CHEMISTRY 2500

Topic #8: Nucleophilic Substitution Reactions (S_N1 and S_N2)

Fall 2014

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Nucleophilic Substitution Reactions (S_N1/S_N2)

- Nucleophilic substitution reactions are reactions in which a leaving group attached to a **tetrahedral** carbon atom is displaced by a nucleophile. Consider the following reaction:

$$I^- \ + \ CH_3Br \ \rightarrow \ CH_3I \ + \ Br^-$$

- We can imagine three possible mechanisms for this reaction:
  - C-I bond is formed first then C-Br bond is broken:

  - C-Br bond is broken first then C-I bond is formed:

  - C-I bond is formed at the same time as C-Br bond is broken:

- One of these mechanisms can quickly be ruled out as impossible. Which one? Why?

Nucleophilic Substitution Reactions (S_N1/S_N2)

- The remaining two mechanisms are reasonable, and there are nucleophilic substitutions which proceed according to each.

    - Substitution reactions in which the leaving group leaves before the nucleophile attacks are referred to as S_N1 reactions.
    - Substitution reactions in which the leaving group leaves at the same time as the nucleophile attacks are referred to as S_N2 reactions.

    The number refers to the number of molecules reacting in the rate-determining step in which the leaving group leaves.

    S = substitution. N = nucleophilic.

- For most reactions, one mechanism will be preferred over the other. This particular reaction proceeds according to an S_N2 mechanism:

S$_N$2 Reactions

- S$_N$2 reactions are generally favoured by 1° (and methyl) substrates. The table below shows the relative rates of reaction for a variety of different alkyl bromides in S$_N$2 reactions.

Substrate	Relative Rate of S$_N$2 Reaction
CH_3Br	100
CH_3CH_2Br	1.31
$CH_3CH_2CH_2Br$	0.81
$(CH_3)_2CHBr$	0.015
$(CH_3)_3CBr$	0.004

Can you rationalize this trend?

S$_N$2 Reactions

- Here is another table showing relative rates of reaction for a variety of different alkyl bromides in S$_N$2 reactions.

Substrate	Relative Rate of S$_N$2 Reaction
CH_3Br	100
CH_3CH_2Br	1.31
$CH_3CH_2CH_2Br$	0.81
$CH_3CH_2CH_2CH_2Br$	0.52
$(CH_3)_2CHCH_2Br$	0.052
$(CH_3)_3CCH_2Br$	0.00001

Can you rationalize this data? Your model kit may be helpful...

S$_N$2 Reactions

- Sketch a reaction profile diagram for each of the following reactions if it were to follow a simple one-step S$_N$2 mechanism. Consider the trends discussed on the previous two pages.

$$I^- + CH_3Br \rightarrow CH_3I + Br^-$$

$$I^- + (CH_3)_3CBr \rightarrow (CH_3)_3CI + Br^-$$
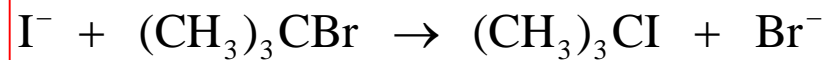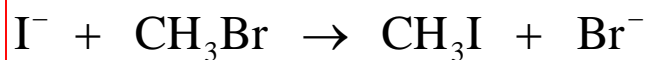
- What is the main difference between the two diagrams, and how does it account for the fact that only one of the reactions will actually proceed according to an S$_N$2 mechanism?
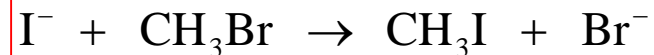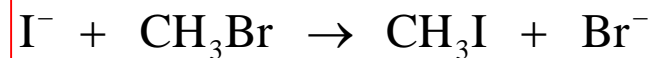
S$_N$2 Reactions and Kinetics

- S$_N$2 reactions are referred to as **second order** reactions. This is because they involve two molecules colliding in the **rate determining step**.

- The rate of a reaction is generally measured as the change in concentration of one of the reactants over a given unit of time:

$$\text{average rate} = -\frac{\Delta[\text{reactant}]}{\Delta t}$$

- Alternatively, it is sometimes reported in terms of product concentration:

$$\text{average rate} = \frac{\Delta[\text{product}]}{\Delta t}$$

- So, for our reaction between CH_3Br and I^-, we would report rate as either the consumption of CH_3Br or as the production of CH_3I. These are, of course, directly proportional!

S$_N$2 Reactions and Kinetics

- What happens to the rate of production of CH_3I if the concentration of I^- is held constant but the concentration of CH_3Br is increased?

- What happens to the rate of production of CH_3I if the concentration of CH_3Br is held constant but the concentration of I^- is increased?
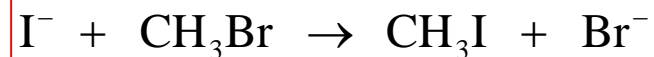
S$_N$2 Reactions and Kinetics

- Looking at the graphs on the previous page, we can write out a **rate law** for this reaction. A rate law is a mathematical equation relating the concentrations of each reactant to the overall rate of reaction. It involves a **rate constant** (k) which must be measured experimentally.

- The rate law for the S$_N$2 reaction between CH$_3$Br and I$^-$ is:

- We already defined S$_N$2 reactions as **second order** based on the number of molecules colliding in the rate determining step. Here is another way to find the order of a reaction: add up the exponents on all concentrations in the rate equation. In this case, we can say that the reaction is _____ order in CH$_3$Br, _____ order in I$^-$ and **second order** overall.

S$_N$2 Reactions and Kinetics

- Rate laws and rate constants are determined experimentally. Known quantities of each reagent are mixed, and the initial rate of reaction is measured. By comparing reaction rates under different reaction conditions, reaction order and rate constant can be calculated.

- A mechanism is a hypothesis that must be consistent with all observed rate data!

- We can use rate data to test whether or not a given reaction might proceed via an S$_N$2 mechanism.

S$_N$2 Reactions and Kinetics

- The substitution reaction between bromoethane and hydroxide is studied, giving the following rate data:

[CH$_3$CH$_2$Br] (M)	[HO$^-$] (M)	Initial Rate (M/s)
0.1	0.1	0.15
0.2	0.1	0.31
0.2	0.2	0.63

Might this reaction proceed via an S$_N$2 mechanism?

S$_N$2 Reactions and Kinetics

- The substitution reaction between 2-chloro-2-methylpropane and water is studied, giving the following rate data:

[(CH$_3$)$_3$CCl] (M)	[H$_2$O] (M)	Initial Rate (M/s)
0.1	0.1	0.0068
0.2	0.1	0.014
0.2	0.2	0.014

Might this reaction proceed via an S$_N$2 mechanism?

S$_N$2 Reactions and Kinetics

- Consider what happens to the concentrations of each reactant as the reaction progresses. What would a plot of reaction rate vs. time look like?

In order to predict the rate of reaction at a future time, it would be necessary to convert this graph into a linear function. Doing so is beyond the scope of this course; however, for second order reactions, plotting $\dfrac{1}{[\text{reactant}]}$ vs time gives a linear plot (slope=k).

S$_N$2 Reactions with Multiple Elementary Steps

- Not all S$_N$2 reactions involve only one step, but they all have the same rate determining step, and they are all second order. Consider the following two-step S$_N$2 reaction:

$$CH_3SH \ + \ CH_3I \ \rightarrow \ CH_3SCH_3 \ + \ H^+ + \ I^-$$

  Provide a mechanism for this reaction and rationalize why the rate determining step is still the step in which the leaving group leaves. Then sketch a reaction profile diagram for this reaction.

S$_N$2 Reactions and Stereochemistry

- So far, all the examples we have considered have involved achiral substrates. If we consider a chiral substrate, we discover that we must consider what happens to the stereochemistry in the reaction.

- If the stereocenter is not the electrophilic site, then there is no change to any of the stereocenters:
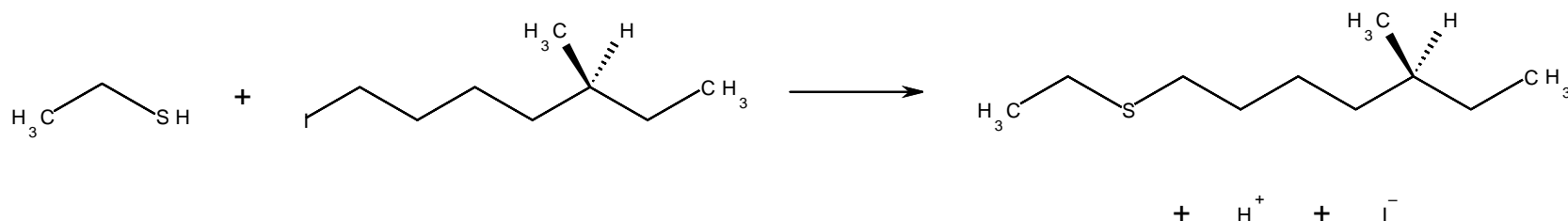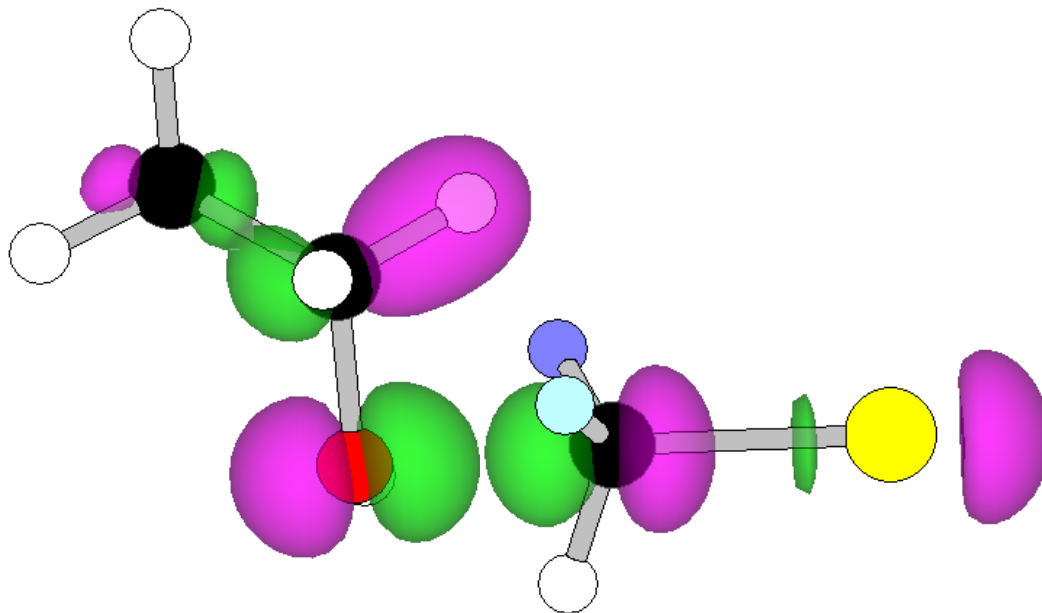

- If, however, the electrophilic site is a stereocenter, it will be inverted:
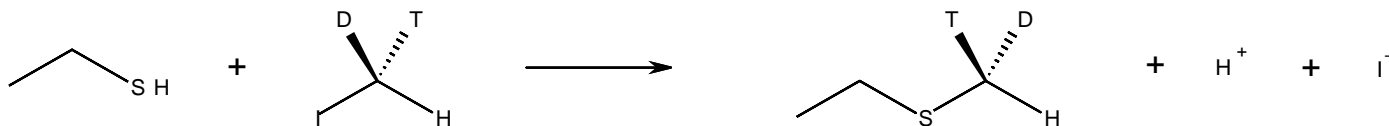
This is because the reaction always proceeds with **backside attack** *(see next page).*

S$_N$2 Reactions and Stereochemistry

- Look at the HOMO for our nucleophile (CH$_3$CH$_2$SH) and the LUMO for our electrophile (CHDTI):

- The only way to get good overlap between these two MOs is for the nucleophilic site to attack the electrophilic site exactly opposite the leaving group. This results in inversion of the stereocenter. This inversion always occurs in an S$_N$2 reaction but can only be observed when the electrophilic site is a stereocenter.

S$_N$2 Reactions and Stereochemistry

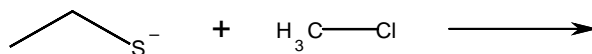■ If we draw the reaction equation including the transition state, we can see how this inversion happens:

■ If we imagine replacing the various hydrogen isotopes with larger groups, we can see that the nucleophile would have a difficult time approaching the electrophilic site <u>and</u> that the transition state would be relatively unstable due to steric effects. This confirms the observation that S$_N$2 reactions occur fastest at methyl electrophiles, reasonably fast at 1° electrophiles, very slowly at 2° electrophiles and not at all at 3° electrophiles.
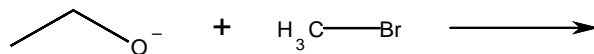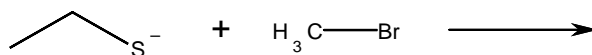
S$_N$2 Reactions and Reactivity

- Other factors to consider include the strength of the nucleophile (nucleophilicity) and leaving group ability.

- For each set of reactions, draw the S$_N$2 products. Then indicate which reaction should proceed more readily and why.
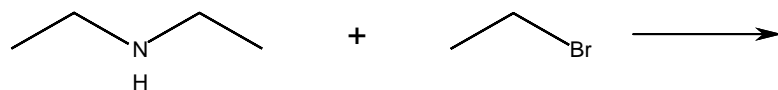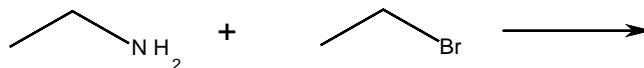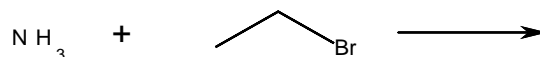
    Reaction Set #1:

    H_3C———Cl   +   S$^-$ →

    H_3C———I   +   S$^-$ →

    Reaction Set #2:

    H_3C———Br   +   S$^-$ →

    H_3C———Br   +   O$^-$ →
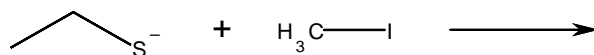
S$_N$2 Reactions and Reactivity

Reaction Set #3:

NH_3 + [CH$_2$CH$_3$Br] ⟶

[CH$_3$CH$_2$NH$_2$] + [CH$_2$CH$_3$Br] ⟶
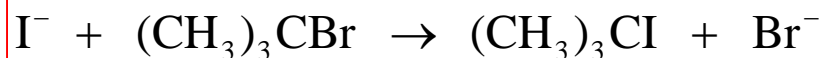
[CH$_3$CH$_2$NHCH$_2$CH$_3$] + [CH$_2$CH$_3$Br] ⟶

What does this tell you about would happen if you mixed ammonia and bromoethane with the hopes of making ethanamine?

S$_N$1 Reactions

■ On page 6 of these notes, we considered the following reaction and determined that it would not proceed according to an S$_N$2 mechanism due to the steric bulk around the electrophilic site:

$$I^- \ + \ (CH_3)_3CBr \ \rightarrow \ (CH_3)_3CI \ + \ Br^-$$

■ This reaction still proceeds, but it goes according to an alternate mechanism – the S$_N$1 mechanism. In an S$_N$1 reaction, there are always multiple steps. In the rate determining step, the leaving group leaves, generating a carbocation. After that, the nucleophile attacks the electrophilic carbocation:

S$_N$1 Reactions

- There may be additional protonation or deprotonation steps, depending on the nucleophile and electrophile:

$$H_2O \ + \ (CH_3)_3CBr \ \rightarrow \ (CH_3)_3COH \ + \ H^+ \ + \ Br^-$$

S$_N$1 Reactions and Reactivity

- In order for an S$_N$1 reaction to proceed, the leaving group must be **very** good. The pK$_a$ of its conjugate acid should be no more than ~1.

- Compare the first step of an S$_N$1 reaction in which the substrate is 2-bromo-2-methylpropane vs. one in which the substrate is 2-methylpropan-2-ol:

Assume that the only other reactant in the flask is a generic nucleophile (Nu:$^-$)

S$_N$1 Reactions and Reactivity

- In order for an S$_N$1 to proceed, the carbocation generated when the leaving group leaves must be relatively stable (compared to other carbocations; it can never be as stable as a neutral molecule).

- One way to stabilize a carbocation is through resonance. As such, allylic and benzylic alkyl halides can undergo S$_N$1 reactions.
 - Draw all resonance structures for the carbocation generated from 3-chloropropene:

S_N1 Reactions and Reactivity

- Draw all resonance structures for the carbocation generated from benzyl chloride ($C_6H_5CH_2Cl$)

- Note that vinyl and aryl carbocations cannot be resonance stabilized because the positive charge is perpendicular to the pi system. As such, it is NOT part of the pi system and cannot be delocalized:

S$_N$1 Reactions and Reactivity

- Another way in which carbocations can be stabilized is through a combination of the inductive effect and a phenomenon known as hyperconjugation.

  - The **inductive effect** suggests that a carbocation surrounded by electron rich groups will be more stable than one which is not as some electron density can be donated through the sigma bonds. As such, we can rank the stability of methyl, 1°, 2 ° & 3 ° carbocations:

  - This effect is enhanced by **hyperconjugation**, a phenomenon in which electron-rich sigma bonding MOs align with the empty p orbital of a carbocation, somewhat delocalizing the positive charge:
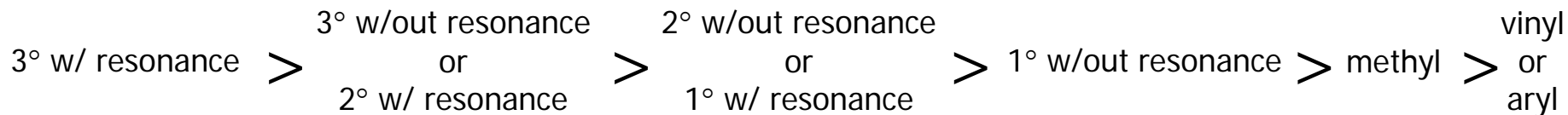

a.

b.
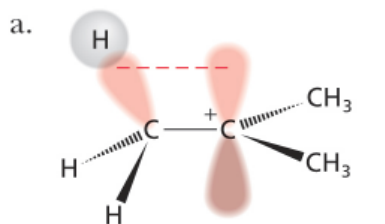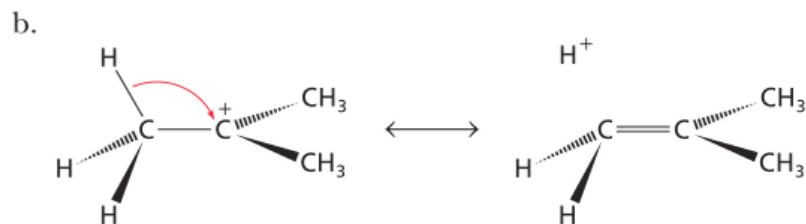
A "no-bond resonance form"
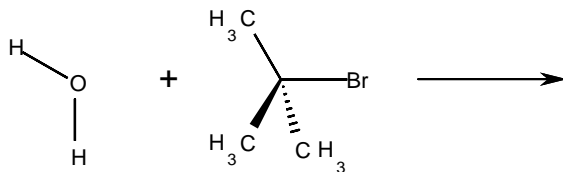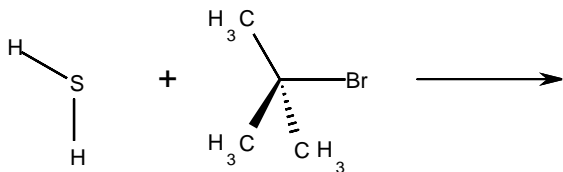
S$_N$1 Reactions and Reactivity

- Just as vinyl and aryl carbocations are NOT stabilized by resonance, they are also NOT stabilized by hyperconjugation. The empty p orbital of the carbocation is simply not aligned with any electron rich C-H sigma bonds.

- **THUS, JUST AS YOU CANNOT DO AN S$_N$2 REACTION AT A NON-TETRAHEDRAL CARBON, YOU CANNOT DO AN S$_N$1 REACTION AT A NON-TETRAHEDRAL CARBON.**

- The overall order of carbocation stability (and, therefore, propensity of a substrate to undergo S$_N$1 reaction) is:

3° w/ resonance > 3° w/out resonance or 2° w/ resonance > 2° w/out resonance or 1° w/ resonance > 1° w/out resonance > methyl > vinyl or aryl

S$_N$1 Reactions and Reactivity

■ For an S$_N$1 reaction to be favourable, it is necessary to have a good leaving group and it is necessary to form a stabilized carbocation.

■ What about the nucleophile? How does the strength of the nucleophile affect the rate of an S$_N$1 reaction?

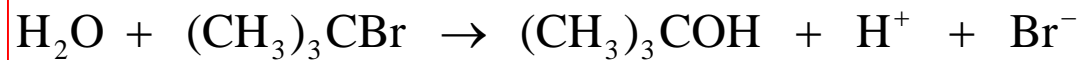Compare the following two S$_N$1 reactions:
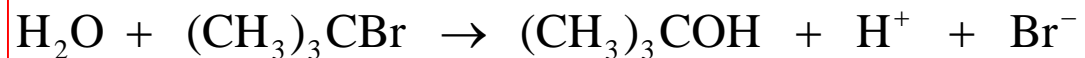
S_N1 Reactions and Kinetics

- What happens to the rate of production of $(CH_3)_3COH$ if the concentration of H_2O is held constant but the concentration of $(CH_3)_3CBr$ is increased?

- What happens to the rate of production of $(CH_3)_3COH$ if the concentration of $(CH_3)_3CBr$ is held constant but the concentration of H_2O is increased?

S$_N$1 Reactions and Kinetics

- Looking at the graphs on the previous page, we can write out a **rate law** for this reaction.

- The rate law for the S$_N$1 reaction between $(CH_3)_3CBr$ and H_2O is:

- S$_N$1 reactions are **first order** based on the number of molecules involved in the rate determining step. Looking at this rate law, we can see that the reaction is _____ order in $(CH_3)_3CBr$, _____ order in H_2O and **first order** overall.
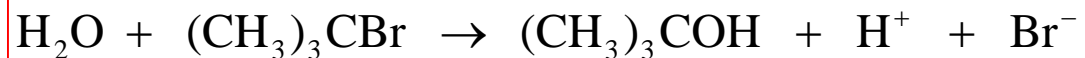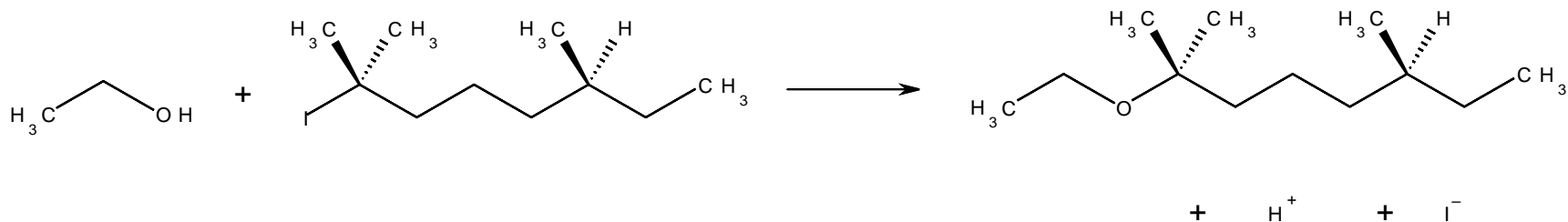
S$_N$1 Reactions and Kinetics

- Consider what happens to the concentrations of each reactant as the reaction progresses. What would a plot of reaction rate vs. time look like?

In order to predict the rate of reaction at a future time, it would be necessary to convert this graph into a linear function. Doing so is beyond the scope of this course; however, for first order reactions, plotting ln[reactant] vs time gives a linear plot (slope=-k).
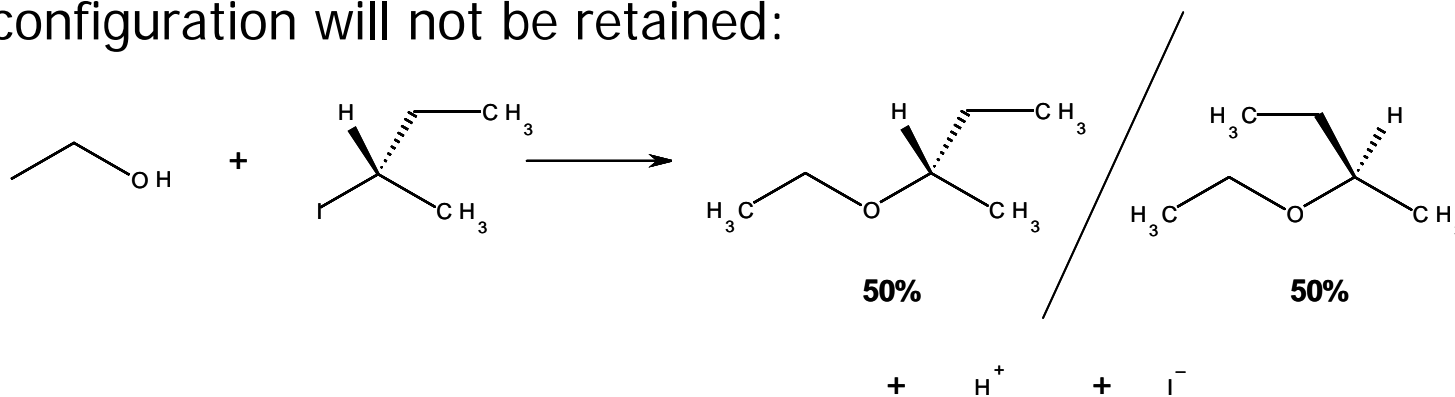
S$_N$1 Reactions and Stereochemistry

- So far, all the examples we have considered have involved achiral substrates. If we consider a chiral substrate, we discover that we must consider what happens to the stereochemistry in the reaction.

- If the stereocenter is not the electrophilic site, then there is no change to any of the stereocenters:

This is consistent with what we saw for S$_N$2 reactions.

S$_N$1 Reactions and Stereochemistry/Isomers

- If, however, the electrophilic site is a stereocenter, its configuration will not be retained:

50%   **50%**

+   H$^+$ +   I$^-$

This was not the case for S$_N$2 reactions. Given the mechanism for an S$_N$1 reaction, why do you think this occurs?

S$_N$1 Reactions and Stereochemistry/Isomers

- Another interesting consequence of the S$_N$1 reaction mechanism is that, occasionally, the product is a constitutional isomer of the one we'd initially expect:
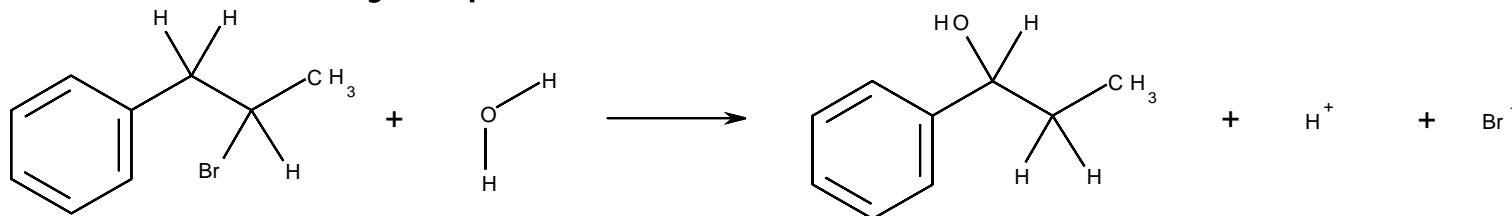

- The mechanism begins as you'd expect; however, once the carbocation is generated, it rearranges to form a more stable carbocation. This is a very fast process and will occur before the nucleophile can attack:
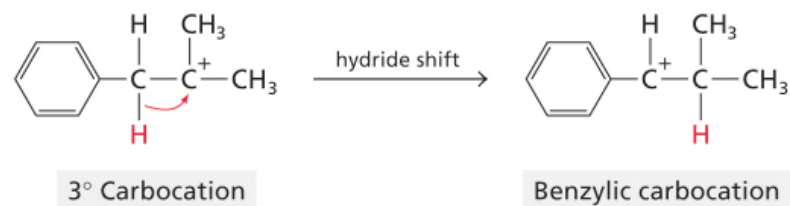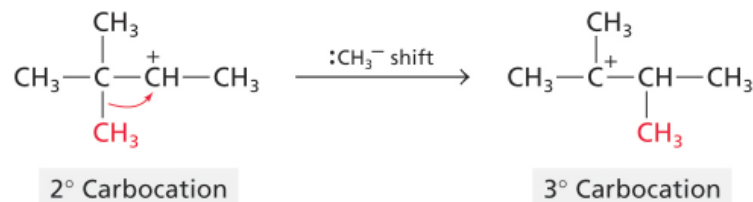
S$_N$1 Reactions and Stereochemistry/Isomers

- Carbocation rearrangements are not limited to S$_N$1 reactions. Any time you propose a reaction mechanism involving a carbocation intermediate, look to see if it can be made significantly more stable through a carbocation rearrangement.

- It is also worth noting that carbocation rearrangements can involve shifting either a hydride ion or a methyl anion.
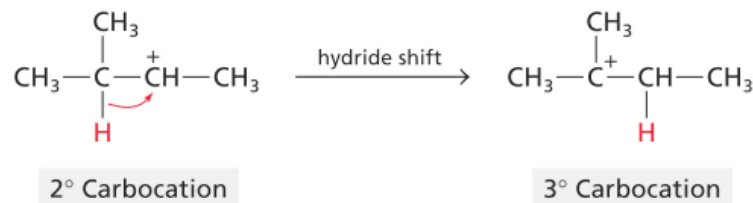
- Pay close attention to the way the curly arrows are drawn in the figure at the right. We should be able to tell if you're proposing a hydride shift or generation of a pi bond by where the arrow points!

$$CH_3-C(CH_3)-\overset{+}{C}H-CH_3 \xrightarrow{\text{hydride shift}} CH_3-\overset{+}{C}(CH_3)-CH(H)-CH_3$$

2° Carbocation → 3° Carbocation

$$CH_3-C(CH_3)-\overset{+}{C}H-CH_3 \xrightarrow{:CH_3^- \text{ shift}} CH_3-\overset{+}{C}(CH_3)-CH(CH_3)-CH_3$$

2° Carbocation → 3° Carbocation

hydride shift

3° Carbocation → Benzylic carbocation

- The following S$_N$1 reaction is done to make a precursor to *trans*-chrysanthemic acid in a senior organic lab at the U. of C.
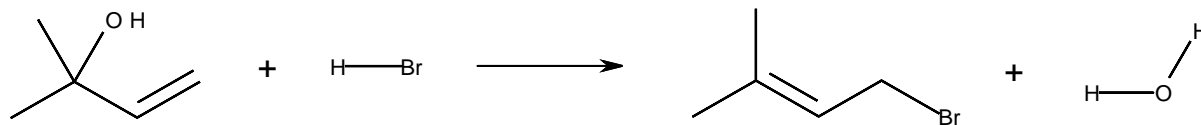
Propose a mechanism consistent with the product formed.

S_N1 vs. S_N2 Reactions: Solvent Effects

- The reaction on the previous page was done using 50% $HBr_{(aq)}$ as the solvent. **S_N1** reactions are usually done in **polar protic** solvents because they help to stabilize the developing charge in the transition state (facilitating formation of the carbocation intermediate):

- Common polar protic solvents include:

S$_N$1 vs. S$_N$2 Reactions: Solvent Effects

- **S$_N$2** reactions are usually done in **polar aprotic** solvents. The solvent must be polar enough to dissolve the nucleophile, but should not be so polar as to render the nucleophile unreactive. (The more stable a compound is, the less reactive it is.)

- Common polar aprotic solvents include:

S_N1 vs. S_N2 Reactions: Comparison

	S_N2	S_N1
Reaction Order	second order reaction	first order reaction
Minimum # Steps	1 or more steps	2 or more steps
Intermediates?	not necessarily	carbocation
Stereochemical Consequences	stereospecific inversion of configuration at electrophilic site	racemization (full or partial) at electrophilic site
Importance of Nucleophile Strength	very important; no reaction for weak nucleophiles like H_2O	unimportant
Importance of Leaving Group	very important; no reaction for weak leaving groups like HO^-	very important; no reaction for weak leaving groups like HO^-
Substrate Structure Dependence	avoid steric hindrance; $CH_3 > 1° > 2°$(slow) $> 3°$ (no); no reaction for aryl/vinyl	need carbocation stabilization; $3° > 2°$ (slow) $> 1°$ (no); resonance stabilization helps; no reaction for aryl/vinyl
Solvent	polar aprotic	polar protic
Competing Reactions	E2	E1, E2, rearrangement

S_N1 vs. S_N2 Reactions

- For each of the following reactions, suggest whether you'd expect it to proceed via S_N1, S_N2, both or neither then draw the appropriate product(s).