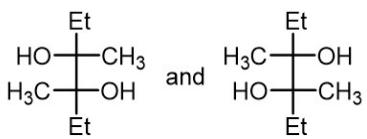
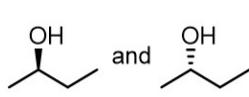
## Optical Isomers

### Optical Activity

The property (displayed by solutions of some compounds) of rotating the plane of polarization of plane-polarized light. This is due to the presence of **chiral** centres (AKA R and S stereocentres).

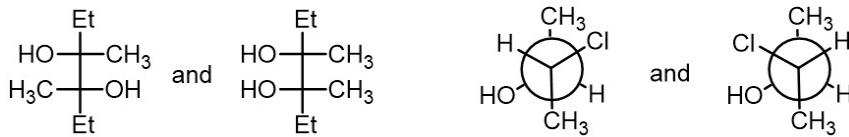
### Enantiomers

Differ by inversion of **every chiral centre**. # of chiral centres: **1 or more**.



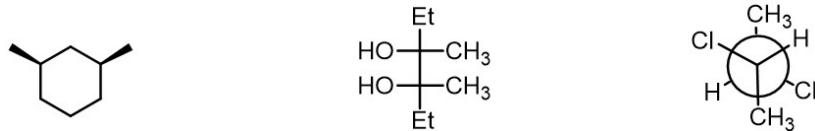
### Diastereomers

Differ by inversion of some (but not all) chiral centres. # of chiral centres: **2 or more.**



### Meso Compounds

Possess chiral centres and a plane of symmetry. This symmetry makes two 'enantiomers' identical and therefore the molecule won't interact with plane-polarized light. # of chiral centres: **2 or more.**

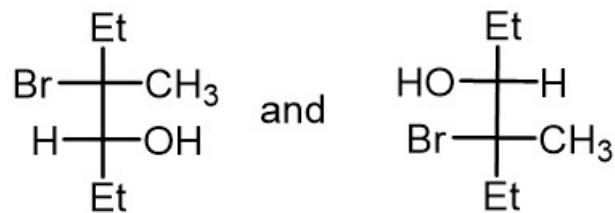
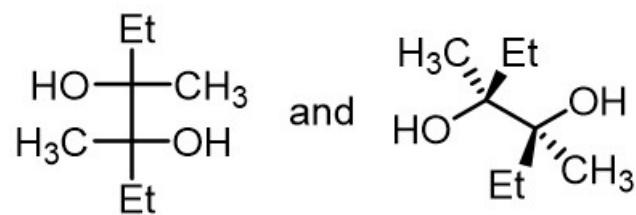


### CONCEPT CLARIFIER

How does plane-polarized light interact with a chiral molecule? A racemic mixture? A meso compound?

### CONCEPT CLARIFIER

What is the relationship (enantiomer, diastereomer, identical) between the following compounds?



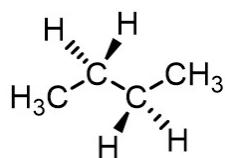
## Conformational Isomers

### Conformational Isomers

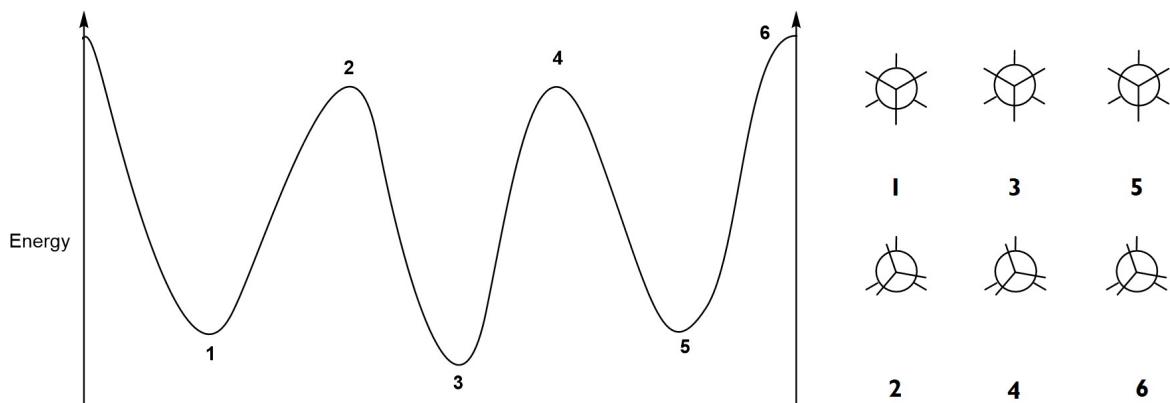
A form of stereoisomerism in which the isomers can be interconverted just by rotations about formally single bonds.



Due to steric interactions different **conformers** (conformational isomers) are favoured for enthalpic reasons. Let's look at butane for example:

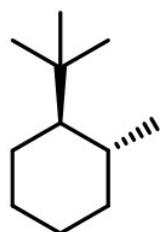


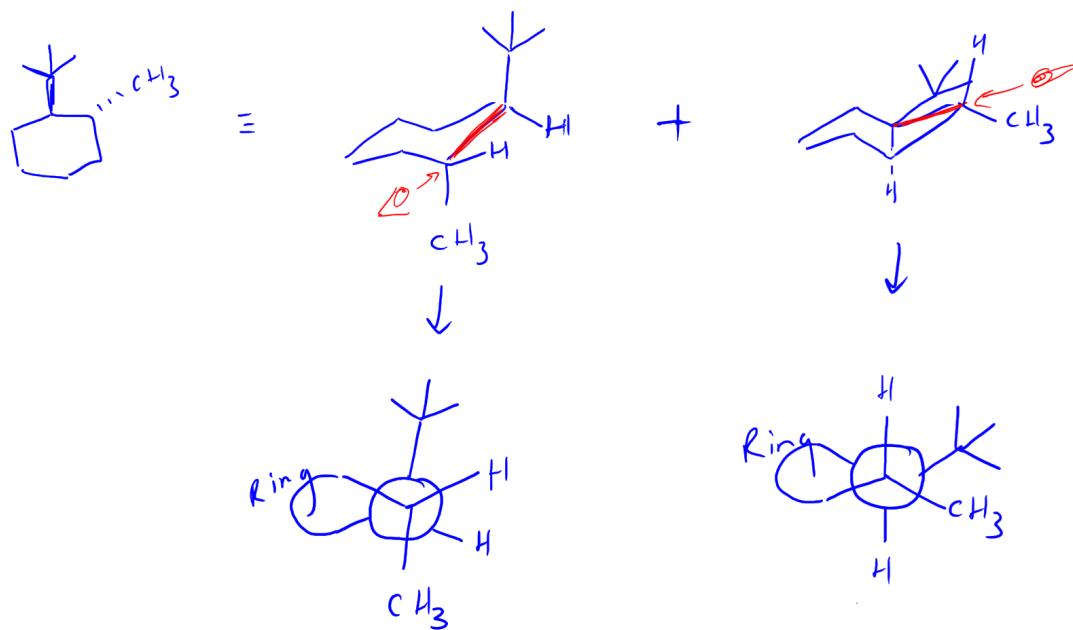
When we look at the Newman projections of butane we see some projections with larger steric interactions and higher relative energy. The main conformations are either **staggered** (1, 3, 5) and **eclipsed** (2, 4, 6). In the staggered orientation the methyl groups can either be **anti** (3) or **gauche** (1, 5).



### CONCEPT CLARIFIER

Draw the main conformational isomers of (1R,2R)-1-(tert-butyl)-2-methylcyclohexane. For each isomer draw a Newman projection looking down the relevant bond.

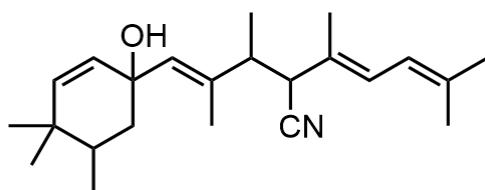




## Determining the Maximum Possible Number of Stereoisomers

There is a classic question you will likely come upon in your chemistry career. An example is shown below:

**What is the maximum number of stereoisomers possible for the following compound.**

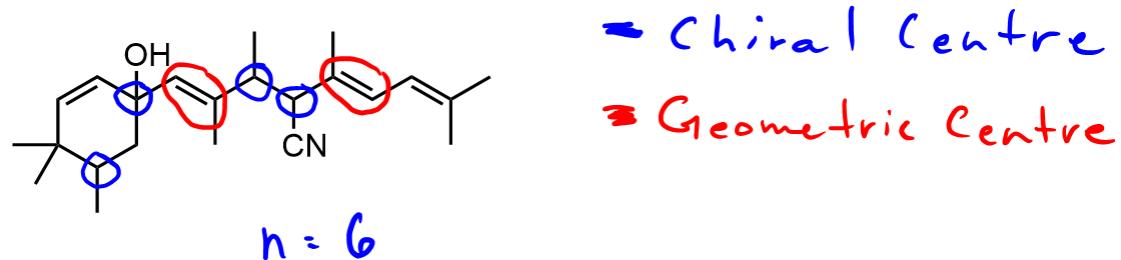


It is important to remember what classifies as a stereoisomer. It includes all versions of a compound with different **chiral centres** (e.g. *R/S*) and **geometric isomers** (e.g. *cis/trans*). In each of those cases there are two options for each

**stereogenic centre:** *R or S* (if a chiral carbon) and *cis or trans* (if geometric). So we can derive an equation for the total number of stereoisomers:

**Number of possible stereoisomers =  $2^n$ , where n = number of stereogenic centres**

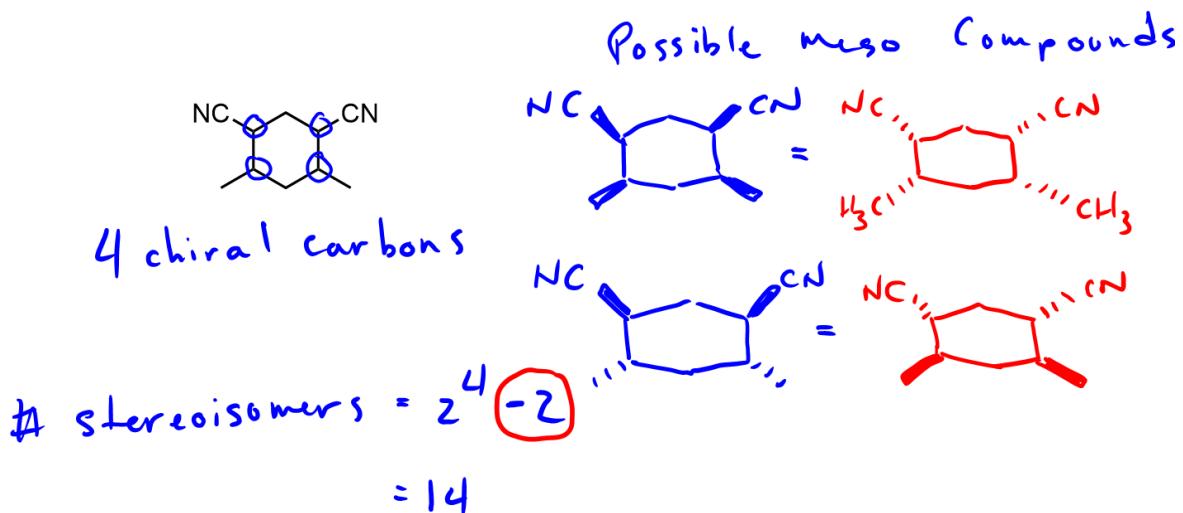
Let's take the above example. First we need to identify all the stereogenic centres:



In this case,  $n = 6$ . There are **4 chiral carbon atoms** and **2 alkenes with cis/trans possibility**. Therefore, the number of possible stereoisomers is  $2^6 = 64$ . Wow.

As you might expect, there are exceptions to this rule. Be on the lookout for **meso compounds!** For every possible meso compound there is one less possible stereoisomer, since two enantiomers are now the same:

**What is the maximum number of stereoisomers possible for the following compound.**



## 02 IUPAC Systematic Naming

### IUPAC Systematic Naming

#### General Naming Rules

1. Identify and name the longest carbon chain
2. If present, assign stereochemistry (*R/S* or *E/Z*)
3. Identify and name any substituents on the carbon chain
4. Give these substituents the appropriate 'address'
5. Add substituent names as a prefix to the carbon chain
6. Change suffix of the carbon chain if necessary (for functional groups)

#### Important Things to Consider

- The length of the longest carbon chain
- The types of C-C bonds in that chain
- The functional groups incorporated in the chain
- The priority of each of those functional groups.

#### The Carbon Chain

The root of the name will always be identified as a number corresponding to the *longest continuous chain of carbon atoms*.

# carbon atoms = root

1 = meth-	6 = hex-
2 = eth-	7 = hept-
3 = prop-	8 = oct-
4 = but-	9 = non-
5 = pent-	10 = dec-

This carbon chain must include any C-C multiple bonds present in the molecule, as this will complete the name of the carbon chain.



**single bonds only**  
-ane

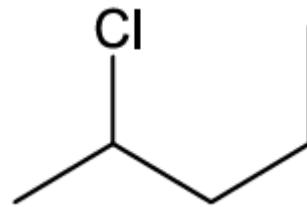
**double bond(s)**  
-ene

**triple bond(s)**  
-yne

#### The Substituents

Lower priority 'functional groups' (alkyl groups, alkoxy groups and halides) that are attached to the carbon chain are listed **before** the name of the carbon chain.

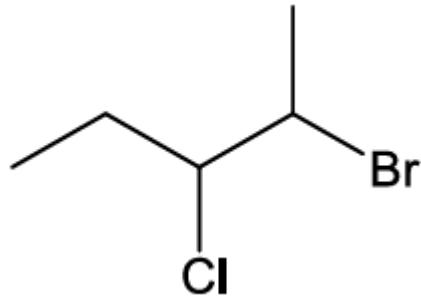
Substituents that have similar priority as the ones listed above must be listed with the lowest possible numbering system, or 'address'. For example:



Going from left to right, the Cl has an address of 2. Going from right to left, the Cl has an address of 4. Since  $2 < 4$ , we have a 2-chloro substituent. '2-chloropentane'

*Note that each number and letter is separated by a hyphen (-).*

If there is more than one substituent, then the two numbers combined must give the lowest possible numbers. For example:



Going from left to right, the Cl is on 3 and the Br is on 4. Going from right to left, the Cl is on 3 and the Br is on 2. Since  $2,3 < 3,4$ , we have 2-bromo-3-chloro. '2-bromo-3-chloropentane'

**Note that the substituents are listed in alphabetical order.**

If there is more than one substituent of the same type, then we don't list them separately, instead we combine them with a prefix. Each number is separated by a comma (,). Also notice that the prefixes used are as follows:

# = prefix	
1 = no prefix	6 = hexa-
2 = di-	7 = hepta-
3 = tri-	8 = octa-
4 = tetra-	9 = nona-
5 = penta-	10 = deca-

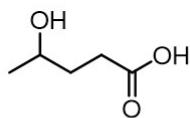
Example: 2,2,4-trimethyloctane

### Functional Groups

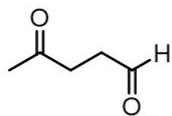
These are higher priority groups that occur along the carbon chain. These often result in a modification of the suffix of the carbon chain. These also effect the 'addressing' of the chain, as many of these groups are **terminal and must start on Carbon-1**. In the previous section, you are responsible for naming the structures in black. Note their type, as well as their suffix. In general, when adding a suffix you drop the "e" from the regular alkane/alkene/alkyne and add the suitable suffix. In the case of alkanes, alkenes, and alkynes the whole suffix is as listed ("-ane", "-ene" and "-yne" respectively). The priorities of these functional groups are listed below:

(*Highest priority*) Carboxylic Acids, Esters, Amides, Aldehydes, Ketones, Alcohols, Thiols, Alkenes, Alkynes, Alkyl Halides, Alkanes (*Lowest priority*)

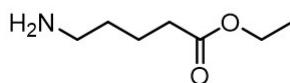
### Examples:



4-hydroxypentanoic acid



4-oxopentanal



ethyl 5-aminopentanoate

Draw:

4-methylpent-3-en-2-one

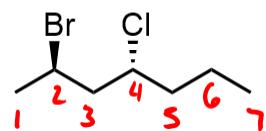
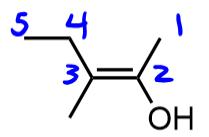
6-bromo-6-chloro-5-ethylheptan-3-ol

## Naming Compounds with Stereochemistry

As a reminder, remember the Wize General Naming Rules:

1. Identify and name the longest carbon chain
2. If present, assign stereochemistry (*R/S* or *E/Z*)
3. Identify and name any substituents on the carbon chain
4. Give these substituents the appropriate 'address'
5. Add substituent names as a prefix to the carbon chain
6. Change suffix of the carbon chain if necessary (for functional groups)

For this lecture we are going to focus on naming compounds with stereochemistry (*R/S* stereogenic centres or *cis/trans* double bonds). Take for example the following two compounds:

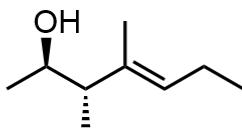


I included the carbon atom numbering, because you know how to do that now! The alkene (with blue numbering) is an *E*-alkene (AKA trans). The IUPAC name is (*E*)-3-methylpent-2-en-2-ol. The *E* notation comes first and is in brackets. Since there is only one double bond, you don't have to designate which alkene has an *E* double bond is.

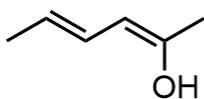
But what about when there's two stereocentres? Let's take the second compound, with numbering shown in red. The IUPAC name is (2*R*,4*R*)-2-bromo-4-chloroheptane. Again, I'm taking for granted your ability to label stereocentres as *R* and *S*... That's covered in another section. Now, due to the presence of two stereogenic centres, we **need** to designate the location of each stereocentre with numbers.

Try your hand at these tricky ones and toggle the answers on:

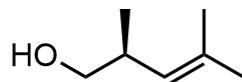
1.



2.



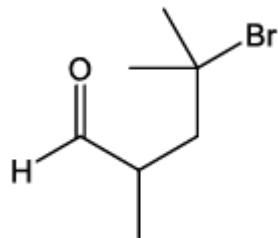
3.



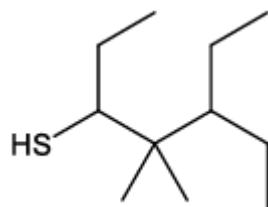
**CONCEPT CLARIFIER**

Name the following molecules using IUPAC systematic naming.

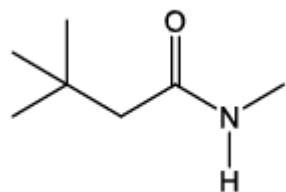
Molecule 1:



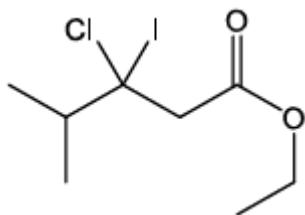
Molecule 2:



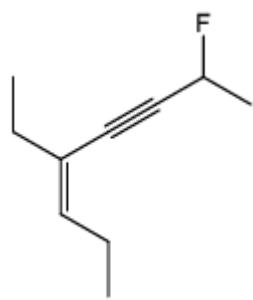
Molecule 3:



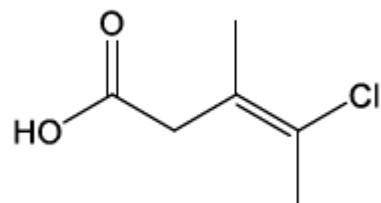
Molecule 4:



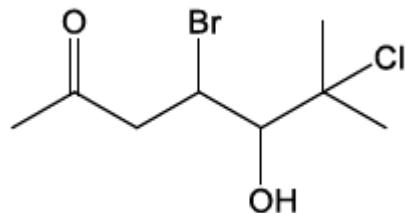
Molecule 5:



Molecule 6:



Molecule 7:





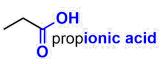
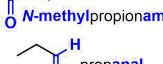
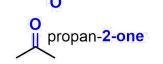
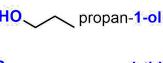
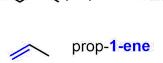
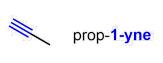
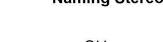
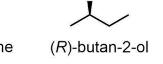
## IUPAC Naming Overview

### General Naming Rules

1. Identify and name the longest carbon chain
2. If present, assign stereochemistry (*R/S* or *E/Z*)
3. Identify and name any substituents on the carbon chain
4. Give these substituents the appropriate 'address'
5. Add substituent names as a prefix to the carbon chain
6. Change suffix of the carbon chain if necessary (for functional groups)

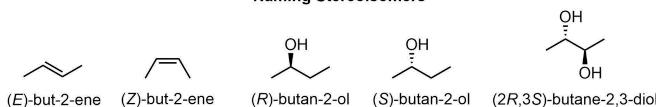
# of Carbons	Name	Structure	
1	Methane	CH <sub>4</sub>	
2	Ethane	H <sub>3</sub> CCH <sub>3</sub>	
3	Propane	H <sub>3</sub> CCH <sub>2</sub> CH <sub>3</sub>	 Butane
4	Butane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	 1-Butene
5	Pentane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	
6	Hexane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	
7	Heptane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	
8	Octane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	
9	Nonane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	
10	Decane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub>	 1-Butyne

### Functional Groups and Priorities

(Highest priority)	Main Chain/Example	Side Chain/Example
Carboxylic Acids		N/A
Esters		3-methoxy-3-oxopropanoic acid
Amides		3-amino-3-oxopropanoic acid
Aldehydes		3-oxopropanoic acid
Ketones		2-oxopropanoic acid
Alcohols		3-hydroxypropanal
Thiols		3-mercaptopropanal
Alkenes		prop-2-en-1-ol
Alkynes		prop-2-yn-1-ol
Alkyl Halides		3-bromoprop-1-ene
Alkanes		2-methylpentane

(Lowest priority)

### Naming Stereoisomers



### Special Carbon Chains

Name	Structure	Example
isopropyl		4-isopropylheptane
sec-butyl		4-(sec-butyl)heptane
tert-butyl		4-(tert-butyl)heptane
isobutyl		4-isobutyloctane
cyclo...	 n = 1,2,3...	1-isopropyl-2-methylcyclopentane  

**03** — **Section Quizzes**

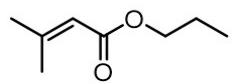
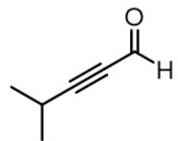
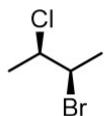
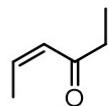
## Wize Quiz

### Isomers Quiz (10 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

**PRACTICE QUESTION #1**

Provide IUPAC names for the following compounds:



# Wize Quiz

## Stereochemistry Section Quiz (12 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

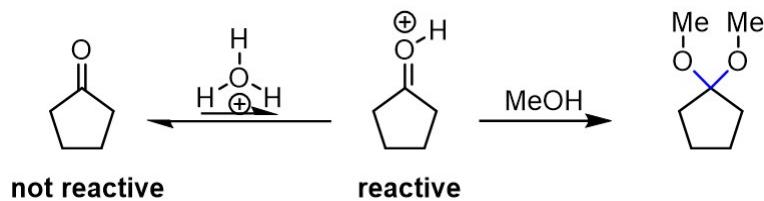
# ACIDS AND BASES

## 01 Acid/Base Equilibrium Fundamentals

### Acid/Base Equilibrium Fundamentals

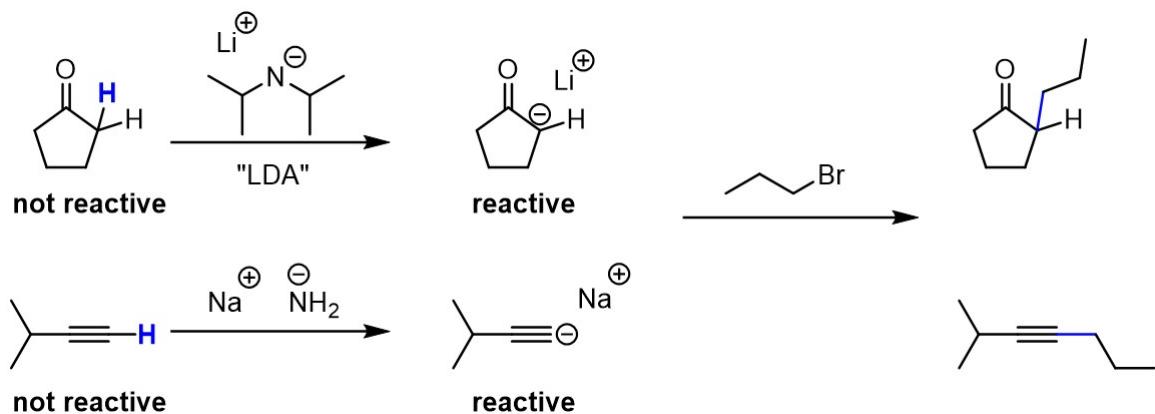
#### Why do we use Acids in Organic Chemistry?

Acids, which are essentially sources of protons ( $H^+$  ions), are key catalysts in a number of organic transformations. Less reactive functional groups (like a **ketone**, see below) are converted to more reactive/electrophilic functionalities by the addition of a strong acid (hydronium in the example below).



#### Why do we use Bases in Organic Chemistry?

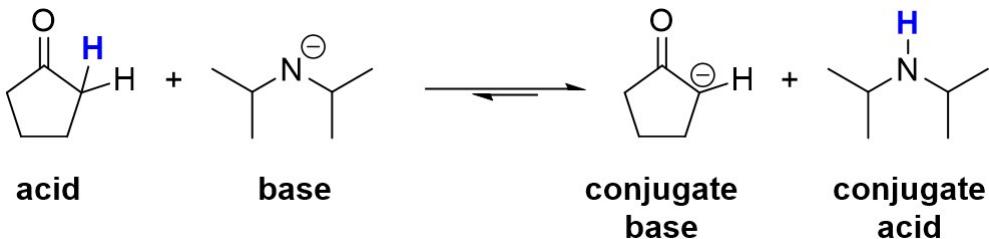
Bases, which are essentially proton removers, are used to deprotonate compounds. The resulting anion is more nucleophilic and can form new bonds. This is a key step in many carbon-carbon bond forming reactions. For example, the  $\alpha$ -proton of a **ketone** or proton of a terminal alkyne can be deprotonated with an appropriate base and reacted with 1-bromopropane to form a new C-C bond.



## Key Definitions

### Bronsted-Lowry Acids/Bases

When an acid and a base react together, the acid will form a **conjugate base** and the base will form a **conjugate acid**. This occurs via the transfer of a proton (see below).



Bronsted-Lowry Acids give up a proton to form a conjugate base  
Bronsted-Lowry Bases take a proton to form a conjugate acid

### Arrhenius Acid

In water, acids will dissociate and produce a hydronium ion ( $\text{H}_3\text{O}^+$ ), see below.



### Arrhenius Base

In water, bases will deprotonate the  $\text{H}_2\text{O}$  molecule and produce a hydroxide ion ( $\text{OH}^-$ ), see below.



Based on the above equilibria, the addition of acids and bases can have an effect on a solution pH. Remember pH is a measure of protons in solution:

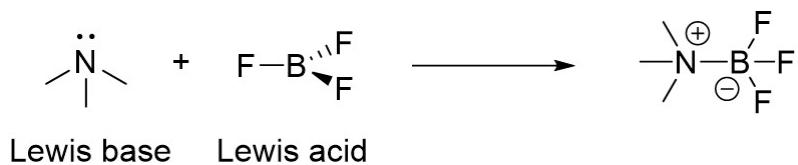
$$\text{pH} = -\log[\text{H}^+]$$

**Arrhenius acids** will increase the concentration of  $\text{H}^+$  ions in solution, and the pH will drop.

**Arrhenius bases** will decrease the concentration of  $\text{H}^+$  ions in solution, and the pH will increase.

### Lewis Acids and Bases

A less common term (in organic chemistry) is Lewis acids and bases. A **Lewis acid** accepts a pair of electrons ( $\text{BF}_3$ , below). A **Lewis base** donates a pair of electrons ( $\text{NMe}_3$ , below).

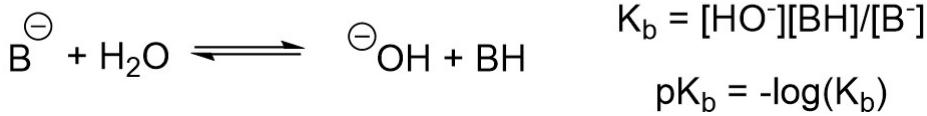
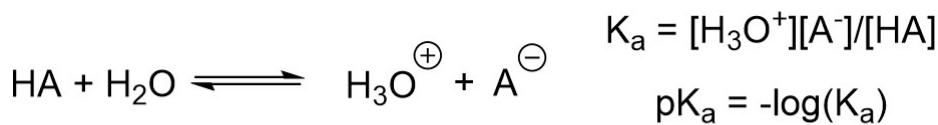


### $K_a$ and $\text{p}K_a$

We need a way to quantify acid strength... enter  $K_a$  and  $\text{p}K_a$ . If you remember your equation for any equilibrium constant, K:

$$K = \frac{[\text{Products}]}{[\text{Reactants}]}$$

Acids and Bases are no different, they are examples of equilibria. A strong acid will dissociate into a larger amount of protons (or products) and have a larger  $K_a$  value (see below). The 'p' of  $\text{p}K_a$  is just an operator that means ' $-\log(x)$ ' and is more commonly used because  $K_a$  values have a large range and can be quite big/small ( $K_a$  range =  $10^{10}$ - $10^{-50}$ ).

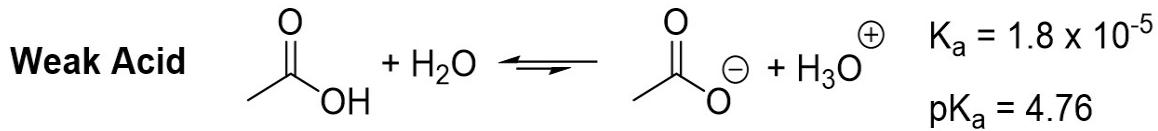
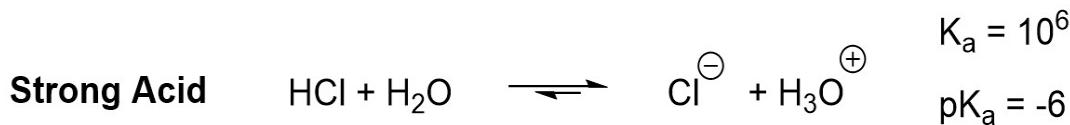


### $K_b$ and $\text{p}K_b$

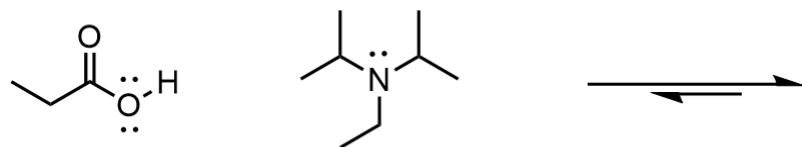
Less commonly discussed is the  $K_b$  and  $\text{p}K_b$  of compounds. This is a measure of base strength (see above) and is represented in a similar fashion as  $K_a$  and  $\text{p}K_a$ . The main difference is the product of this equilibrium is the conjugate acid.

### Strong Acid Versus Weak Acid

Often the terms **strong** and **weak** will be applied to acids. A **strong** acid will dissociate into lots of protons (HCl, see below). As a result, the  $K_a$  value will be **large** and the  $\text{p}K_a$  value will be **very small** (often negative). A **weak** acid will remain largely in its protonated form. As a result, the  $K_a$  value will be **small** and the  $\text{p}K_a$  value will be **large**.



Label the Acid and Base in the following reaction, draw the products, and show a mechanism using the appropriate arrows.

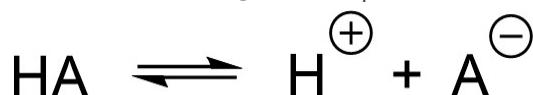


02

## Factors Influencing Acid/Base Strength

### Factors Influencing Acid/Base Strength

A solid understanding of the acid/base equilibrium is important. Not just for exam questions; it's a collection of fundamental chemical properties working together. Basically it all comes down to one thing, this equilibrium:



A strong acid will largely dissociate into 'HA' into  $\text{H}^+$  and  $\text{A}^-$ . So, a **strong acid** needs to form a **very stable conjugate base** ( $\text{A}^-$ , above). What are the factors that **stabilize a conjugate base**?

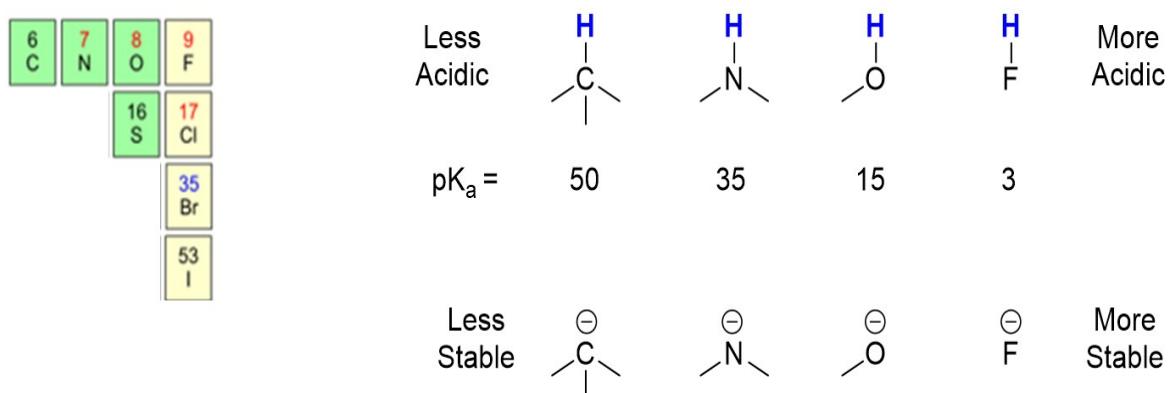
A strong base ( $\text{A}^-$ ) will grab a proton and form a conjugate acid (HA). So, a **stronger base** is essentially a **more unstable  $\text{A}^-$**  (above). What are the factors that lead to a **compound getting protonated**?

### Factors Influencing Acid/Base Strength

1. Electronegativity
2. Atom Size
3. Resonance
4. Hybridization
5. Induction
6. Aromaticity

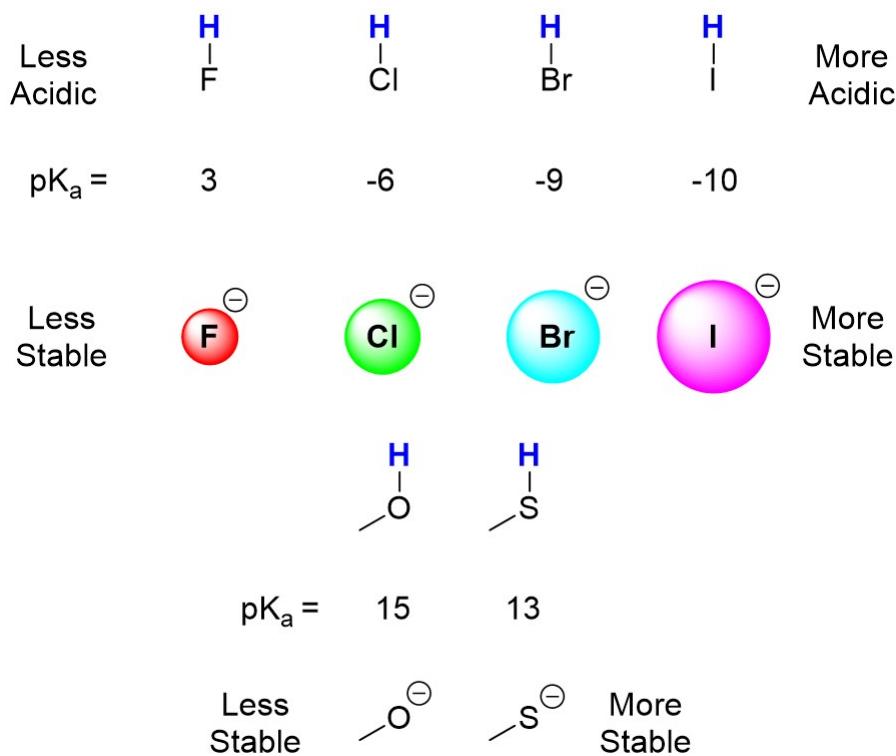
#### 1. Electronegativity

Atom electronegativity is a measure of how well an atom holds electrons to its nucleus (in a bond). If we look at the anions of the 'organic' atoms of the 2nd row (C, N, O, F) we see a trend associated with their relative electronegativity. Carbon, the most electropositive atom of the series, forms the least stable anion and is therefore a poor acid. Fluorine, the most electronegative atom of the series, forms the most stable anion and HF is a much stronger acid than the others. In general, **anions of more electronegative atoms (in the same row)** are **more stable**.



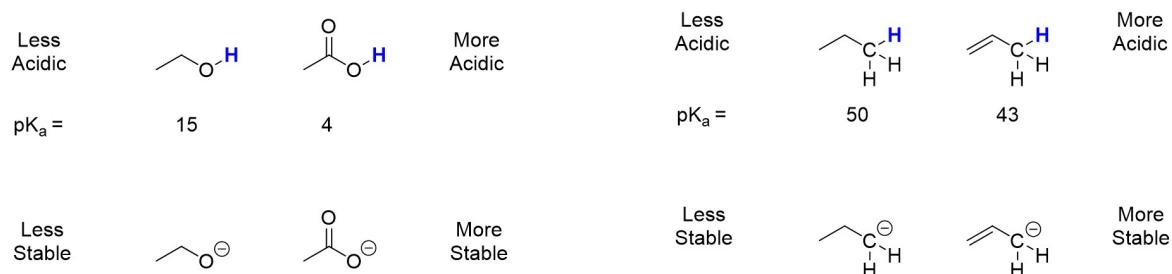
## 2. Atom Size

When comparing the anion stability of atoms in the same group (e.g. halogens, group 17), the **more stable anions are the larger ones**. This may be counter to the electronegativity concept above, but **larger atoms are able to better disperse their negative charge and are therefore more stable**. The same trend can be seen with the chalcogens (O and S, group 16). A thiol ( $\text{R-SH}$ ) is a stronger acid than an alcohol ( $\text{R-OH}$ ).



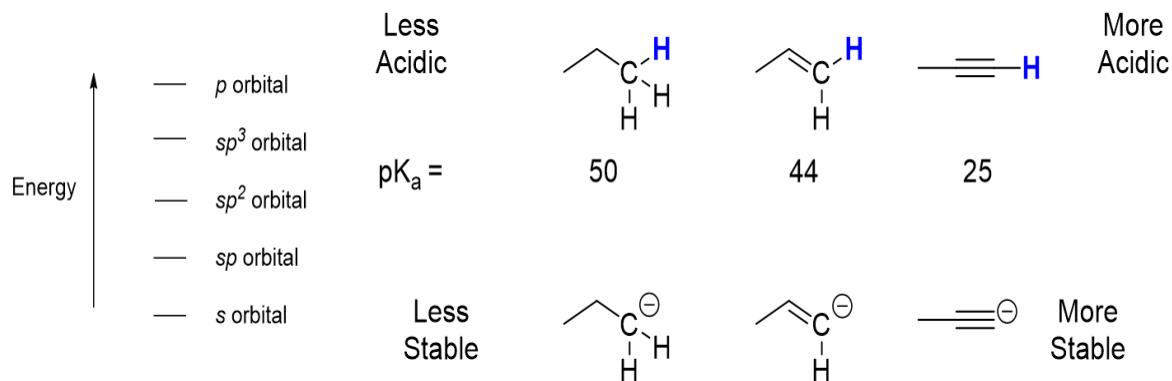
### 3. Resonance

If a negative charge can be dispersed over two or three atoms (e.g. anion has multiple resonance structures) it will be more stabilized. Compare the  $pK_a$  values of an alcohol to a carboxylic acid (below, left) or an alkane C-H to an allylic C-H (below, right).

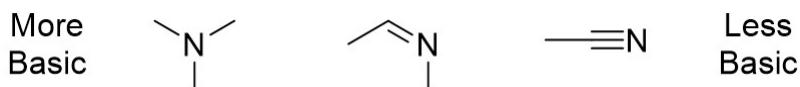


### 4. Hybridization

Atom hybridization plays a role in acid and base strength. For acids, an anion will be more stabilized in a hybrid orbital that has more s-character. For example, a terminal alkyne is exceptionally more acidic than an alkane because a  $sp$  anion is more stable than an  $sp^3$  anion (see below).

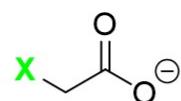


For bases, if the lone pair is in an orbital with more s-character (e.g. an  $sp$  orbital) it will be lower in energy, more stable, and less likely to get protonated. For this reason amines are generally more basic than imines and nitriles (see below).



## 5. Induction

Inductive stabilization is a more complex factor contributing to anion stability. It is commonly observed in carboxylic acid derivatives but the concept applies to any anion. If an electronegative element, nitro group or ammonium functionality (**X**, below) is close to an anion, it can stabilize the anion through induction. You are introducing a dipole in the molecule, and this partial positive charge stabilizes the anion.



**X** = electronegative elements (halogens, O, N)

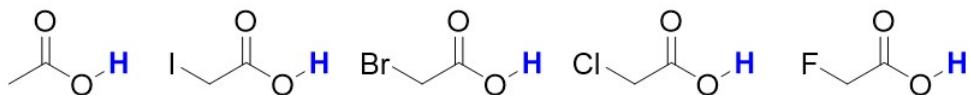


ammonium groups    nitro ( $\text{NO}_2$ ) groups

There are several factors that contribute to the overall inductive stabilization of an anion:

### 5a. Electronegativity

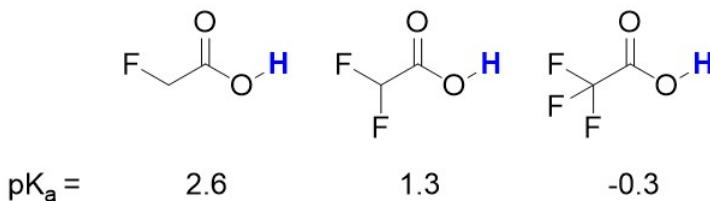
Atoms with greater electronegativity create a stronger dipole and this leads to greater inductive stabilization. For example, fluorine is the most electronegative halogen and the fluoro-derivative of ethanoic acid is the most acidic of all mono-halogenated ethanoic acids (see below).



$\text{pK}_a =$	4.8	3.1	2.9	2.7	2.6
-----------------	-----	-----	-----	-----	-----

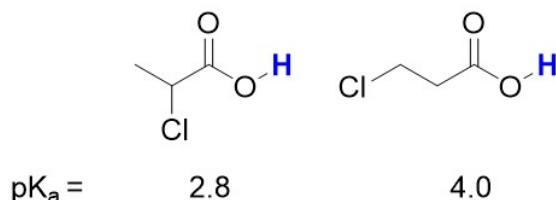
### 5b. Number of Atoms

Additional electronegative atoms will only increase the dipole and this leads to greater inductive stabilization:



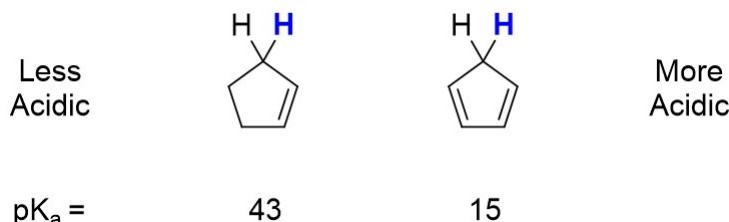
### 5c. Proximity

The closer your inductive stabilizer is to the resulting anion, the **more stable** that anion will be. For example, 2-chloropropanoic acid is more acidic than 3-chloropropanoic acid:

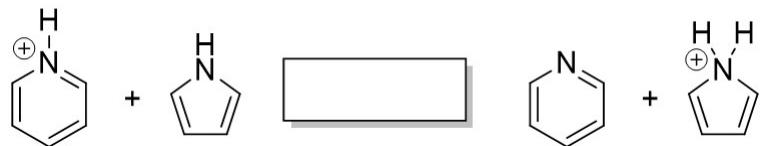


### 6. Aromaticity

If an anion is aromatic it will be stable. This is the case with cyclopentadiene which, when compared to cyclopentene, is a much more acidic compound (see below). Although each anion is resonance stabilized, the cyclopentadienyl anion is aromatic.

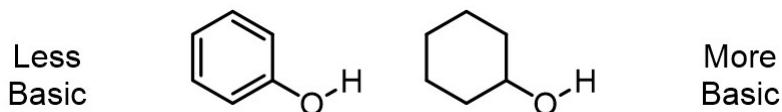


Aromaticity also plays a role in base strength. If a lone pair of electrons is necessary for a compound to be aromatic it will be **less likely** to get protonated. For example, which way does the equilibrium lie in the following example:



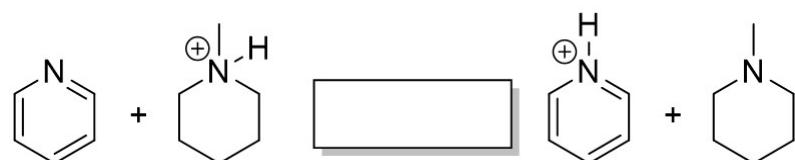
### CONCEPT CLARIFIER

Rationalize the following observation regarding the relative basicity of phenol and cyclohexanol. Which of the two compounds would be more acidic? Why? (hint: use diagrams, not words, to explain your answer).



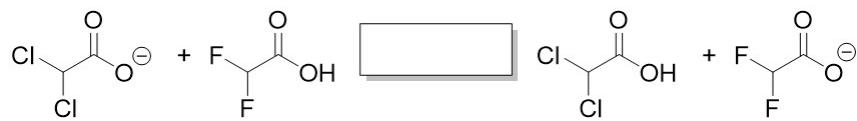
**CONCEPT CLARIFIER**

Which way does the equilibrium lie in the following reaction? Rationalize your answer.



**CONCEPT CLARIFIER**

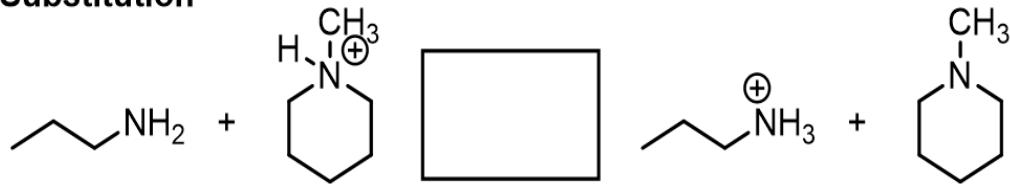
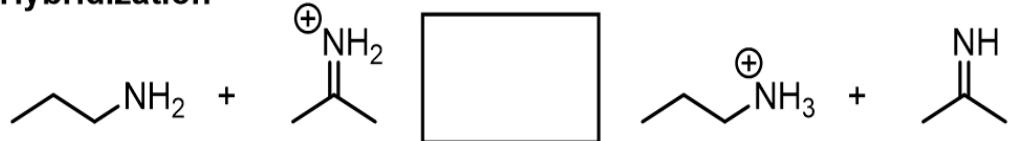
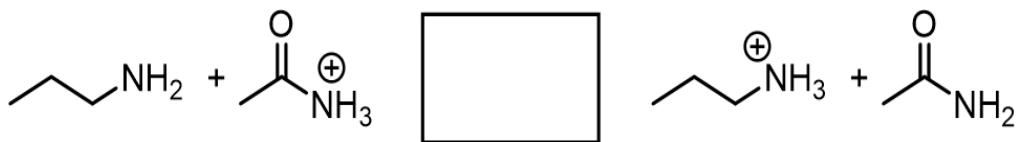
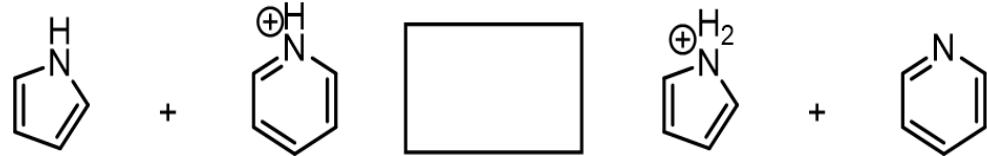
Which way does the equilibrium lie in the following reactions?



## 03 —— Nitrogen-based Bases

### Nitrogen-based Bases

Predict the direction of the equilibrium in each reaction. All four reaction equilibria can be predicted following standard acid/base rules.

**Substitution****Hybridization****Resonance****Aromaticity**

Four factors contribute to the basicity of amines:

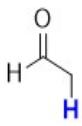
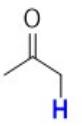
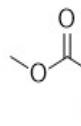
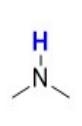
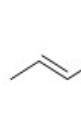
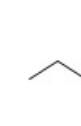
1. **Substitution:** More substitution = better base
2. **Hybridization:** More s-orbital character = worse base
3. **Resonance:** Delocalized lone pairs are less basic
4. **Aromaticity:** Protonation is difficult if it destroys aromaticity

04

## Relationship Between pH and pKa

### Relationship Between pH and pK<sub>a</sub>

#### Important pK<sub>a</sub>s You Should Know

<chem>H2SO4</chem>	<chem>H3O+</chem>				<chem>H2O</chem>	
-9	-2	4	10	10	16	16
<b>pK<sub>a</sub> =</b>						
						
17	20	25	25	40	45	50

A good knowledge of the relative pK<sub>a</sub>s of certain functional groups is vital in Organic Chemistry. In some cases, you can only predict an acid/base equilibrium if you know these values. Like before, the equilibrium will favour the side with the most stable conjugate base. For example, predict the equilibria in the following examples:

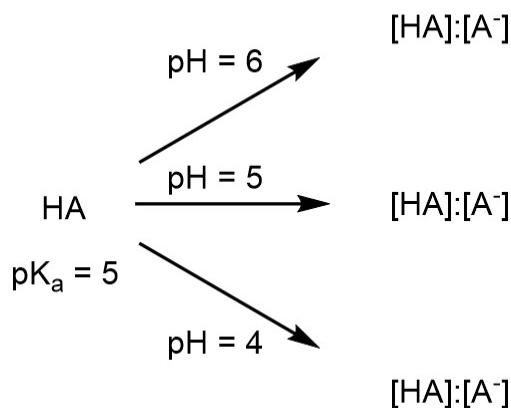


In addition, knowledge of  $pK_a$ s allows you to choose the appropriate base to deprotonate at select sites in a molecule. To completely deprotonate a compound of a given  $pK_a$  you must select the conjugate base of an acid with a higher  $pK_a$ . Select an appropriate base (e.g. not too strong) to perform the following deprotonations:



### Relationship Between pH and $pK_a$

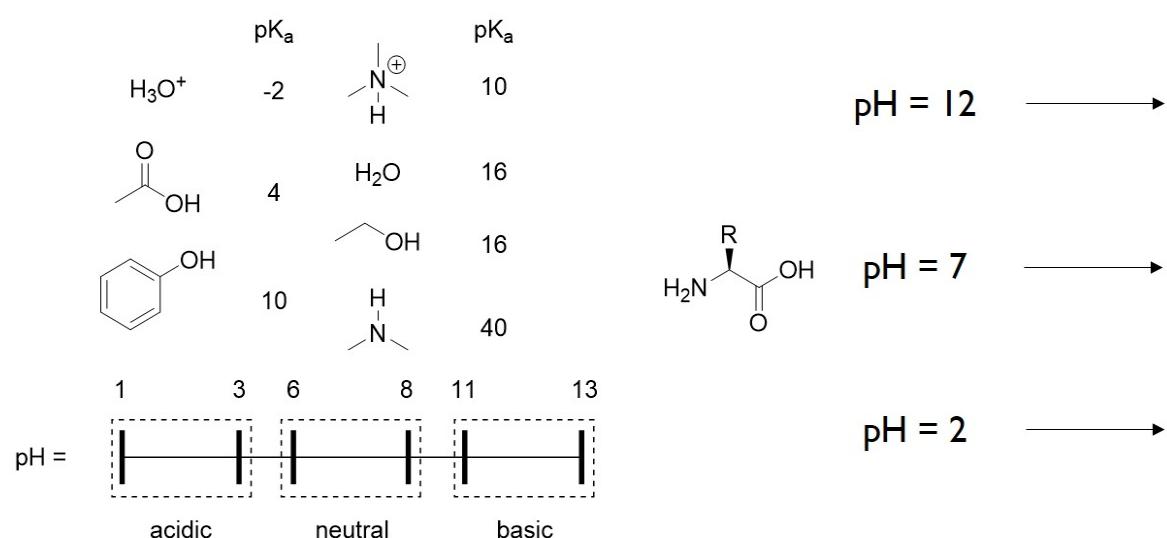
The pH of a solution will have an effect on the predominant structure of an acid. Take for example a generic acid HA shown below:



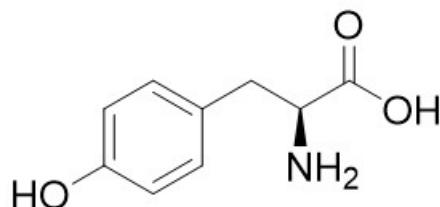
The ratio of the protonated acid (HA) to its conjugate base ( $A^-$ ) will be directly related to the pH (which is a measure of  $H^+$  ions in solution). If  $pH = pK_a$ , the concentration of HA will equal  $A^-$ . In higher (more basic) pH, the quantity of  $A^-$  will increase. In lower (more acidic) pH, the quantity of HA will increase.

## Amino Acids at Different pHs

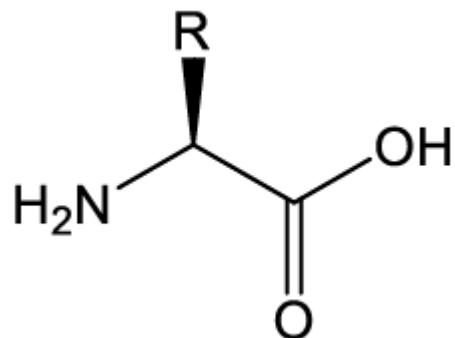
Amino acids, the building blocks of proteins and enzymes, are important biological molecules. They also serve as great tool to explore the relationship of pH to  $pK_a$ . Amino acids are similar in that they all feature an amine and a carboxylic acid functionality. They differ in the structure of their side chain (labelled R, see below), which is a key feature of their reactivity. We can predict the predominant structure of an amino acid in acidic ( $\text{pH} = 1\text{-}3$ ), neutral ( $\text{pH} = 6\text{-}8$ ), and basic ( $\text{pH} = 11\text{-}13$ ) solutions:



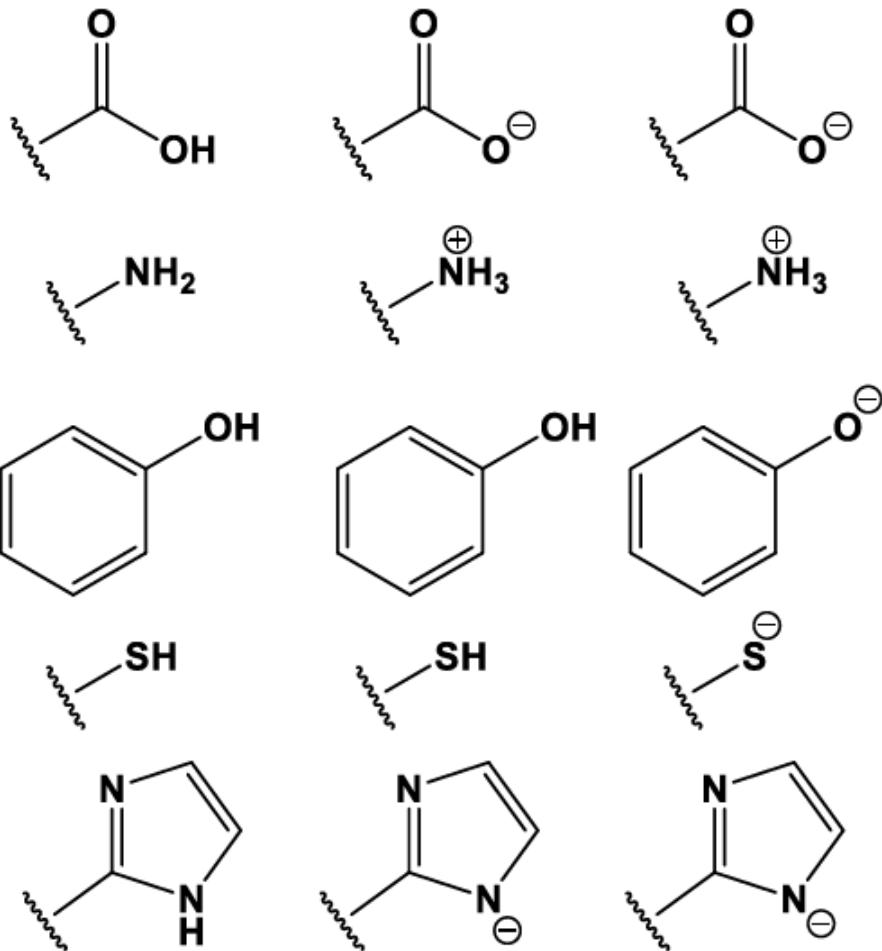
Below is the structure of L-Tyrosine. Draw the major structure of the amino acid at pHs 2, 7, and 12.



## Amino Acids in Solution of Various pH



Amino acids only have a few different functional groups (carboxylic acids, alcohols, thiols, thioethers, amines, amides, (and aromatic imidazole for histidine)). Remember, if the pH is below than the  $\text{pK}_a$ , the functional group is protonated, and if the pH is above the  $\text{pK}_a$ , the functional group is deprotonated. Alcohols, amides, and amines will never be deprotonated in these aqueous solutions (except for alcohols with aromatic stabilization (see below)). So you just need to concern yourself with the groups shown below:

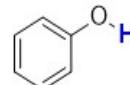
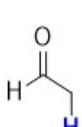
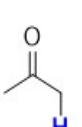
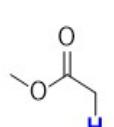
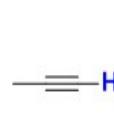
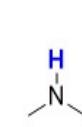
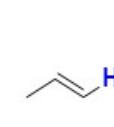
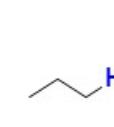
Acidic (pH 1-3)   Neutral (pH 6-8)   Basic (pH 10-12)

05

## pKa's of Common Molecules

### pK<sub>a</sub> Values for Common Functional Groups

Below are the pK<sub>a</sub> values of some of the most important functional groups in organic chemistry. Memorizing an approximate value is more than adequate to predict the appropriate bases to deprotonate any of these acids.

$\text{H}_2\text{SO}_4$	$\text{H}_3\text{O}^+$				$\text{H}_2\text{O}$	
-9	-2	4	10	10	16	16
$\text{pK}_a =$						
						
17	20	25	25	40	45	50

## 06 ————— Section Quiz

# Wize Quiz

## Acid/Base Quiz (15 Qu.)

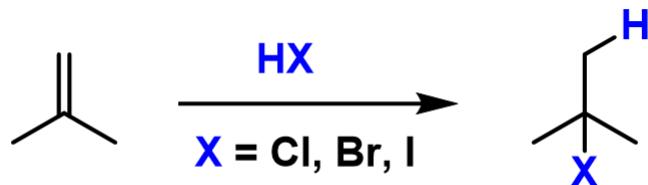
Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](http://wizedemy.com)

# ELECTROPHILIC ADDITION TO ALKENES

## 01 —— Hydrohalogenation

### Hydrohalogenation

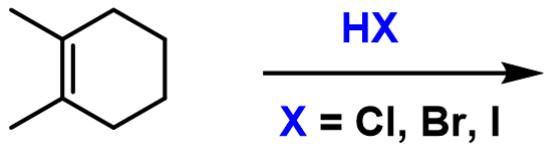
**General Reaction:** Addition of HX (where X is a halogen) across an alkene/alkyne.



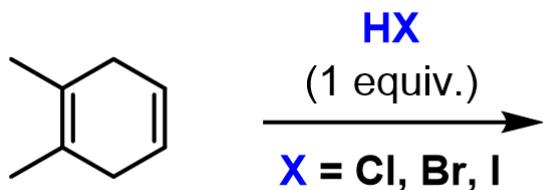
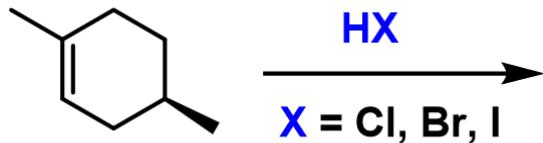
### Mechanism

Hydrohalogenation reactions, like most electrophilic additions with carbon-carbon multiple bonds, proceeds via a **carbocation intermediate**. This has an impact on both **stereoselectivity** (preferential formation of different stereoisomers) and **regioselectivity** (preferential addition at one site over another). In this case, the **Markovnikov product** is favoured.

Take for example the different **stereoisomers** formed in the following reaction:

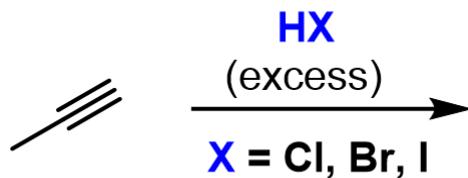


Predict the **regioselectivity** in the following reactions:



**CONCEPT CLARIFIER**

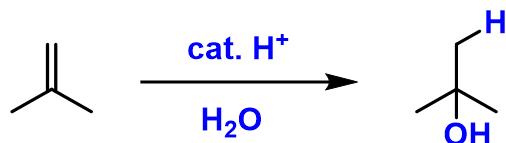
Hydrohalogenation of alkynes is a tool for the synthesis of *geminal* (two atoms bound to the same carbon atom) dihalides. Predict the product of the following reaction. Provide a plausible mechanism for the product formation and rationalize the regioselectivity.



## 02 Acid-Catalyzed Hydration

### Acid-catalyzed Hydration

**General Reaction:** Addition of  $\text{H}_2\text{O}$  across an alkene in the presence of a strong acid-catalyst.

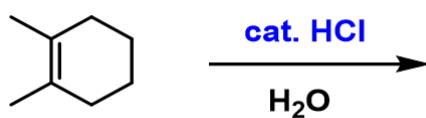


#### Mechanism

You may see any number of **strong acid catalysts** used in this reaction (e.g. HCl,  $\text{H}_2\text{SO}_4$ ). The catalyst is not so important... remember only a small amount is required for the reaction.

Acid-catalyzed hydration, like most electrophilic additions with carbon-carbon multiple bonds, proceeds via a **carbocation intermediate**. This has an impact on both **stereoselectivity** (preferential formation of different stereoisomers) and **regioselectivity** (preferential addition at one site over another). In this case, the **Markovnikov product is favoured**.

Take for example the different **stereoisomers** formed in the following reaction:

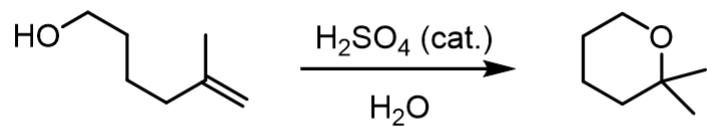


Predict the regioselectivity in the following reaction:



### CONCEPT CLARIFIER

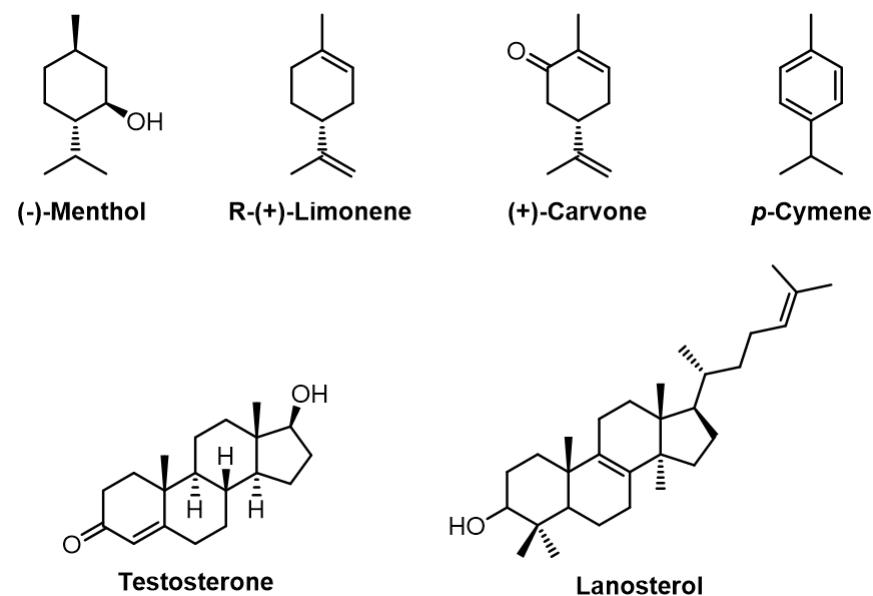
Intramolecular reactions are possible when a compound possesses both an alkene and an alcohol. Draw a possible mechanism for the following reaction:



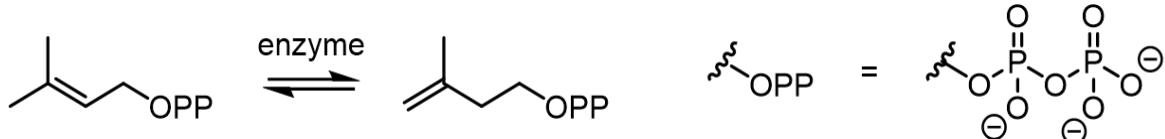
## 03 — **Terpene Biosynthesis**

### Terpene Biosynthesis

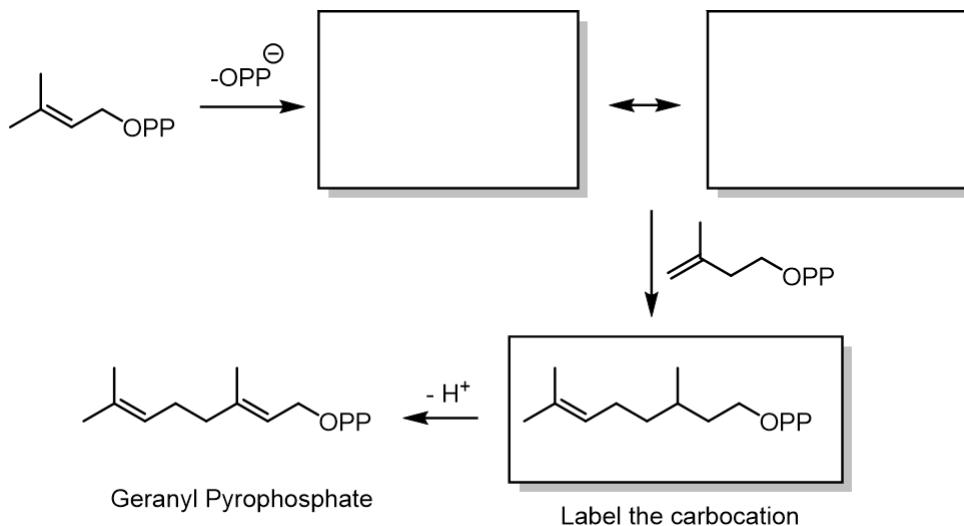
Terpenes are a diverse class of chemical compounds found in nature. They are often very aromatic with a pleasing odour (e.g. limonene). Many are important biological building blocks.



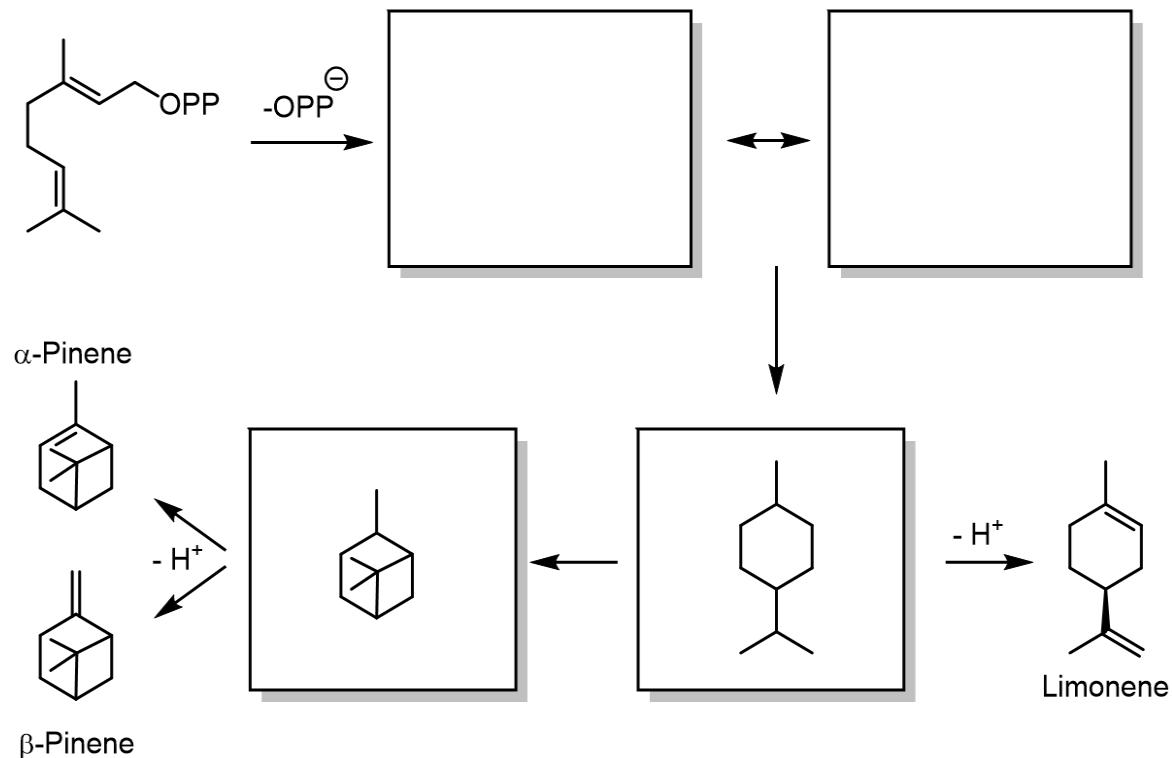
You can recognize **terpenes** because they contain a number of 5-carbon chain 'isoprene' units. In fact, most terpene compounds are all made from the same starting material: Dimethylallyl pyrophosphate (DMAPP) or its constitutional isomer Isopentenyl pyrophosphate (IPP).



A key intermediate in terpene synthesis is Geranyl Pyrophosphate (GPP), which comes from DMAPP. Let's see how its made:



Terpene biosynthesis questions are often given as a **roadmap question**:



04

## Summary of Reactions and Key Ideas

Key Ideas: Hydrohalogenation and Acid-catalyzed Hydration



05

## Section Quiz

# Wize Quiz

## Electrophilic Additions to Alkenes (12 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

# SUBSTITUTIONS AND ELIMINATION REACTIONS

## 01 Important Terms in Substitutions and Eliminations

### Important Terms in Substitutions and Eliminations

#### Key Terms

1. Nucleophile - Species that donates an electron pair to form a new chemical bond
2. Electrophile - Species happy to accept an electron pair in order to bond to a nucleophile
3. Leaving Group - A fragment that departs with a pair of electrons in heterolytic bond cleavage.

#### Example:

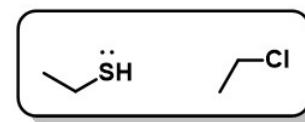
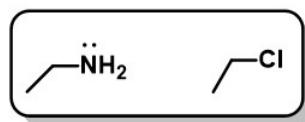
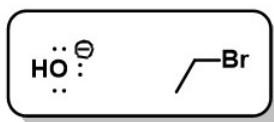


Nucleophile      Electrophile

Leaving Group

#### Nucleophiles

Nucleophiles must have lone pairs to attack an electrophile. We can show that attack, and subsequent bond breakage, using the appropriate arrow:



## General Rules for Nucleophiles

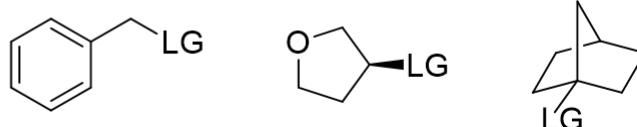
1. Nucleophilicity increases with negative charge:  $\text{HO}^- > \text{H}_2\text{O} >> \text{H}_3\text{O}^+$
2. Nucleophilicity increases with basicity in general:  $\text{H}_3\text{C}^- > \text{H}_2\text{N}^- > \text{HO}^- > \text{F}^-$
3. Nucleophilicity increases with more polarizable atoms (size):  $\text{I}^- > \text{Br}^- > \text{Cl}^- > \text{F}^-$

## Electrophiles

The amount of substitution around a Leaving Group influences sterics. Steric interactions can play a major role in reaction rate (as will be discussed in detail later). We can refer to an electrophile as primary ( $1^\circ$ ), secondary ( $2^\circ$ ), and tertiary ( $3^\circ$ ):

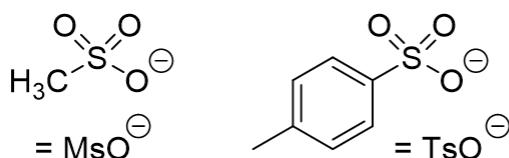
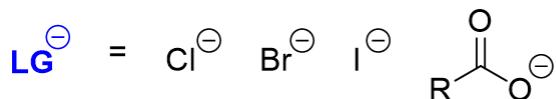
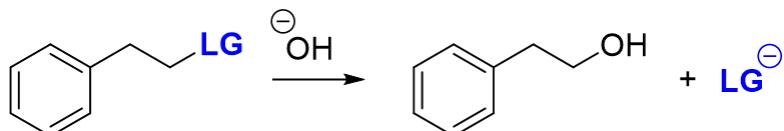
Type of Electrophile:

Example:



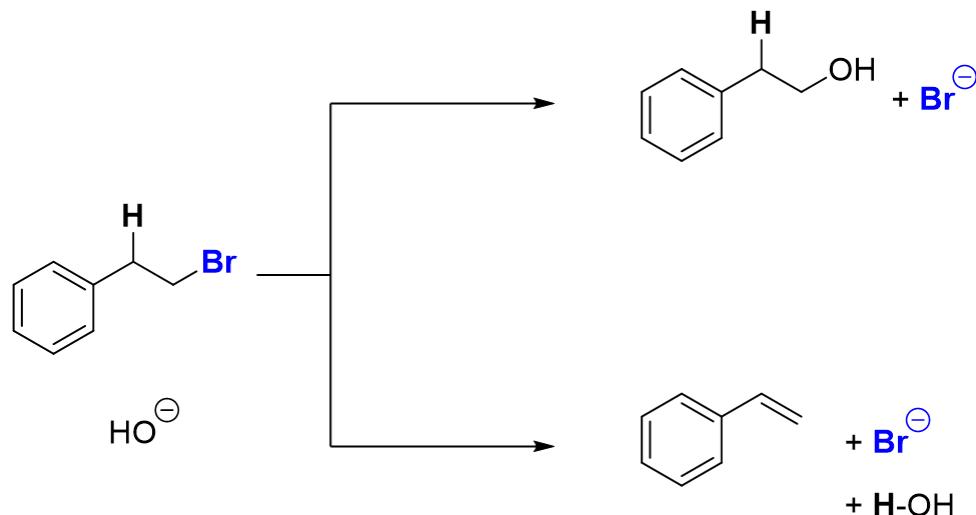
## Leaving Groups

Some leaving groups are better than others. The same factors that influence base stability (resonance, electronegativity, etc.) will also make a leaving group more stable. Typical examples include halogens, acetates, and sulfonates:



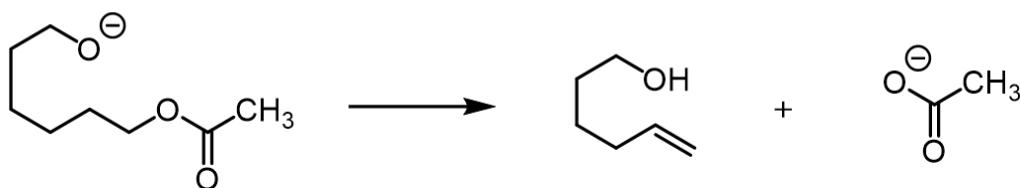
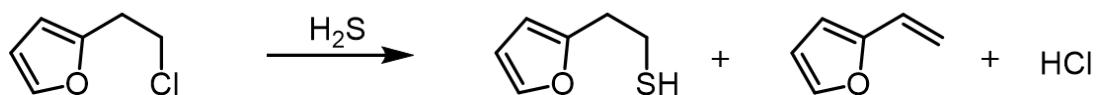
## Elimination Vs Substitution

This concept will be explored in detail later. A substitution involves replacing one group with another and a elimination involves a deprotonation and leaving group migration to form a new multiple bond:



### CONCEPT CLARIFIER

Label the following reactions as substitution, elimination, or both:



02

## Introduction to Substitution Reactions

### Introduction to Substitution Reactions

There are two main substitution reactions to be aware of:  $S_N2$  and  $S_N1$  reactions

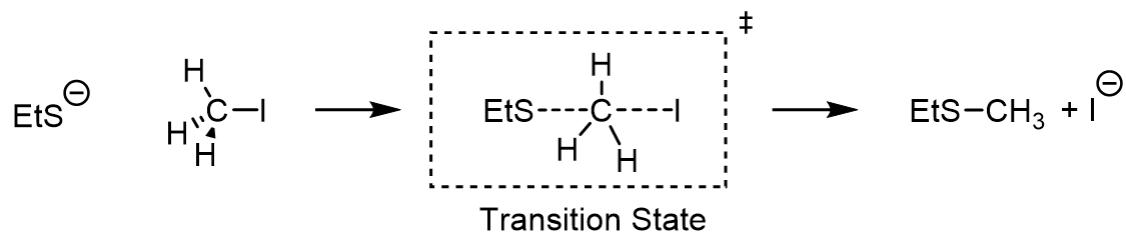
#### $S_N2$ Reactions: Substitution Nucleophilic Bimolecular (2)

$S_N2$  reactions occur between a strong nucleophile ( $\text{NaSEt}$ ) and an electrophile with little steric hinderance ( $\text{Me}-\text{I}$ ). It is a direct substitution of the leaving group with the nucleophile, in a single step:

Example:



#### $S_N2$ Mechanism



**Rate =**

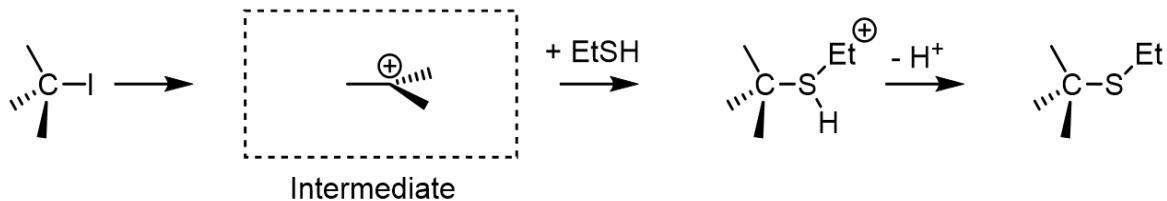
## S<sub>N</sub>1 Reactions: Substitution Nucleophilic Unimolecular (1)

S<sub>N</sub>1 reactions occur between a weak nucleophile (EtSH) and a substituted electrophile [(CH<sub>3</sub>)<sub>3</sub>C-I]. It is a two-step substitution of the leaving group with the nucleophile that occurs via a carbocation intermediate.

**Example:**



### S<sub>N</sub>1 Mechanism



Rate =

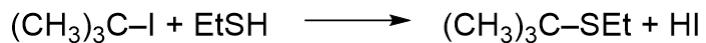
## Reaction Energy Diagrams

We use reaction energy diagrams to show the relative energy of **starting materials**, **intermediate species** (if present), **transition states** and **products**.  $S_N2$  and  $S_N1$  reactions have different reaction energy diagrams and you should be able to identify both. Remember, for a substitution reaction to occur it must be exothermic (the products are lower in energy than the starting material).

Provide a reaction energy diagram for the following reaction:

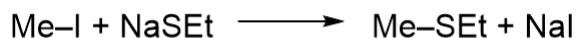


Provide a reaction energy diagram for the following reaction:



### CONCEPT CLARIFIER

Consider the following  $S_N2$  reaction:



Which of the following is true:

1. The rate increases with greater Mel concentration
2. The rate decreases with greater NaSEt concentration
3. If the Mel is replaced with MeBr, the rate decreases

### CONCEPT CLARIFIER

Consider the following S<sub>N</sub>1 reaction:



Which of the following is true:

1. The rate increases with greater (CH<sub>3</sub>)<sub>3</sub>C-I concentration
2. The rate increases with greater EtSH concentration
3. If the EtSH is replaced with EtNH<sub>2</sub>, the substitution rate changes

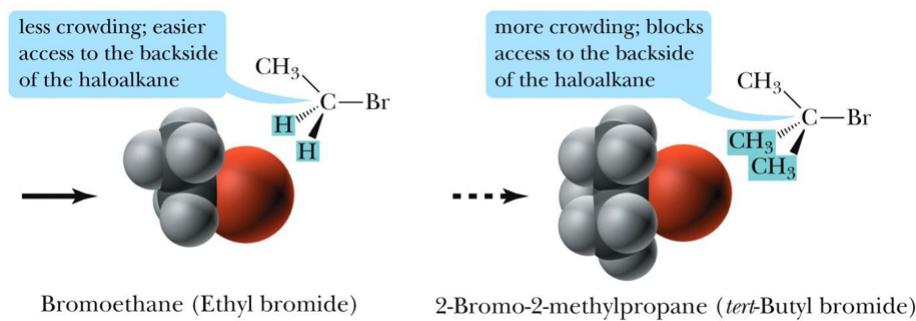
## 03 Choice of Electrophile in Substitution Reactions

### Choice of Electrophile in Substitution Reactions

The electrophile dictates the rate of substitution ( $S_N1$  and  $S_N2$ ) and elimination reactions. There are two key factors to consider: **sterics** (stuff around reaction centre) and **electronics** (quality of leaving group).

#### $S_N2$ Reactions

**It's all about sterics!** Crowding around a reaction centre is going to make nucleophile harder. Harder means slower - AKA decreased rate or less favoured.



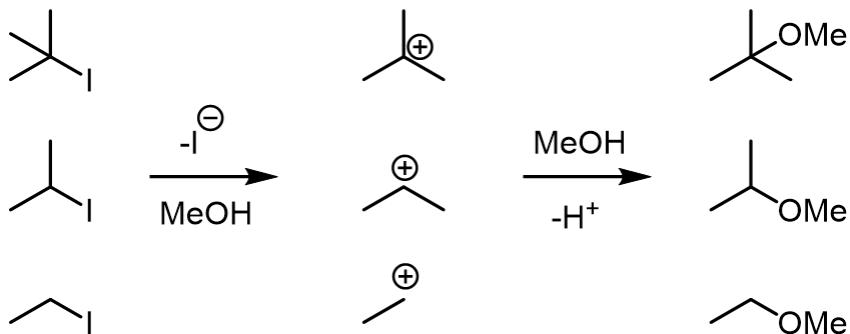
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#### Relative Rates in $S_N2$ Reactions

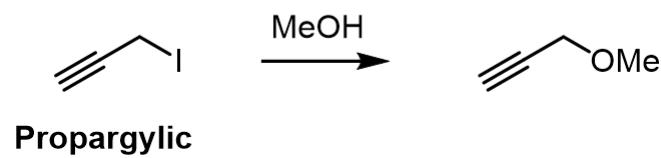
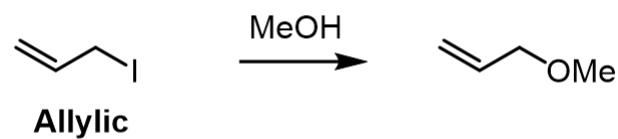
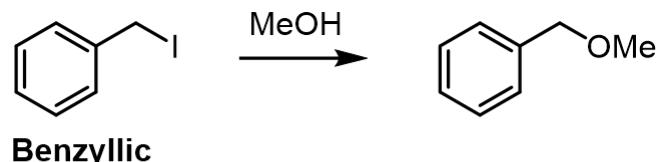
Substrate	Example			Approx. Rate
Methyl	$\text{CH}_3\text{Br}$	$\xrightarrow{\ominus \text{CN}}$	$\text{CH}_3\text{CN}$	$\sim 1000$
Primary		$\xrightarrow{\ominus \text{CN}}$		$\sim 20$
Secondary		$\xrightarrow{\ominus \text{CN}}$		1
Tertiary		$\xrightarrow{\ominus \text{CN}}$		$< 0.001$

## $S_N1$ Reactions

It's important to remember that the rate of  $S_N1$  reactions only depends on the electrophile. Also, you are forming a carbocation intermediate! So a more stable carbocation will lead to an increased rate of reaction. More substituted carbocations are more stable:

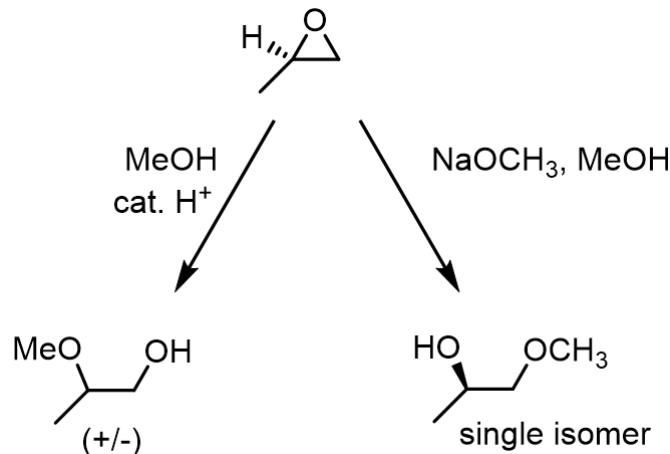


In fact, simple primary organohalides will never undergo a  $S_N1$ -type substitutions. However, below you will see examples of  $S_N1$ -substitutions that appear to take place with primary organohalides? In this case, it is important to consider **resonance contributions** that stabilize the carbocation. They often have special names:



## Tough Example - Epoxides

Rationalize the products of the following additions to an epoxide

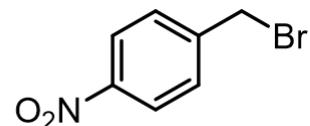
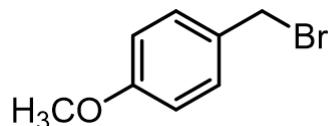


## Electrophiles Review

	<b>SN1</b>	<b>SN2</b>
	Primary ( $1^\circ$ )	
	Secondary ( $2^\circ$ )	
	Tertiary ( $3^\circ$ )	
	Allylic/Benzyllic...	

**CONCEPT CLARIFIER**

One of the electrophiles below is good for  $S_N1$  substitutions. The other only suitable for  $S_N2$  substitutions. Rationalize this observation (use pictures).

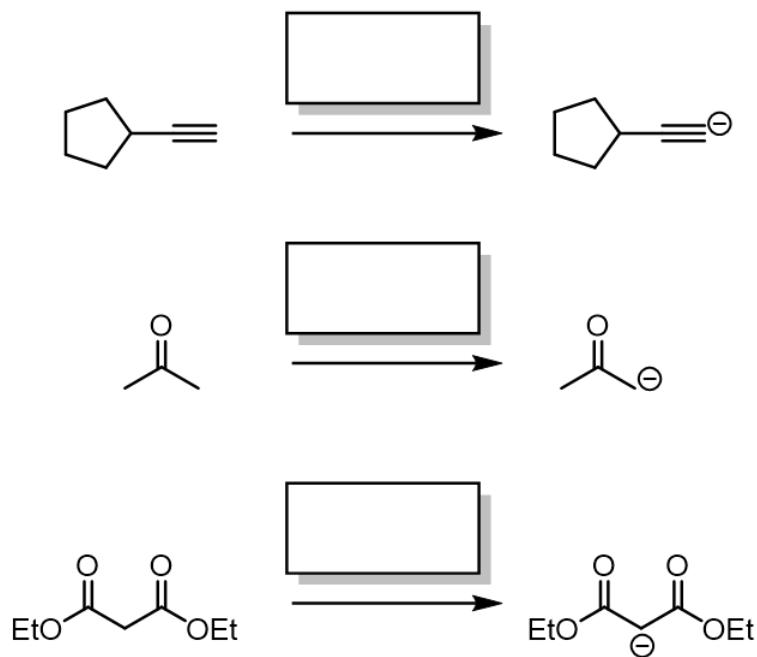


## 04 — **Choice of Nucleophile in Substitution Reactions**

## Choice of Nucleophile in Substitution Reactions

The choice of nucleophile directly impacts the rate of  $S_N2$  reactions. As a result, strong nucleophiles will increase the rate of  $S_N2$  substitutions. Conversely, strong nucleophiles do not benefit  $S_N1$  substitutions. Unwanted side reactions will likely occur.

Often strong nucleophiles are generated *in situ* before a suitable electrophile for a  $S_N2$  substitution is added. This takes advantage of the principles of Acid/Base equilibria. It is important to recognize or select the appropriate base to generate strong nucleophiles:

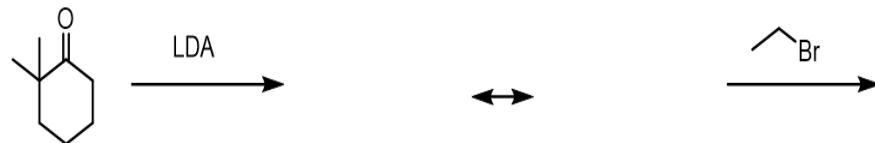


Fill in the blanks in the following reactions:

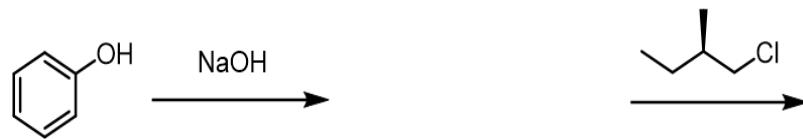
**Example 1**



**Example 2**



**Example 3**



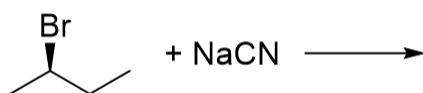
05

## Stereochemistry in Substitution Reactions

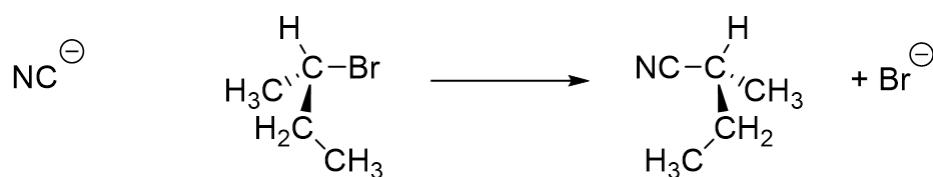
### Stereochemistry in Substitution Reactions

Different substitution reaction mechanisms ( $S_N2$  and  $S_N1$ ) often lead to different stereochemical outcomes. For example,  $S_N2$  is a single step reaction and occurs with inversion of stereocentre.

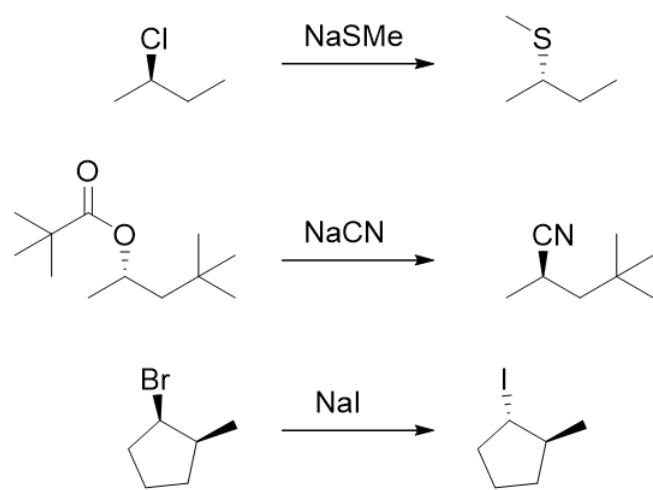
#### Predict the Product



#### Mechanism

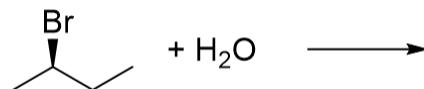


We can always spot an  $S_N2$  reaction because it occurs with inversion and gives a single stereoisomer as a product:

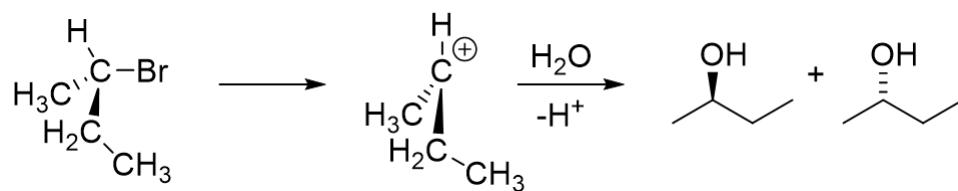


$S_N1$  reactions differ because they proceed via a carbocation intermediate. If there is a newly formed chiral centre, this leads to a racemic centre.

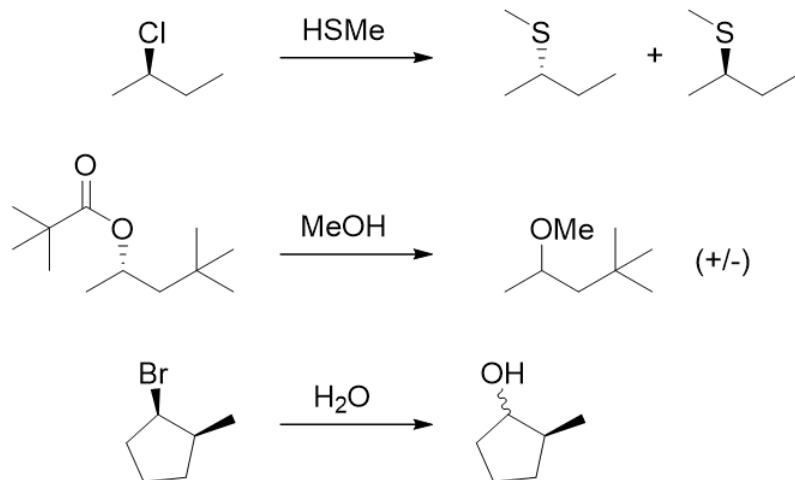
### Predict the Product



### Mechanism



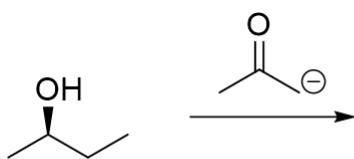
We can always spot an  $S_N1$  reaction because it occurs with **racemization** (if a chiral centre is being formed) and (often) gives **multiple stereoisomers** as a product:



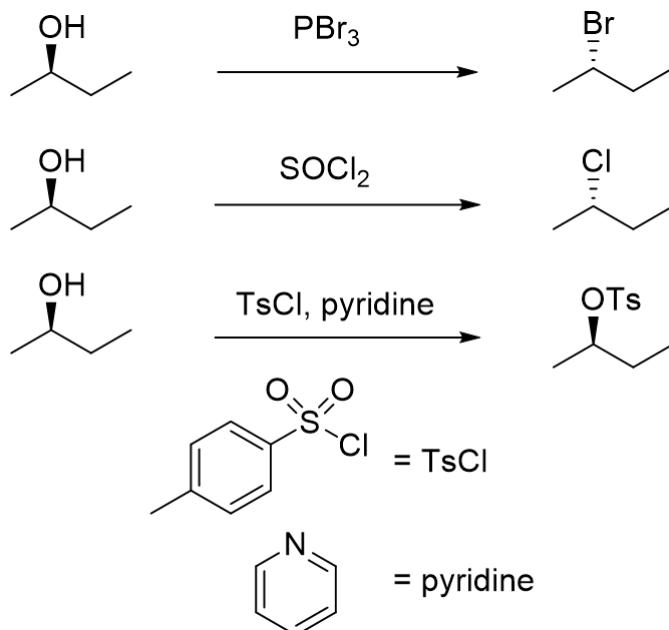
## 06 — Alcohol As a Leaving Group

### Alcohol As a Leaving Group

Alcohols are **terrible leaving groups**. Remember that they are weakly acidic ( $pK_a = 15$ ), so if you treat an alcohol with a strong nucleophile you'll undergo an acid/base reaction. Take for example the following reaction:



Alcohols need to be converted to a good leaving group before they can be used for substitution or elimination reactions. There are three main strategies:



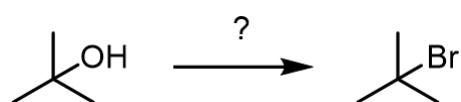


The choice of leaving group you convert your alcohol to can often matter. Remember in each  $S_N2$  reaction a chiral centre can be inverted. Fill in the blanks for the two examples below:



### CONCEPT CLARIFIER

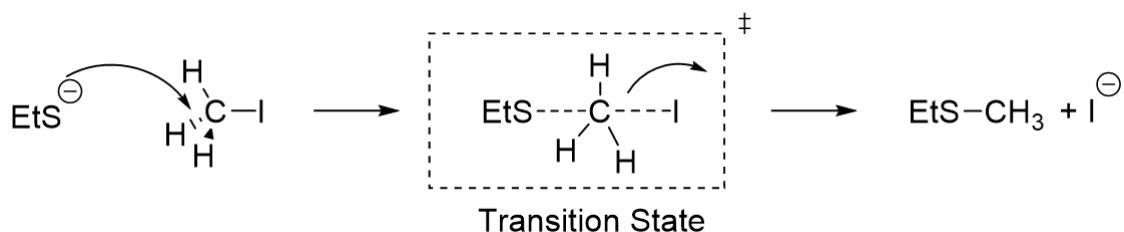
Provide a reagent (or reagents) for the reaction shown below:



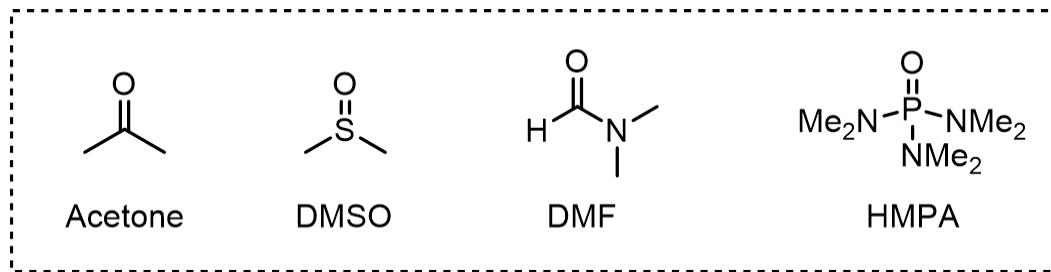
**07****Solvent Effects in Substitution Reactions****Solvent Effects in Substitution Reactions**

Different solvents can have beneficial effects on substitution reactions. Remember,  $S_N1$  and  $S_N2$  reactions proceed via highly charged intermediates and transition states, respectively. Solvents that are capable of stabilizing these high energy species are going to increase reaction rate.

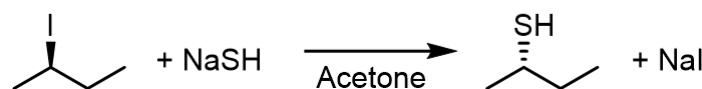
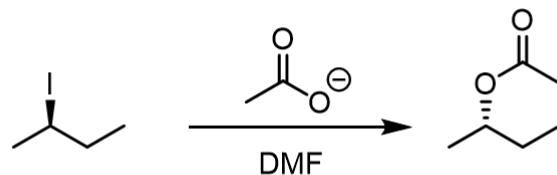
Take for example the mechanism of a standard  $S_N2$ -type reaction:



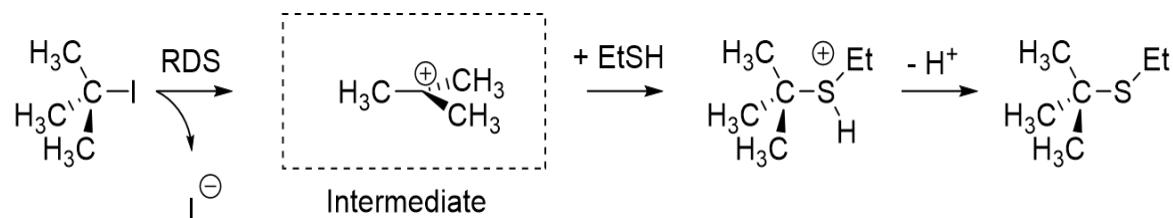
$S_N2$  reactions have *charged*, high-energy *transition states*. They also often utilize *strong nucleophiles*. To stabilize the charged species it is beneficial to use *polar* molecules. However, because of the strong nucleophiles, there shouldn't be any acidic protons present (AKA *nonprotic solvent*). Examples of *polar, nonprotic solvents* include Acetone, Dimethylsulfoxide (DMSO), Dimethylformamide (DMF), and Hexamethylphosphoramide (HMPA).



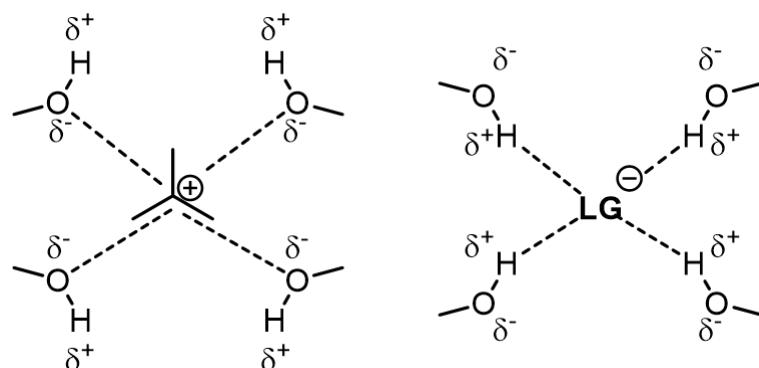
In general, anytime you see some acronym solvent you don't recognize there's likely an  $S_N2$  reaction afoot:



Now take for example the mechanism of a standard  $S_N1$ -type reaction:

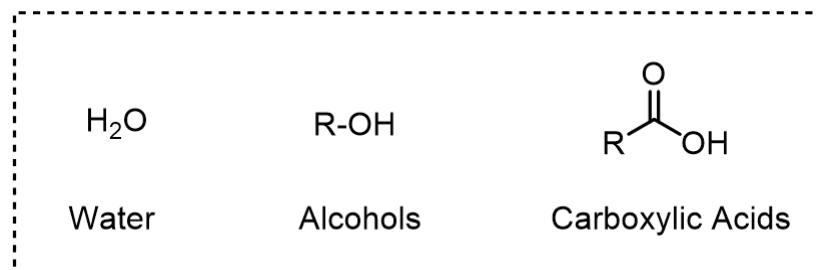


$S_N1$  reactions have **charged**, high-energy **intermediates**. The rate of  $S_N1$  reactions are dictated by stabilization of **leaving group** and **carbocation**. To stabilize the charged carbocation it is beneficial to use **polar molecules**. In addition, to help stabilize the leaving group **protic** compounds are best. This way there can be hydrogen bonding with the leaving group:



Typically for  $S_N1$  reactions the solvent is the nucleophile. Still, we can define the beneficial solvents as **polar and protic**. Examples include water, alcohols,

carboxylic acids:



08

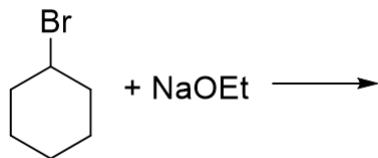
## Introduction to Elimination Reactions

### Introduction to Elimination Reactions

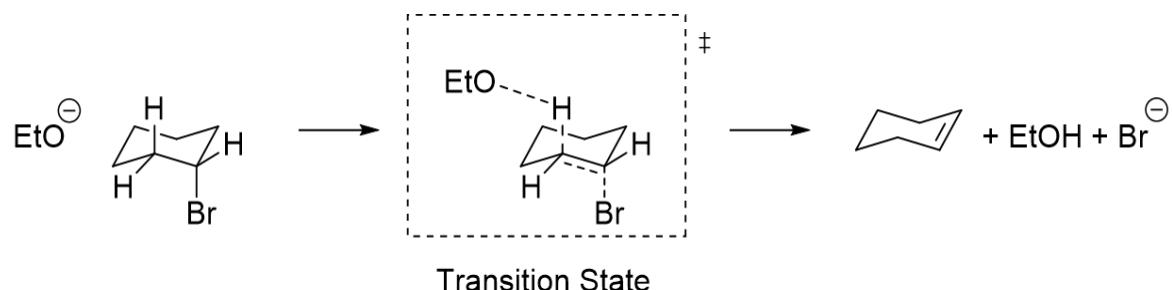
Eliminations, similar to substitution reactions, can be classified in two major categories: E2 and E1 reactions.

#### E2 Reactions: Elimination Bimolecular (2)

Example:

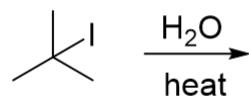


#### E2 Mechanism

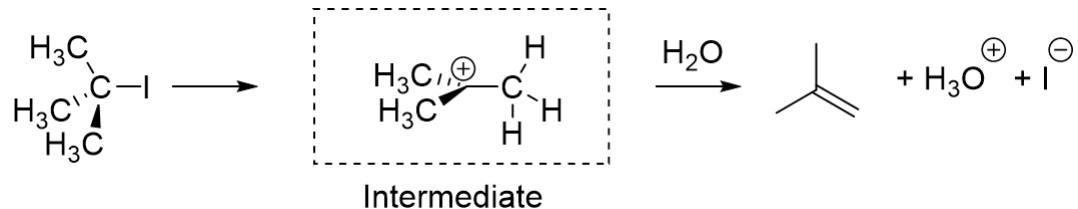


### E1 Reactions: Elimination Unimolecular (1)

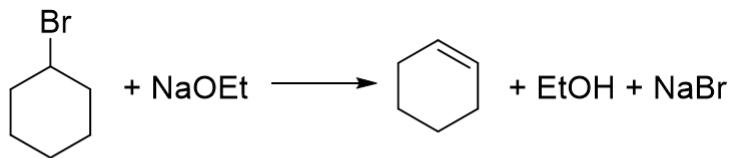
**Example:**



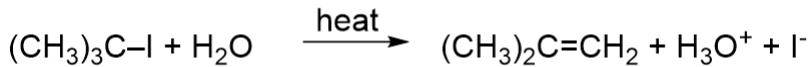
### E1 Mechanism



Similar to substitution reactions, there is a unique rate law for each type of elimination reaction:



**Rate =**



**Rate =**

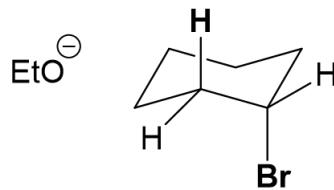
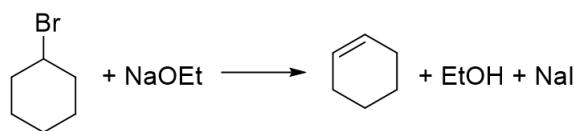
## 09 Selectivity in Elimination Reactions

### Selectivity in Elimination Reactions

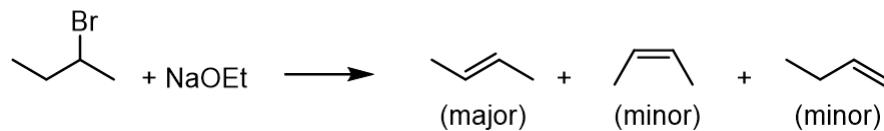
Elimination reactions can display both regioselectivity (preferential elimination at one site over another) and stereoselectivity (preferential formation of one stereoisomer over another).

#### Selectivity in E2 reactions

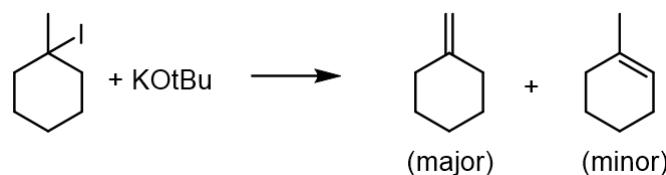
E2 reactions require an anti-periplanar arrangement of the proton and leaving group. Take the following reaction:



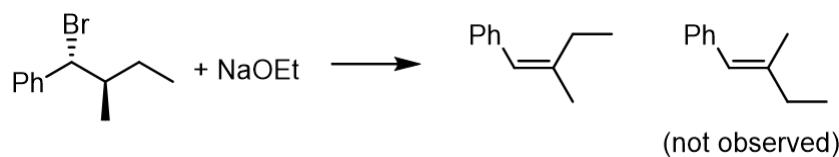
In general, unless a bulky base is being used E2 will occur to give the **most substituted double bond**. This is an example of **Zaitsev's rule**. In addition, if multiple protons are present, the trans double bond will be favoured:



If a **bulky base** is used (e.g. KOtBu), elimination will occur to limit steric interaction. This is an example of **Hofmann's rule**:

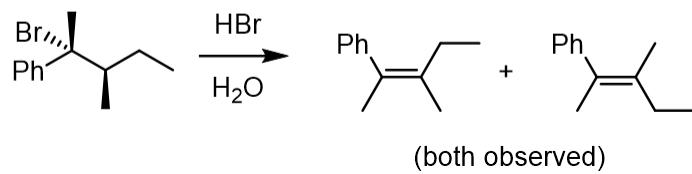
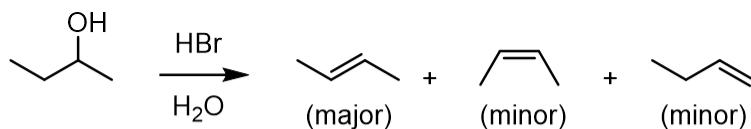


If only one proton is available, it's important to remember that **E2 reactions** proceeds via the **anti-periplanar** arrangement of the proton and leaving group. This will sometimes lead to a **single stereoisomer** (either cis or trans). Take for example:



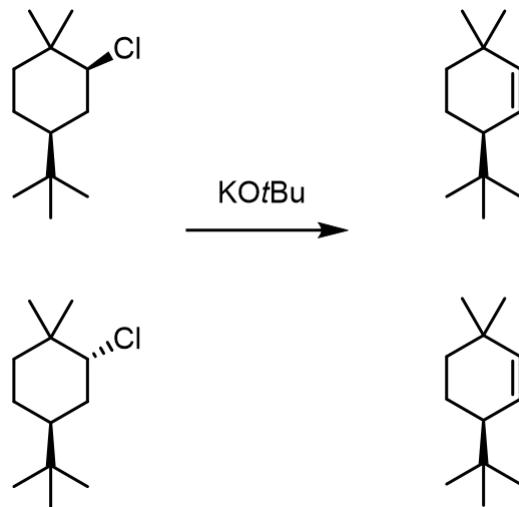
### Selectivity in E1 reactions

Selectivity is also observed in E1 elimination reactions, but they differ since there is an **intermediate carbocation species**. This can lead to similar product distributions (Zaitsev product) as related E2 reactions (top example) or a mix of stereoisomers where only one product might be formed in an E2 reaction (bottom example).



### CONCEPT CLARIFIER

Both alkyl halides below eliminate to form a cyclohexene derivative, however one species eliminated more rapidly than the other. How can you rationalize this observation? (hint: use pictures... draw the chair conformations)



10

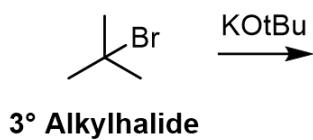
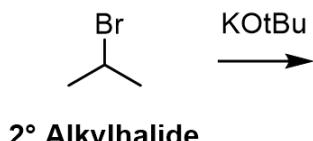
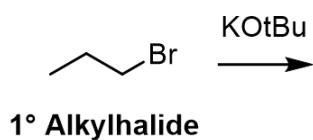
## Favouring Elimination over Substitution

### Favouring Elimination over Substitution

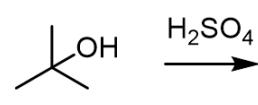
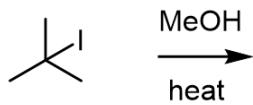
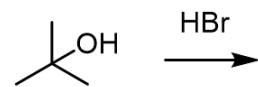
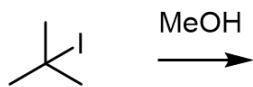
One of the biggest issues students face is deciding if a reaction will be an elimination or a substitution. There are certain reagents that can be used to favour elimination (or substitution). For example, **alcohols versus alkoxides**. Alcohols are weak nucleophiles/bases so they tend to favour **substitution reactions**. Alternatively, **alkoxides** are small and reactive (compared to halogens/thiolates) and tend to favour **elimination reactions**. The **best alkoxides for elimination reactions are bulky (KOtBu)**. Take for example the product distribution in the following reactions:



Even if you use bulky bases it is difficult to favour E2 over SN2 on primary alkylhalides. After that, more substituted alkylhalides will elimination preferentially:



E1 elimination can be favoured over SN1 substitution using two techniques: (1) Heat and (2) Strong acid, weak nucleophile. Take for example the products of the following reactions:



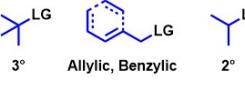
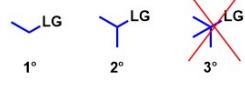
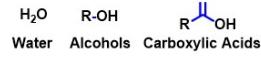
## 11

## Summary and Key Ideas - Substitution and

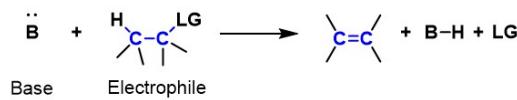
# Elimination

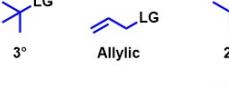
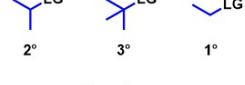
## Substitutions – S<sub>N</sub>1 and S<sub>N</sub>2



	<b>S<sub>N</sub>1</b>	<b>S<sub>N</sub>2</b>
Rate Law	k[electrophile]	k[electrophile][nucleophile]
Reaction Energy Diagram	2 transition states and 1 intermediate	1 transition state
Electrophiles	3° and resonance stabilized best, 2° sometimes  3°      Allylic, Benzylic      2°	1° best, 2° good, 3° never  1°      2°      3°
Nucleophiles	Not strong	Strong (anionic) preferred, sterics matter
Solvent	Polar, <b>Protic</b> 	Polar, <b>Aprotic</b> 

## Eliminations – E1 and E2



	<b>E1</b>	<b>E2</b>
Rate Law	k[electrophile]	k[electrophile][base]
Reaction Energy Diagram	2 transition states and 1 intermediate	1 transition state
Electrophiles	3° and resonance stabilized best, 2° sometimes  3°      Allylic      2°	2° and 3° good, 1° more difficult  2°      3°      1°
Base and conditions	Weak base + heat or strong acid (LG = OH)	Alkoxides (~OR), Bulk helps
Double Bond Stereochemistry	(E) preferred, (Z) rare	(E) preferred, (Z) rare <b>unless</b> orbitals require it
Regiochemistry	Always form most substituted double bond <b>(Zaitsev product)</b>	Always <b>Zaitsev</b> product <b>unless</b> a bulky base is used, then <b>Hofmann</b> (least substituted) product

**12** **Section Quizzes**

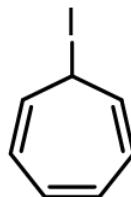
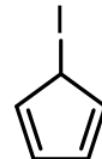
## Wize Quiz

### Substitutions and Eliminations (14 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](http://wizedemy.com)

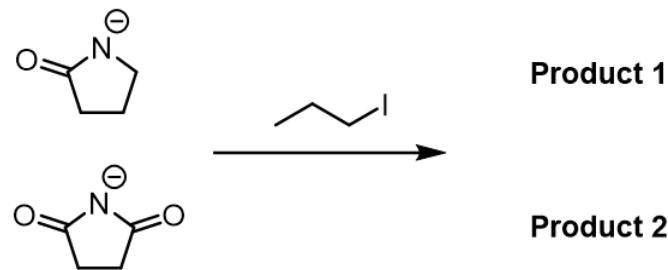
#### PRACTICE QUESTION #1

Compound A and B were each reacted with MeOH. It was observed that the rate of substitution greatly differed between each substrate. (1) Draw the substitution products, (2) Circle the product that forms quicker, (3) Justify your answer using a picture.

**A****B**

### PRACTICE QUESTION #2

Draw the structures of product 1 and product 2. Which product forms faster? Justify your answer using pictures!!

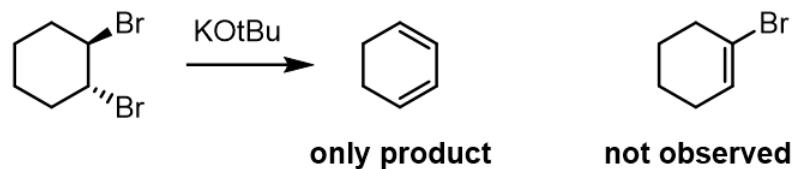






**PRACTICE QUESTION #3**

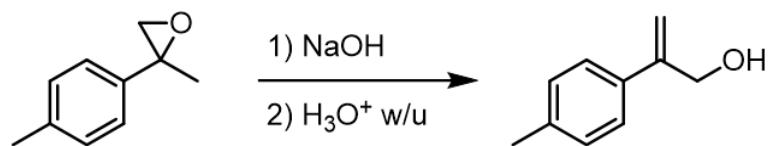
Explain the following observation using pictures:





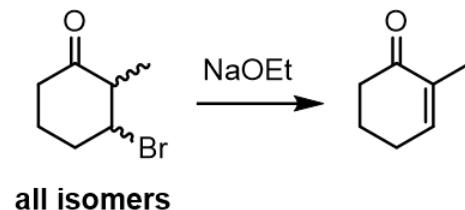
**PRACTICE QUESTION #4**

Draw a mechanism for the following reaction. What type of elimination reaction is this?



**PRACTICE QUESTION #5**

Explain the following observation. Explain using a mechanism:





# CARBOHYDRATES

## 01 Nomenclature

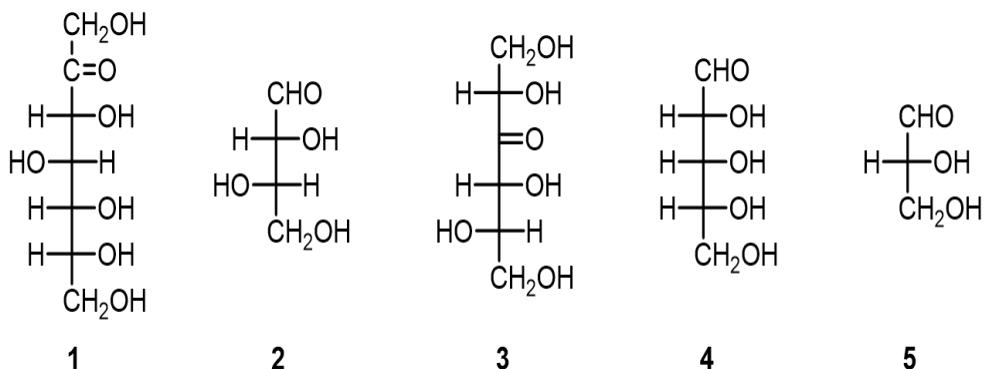
### Nomenclature

A carbohydrate (i.e. sugar molecules) is a biomolecule consisting of carbon, hydrogen and oxygen atoms, usually with a hydrogen–oxygen atom ratio of 2:1. The standard example is glucose -  $C_6H_{12}O_6$ .

#### Classification of Carbohydrates

1. **Chain Length:** Carbohydrates are named according to the number of carbon atoms in the main chain (carbon atoms in a row). They have similar prefixes to those used in IUPAC naming: 3 (tri), 4 (tetr), 5 (pent), 6 (hex), 7 (hept), and will all end in 'ose.'
2. **Aldose or Ketose:** Carbohydrates are classified as aldose (aldehyde) or ketose (ketone) depending on the carbonyl group present within the molecule.
3. **D Versus L:** Carbohydrates are classified as D or L. To do so: (1) the Fischer projection is drawn so the **highest oxidation state carbon is at the top**, (2) the  $-CH_2OH$  group is on the **bottom**, (3) if the next OH up is on the **Left = L**, **Right = D**.

Let's try naming these following carbohydrates:

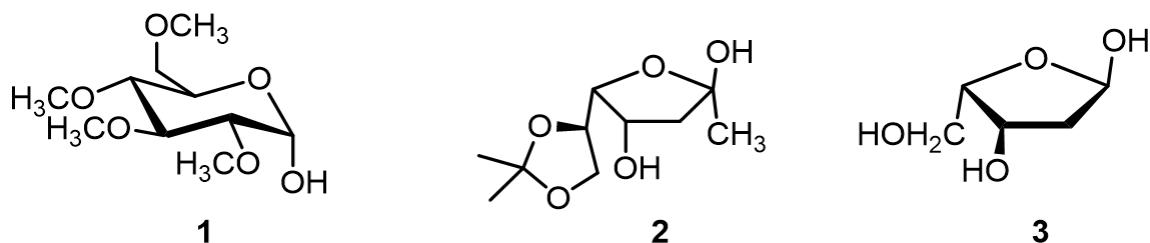


Chain length: 1. \_\_\_\_\_ose, 2. \_\_\_\_\_ose, 3. \_\_\_\_\_ose, 4. \_\_\_\_\_ose, 5. \_\_\_\_\_ose

Aldose or ketose: 1. \_\_\_\_\_ose, 2. \_\_\_\_\_ose, 3. \_\_\_\_\_ose, 4. \_\_\_\_\_ose, 5. \_\_\_\_\_ose

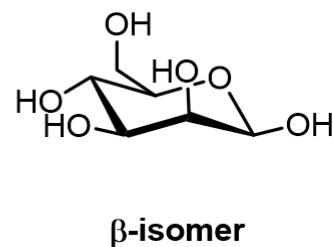
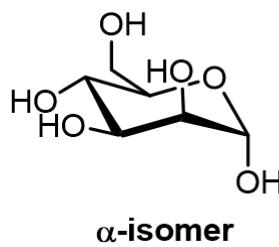
D or L: 1. \_\_\_\_\_, 2. \_\_\_\_\_, 3. \_\_\_\_\_, 4. \_\_\_\_\_, 5. \_\_\_\_\_

It's easy to assign nomenclature to the acyclic Fischer projections, but carbohydrates exist in equilibrium between their **acyclic carbonyl** and **cyclic hemiketal/hemiacetal** form. The most common ring sizes are **six-member (Pyranose)** and **five-member (Furanose)**. Let's try naming the following sugar molecules by chain length, aldose/ketose, pyranose/furanose. Be sure to number the carbon atoms appropriately!



### Alpha Versus Beta

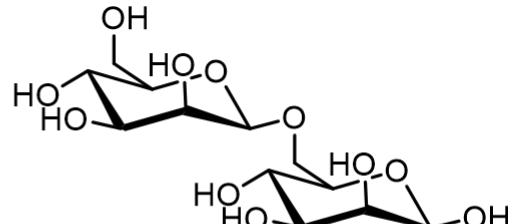
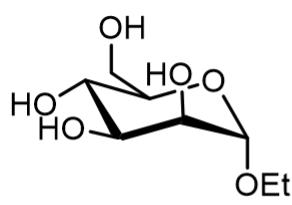
The anomeric centre, the carbon with the hemiacetal/hemiketal or acetal/ketal, can exist in two different forms: alpha or beta. The naming is related to the orientation of the (1) oxygen off the ring and the (2) CH<sub>2</sub>OH group on the other side of the molecules. **Alpha = opposite (vowels)**, **Beta = same**:



What is the relationship between these two compounds:

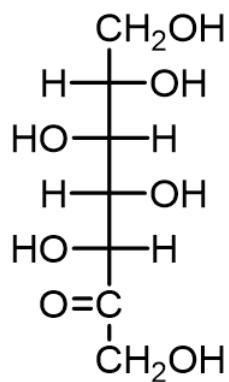
### Glycosidic Bonds

When you have a ketal/acetal instead of a hemiketal/hemiacetal you have created a **glycosidic bond**. Glycosidic bonds are named in a similar fashion to anomers (alpha or beta):

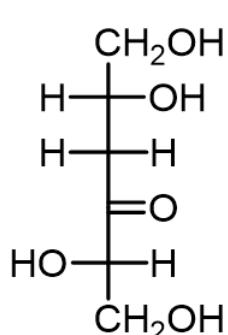


### CONCEPT CLARIFIER

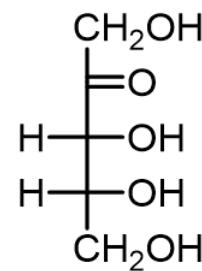
Name the following by: 1) chain length, 2) Aldose/ketose, 3) D/L:



**1**



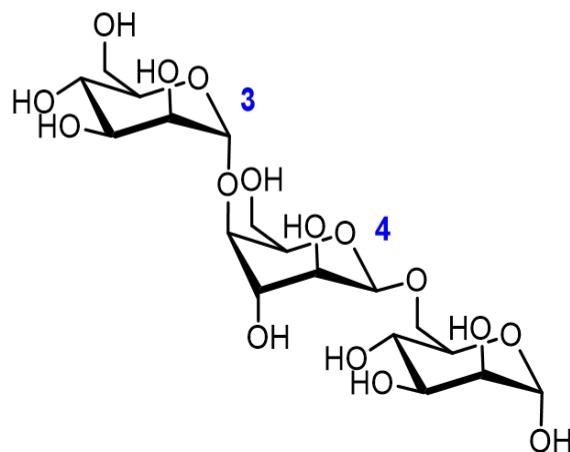
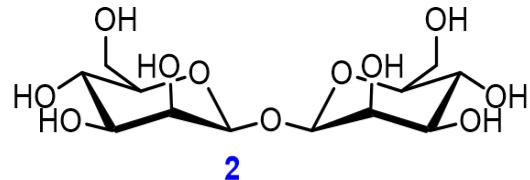
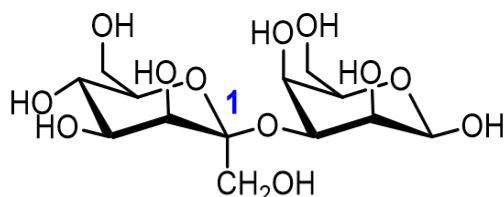
**2**



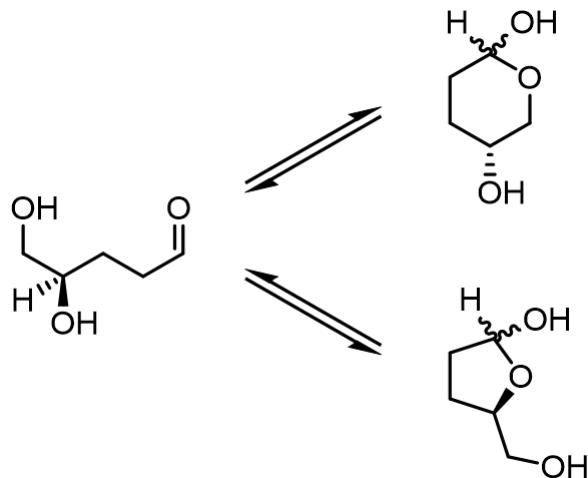
**3**

**CONCEPT CLARIFIER**

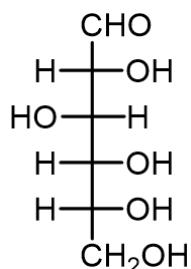
Label the following glycosidic bonds:

**02 ————— Converting Fischer Structures****CONCEPT CLARIFIER****Converting Fischer Structures**

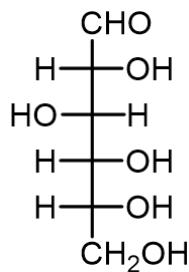
Carbohydrates are interesting molecules because they can **rapidly interconvert** between their **closed and open forms** to form either a pyranose (6-membered) or furanose (5-membered) ring:



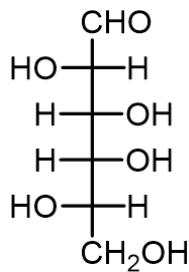
One of the classic exam questions (and bioorganic chemistry skills in general) is the ability to transform a Fischer projection into a pyranose/furanose ring and draw them in the appropriate chair conformation. Let's take a look at D-glucose (shown below). Can you draw D-glucose as a  $\beta$ -pyranose? What is the structure of L-glucose?



The most common cyclic structure we see for carbohydrates is the pyranose form, but the furanose form also persists. Can you draw D-glucose as a  $\beta$ -furanose?

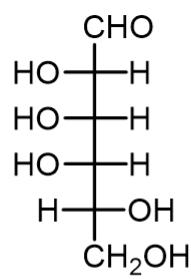


One last example to practice together: Can you draw L-Galactose (shown below) as an  $\alpha$ -pyranose? The trick with L-carbohydrates is we **rotate the Fischer projections to the left** in the first step.

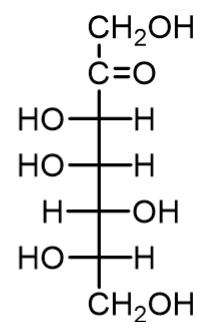


### CONCEPT CLARIFIER

Draw the carbohydrates below in the appropriate chair conformations:



Draw as an  $\alpha$ -pyranose.



Draw as an  $\beta$ -pyranose.

## 03 — Carbohydrate Reactions

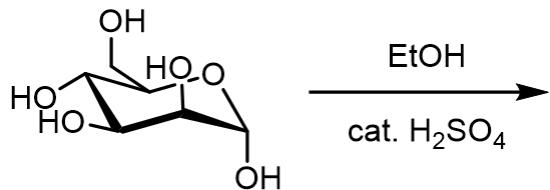
### Reactions Part 1

There are a number of reactions that can be done with sugar molecules, but for now we are only going to concern ourselves with two: **Glycosidic bond formation (and Hydrolysis)** and Tollen's Reagent

### 1. Glycosidic Bond Formation/Hydrolysis

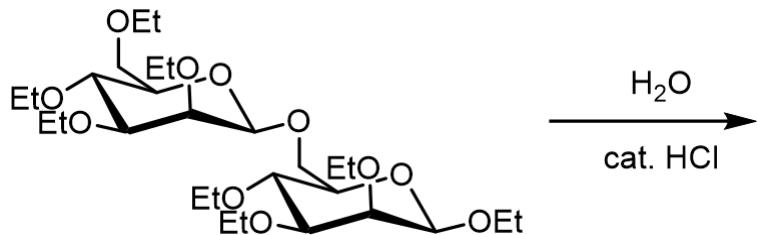
Carbohydrates exist mainly in their hemiacetal or hemiketal form. This means that they can be **treated** with an **alcohol** in a **catalytic amount of acid** to form an **acetal** or **ketal**. This is one technique to **stop the equilibrium** between cyclic and acyclic forms. We call this **formation of a glycosidic bond**. You could imagine another carbohydrate molecule is the alcohol and you could make a **disaccharide!**

Provide a product and mechanism for the following reaction:



Conversely, glycosidic bonds can be hydrolyzed (just like acetals/ketals) using water and a catalytic amount of strong acid. Remember the final product will be the hemiacetal/hemiketal since these are more stable than the related aldehyde/ketone.

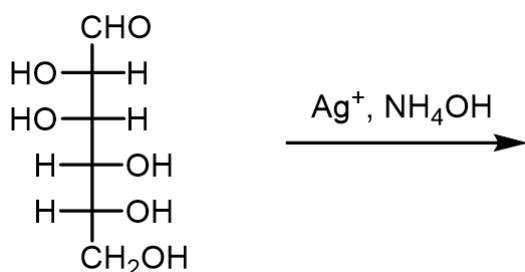
Try to predict the products of the following reaction:



## 2. Tollen's Reagent

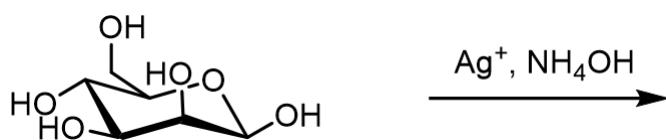
Tollen's reagent ( $\text{Ag}^+$ ,  $\text{NH}_4\text{OH}$ ) is used to identify the presence of aldehydes in carbohydrates. Aldehydes are oxidized to carboxylic acids, while everything else remains the same, using this reagent. The byproduct of the reaction is  $\text{Ag}^0$ , the same silver we covet for our kitchenware and necklaces, and can be quickly identified (it's shiny).

Predict the product:



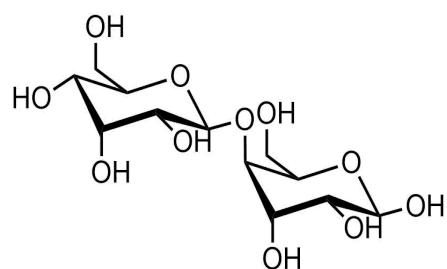
Carbohydrates exist in equilibrium between cyclic and acyclic forms. As soon as an aldehyde is formed it will oxidize in the presence of Tollen's reagent. We use this test to identify **Reducing Sugars**, which are any carbohydrates that possess a hemiacetal/hemiketal... anywhere on the molecule. This includes long chains of sugars that only have one hemiacetal/hemiketal.

Predict the product. Is the carbohydrate a reducing sugar?

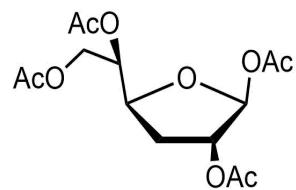


### CONCEPT CLARIFIER

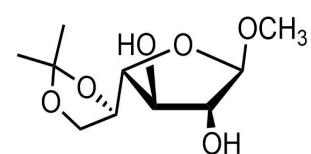
Label the following (1-5) as either a reducing or non-reducing sugar:



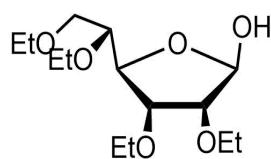
1



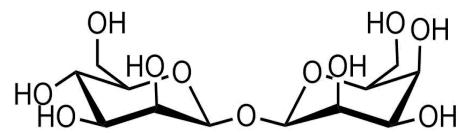
2



3



4



5

## 04

## Section Quiz

# Wize Quiz

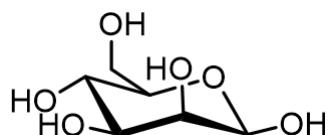
## Carbohydrates (6 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

### PRACTICE QUESTION #1

Pure  $\beta$ -D-mannopyranose (shown below) has optical activity (specific rotation,  $\alpha$ , =  $-17.0^\circ$ ).

In water, the optical activity rapidly changes until after 3 hours  $\alpha$  =  $+14.6^\circ$ . What is going on? (Use pictures)





# NUCLEOPHILIC ADDITION TO CARBONYLS

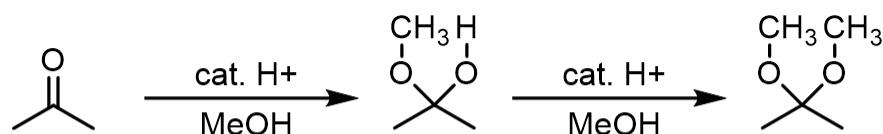
## 01 — Ketals and Acetals

### Introduction to Ketals and Acetals

Ketals and Acetals are formed by acid-catalyzed addition of alcohols to ketones and aldehydes, respectively. In a mechanism we'll dive into in detail later, the synthesis of a ketal/acetal proceeds via a **hemiketal** or **hemiacetal**. It is important to recognize acyclic hemiketals and hemiacetals can't be isolated experimentally... you'll isolate either the carbonyl or disubstituted product.

You can always recognize Ketals/Acetals following these two steps:

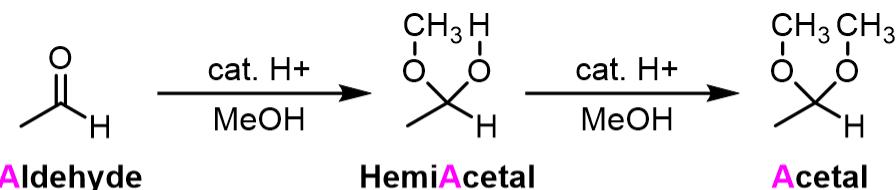
- (1) Look for carbon atoms with 2 C-O single bonds (If there's an OH it's a **hemi**\_\_)
- (2) Look at the other 2 bonds from that carbon: is there an H?? (**Ketal vs. acetal**)



Ketone

HemiKetal

Ketal



Aldehyde

HemiAcetal

Acetal

**Note:** The above hemiketal and hemiacetal  
cannot be isolated experimentally

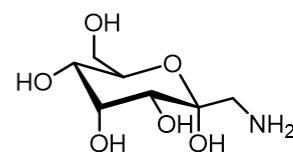
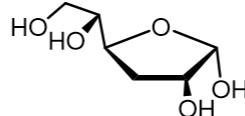
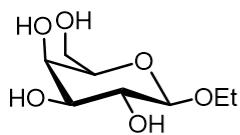
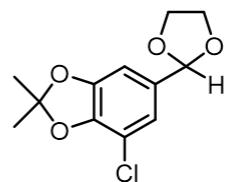
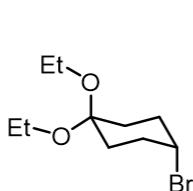
### CONCEPT CLARIFIER

You can always recognize Ketals/Acetals following these two steps:

(1) Look for carbon atoms with 2 C-O single bonds (If there's an OH it's a hemi\_\_\_\_)

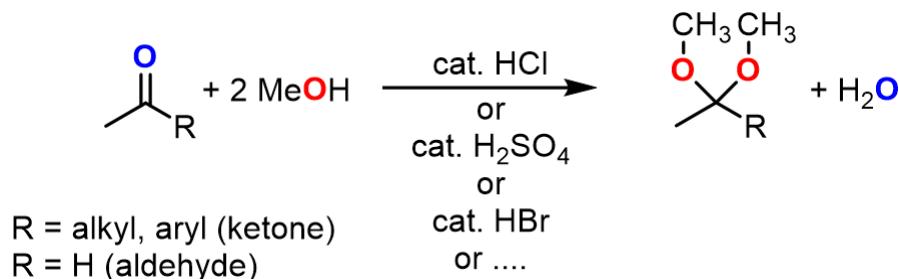
(2) Look at the other 2 bonds from that carbon: is there an H?? (Ketal vs. acetal)

Identify any Ketals/acetals or hemiketals/hemiacetals in the following compounds:

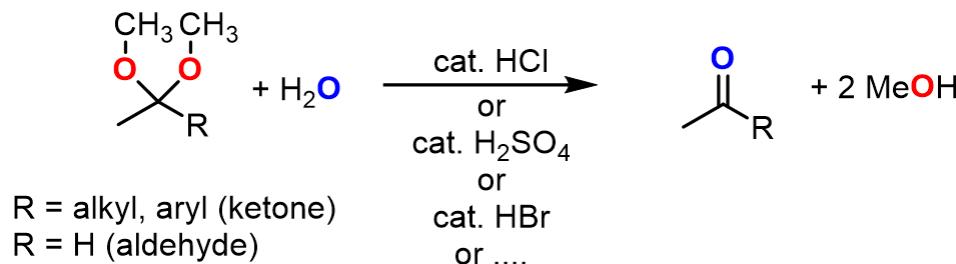


## General Synthesis/Hydrolysis of Ketals and Acetals

The synthesis of a ketal or acetal requires three things: (1) Ketone or Aldehyde, (2) Alcohol (reagent or solvent), and (3) strong acid catalyst. The options are limitless!

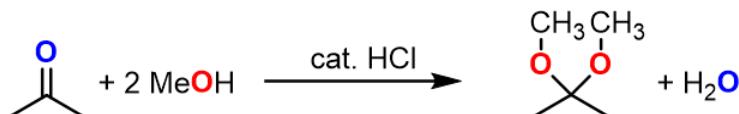


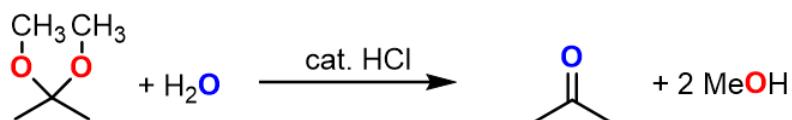
Ketals/Acetals are stable under basic conditions (alkoxides are poor leaving groups). If you wish to hydrolyze a ketal or acetal treat it with a **strong acid catalyst** in water:



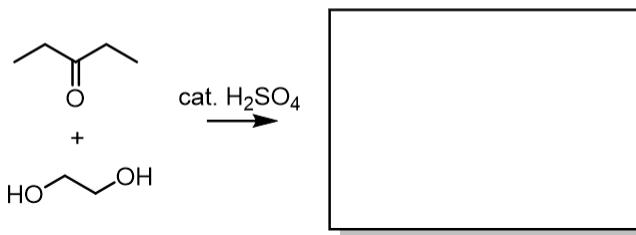
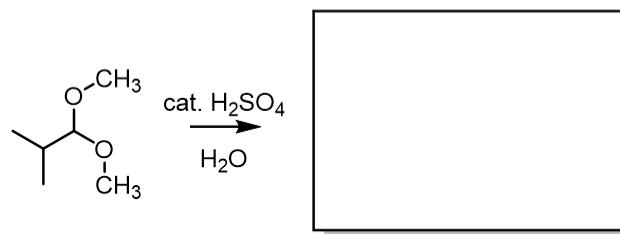
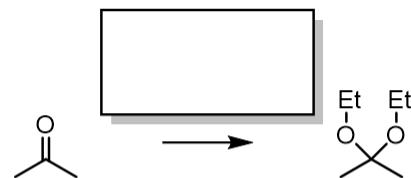
## Mechanism: Synthesis/Hydrolysis of Ketals and Acetals

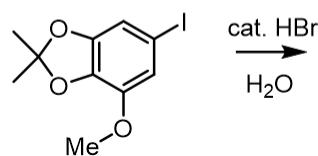
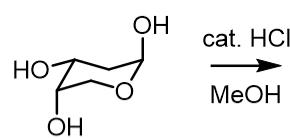
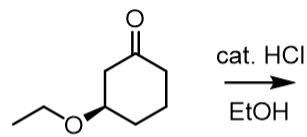
Provide a mechanism for the following two reactions:



**PRACTICE QUESTION #1**

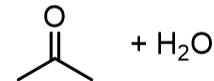
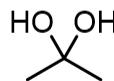
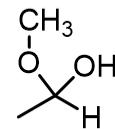
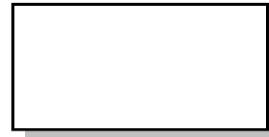
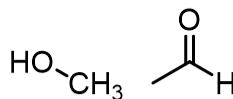
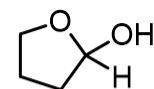
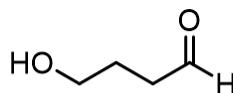
Fill in the blanks for the following reactions:





## Stability of Hemiketals and Hemiacetals

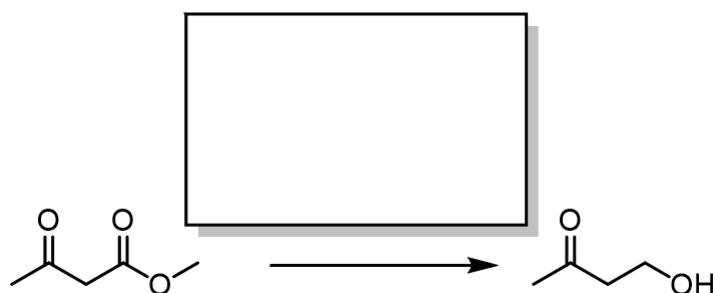
Although the 'hemi' form of ketals and acetals aren't usually stable, there are examples where they can be isolated synthetically. Take for example the following equilibria:



The carbonyl bond ( $\text{C}=\text{O}$ ) is very strong. On the other hand, the formation of a five- or six-membered ring is also thermodynamically favoured. The stability of the ring is greater than the strength of the  $\text{C}=\text{O}$  carbonyl group.

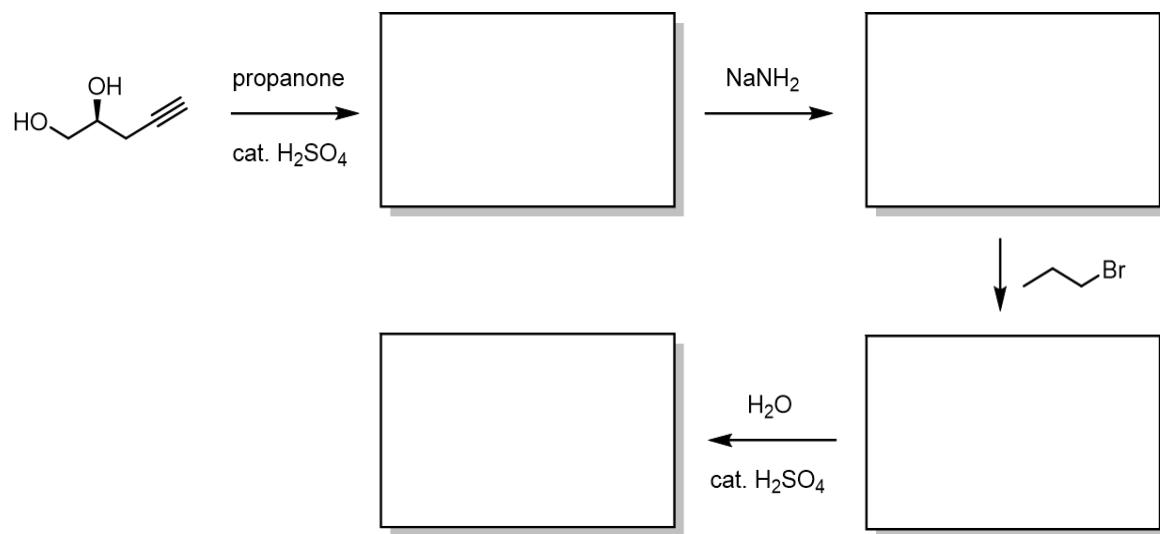
## Ketals and Acetals as Protecting Groups

The synthetic application of ketals and acetals is primarily are protecting groups. This is because they are easy to **install** (ketone, alcohol, acid), easy to **remove** (ketal, acid, water), and stable under strongly basic and reducing (e.g.  $\text{NaBH}_4$ ,  $\text{LiAlH}_4$ ) conditions. Take for example a question that asks you to propose reagents for the following reaction:



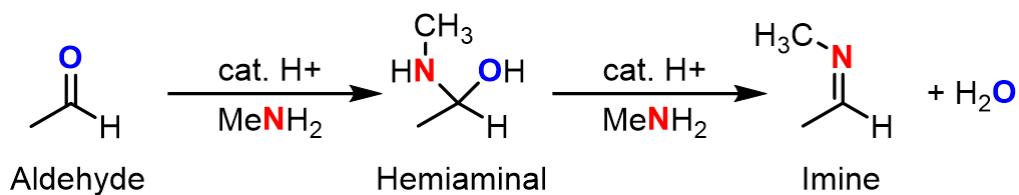
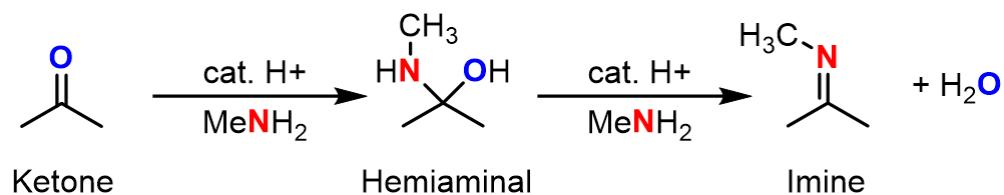
**CONCEPT CLARIFIER**

Fill in the blanks for the following synthetic scheme:

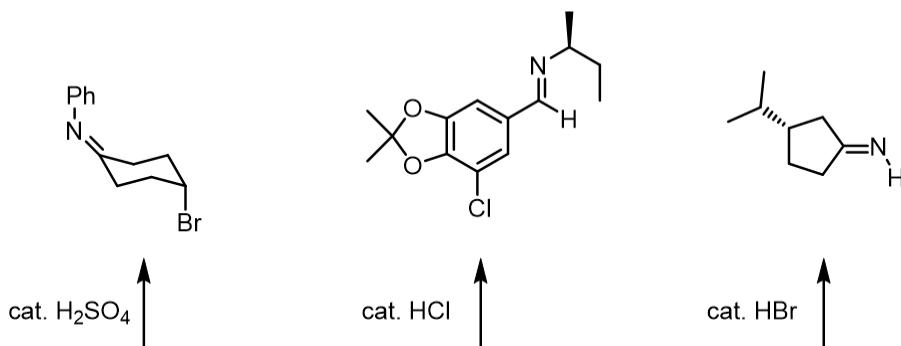
**02** **Imines****Synthesis and Hydrolysis of Imines**

## Synthesis of Imines

Imines are formed by acid-catalyzed addition of amines to ketones and aldehydes. In a mechanism we'll dive into in detail later, the synthesis of an imine proceeds via a **hemiaminal**. It is important to recognize **hemiaminals** can't be isolated experimentally... you'll isolate either the carbonyl or imine product. Three things you need to make an imine: (1) Ketone or aldehyde, (2) Amine, and (3) Strong acid catalyst.

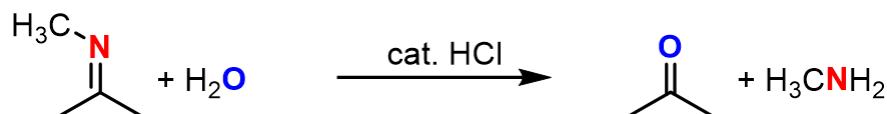


Predict the starting materials:

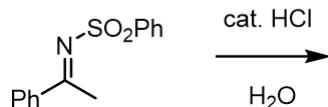
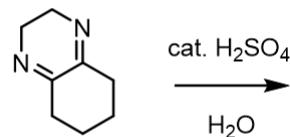
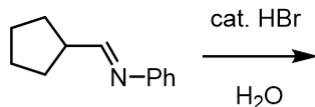


## Hydrolysis of Imines

If you wish to hydrolyze an imine treat it with a strong acid catalyst in water:

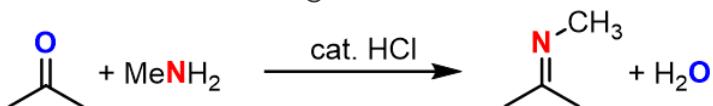


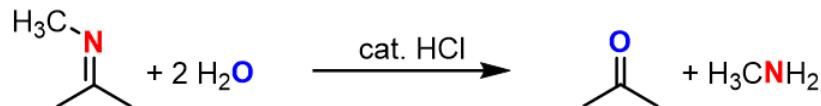
Predict the product:



## Mechanism of Synthesis and Hydrolysis of Imines

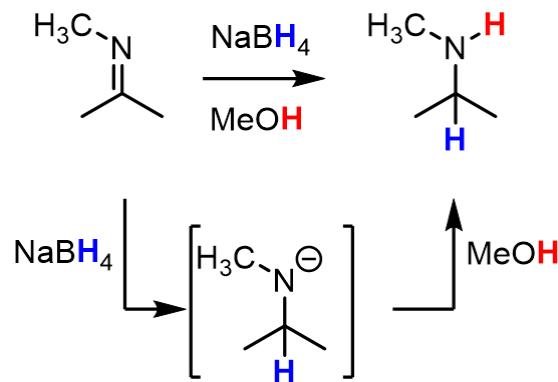
Provide a mechanism for the following two reactions:





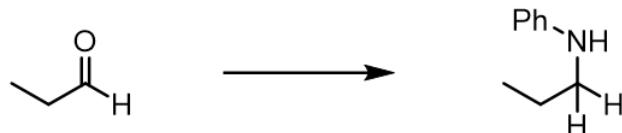
## Reductive Amination

Remember when I told you only ketones and aldehydes could be reduced by  $\text{NaBH}_4$ ? I lied... Imines can be reduced under similar conditions. Take for example the reaction shown below:

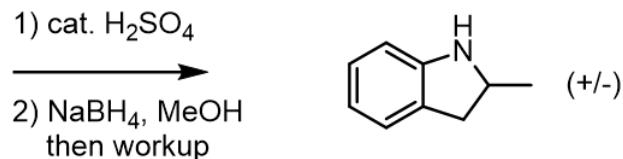


This allows for the synthesis of amines in one-pot (without isolating anything from the reaction mixture).

**Provide reagents for the following transformation**



Predict the starting material for the following reaction



Chemical Formula: C<sub>9</sub>H<sub>11</sub>NO

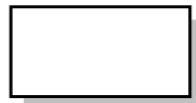
## 03 Tautomerization

### Tautomerization

Tautomerization refers to the interconversion of two **constitutional isomers**, called tautomers. It involves the rapid equilibrium between a carbonyl (keto-form) and vinyl alcohol (enol-form). In general, this equilibrium favours the keto-form because the C=O pi-bond is thermodynamically more stable.



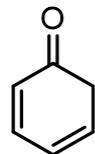
Keto-form



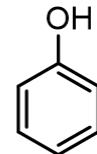
Enol-form

There are cases when the **enol-form** is favoured over the **keto-form** due to some contributing thermodynamic property. The main reasons are: (1) Aromaticity and (2) Hydrogen Bonding:

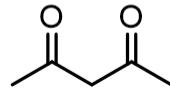
Keto-form



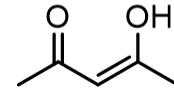
Enol-form



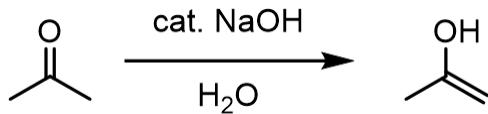
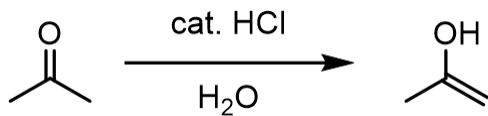
Keto-form



Enol-form

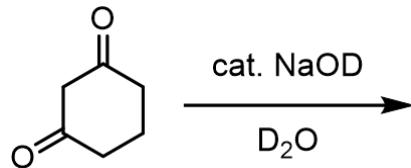


Although the interconversion between keto-form and enol-form occurs in neutral pH, the rate of this reaction is increased in dilute acid or base. The mechanism of the acid- and base-catalyzed tautomerization of a ketone is important to be familiar with:



### CONCEPT CLARIFIER

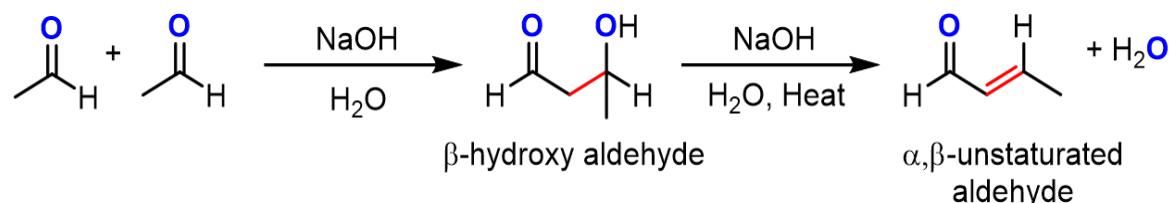
The following compound is left to equilibrate for a *long* time. (1) What is the maximum number of deuterium atoms that can be incorporated. (2) Provide a mechanistic example of the deuteration reaction.



## 04 — The Aldol Reaction

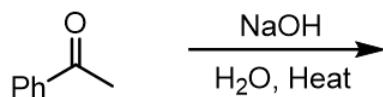
### Aldol Reaction Overview

The Aldol reaction is a very useful carbon-carbon bond forming reaction. It requires a ketone/aldehyde with alpha-protons, a strong base (typically NaOH), and heat. The reaction is typically done in water:

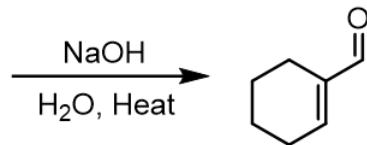


We can recognize aldol reactions from the **reagents** (NaOH, heat in H<sub>2</sub>O) or from the **products** ( $\alpha,\beta$ -unstaturated aldehyde or ketone):

Predict the product(s)

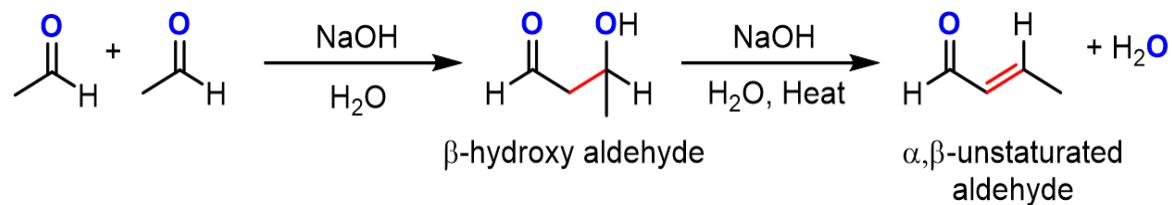


Predict the starting material



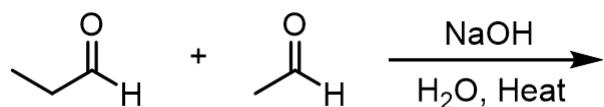
## Mechanism: Aldol Reaction

Provide a mechanism for the following reaction:

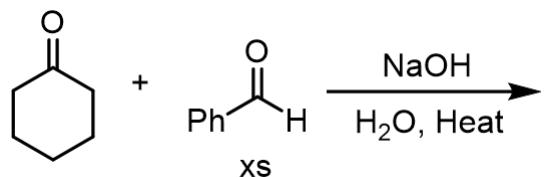


## Mixed Aldol Reactions

Mixed Aldol reactions refer to an Aldol reaction between two different compounds. This can sometimes lead to multiple products:

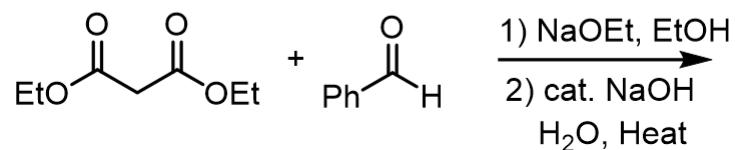
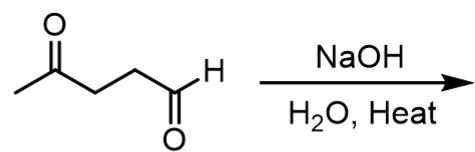


There are situations when only one of the compounds has enolizable protons. In this case you can get a single aldol product from two different compounds:



#### CONCEPT CLARIFIER

Predict the product(s) of the following reactions:



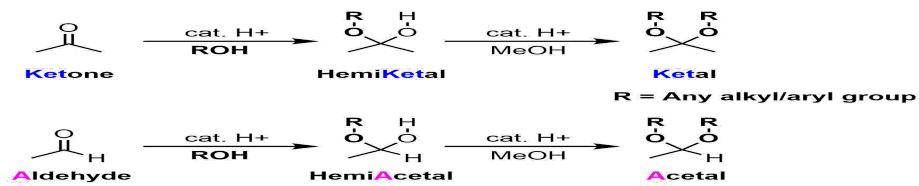


**05**

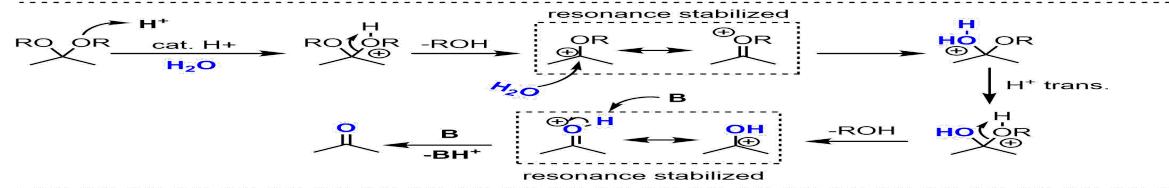
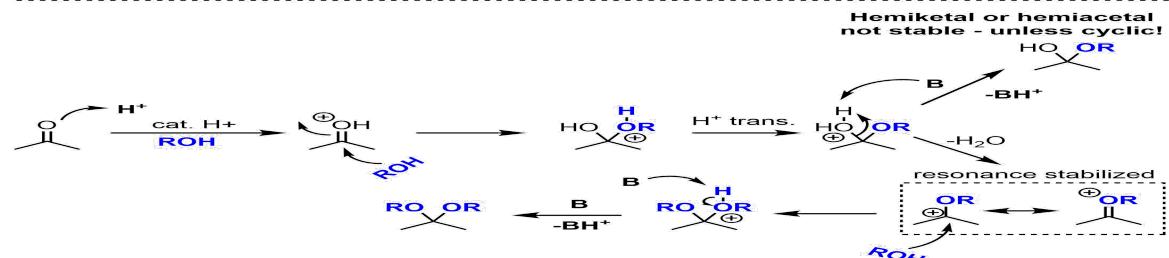
## Summary of Reactions and Key Ideas

## Nucleophilic Addition to Ketones/Aldehydes

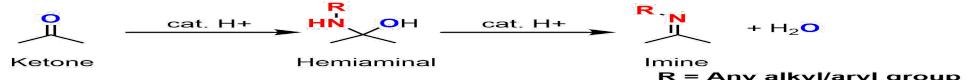
### 1. Ketals and Acetals



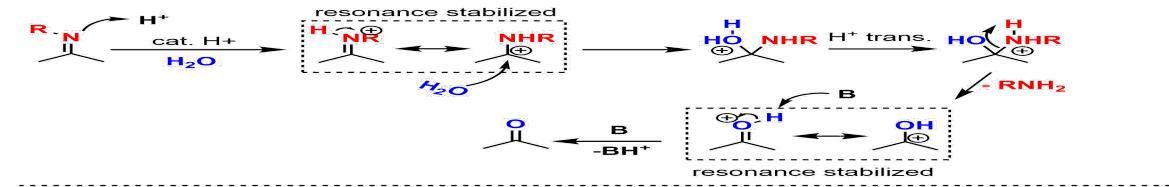
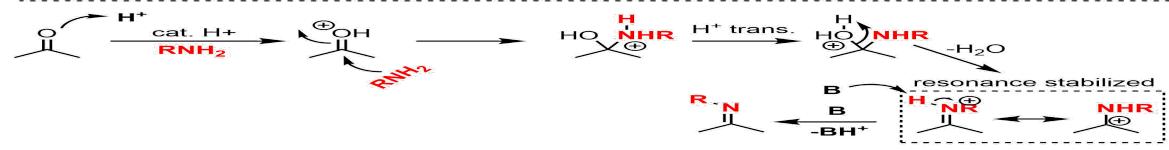
### General Mechanism: Formation and Hydrolysis



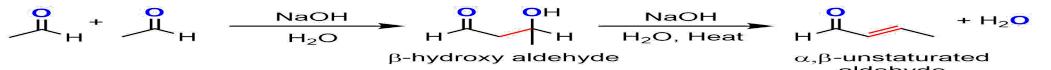
### 2. Imines



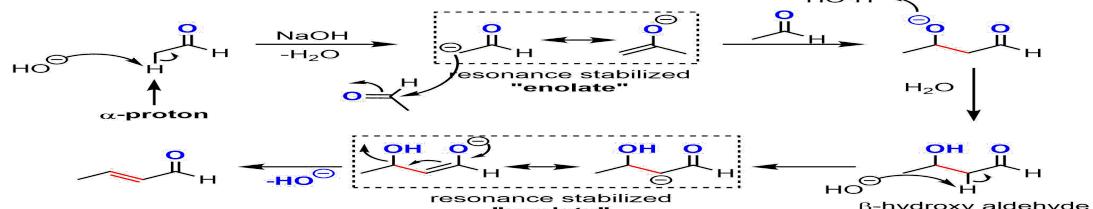
### General Mechanism: Formation and Hydrolysis



### 3. Aldol Reaction



### General Mechanism



**06** — **Section Quiz**

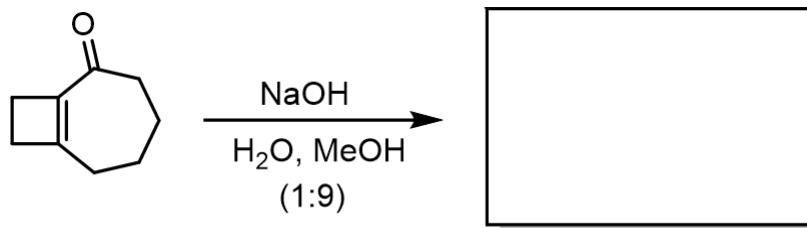
## Wize Quiz

### Nucleophilic Addition to Carbonyl Compounds (6 Qu.)

Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

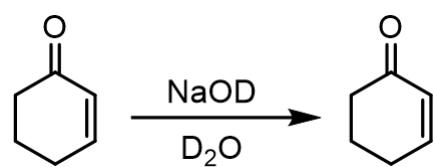
**PRACTICE QUESTION #1**

The following compound was left to equilibrate in a basic solution. Within 3 hours a new bicyclic compound was obtained. What is the structure of this new compound and why does it form?



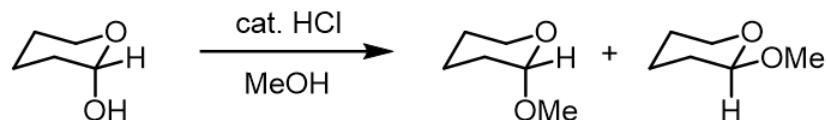
### PRACTICE QUESTION #2

The following compound was dissolved in basic deuterium oxide for an extended period. After workup, deuterium incorporation was observed at multiple sites. Where? Clearly label all possible deuterium location(s).

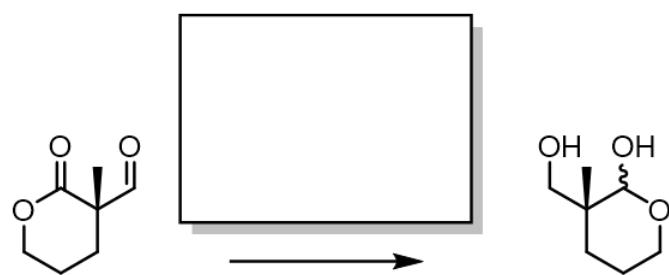


**PRACTICE QUESTION #3**

What is the mechanism of the following transformation? Why do the products form as a mixture of stereoisomers?

**PRACTICE QUESTION #4**

Provide reagent(s) for the following transformation. Rationalize the formation of the product (show the product after each reaction).

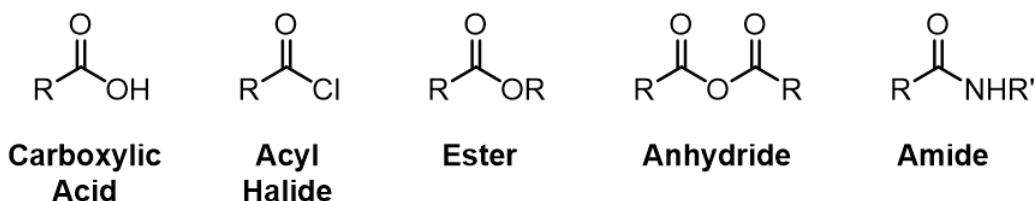


# CARBOXYLIC ACID DERIVATIVES

## 01 — Carboxylic Acid Derivatives

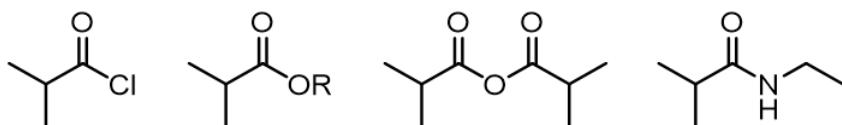
### Carboxylic Acid Derivatives

The **Carboxylic Acid derivatives** represents a group of compounds that all possess the **same oxidation state** as, and look similar to, a carboxylic acid! This group includes: **carboxylic acids**, **acyl (or acid) halides**, **esters**, **anhydrides** and **amides** (shown below).



These functionalities can be converted from one to another using reactions that will be covered in this section. In all cases, the carboxylic acid derivative will act as an **electrophile at the carbon atom** (in some cases after addition of a suitable acid-catalyst).

With that in mind, how do we assess the electrophilicity of the different carboxylic acid derivatives? To put it in more of an exam-type question format, rank the following in terms of rate of reaction with a nucleophilic reagent:

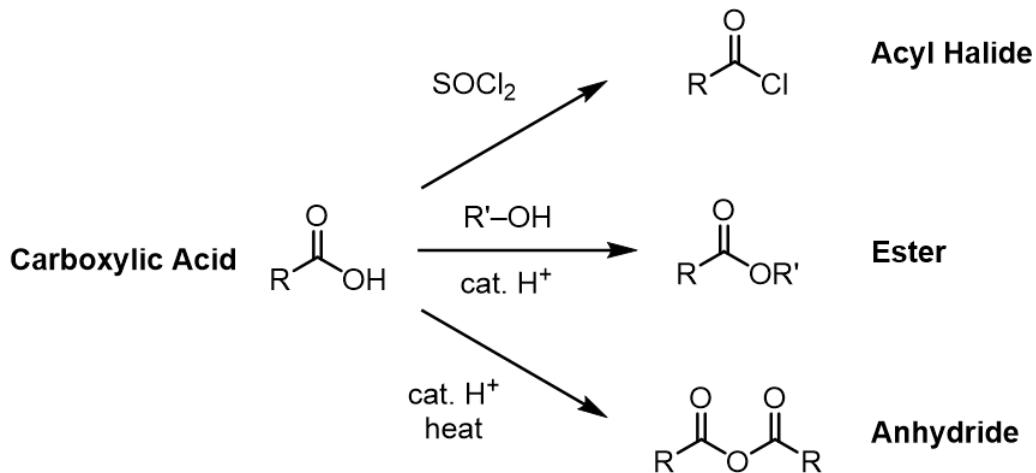


## 02 Carboxylic Acids

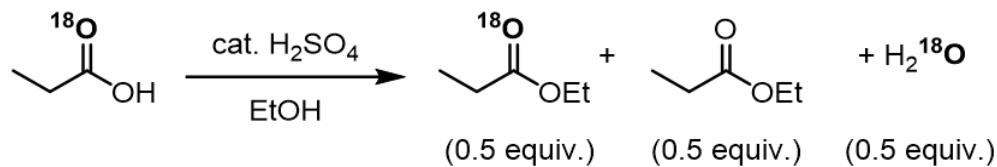
### Carboxylic Acids

The key functionality that ties all these compounds together (the group is named after the carboxylic acid!), the carboxylic acid is a **versatile building block** that can be converted to any other member of the group in 1 or 2 steps (2 steps for amide). When unsure which reagents to use, just make a carboxylic acid and take it from there!

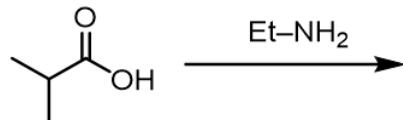
#### Overview of Important Carboxylic Acid Transformations



The most common method for synthesis of **esters** and **anhydrides** from carboxylic acids requires the addition of a strong acid-catalyst. Ultimately, either oxygen can be transformed to a leaving group, as we see with the example shown below. **How do we rationalize the product distribution below with a mechanism?**



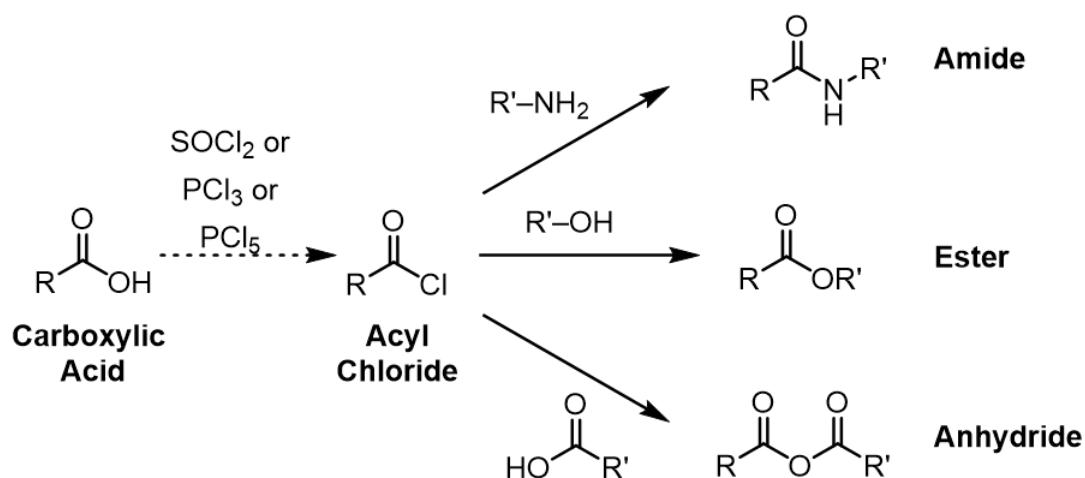
Synthesis of an amide from a carboxylic acid usually proceeds via an acyl halide (which will be looked at in detail later). Simple mixing of an amine and carboxylic acid doesn't have the desired effect:



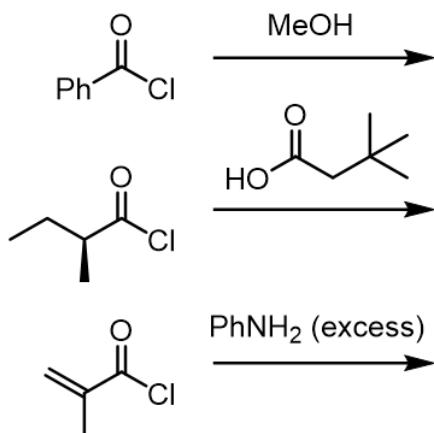
## 03 — Acyl Halides

### Acyl Halides

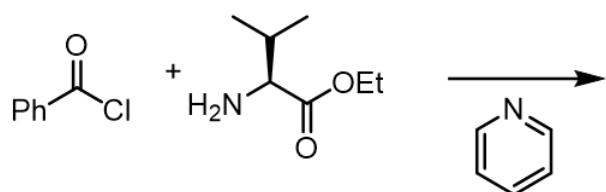
The simplest way to make an acyl halide is by refluxing a carboxylic acid in thionyl choride (SOCl<sub>2</sub>), but PCl<sub>3</sub> or PCl<sub>5</sub> will also accomplish the transformation. With an acid chloride, there is no limit to the compounds you can make! Treatment with the appropriate nucleophile will give amides, esters, anhydrides or carboxylic acids.



For example, predict the products of the following reactions between different nucleophiles and acyl halides:



It's important to recognize that the synthesis of amides from acid chlorides requires either an excess of amine (as seen above) or a sacrificial base (often pyridine or triethylamine,  $\text{NEt}_3$ ). What is the role of this extra base? Show it with a mechanism for the reaction below:



## 04 — Esters and Anhydrides

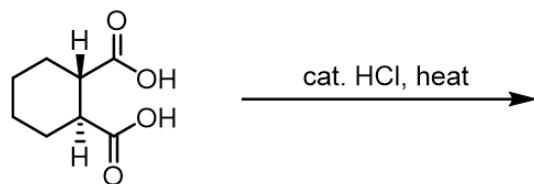
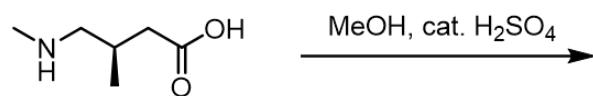
### Esters and Anhydrides

**Esters and Anhydrides** are often made from carboxylic acids. The name anhydride is a contraction of the full name 'acid anhydride' which is in reference to the dimerization of a carboxylic acid with the loss of water.

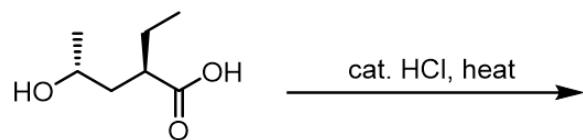
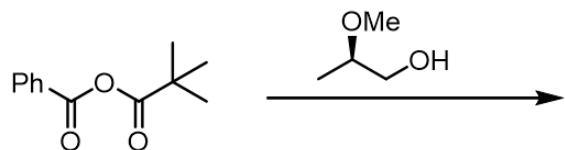
Which compound undergoes hydrolysis faster in dilute NaOH? Justify your answer and provide a mechanism.



Esters can react with amines to form amides. Predict the products of the following reactions:



Sterics are a factor in reactions with **mixed anhydrides** (non-symmetrical anhydrides). Predict the products of the following reactions:

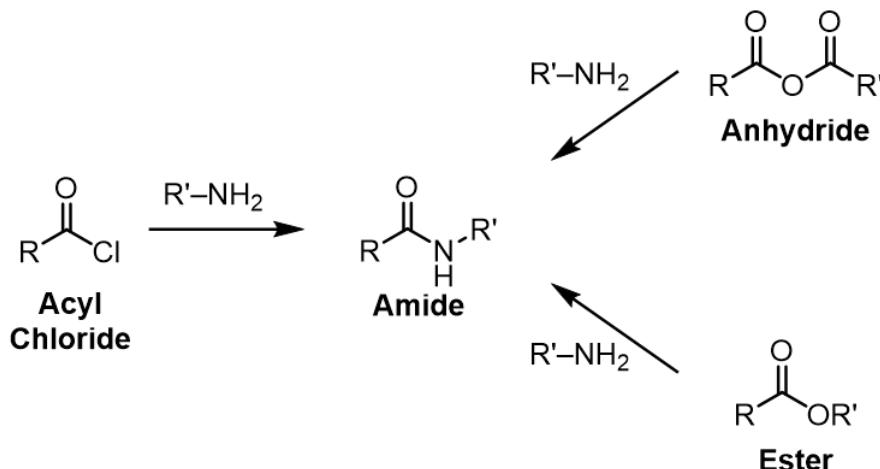


## 05 — Amides

### Amides

The most efficient method to synthesize an amide is from an acyl chloride. In general, the strategy is to react an amine with a suitable electrophile. It follows that anhydrides are the next most effective electrophile and esters will only work sometimes.

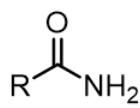
### Synthesis of Amides



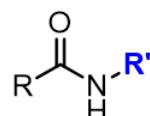
### Amide Nomenclature

Amides can be defined by their substituents, similar to amines and halides. They are either primary ( $1^\circ$ ), secondary ( $2^\circ$ ), and tertiary ( $3^\circ$ ).

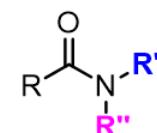
#### $1^\circ$ Amide



#### $2^\circ$ Amide

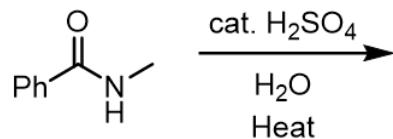


#### $3^\circ$ Amide



The amide bond is strong! The delocalization of the nitrogen lone pair results in a very stabilized carbon-nitrogen bond. The best strategy to hydrolyze (break) an

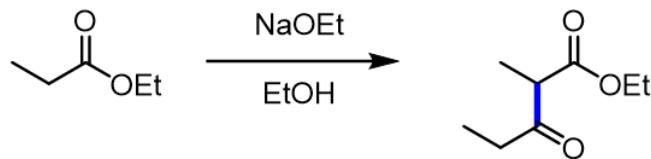
amide bond is high temperature acid hydrolysis. Predict the products of the following reaction and provide a mechanism



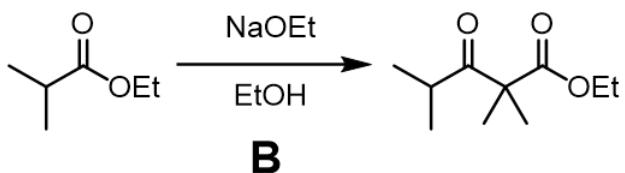
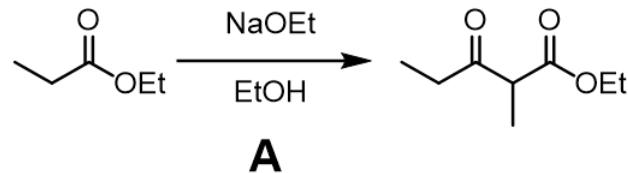
## 06 —— Claisen Reactions

### Claisen Reactions

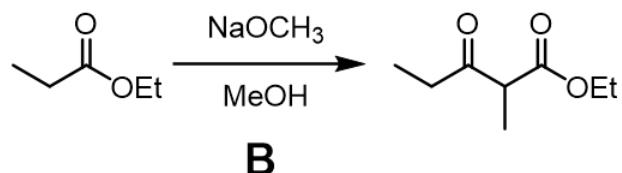
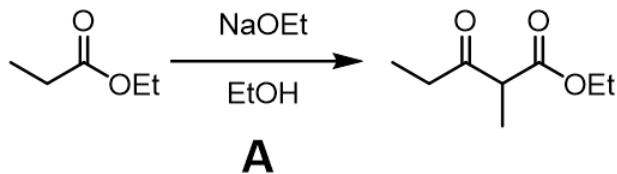
The **Claisen reaction** is a carbon-carbon bond forming reaction akin to the **Aldol reaction**, except using ester derivatives. A comparatively weak base, an **alkoxide**, is used to deprotonate the alpha-protons of the ester. Let's look at the mechanism of the following reaction:



An important consideration for Claisen reactions is that we need two alpha-protons on the ester reactant! For example, the reaction A will proceed as written, but reaction B will not proceed. Why?

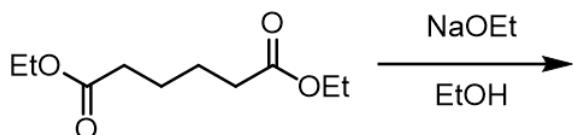


In addition, the choice of base is important because the ester functionality can still undergo substitution reactions. For example, the reaction A will give a high yield of the product as written, but reaction B will not give just one product. Why?



### Dieckmann Condensation

A special named reaction is the **Dieckmann Condensation**, which is just a fancy way of saying **intramolecular Claisen reaction**. Predict the product of the following Dieckmann condensation reaction.



**07** **Section Quizzes**

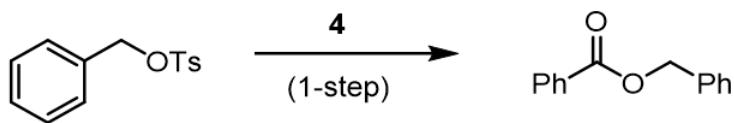
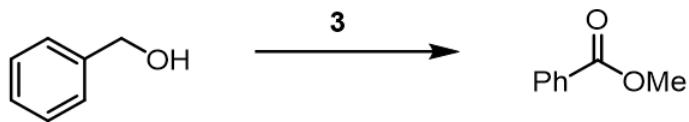
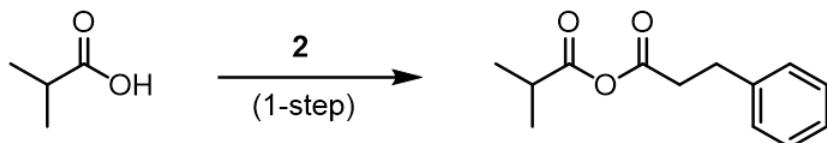
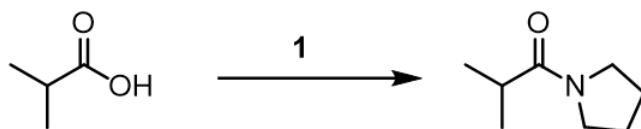
## Wize Quiz

### Carboxylic Acid Derivatives (9 Qu.)

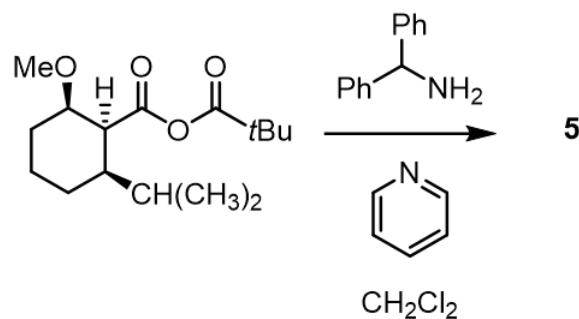
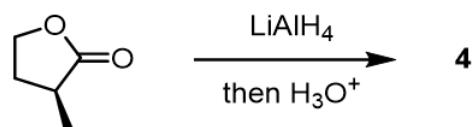
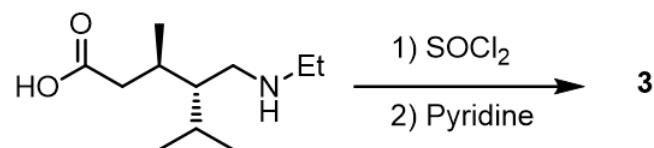
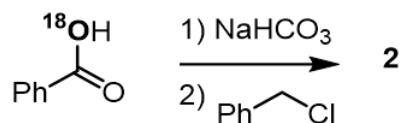
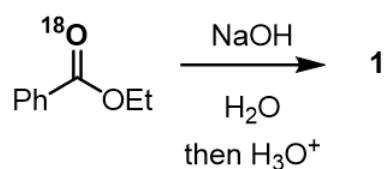
Find the full exam-like practice quiz  
with step-by-step solutions on  
[wizedemy.com](https://wizedemy.com)

#### PRACTICE QUESTION #1

Provide the reagents for the following transformations:



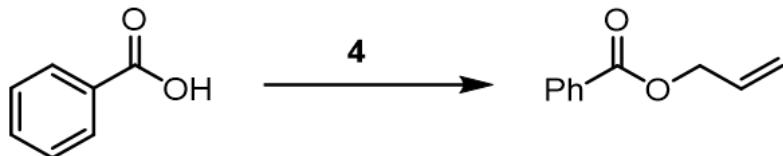
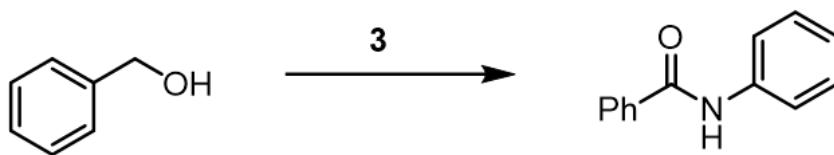
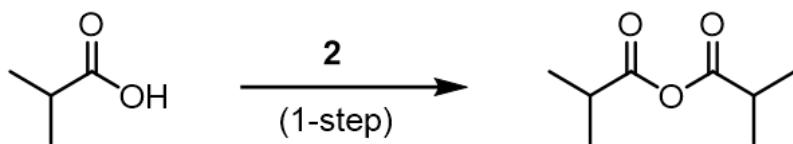
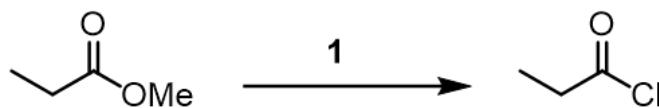
### PRACTICE QUESTION #2



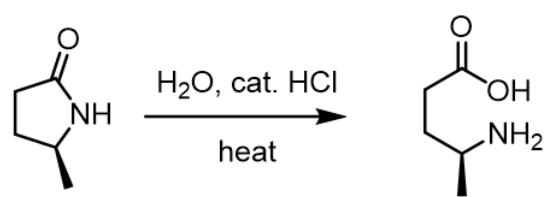


**PRACTICE QUESTION #3**

Provide reagent(s) for the following transformations:

**CONCEPT CLARIFIER**

Provide a mechanism for the following reaction:



# REDUCTION AND OXIDATION REACTIONS

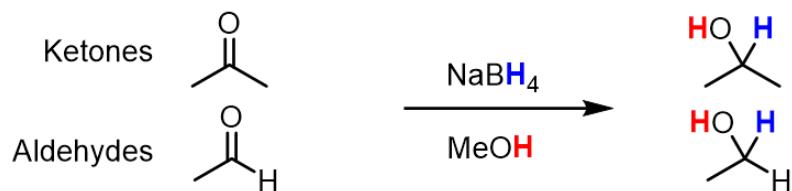
## 01 Reductions - NaBH<sub>4</sub> and LiAlH<sub>4</sub>

### Reductions - NaBH<sub>4</sub> and LiAlH<sub>4</sub>

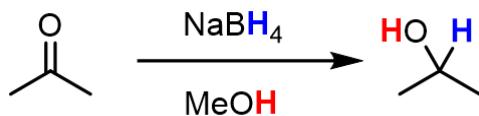
There are two key reagents useful for reduction of carbonyl-containing (C=O) compounds like aldehydes, ketones, esters, amides, and carboxylic acids: NaBH<sub>4</sub> and LiAlH<sub>4</sub>

#### NaBH<sub>4</sub> - Sodium Borohydride

NaBH<sub>4</sub> is the milder reductant. It is only used for reduction of ketones and aldehydes to alcohols. This makes the reduction reaction **selective**:

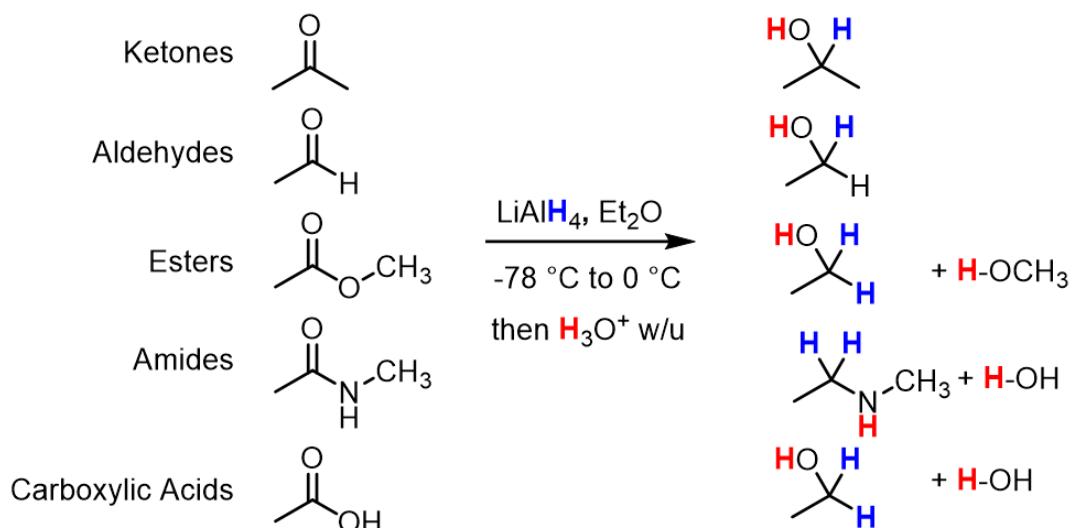


The mechanism, similar to other hydride additions to carbonyls, involves nucleophilic addition of a hydride to the electrophilic carbon of the carbonyl. The typical **solvent** is an **alcohol** since the conditions are relatively mild. Practice drawing the mechanism for the reaction below:

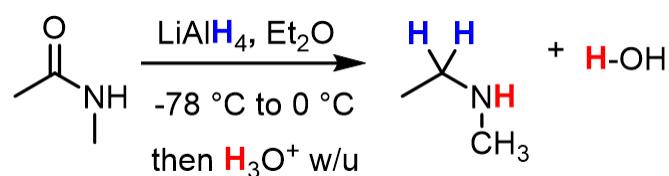


## $\text{LiAlH}_4$ - Lithium Aluminum Hydride

$\text{LiAlH}_4$  is the harsher reductant. It is used for reduction of ketones, aldehydes, esters, amides and carboxylic acids. In most cases the final product is an alcohol, except amides which will give amines (more on this later). This makes the reduction reaction **unselective** since all these different functional groups will react:

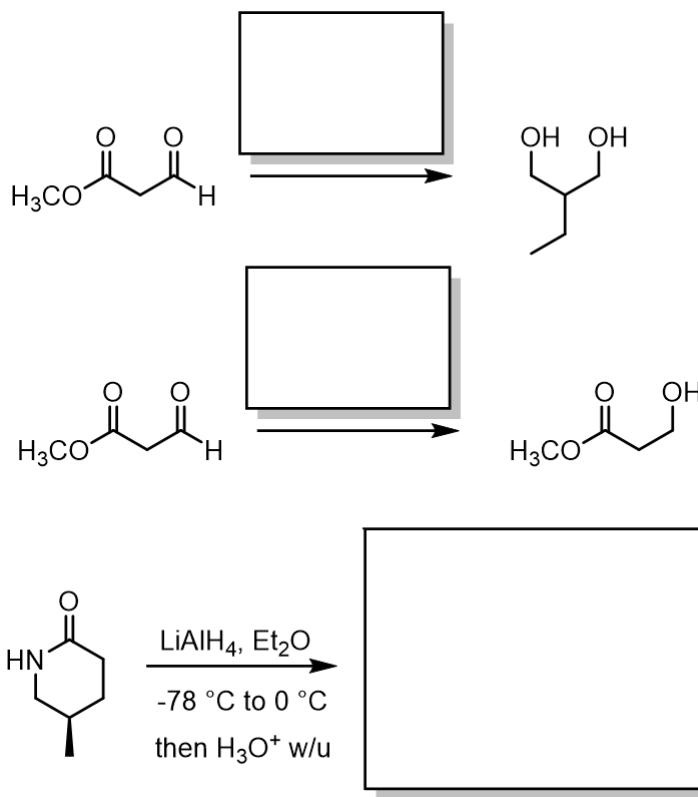


Like  $\text{NaBH}_4$ , the mechanism involves **nucleophilic addition** of a hydride to the **electrophilic carbon** of the carbonyl. However, alcoholic solvents or water can't be used because  $\text{LiAlH}_4$  will react to give  $\text{H}_2$  gas. Therefore, the reactions are most commonly performed with **nonprotic polar solvents** like ethers (e.g.  $\text{Et}_2\text{O}$  or THF). The most difficult mechanism is found with the reduction of an amide:



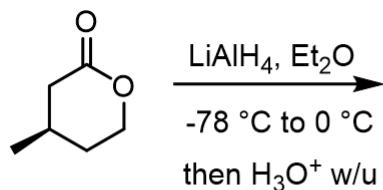
### CONCEPT CLARIFIER

Fill in the blanks for the following reactions. In some cases, multiple reaction steps may be necessary:



### CONCEPT CLARIFIER

Predict the product(s) of the following reaction. Is the product optically active?



Does the product rotate plane-polarized light?  
(is it optically active?)

02

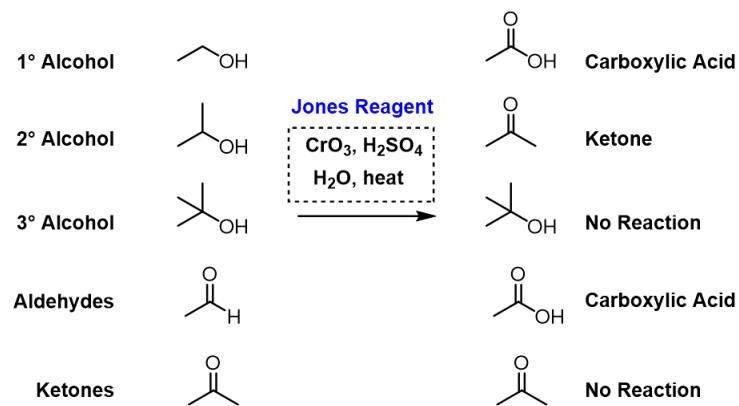
## Oxidation - Jones Reagent and PCC

### Oxidation - Jones Reagent and PCC

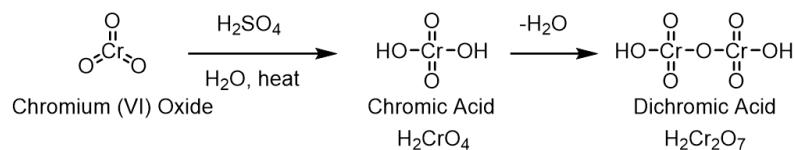
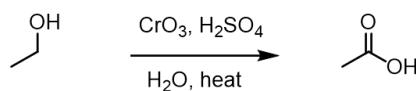
There are two key reagents useful for oxidation of alcohols into carbonyl-containing ( $C=O$ ) compounds like aldehydes, ketones, and carboxylic acids: Jones Reagent and PCC

#### Jones Reagent - $\text{CrO}_3$ in $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$

Jones reagent is chromium (VI) oxide in fuming  $\text{H}_2\text{SO}_4/\text{H}_2\text{O}$ . These conditions are harsh, which can make functional group tolerance a concern. Nevertheless, Jones reagent is a great oxidant. Of note, primary alcohols and aldehydes are oxidized to carboxylic acids.



Let's look at the Jones reaction mechanism in detail:

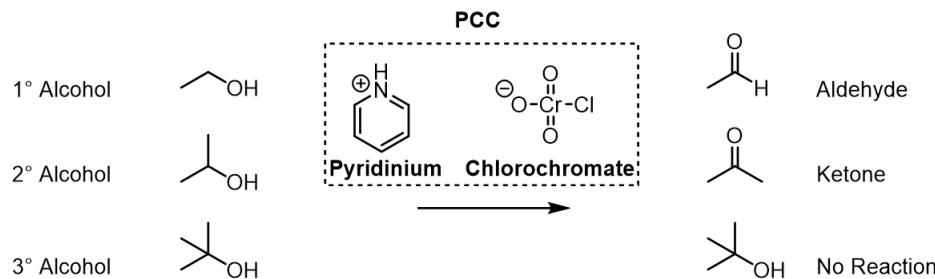


The mechanism of oxidation first involves the formation of **chromic acid** ( $\text{H}_2\text{CrO}_4$ ) which will disproportionate into **dichromic acid** ( $\text{H}_2\text{Cr}_2\text{O}_7$ ). Sometimes the Jones reagent is just written as  $\text{H}_2\text{CrO}_4$  or  $\text{H}_2\text{CrO}_7$ . Alternatively, dichromate salts like **potassium dichromate** ( $\text{K}_2\text{Cr}_2\text{O}_7$ ) can be used in place of the hygroscopic  $\text{CrO}_3$  in the Jones reaction.

### PCC - Pyridinium Chlorochromate

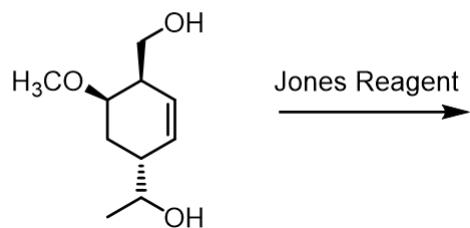
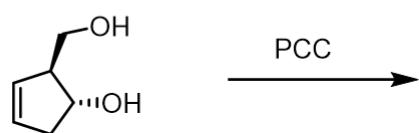
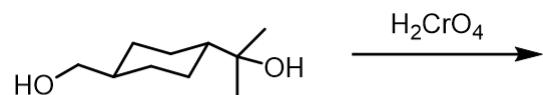
Primary alcohols and aldehydes are oxidized to carboxylic acids with the Jones reagent because of the **hydration of the carbonyl group** in the  $\text{H}_2\text{O}$  solvent.

What if the reactions were done **anhydrous** (without water)?! Enter **PCC** (Pyridinium Chlorochromate), a one stop electrophilic oxidation reagent. PCC stops at aldehydes:



**CONCEPT CLARIFIER**

Predict the product(s) of the following reactions

**03 ————— Hydrogenations**

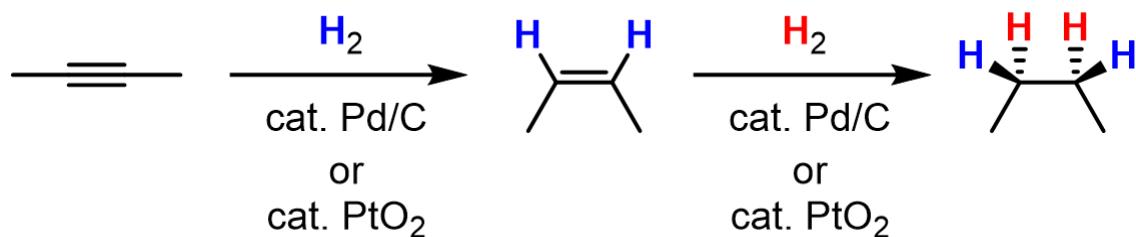
## Hydrogenation

**Key Reactions (3):** 1. Metal-catalyzed Hydrogenation; 2. Lindlar Catalyst; 3. Metal/Liquid Ammonia

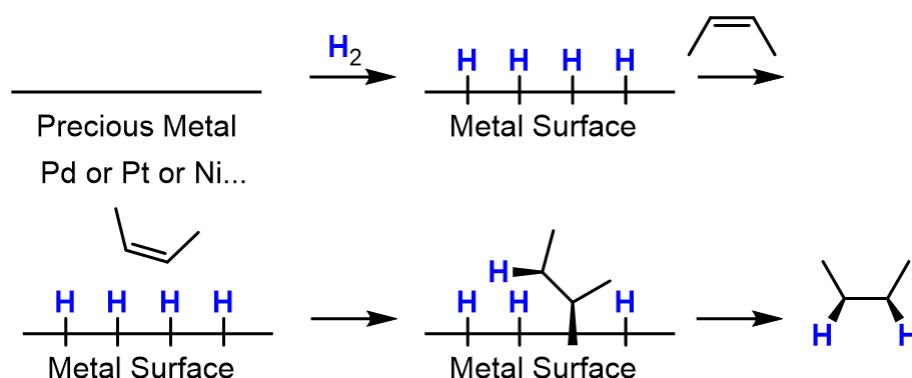
Hydrogenation refers to a type of reduction reaction where two hydrogen atoms are added across a **multiple bond**. In this case it refers to the reduction of alkenes and alkynes, but other functional groups (e.g. imines, ketones) can be reduced.

### 1. Metal-catalyzed Hydrogenation

The most general type of hydrogenation involves hydrogen gas ( $H_2$ ) and a metal catalyst (most commonly Pd, Pt, Ni), see below. Due to the reaction conditions the reaction can't be stopped (if starting with an alkyne), everything is reduced to an alkane.

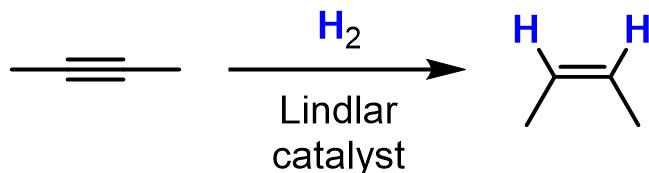


Metal-catalyzed hydrogenation is an example of **heterogeneous catalysis** (a process involving substances in different phases). In this case, **gaseous  $H_2$**  reacts with the metal surface to create **metal hydrides** that react with alkenes/alkynes. Due to the mechanism, the hydrogen atoms are delivered ***syn***.

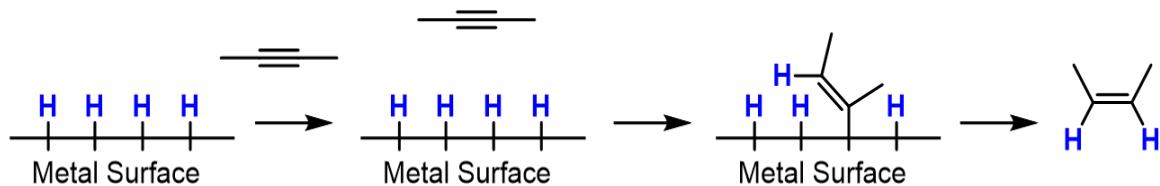


## 2. Lindlar Catalyst

There are scenarios when you will want to reduce alkynes to alkenes. Simple metal-catalyzed hydrogenation won't work since the reaction can't stop at an alkene! The **Lindlar catalyst**, a poisoned catalyst, was developed to stop the reduction at the *cis*-alkene. [Lindlar catalyst = Pd-CaCO<sub>3</sub>, Pb(CO<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, Quinoline].

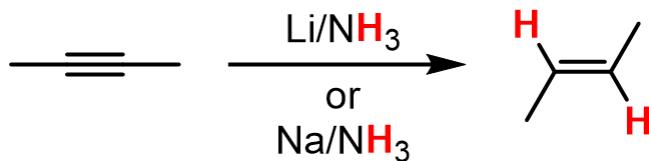


The reaction is still technically follows the same mechanism as metal-catalyzed hydrogenation (see below), but the catalyst design stops the reaction after the alkene is produced. The result is a *cis*-alkene.



## 3. Metal/Liquid Ammonia

What about trans-alkenes? These can be synthesized from alkynes using a reduction reaction with Lithium (Li) or Sodium (Na) metal in liquid Ammonia (NH<sub>3</sub>).

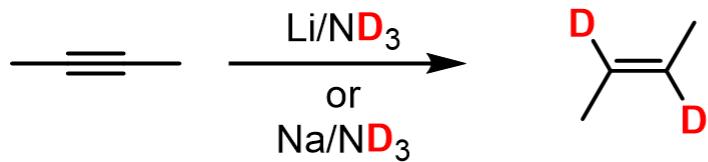
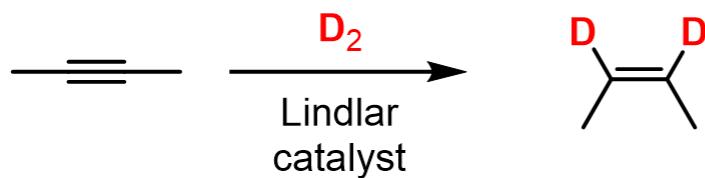
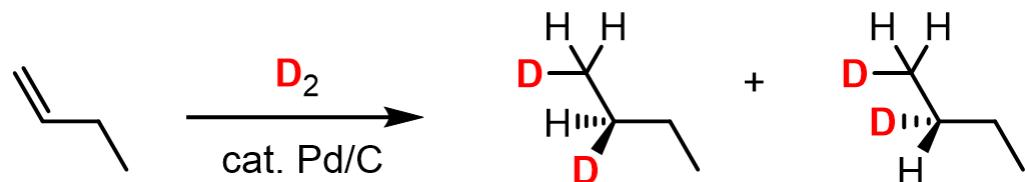


It's important to recognize the difference between sodium amide (NaNH<sub>2</sub>) and sodium/ammonia (Na/NH<sub>3</sub>). They both have applications in alkyne chemistry, but have completely different reactivities:



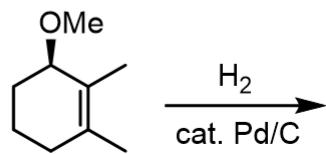
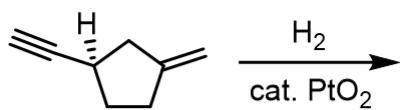
### Deuterium atoms in Hydrogenation Reactions

Deuterium, a heavier isotope of hydrogen (abbreviated  $^2\text{H}$  or D), reacts in the same way as the hydrogen atom. Sometimes deuterium atoms will appear in exam questions to check your understanding of certain reactions. Deuterium is different from hydrogen, so it can create chiral centres (top example)!



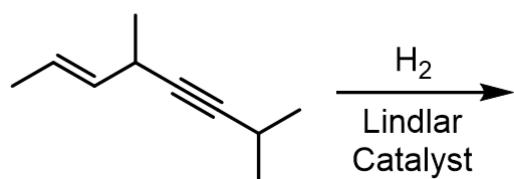
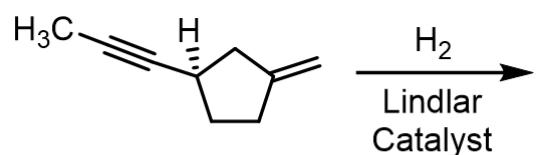
### CONCEPT CLARIFIER

Predict the products of the following reactions:



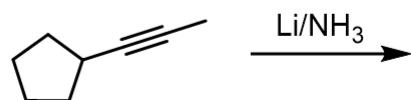
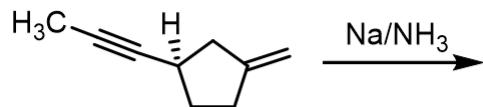
### CONCEPT CLARIFIER

Predict the products of the following reactions:



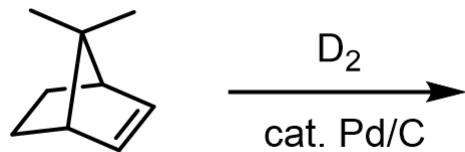
### CONCEPT CLARIFIER

Predict the products of the following reactions:



**CONCEPT CLARIFIER**

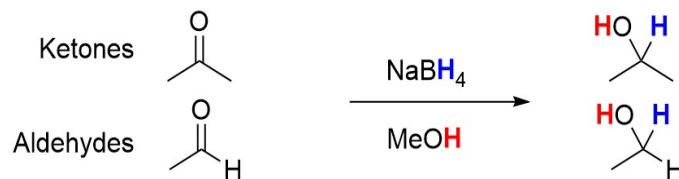
Predict the product of the following reaction. If multiple products form, select the major product. Why does it form preferentially?



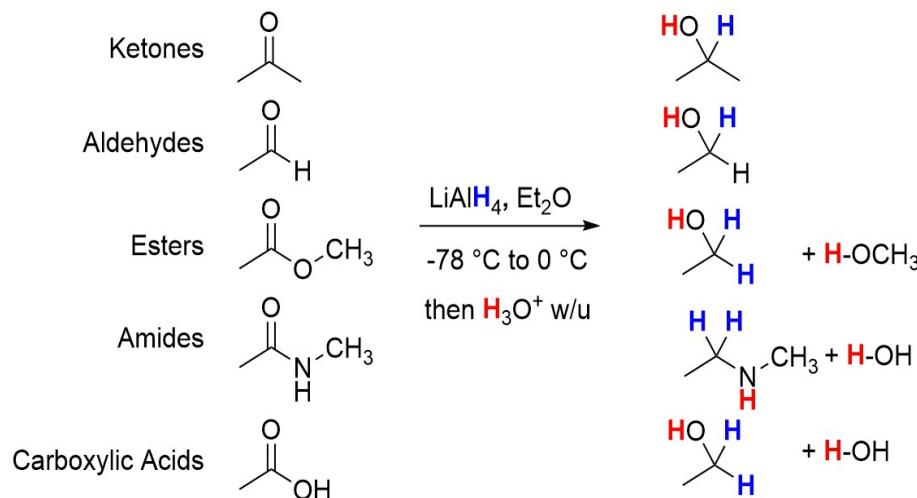
## 04 — Summary of Reactions and Key Ideas

# Reductants

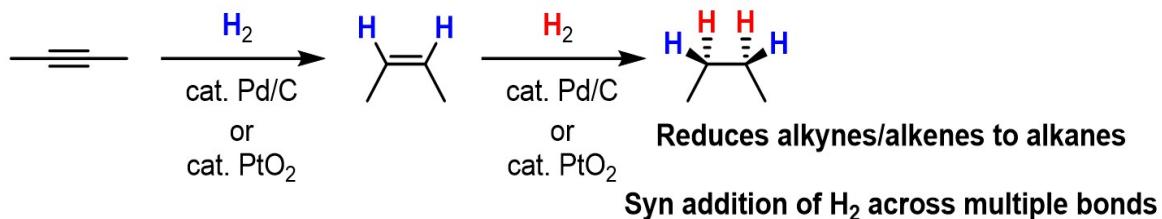
## 1. Sodium Borohydride, $\text{NaBH}_4$



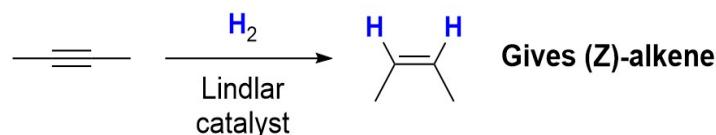
## 2. Lithium Aluminum Hydride, $\text{LiAlH}_4$



## 3. $\text{H}_2$ with Pd/C (or Pt or Ni)

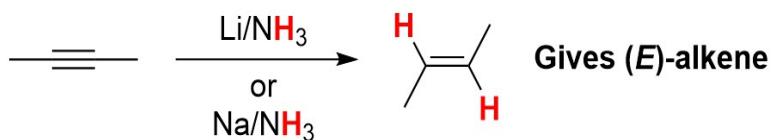


## 4. $\text{H}_2$ with Lindlar Catalyst (Pb-poisoned Pd Catalyst))



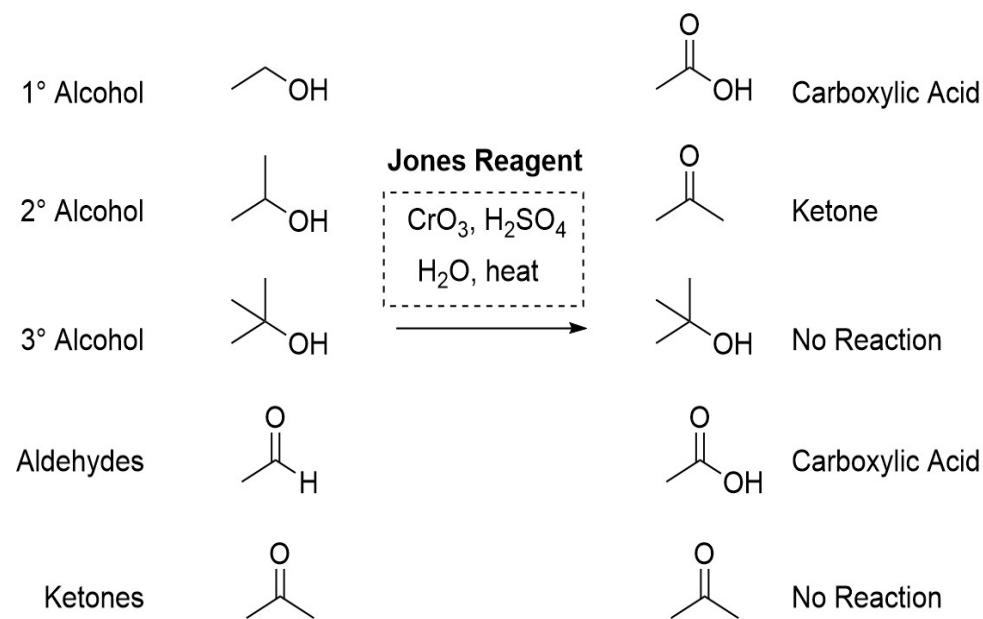


### 5. Li or Na with liquid NH<sub>3</sub>

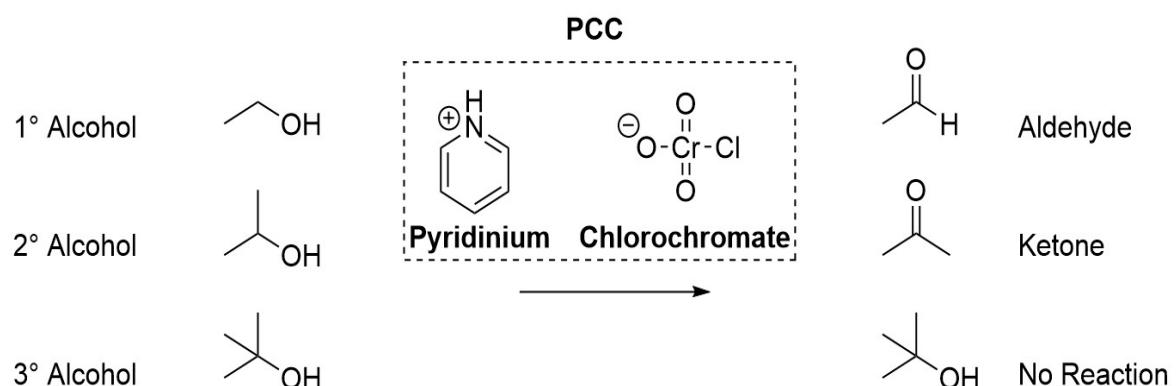


## Oxidants

### 1. Jones Reagent (CrO<sub>3</sub>, H<sub>2</sub>SO<sub>4</sub>, H<sub>2</sub>O)



### 2. Pyridinium Chlorochromate (PCC)



**05** — **Section Quizzes**

# CHEATSHEETS AND REVIEW

## 01 Review

### Bonding

#### Lewis Structures and Formal Charge

##### WIZE's Rules for Drawing Lewis Structures

1. Position most electropositive atom in the middle, with more electronegative atoms around it
2. Add valence electrons (be aware of overall molecule charge) and form bonds between the central and terminal atoms (1 bond = 2 electrons)
3. Complete the octets of the terminal atoms by moving electrons out from the central atom
4. Calculate formal charges and add double bonds if necessary
5. Check to make sure all atoms have complete octets, and that if they don't it is allowed\*

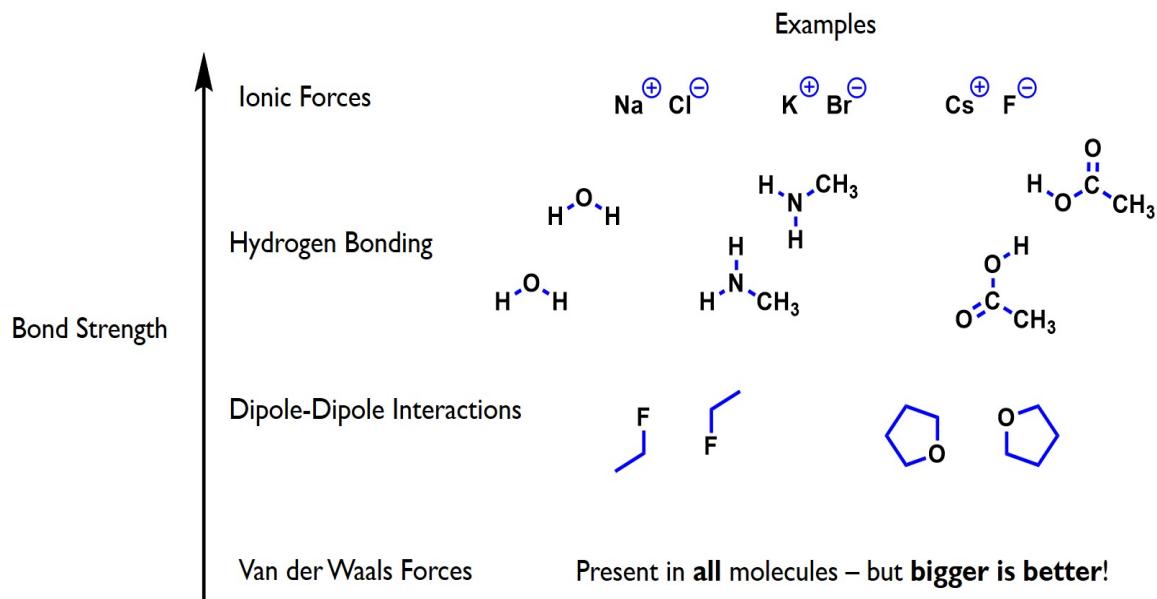
*Carbon and Nitrogen can ONLY form 4 bonds!!!*

**Formal charge is calculated using the following equation**

$$\text{FC(atom)} = \# \text{ valence e}^- - (\text{lone pair e}^- + \text{number of bonds})$$

### Key Terms

- **Valence Bond Theory:** Defines the orbitals involved in bonding for each atom in a compound.
- **Hybridization:** The combination of atomic orbitals (usually *s* and *p* orbitals) to form *bonding* orbitals
- **Molecular Orbital (MO) Theory:** How the (usually *hybridized*) atomic orbitals **combine** to form bonds. Each bond involves the formation of a bonding (either a  $\sigma$ -bond or  $\pi$ -bond) and a related antibonding ( $\sigma^*$ -bond or  $\pi^*$ -bond) orbital by overlapping orbitals.
- **Resonance:** The state attributed to certain molecules of having a structure that cannot adequately be represented by a single structural formula but is a composite of two or more structures of higher energy.
- **Valence-Shell Electron-Pair Repulsion (VSEPR):** The geometry and shape of a molecule is dictated by the atom's hybridization (number of  $\sigma$ -bonds and  $\pi$ -bonds). It is important to consider lone pairs, they also occupy space!
- **Electronegativity:** Tendency of an atom to bring electrons close, in a bond.
- **Polarity:** For a molecule to be overall polar (posses a net dipole) it needs: 1. A Polar Covalent Bond 2. Appropriate Geometry.
- **Intermolecular Forces:** Attractions between compounds holding them together that influence their relative boiling and melting points. More (stronger) intermolecular forces = higher boiling/melting points.



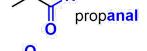
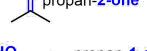
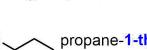
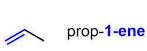
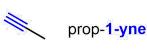
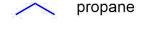
## IUPAC Naming Overview

### General Naming Rules

1. Identify and name the longest carbon chain
2. If present, assign stereochemistry (*R/S* or *E/Z*)
3. Identify and name any substituents on the carbon chain
4. Give these substituents the appropriate 'address'
5. Add substituent names as a prefix to the carbon chain
6. Change suffix of the carbon chain if necessary (for functional groups)

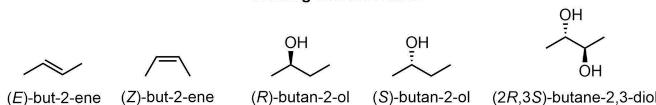
# of Carbons	Name	Structure	
1	Methane	CH <sub>4</sub>	
2	Ethane	H <sub>3</sub> CCH <sub>3</sub>	
3	Propane	H <sub>3</sub> CCH <sub>2</sub> CH <sub>3</sub>	 Butane
4	Butane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>2</sub> CH <sub>3</sub>	 1-Butene
5	Pentane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>3</sub> CH <sub>3</sub>	
6	Hexane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>4</sub> CH <sub>3</sub>	
7	Heptane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>5</sub> CH <sub>3</sub>	
8	Octane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>6</sub> CH <sub>3</sub>	
9	Nonane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>7</sub> CH <sub>3</sub>	
10	Decane	H <sub>3</sub> C(CH <sub>2</sub> ) <sub>8</sub> CH <sub>3</sub>	 1-Butyne

### Functional Groups and Priorities

(Highest priority)	Main Chain/Example	Side Chain/Example
Carboxylic Acids		N/A
Esters		3-methoxy-3-oxopropanoic acid
Amides		3-amino-3-oxopropanoic acid
Aldehydes		3-oxopropanoic acid
Ketones		2-oxopropanoic acid
Alcohols		3-hydroxypropanal
Thiols		3-mercaptopropanal
Alkenes		prop-2-en-1-ol
Alkynes		prop-2-yn-1-ol
Alkyl Halides		3-bromoprop-1-ene
Alkanes		2-methylpentane

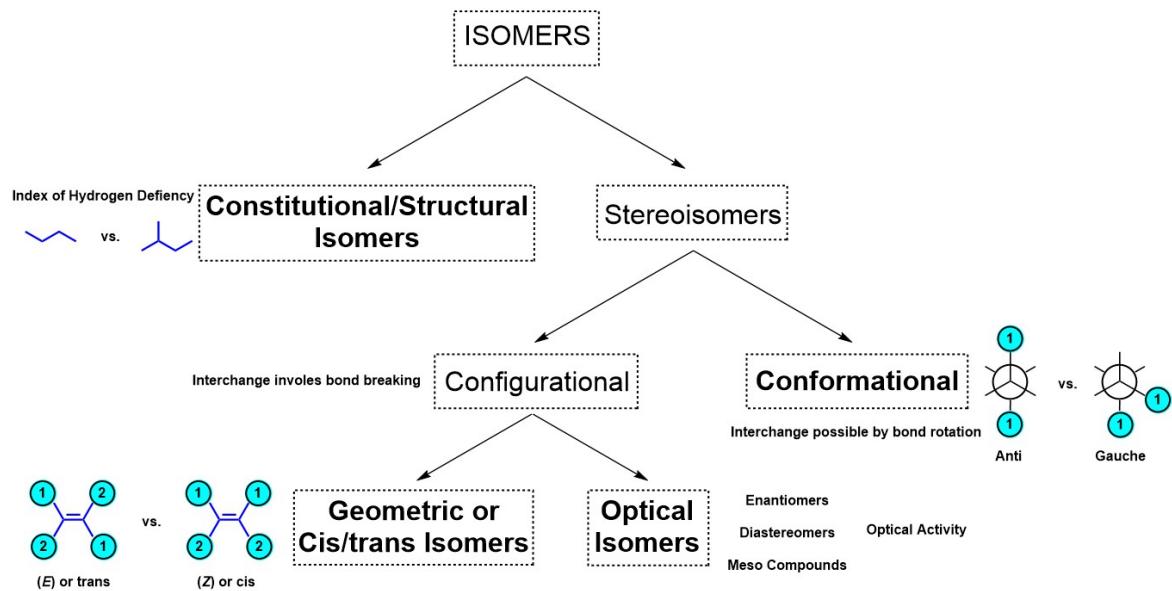
(Lowest priority)

### Naming Stereoisomers

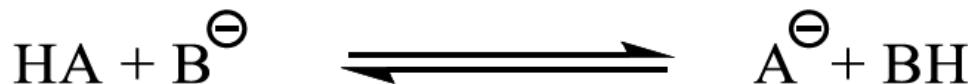


### Special Carbon Chains

Name	Structure	Example
isopropyl		4-isopropylheptane
sec-butyl		4-(sec-butyl)heptane
tert-butyl		4-(tert-butyl)heptane
isobutyl		4-isobutyloctane
cyclo...	 n = 1,2,3...	1-isopropyl-2-methylcyclopentane  
		3-isopropyl-4-methylcyclopent-1-ene



## Acid/Base Equilibrium



The equilibrium is going to tend towards the side that has the **most stable species** (is  $\text{A}^-$  or  $\text{B}^-$  more stable?).

Factors that can increase the stability of an anion:

### 1. Atom Size

If you are dealing with atoms in the **same group** of the periodic table:  
The **larger the atom**, the **weaker the H-X bond** and the **more stable** the **conjugate base** will be.



This comes from a *lower charge density* on the conjugate base/anion.

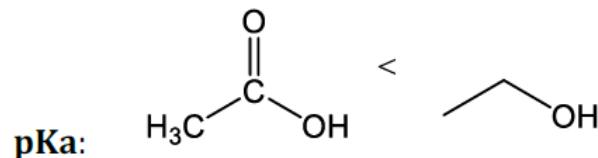
## 2. Atom Electronegativity

If you are dealing with atoms *in the same period/row*, the more electronegative the anion is the more stable of a conjugate base it will be. This is because being more electronegative means the ion can hold the negative charge better.



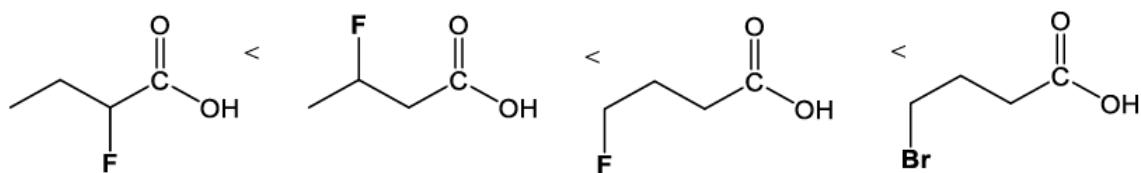
## 3. Resonance

Any conjugate base that exhibits resonance will be more stable than one that does not.



## 4. Induction

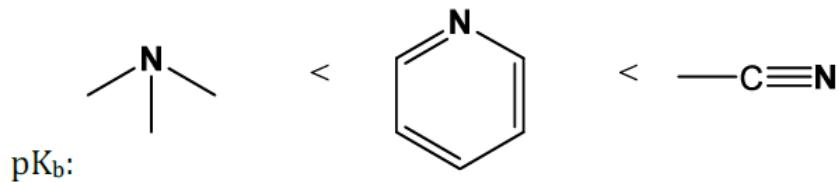
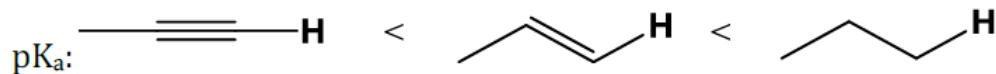
Electronegative atoms create a dipole which stabilizes the negative charge of the conjugate base.



## 5. Hybridization and Aromaticity

(most stable orbital) s < sp < sp<sup>2</sup> < sp<sup>3</sup> < p (less stable orbital).

If an anion is put in an orbital with more '*s-character*' it is more stable.

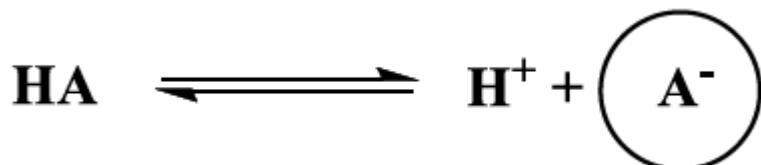


#### Wize's Points to Remember:

1. Big  $K_a$  = good acid! (recall that  $K_x$  is often rate of 'x' thing)

$$pK_a = -\log(K_a) \rightarrow \text{low } pK_a = \text{good acid!}$$

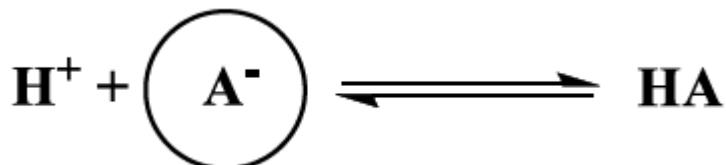
2. The best acids have the most stable conjugate base.



Things that stabilize conjugate bases:

- (1) Size, (2) Electronegativity, (3) Resonance, (4) Induction, (5) Hybridization

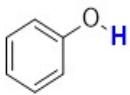
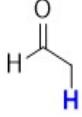
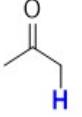
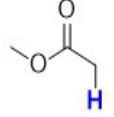
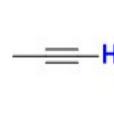
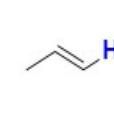
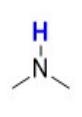
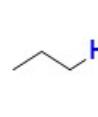
3. The best bases are the most unstable 'conjugate bases'



Mostly anions (and some neutral compounds) that are:  
(1) not big ( $-\text{OH}$  vs.  $-\text{SH}$ ), (2) not electronegative ( $-\text{CR}_3$  vs.  $-\text{NR}_2$ ), (3) no resonance, (4) no inductive stabilization, (5) available lone pair

## pK<sub>a</sub> Values for Common Functional Groups

Below are the pK<sub>a</sub> values of some of the most important functional groups in organic chemistry. Memorizing an approximate value is more than adequate to predict the appropriate bases to deprotonate any of these acids.

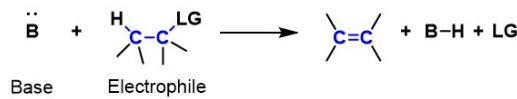
H <sub>2</sub> SO <sub>4</sub>	H <sub>3</sub> O <sup>+</sup>				H <sub>2</sub> O	
-9	-2	4	10	10	16	16
<p>pK<sub>a</sub>=</p>						
						
17	20	25	25	40	45	50

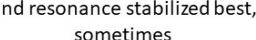
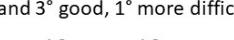
## Substitutions – $S_N1$ and $S_N2$

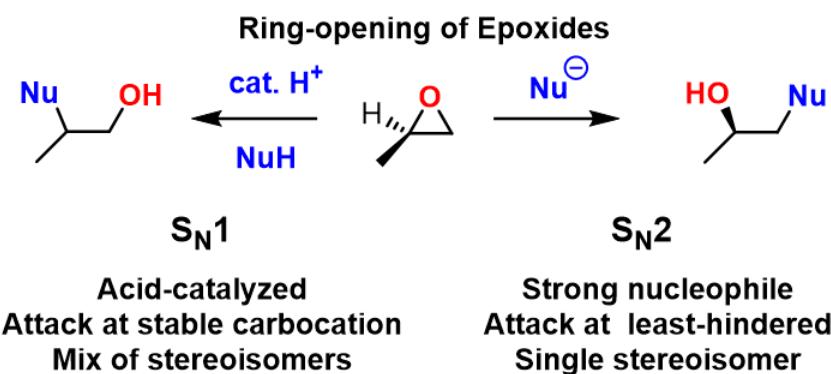


	<b>S<sub>N</sub>1</b>	<b>S<sub>N</sub>2</b>
Rate Law	$k[\text{electrophile}]$	$k[\text{electrophile}][\text{nucleophile}]$
Reaction Energy Diagram	2 transition states and 1 intermediate	1 transition state
Electrophiles	3° and resonance stabilized best, 2° sometimes	1° best, 2° good, 3° never
	 3°      Allylic, Benzylic      2°	 1°      2°      3°
Nucleophiles	Not strong	Strong (anionic) preferred, sterics matter
Solvent	Polar, Protic	Polar, Aprotic
	$\text{H}_2\text{O}$ Water $\text{R-OH}$ Alcohols $\text{R-COOH}$ Carboxylic Acids	 Acetone      DMSO      DMF      HMPA

## Eliminations – E1 and E2



	E1	E2
Rate Law	$k[\text{electrophile}]$	$k[\text{electrophile}][\text{base}]$
Reaction Energy Diagram	2 transition states and 1 intermediate	1 transition state
Electrophiles	3° and resonance stabilized best, 2° sometimes  3°                                    Sometimes Allylic                            2°	2° and 3° good, 1° more difficult  2°                                    3°                                    1°
Base and conditions	Weak base + heat or strong acid ( $\text{LG} = \text{OH}$ )	Alkoxides ( $\text{-OR}$ ), Bulk helps
Double Bond Stereochemistry	(E) preferred, (Z) rare	(E) preferred, (Z) rare <b>unless</b> orbitals require it
Regiochemistry	Always form most substituted double bond <b>(Zaitsev product)</b>	Always <b>Zaitsev</b> product <b>unless</b> a bulky base is used, then <b>Hofmann</b> (least substituted) product



## Electrophilic Addition

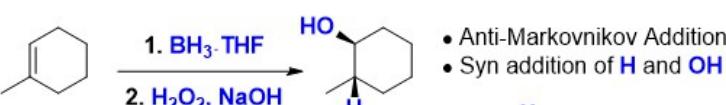
### 1. Hydrohalogenation



### 2. Acid-catalyzed Hydration



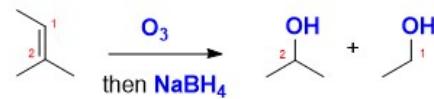
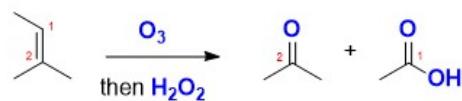
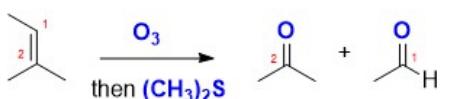
### 3. Hydroboration



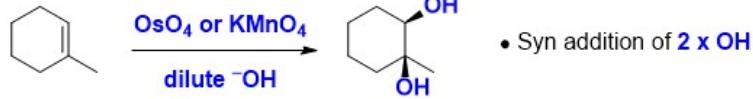
### 4. Halogenation



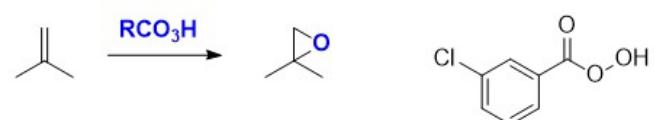
### 5. Ozonolysis



### 6. Dihydroxylation



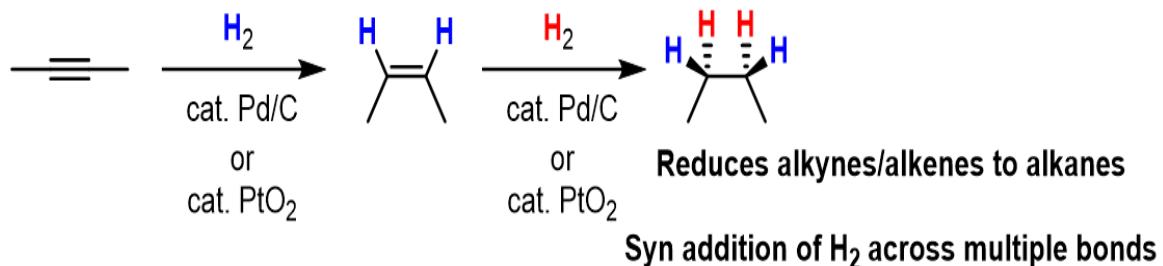
### 7. Epoxidation



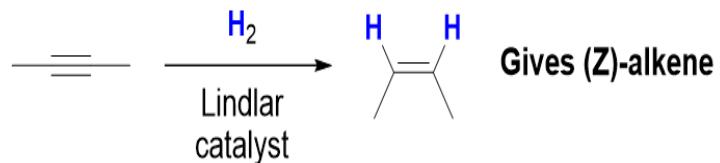
Most common epoxidation reagent, **mCPBA**

## Hydrogenations

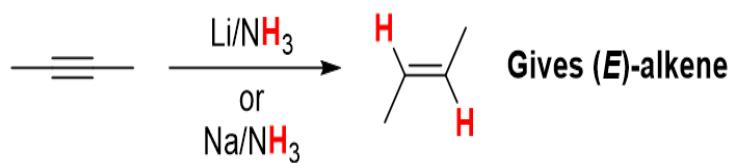
**H<sub>2</sub> with Pd/C (or Pt or Ni)**



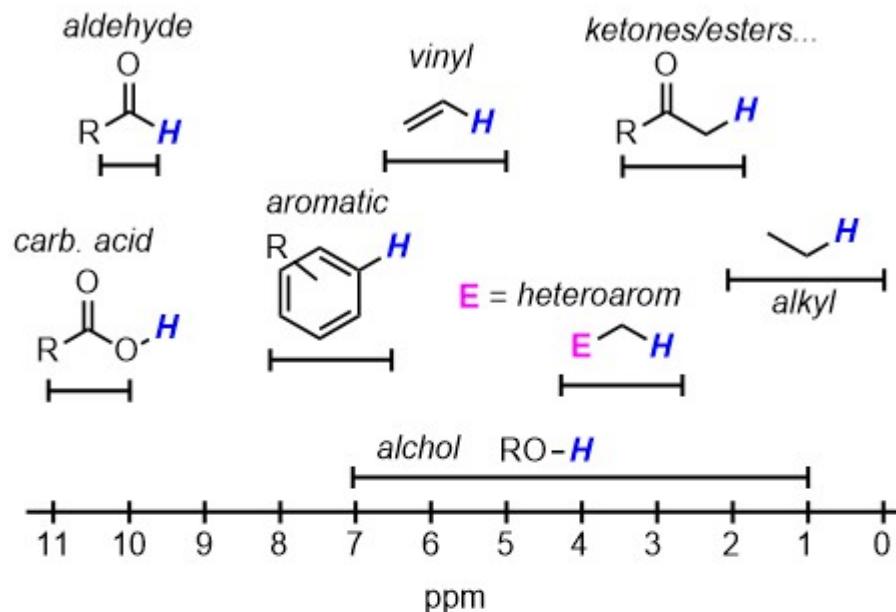
**H<sub>2</sub> with Lindlar Catalyst (Pb-poisoned Pd Catalyst))**



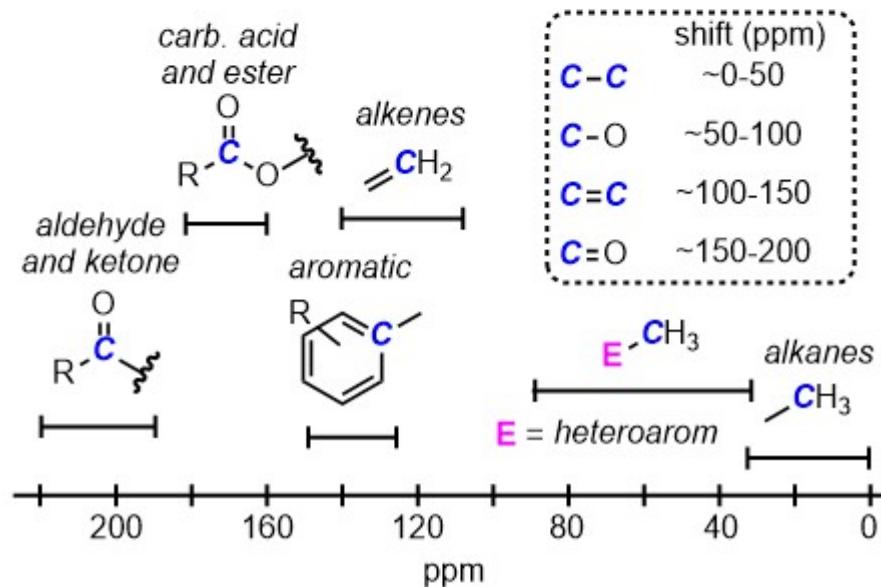
**Li or Na with liquid NH<sub>3</sub>**



### Common $^1\text{H}$ NMR Shifts



### Common $^{13}\text{C}$ NMR Shifts



# PRACTICE EXAM

## 01 Exam

Wize Quiz

Practice Exam 1 (21 Qu.)

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with step-by-step solutions on  
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