

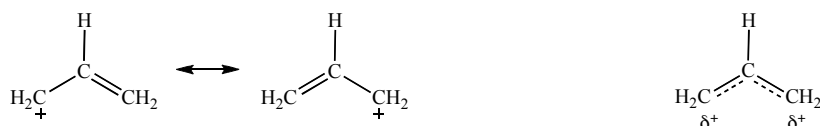


8. Which step in this mechanism is rate determining? Explain.
9. Give the rate law for this reaction.
10. Briefly discuss the stereochemistry of the product.
11. What is the effect on the rate of the reaction when the leaving group is replaced with chloride?
12. What is the effect on the rate of the reaction when the ethyl group is replaced with a hydrogen atom?
13. What is the effect on the rate of the reaction when the solvent is changed to ethanol?
14. List the three requirements for a substitution reaction to proceed via the  $S_N1$  mechanism.
15. When determining the mechanism for any nucleophilic substitution reaction, why is  $S_N2$  considered before  $S_N1$ ?

### Concept Focus Questions Solutions

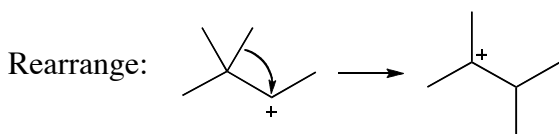
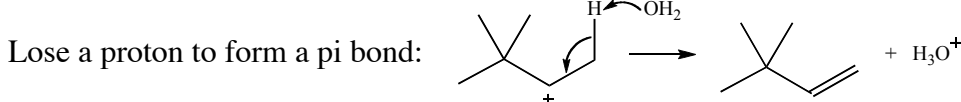
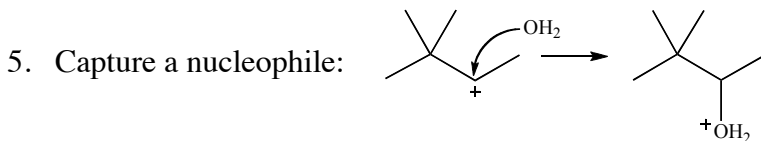
1. Illustrated definitions can be found at the Illustrated Glossary of Organic Chemistry available at the course web site.
  - (a) Carbocation: A structure in which a carbon atom has three covalent bonds and a positive formal charge.
  - (b) Inversion of configuration: A process at a stereocenter that results in a change to the absolute configuration of that stereocenter.
  - (c) Oxonium ion: A structure in which an oxygen atom has three covalent bonds and a positive formal charge.
  - (d) Rate-determining step (rds): The mechanism step which has the largest energy of activation and hence the slowest rate.
  - (e) Retention of configuration: A process at a stereocenter that results in a no change to the absolute configuration of that stereocenter.
  - (f)  $S_N1$  mechanism: A substitution reaction mechanism in which a carbon/leaving group bond scission step occurs before the carbocation/nucleophile bond-forming step. Proceeds via carbocation, and is never concerted.
  - (g) Solvolysis: A reaction in which the solvent participates as a reactant.

- The single most important factor that controls the reactions of any carbocation is the driving force to fill the open octet on the carbon bearing the positive charge.
- Resonance stabilizes a carbocation if the resonance leads to delocalization of charge. The allyl carbocation has two resonance contributors. The resonance hybrid shows the positive charge shared by two carbon atoms. In the absence of resonance a single carbon atom carries the charge.

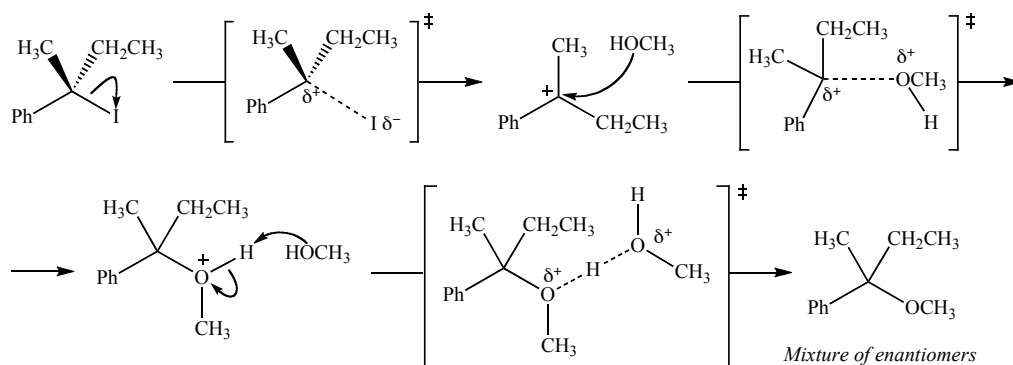


Allyl carbocation resonance contributors      Allyl carbocation resonance hybrid

- A carbocation contains an electron deficient carbon that can be stabilized by electron donating groups. Alkyl groups are weak electron-donating groups. Thus increasing the number of alkyl groups that are directly attached to the carbon with the open octet stabilizes the carbocation. Order of stability:  $\text{H}_3\text{C}^+$  (methyl; least stable) <  $\text{CH}_3\text{CH}_2^+$  (primary,  $1^\circ$ ) <  $(\text{CH}_3)_2\text{CH}^+$  (secondary,  $2^\circ$ ) <  $(\text{CH}_3)_3\text{C}^+$  (tertiary,  $3^\circ$ ; most stable).



## 6. Mechanism:

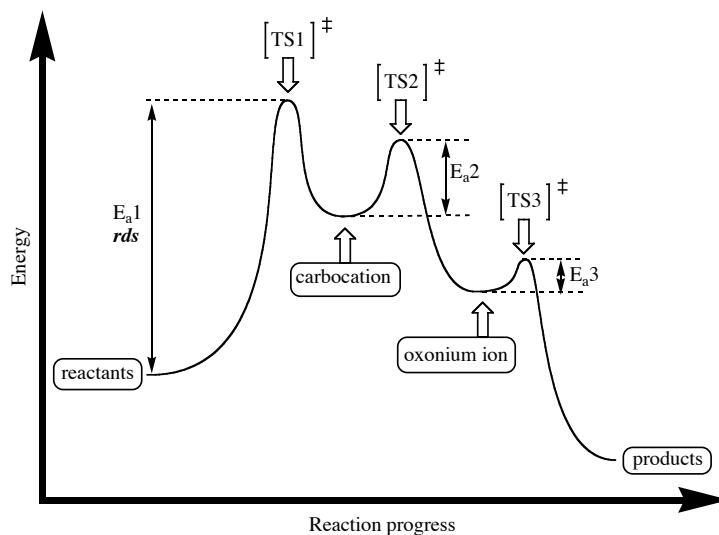


Product stereochemistry: The carbocation intermediate can capture methanol from either face, leading to a mixture of enantiomers for the product. As it leaves I provides some steric hindrance to attack on the carbocation face that it departs from. Therefore the product in which the methoxy group is on the opposite face from which the iodide ion departed (i.e., inversion) is formed in a greater amount than the other stereoisomer (retention) of the product.

That the product consists of a mixture of configurations at the stereocenter is indicated by the lack of solid wedge and broken wedge notation. This way of indicating that the stereochemistry is a mixture can be used for any structure. (The lack of solid and broken wedges may also mean that the stereochemistry is unknown.)

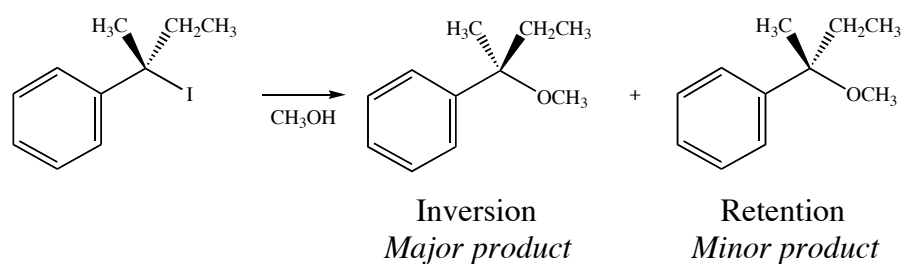
As shown in the mechanism, the  $S_N1$  reaction does not stop at the oxonium ion stage. The oxonium ion intermediate is deprotonated by  $\text{CH}_3\text{OH}$  (the solvent) to give the alcohol product and  $\text{CH}_3\text{OH}_2^+$ , another oxonium ion. These oxonium ions are of roughly equal stability, but due to Le Chatelier's principle the large excess of  $\text{CH}_3\text{OH}$  drives the equilibrium as shown in the mechanism.

7. The reaction energy profile has three transition state humps because the reaction mechanism has three steps.



8. Energy of activation controls the rate of any mechanism step. The step with the greatest energy of activation proceeds at the slowest rate. In the first step of the mechanism, the carbon-iodine bond is lost, and no new bond is gained. In the second step, a carbon-oxygen bond is gained and no bond is lost. The first step is energetically more expensive than the second step. Thus the first step, ionization of the carbon-leaving group bond, is the rate-determining step (rds). The energy difference between these steps may be tens of  $\text{kcal mol}^{-1}$ , so the rate difference is huge. The second step might be a million times faster than the first.

9. Rate =  $k [R_3C-I]$ . Because the second step is so much faster than the first, it does not enter into the rate law.
10. The stereochemistry of the product is determined by which face of the carbocation is attacked by the nucleophile. The products that result from attacking the different faces are (in this case) enantiomers. Remember that the carbocation carbon is planar, so in the absence of other factors, the nucleophile is captured on either face of the carbocation at the same rate. However, the departing leaving group provides some hindrance, so attack leading to inversion of stereochemistry is favored over attack leading to retention. The exact ratio of inversion to retention is influenced by many factors (a complete study of which is beyond the scope of Chemistry 14D), but inversion usually dominates



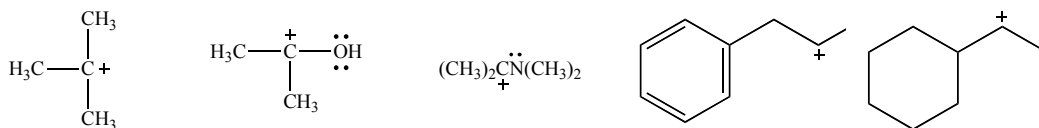
11. Chloride ion has a smaller atomic radius than iodide ion, and therefore a chloride ion is a poorer leaving group. A poorer leaving group makes ionization of the carbon-leaving group bond more difficult. The transition state is less stable and the energy of activation is higher. This ionization is the rate-determining step of the  $S_N1$  mechanism, so replacing a good leaving group with a poorer leaving group causes the  $S_N1$  reaction to be slower.
12. The transition state of the rate-determining step has some carbocation character ( $\delta^+$  on the carbon that becomes the carbon with the open octet in the carbocation). Replacing the ethyl group with a hydrogen atom results in a structure that cannot stabilize this positive charge as easily (less substituted carbocation). This destabilizes the transition state and raises the energy of activation, resulting in a slower reaction.
13. The magnitude of charge on individual atoms is higher in the transition state than in the reactants. A polar solvent stabilizes charges through electrostatic interactions and hydrogen bonding. A more polar solvent stabilizes the charges more effectively, thus lowering the energy of activation and resulting in a faster reaction. Ethanol is less polar than methanol, so the reaction is slowed by this solvent change.
- The solvent also acts as a nucleophile in this reaction. However, the rate at which the carbocation captures the nucleophile is not rate determining, so the relative nucleophilicity of methanol and ethanol is irrelevant.
14. The three requirements for an  $S_N1$  substitution reaction are moderate or better leaving group, stable carbocation intermediate (secondary or better) and polar solvent.

15. In most cases, the rate-determining step of the  $S_N2$  reaction is not as energetically expensive as the  $S_N1$  rate-determining step. This is because bonds are gained and lost in the  $S_N2$  rds, whereas there is only bond loss in the  $S_N1$  rds. The molecules follow the lowest energy pathway when reacting. (If  $S_N2$  is always less energetically expensive than  $S_N1$ ,  $S_N1$  would never occur.) There are examples in which the  $S_N2$  reaction may be a poor one (modest nucleophile, modest leaving group, secondary substrate), and the corresponding  $S_N1$  might be good (good carbocation, polar solvent). In these circumstances, it is possible for an  $S_N1$  reaction to be favored over an  $S_N2$  reaction.

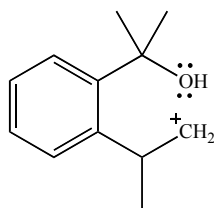
### OWLS Problems

Carbocations are reactive intermediates in a wide range of common organic reactions, so it is important for you be intimately familiar with their structure, relative stabilities, and modes of reaction (the three carbocation fates).

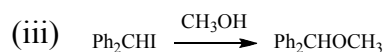
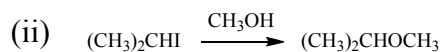
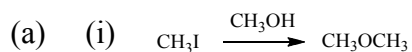
- For the carbocations shown below:
  - Draw all of the significant resonance contributors for each of these carbocations.
  - Arrange the carbocations in order of their relative stabilities.
  - Draw a complete  $S_N1$  reaction of your choice that utilizes the most stable of these carbocations. Include the mechanism with all curved arrows.

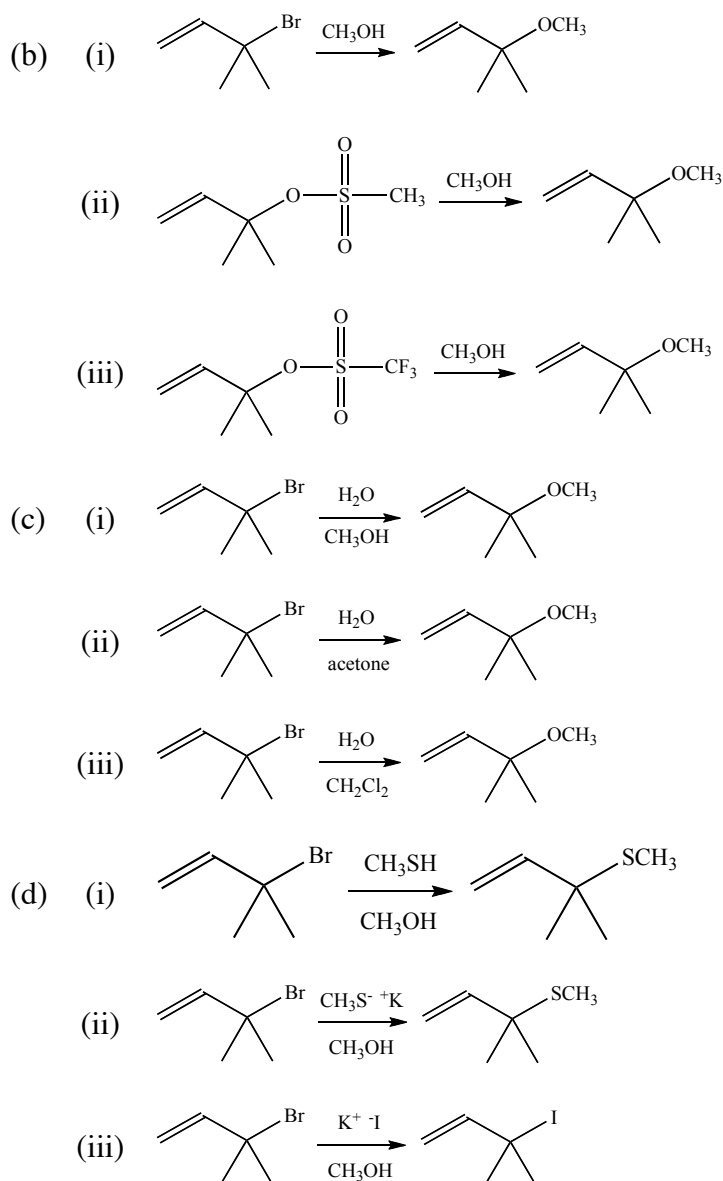


- Name the three carbocation fates discussed in lecture. Illustrate each fate using the carbocation shown below as the only reactant. (No additional nucleophile or base is needed, as these are built into the molecule!) Include curved arrows and products for each fate.

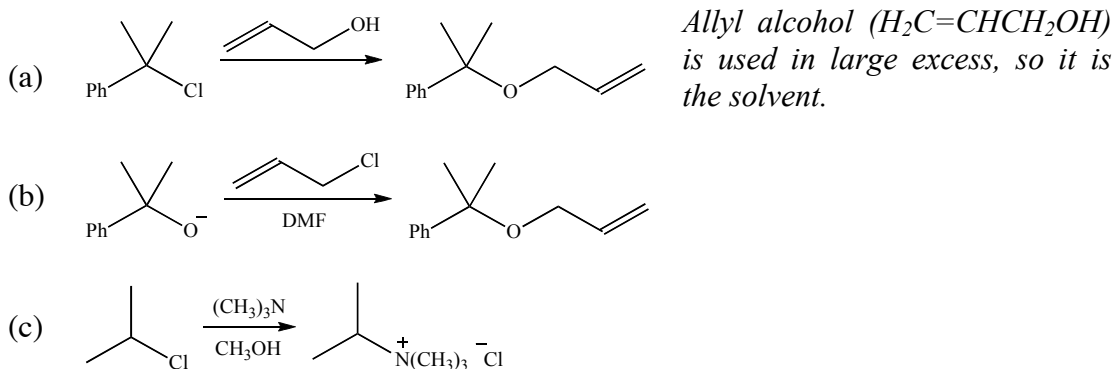


- In each set of reactions, select the fastest one. Be prepared to explain your choice. Assume each reaction occurs by the  $S_N1$  mechanism (even though this may not be a good assumption in reality).



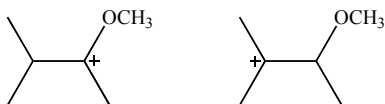


4. In each case, decide whether the reaction proceeds by the  $S_N1$  or the  $S_N2$  mechanism. Draw the reaction mechanism but do not include any transition states.

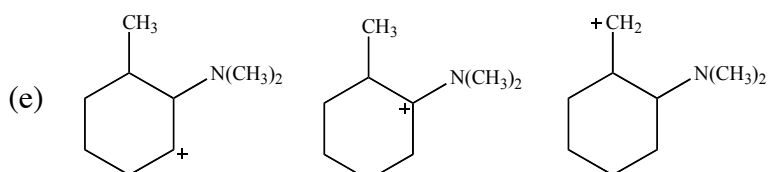
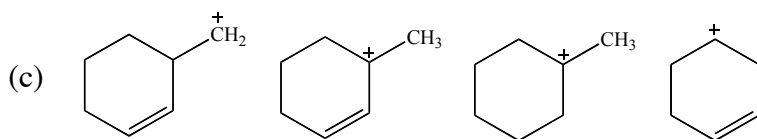
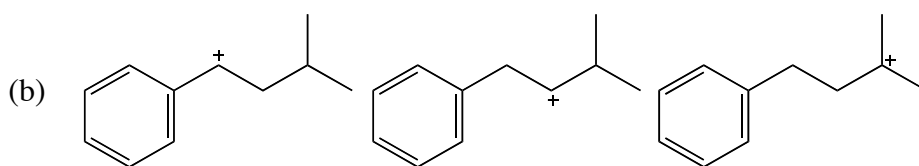
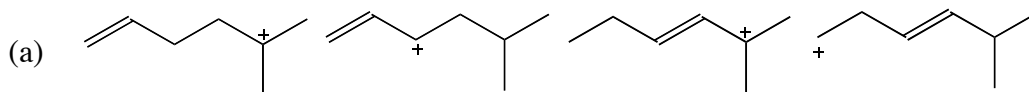


### Practice Problems

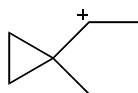
- Briefly but thoroughly explain why a tertiary carbocation is more stable than a secondary carbocation.
- Select the more stable carbocation and briefly explain your choice.



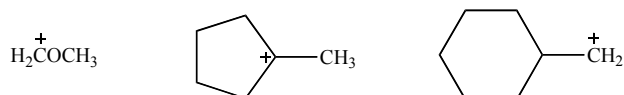
- Select the most stable carbocation in each set.



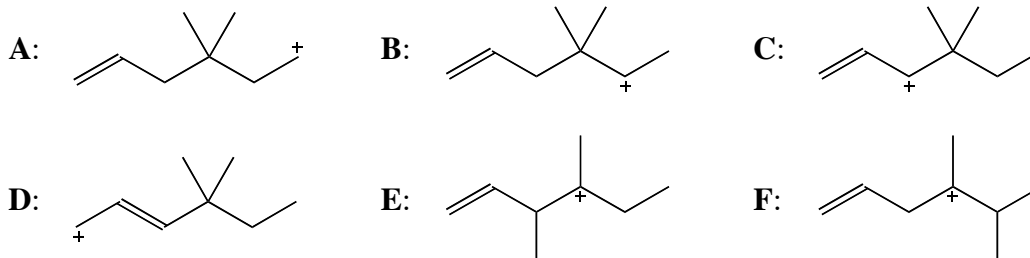
- Use the carbocation shown below to name and illustrate the three common fates of a carbocation. In each case, use curved arrows and specific reagents, and no abbreviations of any type.



- Using each of the following carbocations only once, name and clearly illustrate the three fundamental fates of a carbocation.

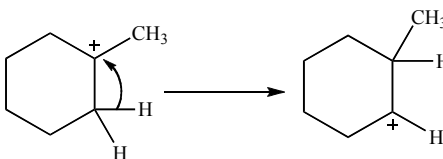


6. Consider the carbocations **A-F**, shown below.

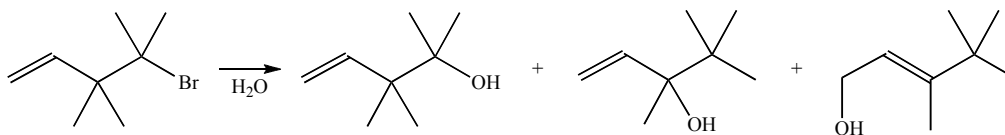


- Arrange these carbocations in order of increasing stability.
- Draw energy profiles for each of the following changes: **A**  $\rightarrow$  **B**; **B**  $\rightarrow$  **F**; **E**  $\rightarrow$  **C**; **A**  $\rightarrow$  **F**; and **C**  $\rightarrow$  **D**. Make sure the carbocation energies (i.e., stabilities) are consistent throughout all the energy profiles.
- Based on your energy profiles, which changes have  $K_{eq} > 1$  (i.e., which changes occur readily)?

7. Does the following mechanism step occur as written, or is something else more likely to occur? Briefly explain your answer.



- Provide definitions of “ $S_N2$  reaction” and “ $S_N1$  reaction” that allows us to distinguish between them based *only* on their written mechanisms, and not on any sort of empirical evidence such as rate studies.
- Draw a detailed curved arrow mechanism that accounts for the formation of all products of the reaction shown below.



- Name the three fundamental requirements for an  $S_N1$  reaction to occur. Briefly describe how each factor controls the rate of an  $S_N1$  reaction. Sample reactions may help clarify your discussions.
- Which reacts slowest in an  $S_N1$  reaction:  $\text{CH}_3\text{I}$ ,  $\text{CH}_3\text{CH}_2\text{I}$ , or  $(\text{CH}_3)_2\text{CHI}$ ?
- Briefly explain why allyl bromide ( $\text{H}_2\text{C}=\text{CHCH}_2\text{Br}$ ) undergoes rapid substitution under either  $S_N1$  or  $S_N2$  reaction conditions.

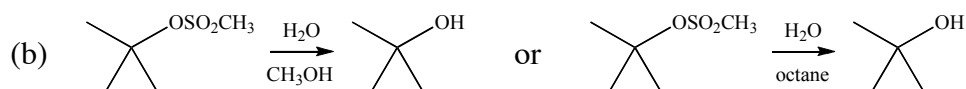
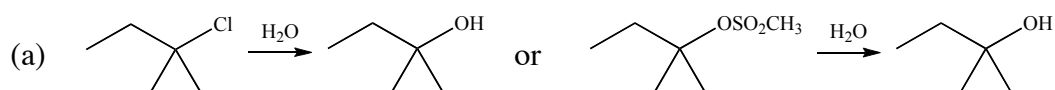
13. Consider reaction of 2-chloropropane with potassium bromide in DMSO, to give 2-bromopropane. Assume it occurs via the  $S_N1$  mechanism.

(a) Using curved arrows, draw the rate-determining mechanism step of this reaction. Briefly explain your choice of rate-determining step.

(b) Draw a potential energy diagram for this endothermic reaction. Label all the important parts of the diagram.

(c) Is the  $S_N1$  mechanism assumption reasonable?

14. For each pair of reactions select the faster reaction. Write a very similar reaction that occurs by the same mechanism but is obviously faster.

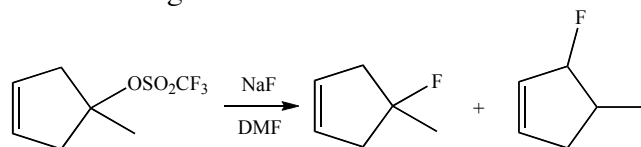


15. For the reaction shown below:

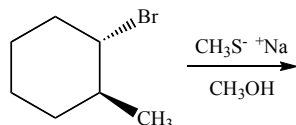
(a) Briefly discuss two reasons why this reaction cannot proceed by the  $S_N2$  mechanism.

(b) Provide a detailed curved arrow mechanism that accounts for the formation of both products. Write "rds" above the reaction arrow for the rate-determining step.

(c) Briefly explain your choice of rate-determining step. Be sure to explain why other steps are not rate-determining.



16. Select the more probable mechanism ( $S_N2$  or  $S_N1$ ), and briefly explain your choice.

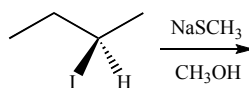


17. For the reaction shown below:

(a) Write the  $S_N2$  mechanism for this reaction.

(b) Write the  $S_N1$  mechanism for this reaction.

(c) Select the more probable mechanism ( $S_N2$  or  $S_N1$ ). Explain your choice.



18. For the reaction shown below:

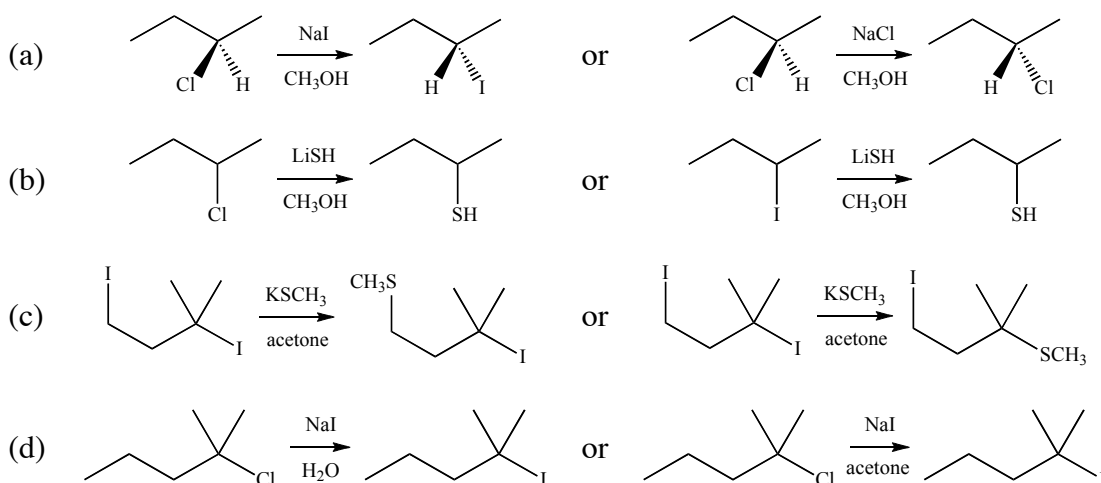
(a) Select the more probable mechanism ( $S_N2$  or  $S_N1$ ). Briefly explain your choice.

- (b) Write the  $S_N1$  mechanism for this reaction.  
 (c) Write a substitution reaction that is very similar, but clearly faster.

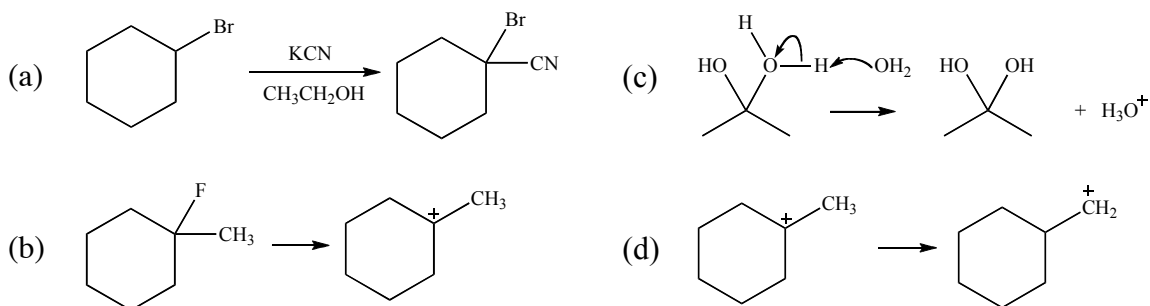


19. For each pair of reactions shown below:

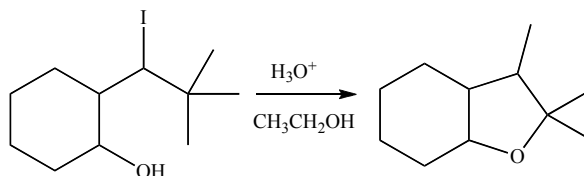
- (i) Decide which reaction is faster. Briefly explain your choice.  
 (ii) Does the faster reaction occur by the  $S_N1$  or  $S_N2$  mechanism? Briefly explain.  
 (iii) Draw a detailed curved arrow mechanism for the faster reaction.  
 (iv) Design a reaction that is similar to, but faster, than the faster reaction of part (i). Briefly explain why your designer reaction is faster.



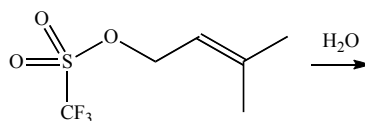
20. Each mechanism step shown below may contain a significant problem or error. Very briefly describe the error, then write the corrected version of the mechanism step. Try to keep your corrected version as close to the original as possible. If nothing is wrong with the step, write "OK." Do not consider missing curved arrows or products.



21. Propose a mechanism.

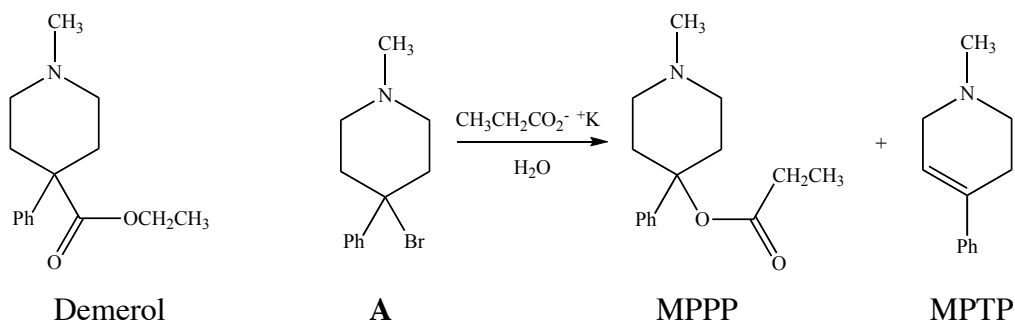


22. Whenever we encounter a carbocation, our “mechanistic mantra” is this: “Every time you see a carbocation in a reaction mechanism, regardless of its origin, consider resonance, then the three fates.” We think about resonance first because it tells us something about the carbocation’s stability (and therefore how easily it can be formed). Resonance must also be considered because different resonance contributors can lead to different products. With this idea in mind, consider this  $\text{S}_{\text{N}}1$  reaction:



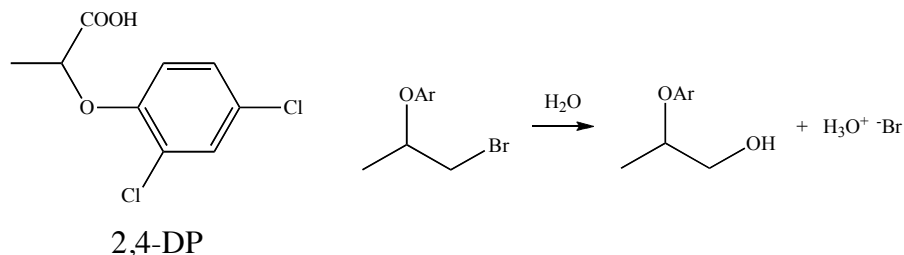
- How readily is the carbocation formed?
- Suggest two products and write the mechanism for their formation.

23. In 1976 an ex-graduate student in Maryland began making his living by selling MPPP (an analog of the analgesic drug Demerol) to heroin addicts. After self-injecting his product, he developed severe symptoms of Parkinson's disease. Chemists found that his meperidine was impure, containing several by-products, including MPTP, which, when independently prepared and injected into primates, caused the same symptoms. (Ironically, this has been one of the most significant advances in Parkinsonism research.) The reaction that forms MPPP and MPTP is shown below.

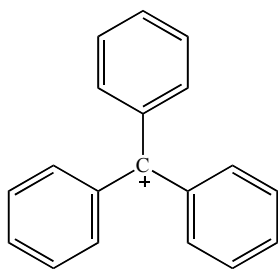


- Provide mechanisms for the formation of MPPP and MPTP from bromide **A**.
- Briefly explain your choice of mechanism for the conversion of **A** into MPPP.
- Based on your mechanism draw the structure of another product that might be formed during the conversion of bromide **A** into MPPP and MPTP.
- Changing only the nucleophile or electrophile (but not both), write a reaction that is similar to, but obviously faster than the conversion of bromide **A** into MPPP.

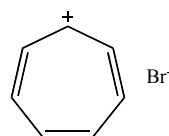
24. 2,4-DP is an herbicide, a chemical that is used to kill plants. A portion of a proposed synthesis of 2,4-DP is shown below. (“Ar” is an abbreviation for an aromatic ring.)



- (a) Very briefly explain why this reaction does not give the primary alcohol shown above.
- (b) Draw the structure(s) of the actual major product(s) of this reaction, and a complete mechanism to show how they are formed.
25. Answer this common student question: Why does the carbon bearing the leaving group have a  $\delta^+$  in the rate-determining transition state for an  $S_N1$  reaction but not for an  $S_N2$  reaction?
26. The  $S_N1$  reaction of 2-iodobutane with methanol gives two products whereas the  $S_N1$  reaction of 3-iodopentane with methanol gives only one product. Explain.
27. Carbocations are generally much too unstable to be reaction products, even resonance-stabilized carbocations such as the triphenylmethyl carbocation. These carbocations satisfy their instability by capturing a nucleophile. The tropylium cation is an exception; the salt tropylium bromide is sufficiently stable that it can be easily isolated and stored. To what does tropylium bromide owe its unusual stability?



Triphenylmethyl carbocation

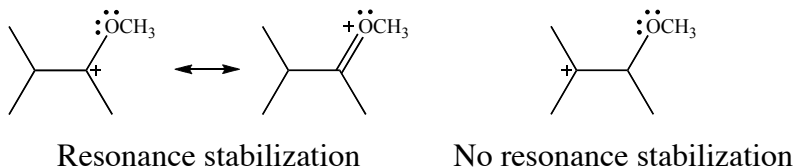


Tropylium bromide

### Practice Problems Solutions

- Carbocations bear a carbon atom with an incomplete octet and a formal charge of +1. This carbon is therefore electron poor, and is stabilized by electron-donating groups. Alkyl groups are weak electron donors. Everything else being equal, a carbocation bearing a greater number of alkyl groups on the electron deficient carbon is more stable. A secondary carbocation has two alkyl groups on this carbon; a tertiary carbocation has three. Thus, a tertiary carbocation is more stable than a secondary carbocation.

2. The carbocation on the left is more stable. In both instances, the carbon bearing the positive charge is attached to three electron-donating groups (alkyl or ether). The ether group is a much better electron donor (by resonance) than an alkyl group (which donates electron density by inductive effects).



3. (a) This is the only carbocation in the set that is 3° with resonance.

- (b) A carbocation that is 2° with resonance is generally more stable than an isomeric carbocation that is 3° and lacks resonance.

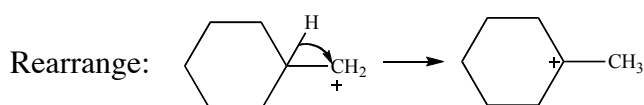
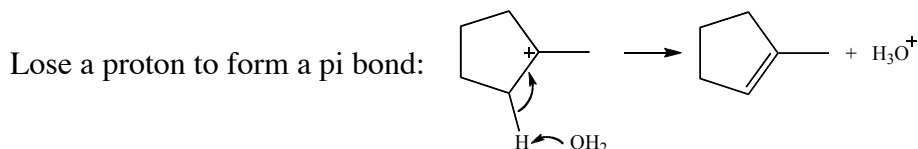
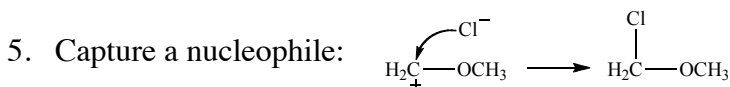
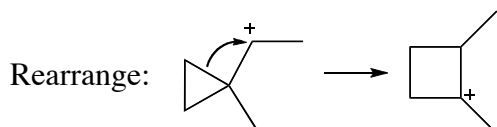
- (c) This is the only carbocation in the set that is 3° with resonance.

- (d)  $\text{H}_2\text{CNH}_2^+$ . All the carbocations in this set are methyl or substituted methyl carbocations. Two have significant resonance and are therefore more stable. The main difference between these two resonance-stabilized carbocations is the atom that supplies the lone pair to complete the carbon atom's octet. Nitrogen is less electronegative than oxygen, and therefore nitrogen shares its electron pair more effectively. Thus  $\text{H}_2\text{CNH}_2^+$  is more stable than  $\text{H}_2\text{COH}^+$ .

- (e) This is the only carbocation in the set that is secondary with resonance (from the nitrogen lone pair).

4. Capture a nucleophile:

- Lose a proton to form a pi bond:

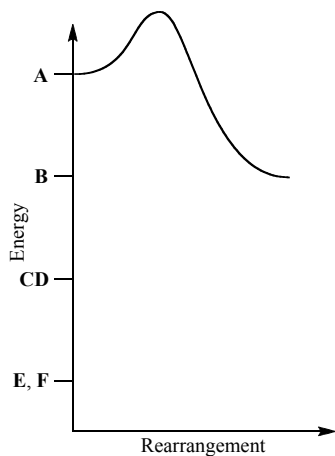


6. (a) Carbocations **C** and **D** are resonance contributors of the same molecule, so we cannot rank their stabilities separately. Instead we will combine them into carbocation **CD**. The stability of **CD** is determined by its resonance hybrid (i.e., the weighted average stability of its resonance contributors). Therefore the stability of **CD** is somewhere between 1° with resonance and 2° with resonance.

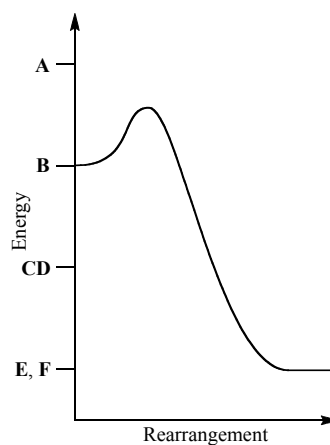
Carbocations **E** and **F** are both 3°, and thus of very similar stability.

The stability ranking is: **A** (least stable) < **B** < **CD** < **E** and **F** (tie for most stable).

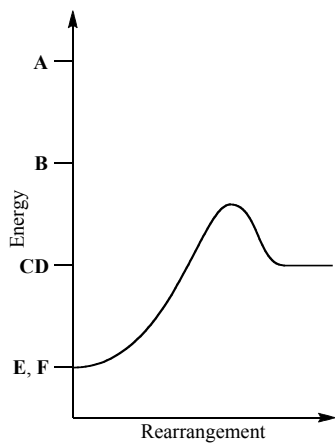
- (b) Just like every other mechanism step, carbocation rearrangements also have transition states and corresponding  $E_{\text{act}}$  values (i.e., one or more humps in the energy profile).



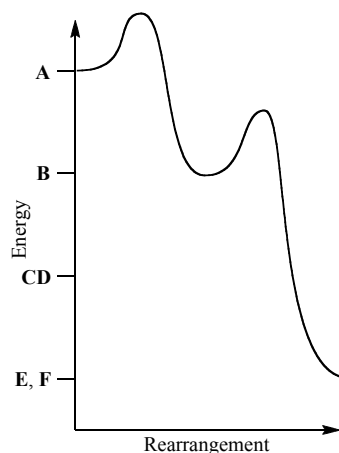
**A → B**



**B → F**



**E → C**



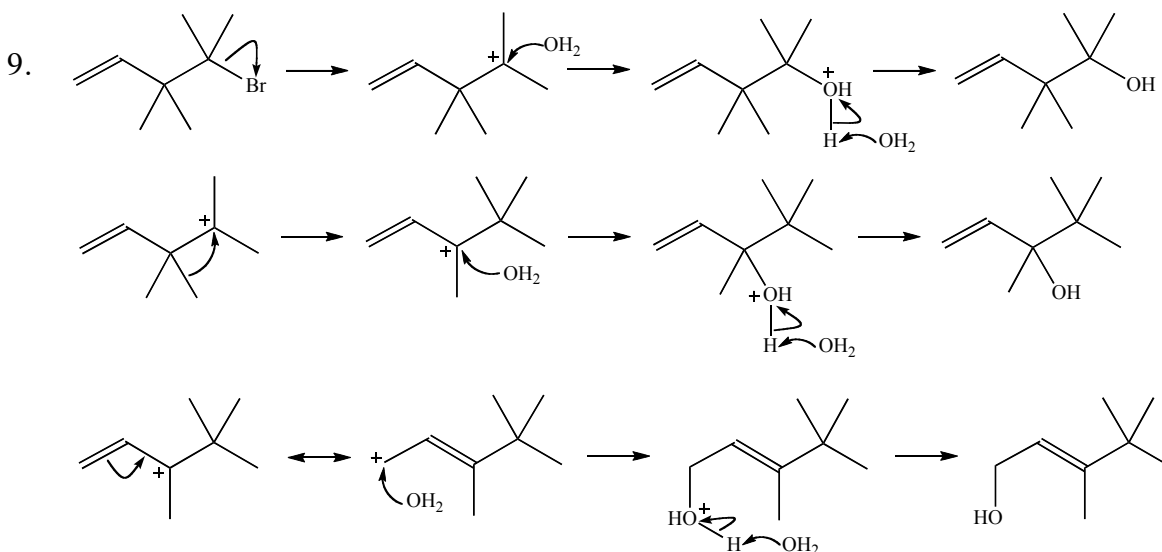
**A → F**

**C → D:** Carbocations **C** and **D** are resonance contributors: different representations of the same structure. Therefore **C** does not rearrange into **D**, or vice versa. In fact, **C** and **D** do not actually exist, and the molecule is actually a resonance hybrid of these structures.

(c)  $K_{eq} > 1$  when the energy of the products is lower than the energy of the reactants (i.e., when the starting carbocation is less stable than the rearranged carbocation). In this case,  $K_{eq} > 1$  for **A** → **B** ( $1^\circ \rightarrow 2^\circ$ ), **B** → **F** ( $2^\circ \rightarrow 3^\circ$ ), and **A** → **F** ( $1^\circ \rightarrow 3^\circ$  in two steps).

7. This mechanism step does not occur as written. This mechanism step is one of the three carbocation fates: the rearrangement of a tertiary carbocation into a secondary carbocation. A secondary carbocation is less stable than a tertiary carbocation, so the rearrangement is unlikely to occur.
8.  $S_N2$  reaction: ionic substitution at an  $sp^3$  carbon in which the carbon to leaving group bond scission occurs simultaneously with carbon to nucleophile bond formation. The reaction does not involve a carbocation.

$S_N1$  reaction: ionic substitution at an  $sp^3$  carbon in which the carbon to leaving group bond scission does not occur in the same mechanism step as carbon to nucleophile bond formation. The reaction involves a carbocation intermediate.



10. **Moderate or better leaving group.** The rate-determining step of an  $S_N1$  reaction is ionization of the leaving group-carbon bond. A better leaving group facilitates ionization, making the reaction go faster.

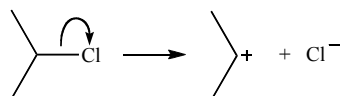
**Stable carbocation.** The rate-determining step of an  $S_N1$  reaction is ionization of the leaving group-carbon bond. A more stable carbocation facilitates ionization, making the reaction go faster.

**Polar solvent.** The rate-determining step of an  $S_N1$  reaction is ionization of the leaving group-carbon bond. A solvent with a higher dielectric constant facilitates ionization by assisting the separation of the ions as well as by stabilizing the leaving group and carbocation, thus making the reaction go faster.

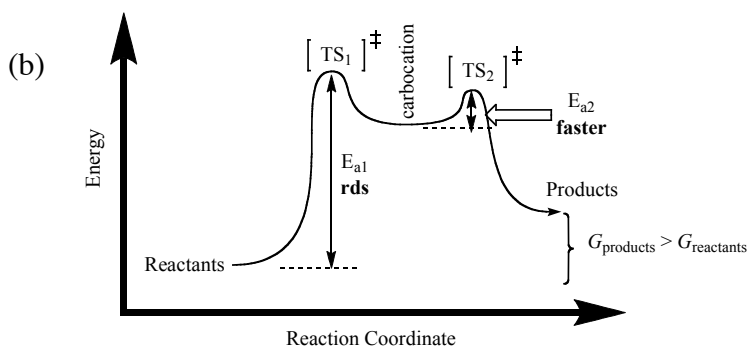
11. The rate-determining step of the  $S_N1$  reaction is ionization of the carbon-leaving group bond to form a carbocation. The reaction is faster when the carbocation is more easily formed, which occurs when the carbocation carbon bearing the positive charge has a greater number of electron donating alkyl groups attached. Thus the  $S_N1$  reaction of methyl iodide, which proceeds via a methyl carbocation, is slower than the similar reaction of ethyl iodide (primary carbocation) or isopropyl iodide (secondary carbocation).

12. Allyl bromide reacts rapidly in an  $S_N2$  reaction because it is a primary halide. It also reacts rapidly in a  $S_N1$  reaction because the corresponding carbocation has resonance stabilization, and is thus easily formed.

13. (a) The rate-determining step of the  $S_N1$  mechanism is the ionization of the carbon-leaving group bond.



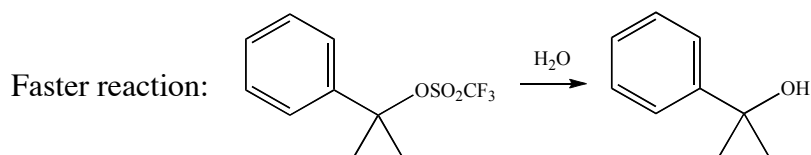
The rate-determining step for any reaction is the step with the highest  $\Delta G^\ddagger$ . By using the approximation  $\Delta G \approx \Delta H$  at lower temperatures, we can determine the rate-determining step by considering the bond changes occurring in each step. The first step, ionization of the carbon-leaving group bond, is endothermic because the C–Cl bond is lost and no new bonds are formed. The second step, capture of bromide ion by the carbocation, is exothermic because the C–Br bond is formed and no bonds are lost. Thus, the ionization of the leaving group has the largest  $\Delta G^\ddagger$  and is rate-determining.



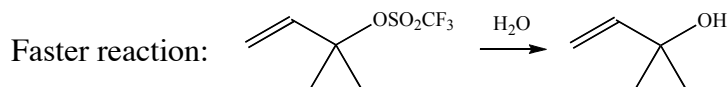
The energy of the products must be higher in energy than the reactants, because the reaction is stated to be endothermic.

(c) For the reaction to proceed by the  $S_N1$  mechanism the  $S_N2$  mechanism must be less favorable and the  $S_N1$  mechanism must be reasonable. The reaction involves a reasonable nucleophile ( $\text{Br}^-$ ), moderate leaving group ( $\text{Cl}^-$ ), a polar aprotic solvent (DMSO), and a secondary carbon. Thus  $S_N2$  is a reasonable reaction pathway. In the  $S_N1$  mechanism, a reasonably stable (secondary) carbocation is involved, a moderate leaving group ( $\text{Cl}^-$ ), and a polar solvent (DMSO). Both reaction mechanisms are reasonable, and neither has an obviously significant advantage. (The actual mechanism in cases like is probably not pure  $S_N2$  or  $S_N1$  but rather something between the two. Saul Winstein of UCLA pioneered this “unified ionic substitution” mechanism.)

14. (a) These reactions must be  $S_N1$  because the substitution is occurring at a tertiary carbon. The difference between the two is the leaving group. Methanesulfonate ion ( $\text{CH}_3\text{SO}_3^-$ ) is a better leaving group than chloride ion because of significant resonance stabilization. Therefore the second reaction is faster. When designing a faster reaction, we can consider a reaction that involves a more stable carbocation (tertiary with resonance), or a better leaving group (trifluoromethanesulfonate, also called triflate,  $\text{CF}_3\text{SO}_3^-$ ). Both factors are incorporated below.



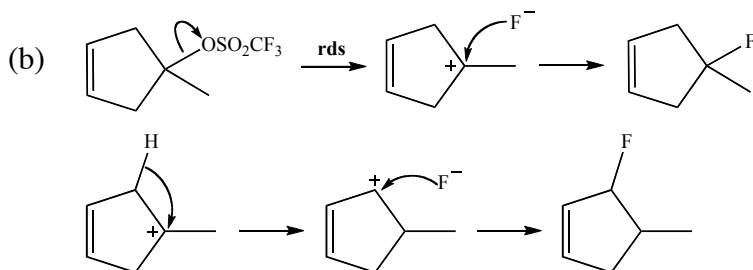
- (b) This reaction must occur by the  $S_N1$  mechanism because the substitution is occurring at a tertiary carbon. The only difference between these two reactions is the solvent. In the  $S_N1$  reaction, a solvent with high dielectric constant ( $\epsilon$ ) is needed to assist ionization of the leaving group to form a carbocation. Methanol ( $\text{CH}_3\text{OH}$ ,  $\epsilon = 33$ ) favors ionization much more than octane ( $\text{CH}_3(\text{CH}_2)_6\text{CH}_3$ ,  $\epsilon \approx 0$ ), so the first reaction is faster. Using a solvent with even greater dielectric constant (water  $\epsilon = 80$ ), use of a better leaving group, or a more stable carbocation intermediate all accelerate the reaction. All of these factors are included in the faster reaction below.



15. (a) Reason #1: Fluoride is a good nucleophile in DMF. This fact does not prevent the  $S_N2$  pathway.

Reason #2: The carbon undergoing substitution is tertiary. The  $S_N2$  reaction cannot proceed on a sterically hindered carbon.

Reason #3: The allyl fluoride product (second product) clearly results from a carbocation rearrangement. There are no carbocations in the  $S_N2$  reaction, so at least some portion of the reactants must proceed through the  $S_N1$  mechanism.



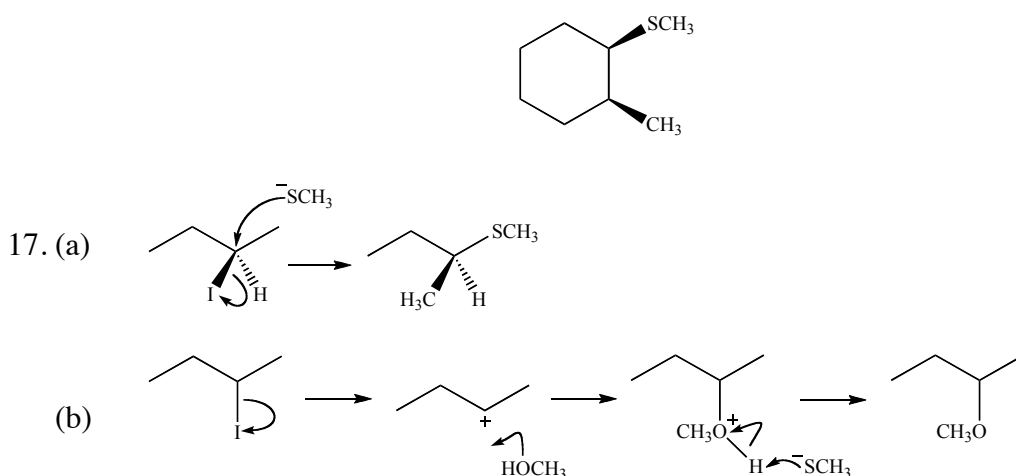
- (c) In the step labeled as rds, triflate leaves and no new bonds are formed. In all other steps, bonds are formed. Thus, ionization is the most energetically expensive step, and thus the slowest.

16. There are two possible ionic substitution mechanisms for this reaction,  $S_N2$  and  $S_N1$ . The  $S_N2$  mechanism avoids carbocation formation, so (generally speaking) is energetically less expensive than  $S_N1$ . (If  $S_N2$  were always energetically less expensive than  $S_N1$ , then ionic substitution reactions would always occur by the  $S_N2$  mechanism and never by the  $S_N1$  mechanism.) If the requirements for the  $S_N2$  mechanism are met, then it is most probable that the substitution proceeds by this pathway. The  $S_N2$  requirements are:

- Moderate or better leaving group: Bromide is a moderate leaving group.

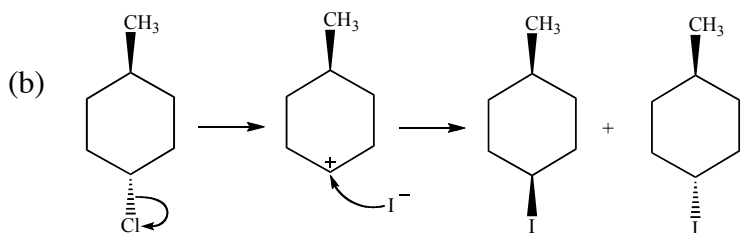
- Good nucleophile: Methanethiolate ( $\text{CH}_3\text{S}^-$ ) is a reasonable nucleophile due to the low electronegativity of sulfur (which is somewhat counteracted by its large atomic radius).
- Not tertiary: The carbon undergoing substitution is secondary, but has some  $\beta$ -branching (the methyl group) that slows it somewhat.
- Solvent: The solvent is polar and protic. The proticity slows the reaction, but does not necessarily prevent it from occurring.

The  $\text{S}_{\text{N}}2$  requirements are reasonably met, so the reaction probably proceeds via the  $\text{S}_{\text{N}}2$  mechanism, providing the product shown below. Note inversion of stereochemistry at the carbon undergoing substitution.



Methanethiolate ( $\text{CH}_3\text{S}^-$ ) is a stronger nucleophile than methanol. However, recall that a carbocation is highly reactive and therefore not very selective in what nucleophile it captures. There is a higher probability the carbocation will capture the solvent ( $\text{CH}_3\text{OH}$ ) because it is more prevalent.

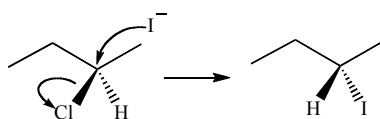
- (c) We consider  $\text{S}_{\text{N}}2$  before  $\text{S}_{\text{N}}1$  because the former is less energetically expensive (no carbocations are formed).  $\text{S}_{\text{N}}2$  requires moderate or better leaving group ( $\text{I}^-$ ), good nucleophile ( $\text{H}_3\text{CS}^-$ ), and not tertiary (is secondary in this case). All of these requirements are met, so the reaction proceeds via the  $\text{S}_{\text{N}}2$  mechanism. The solvent ( $\text{CH}_3\text{OH}$ ) is polar and protic. These factors slow (but do not prevent) the  $\text{S}_{\text{N}}2$  pathway.
18. (a) When deciding between  $\text{S}_{\text{N}}2$  and  $\text{S}_{\text{N}}1$ , we consider  $\text{S}_{\text{N}}2$  first, because it is energetically less expensive (no carbocation is involved).  $\text{S}_{\text{N}}2$  requires a moderate or better leaving group ( $\text{Cl}^-$  is a moderate leaving group), good nucleophile ( $\text{I}^-$  is a moderate nucleophile), and low steric hindrance (not tertiary; the molecule in question is secondary). All of these conditions are met, so the reaction proceeds by the  $\text{S}_{\text{N}}2$  mechanism. The solvent (acetone) is just barely polar ( $\epsilon = 21$ ) and aprotic, factors that also favor the  $\text{S}_{\text{N}}2$  mechanism.



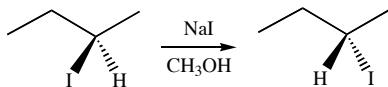
(c) There are many possible answers, including changing to a better leaving group (shown below).



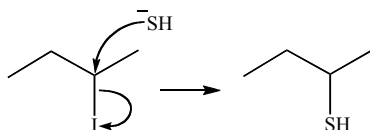
19. (a) The first reaction is faster because iodide is a better nucleophile than chloride in a protic solvent. This reaction has a good nucleophile and a 2° alkyl halide, so it probably occurs by the  $S_N2$  mechanism, which is shown below.



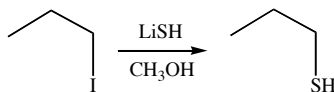
Replacing chloride with a better leaving group (iodide) makes the reaction faster:



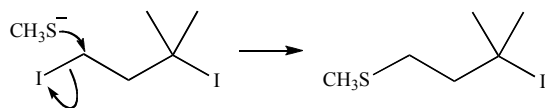
(b) The second reaction is faster, because iodide ion (larger atomic radius) is a better leaving group than chloride ion. The reaction occurs by the  $S_N2$  mechanism because it involves a good nucleophile and a 2° alkyl halide. The mechanism is shown below.



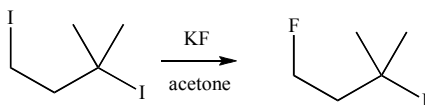
Replacing the 2° halide with a 1° halide makes an  $S_N2$  reaction go faster, because of less steric hindrance to nucleophilic attack:



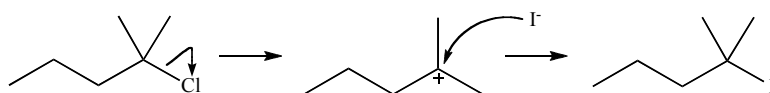
(c) The first reaction occurs more quickly. Given a choice between  $S_N1$  and  $S_N2$ ,  $S_N2$  is preferred (if possible) because it is the less energetically expensive reaction pathway.  $S_N2$  can occur here (1° alkyl halide, more effective leaving group and better nucleophile). The mechanism is shown below.



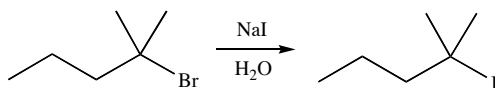
Changing  $\text{CH}_3\text{S}^-$  into  $\text{F}^-$  (in aprotic solvent, a better nucleophile) makes the reaction faster.



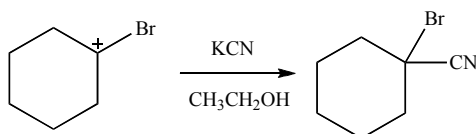
- (d) The first reaction is faster. This reaction must occur by the  $\text{S}_{\text{N}}1$  mechanism ( $3^\circ$  alkyl chloride). The  $\text{S}_{\text{N}}1$  mechanism occurs more readily in more polar solvents, which assist ionization of the leaving group in the first and rate-determining step of the reaction. The mechanism is shown below:



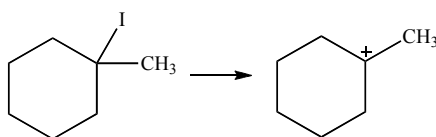
The reaction is faster when chloride is changed to bromide, a better leaving group:



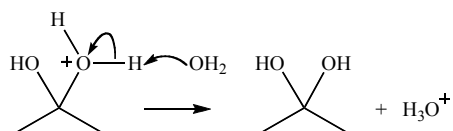
20. (a) This addition cannot occur, because the carbon atom that gains the CN already has a full octet. Solution: remove the H so the carbon has an incomplete octet (shown below) or show the Br leaving (an  $\text{S}_{\text{N}}2$  reaction).



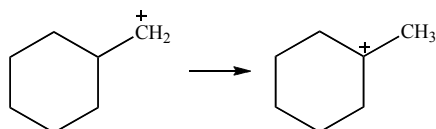
- (b) Fluoride ion is a very poor leaving group. Solution: fluoride can leave if the resultant carbocation is *very* stable or the fluoride is changed to a better leaving group such as iodide (shown below).



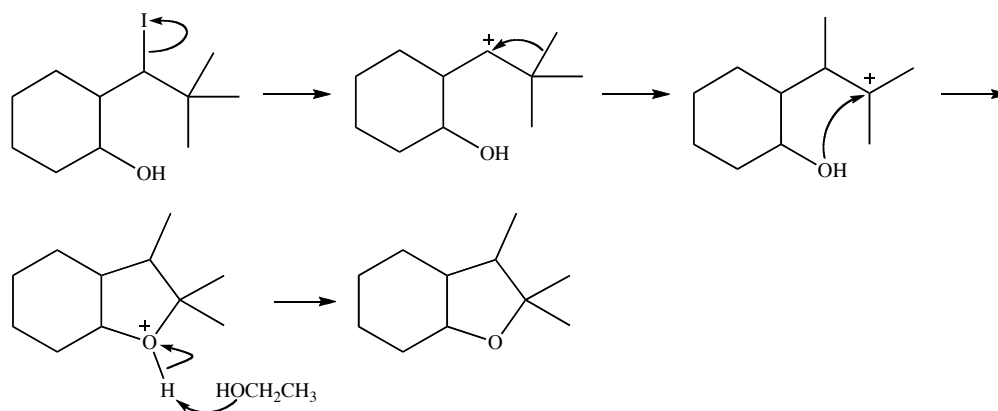
- (c) The oxygen bearing two hydrogens is missing a formal positive charge. Solution: include the positive charge (shown below) or remove one of the hydrogen atoms.



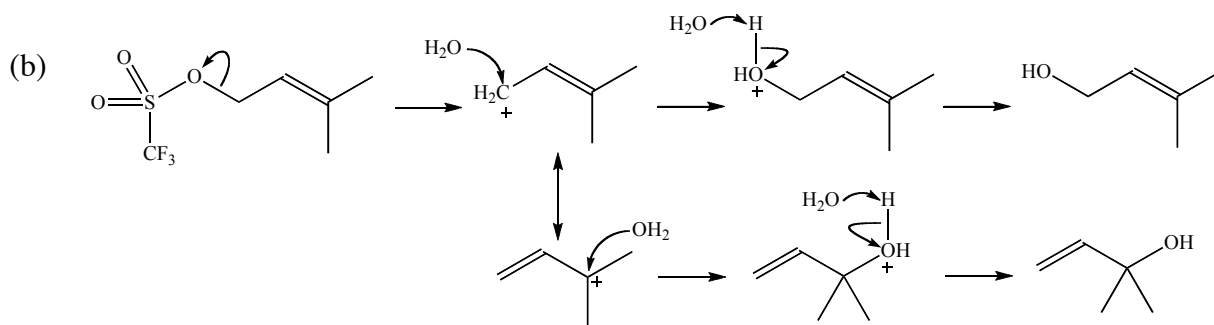
- (d) This is a very unlikely (although not impossible) rearrangement, as the carbocation is becoming less stable. Solution: modify the structure so that the rearrangement product is more stable than the initial tertiary carbocation or reverse the direction of the rearrangement (shown below).

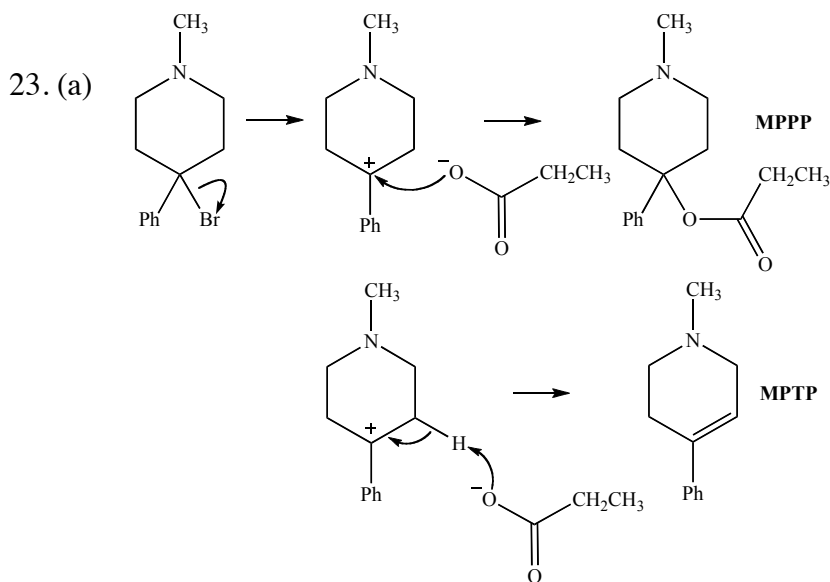


21. The skeletal rearrangement suggests that this reaction involves a carbocation.



22. (a) The more important resonance contributor of the carbocation is tertiary with resonance (as shown below). This is the most stable category of carbocations, and therefore the easiest to form.



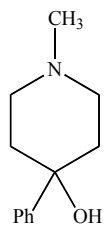


(b) The conversion of **A** into MPPP is a reaction involving substitution at carbon, for which the mechanism choices are  $S_N2$  and  $S_N1$ .  $S_N2$  is considered first because it avoids the highly endothermic carbocation formation step.  $S_N2$  requires:

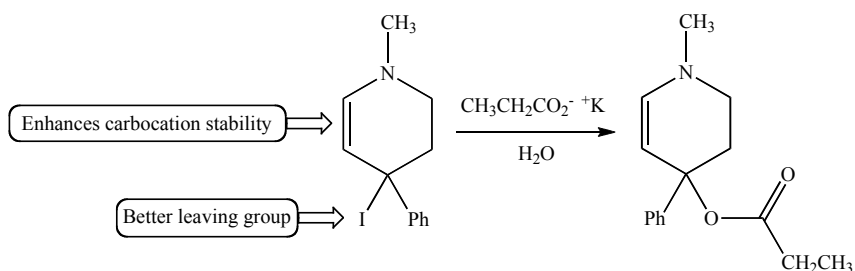
- Good nucleophile ( $\text{CH}_3\text{CH}_2\text{CO}_2^-$  is a modest nucleophile due to small atomic radius but high electronegativity of oxygen and charge stabilization by resonance),
- Moderate or better leaving group ( $\text{Br}^-$  is a moderate leaving group due to atomic radius and electronegativity),
- The carbon undergoing substitution must not be tertiary (the carbon bearing the bromine is tertiary), and
- A moderately polar, aprotic solvent (for most  $S_N2$  reactions; water is very polar and strongly protic which disfavors this particular  $S_N2$  reaction).

Because the steric hindrance and solvent requirements are not met, the reaction cannot proceed by the  $S_N2$  mechanism. This does not automatically mean the reaction must be  $S_N1$  by default; we must see if  $S_N1$  is still possible. The  $S_N1$  requirements are moderate or better leaving group (bromide is a moderate leaving group), stable carbocation (the carbocation formed by departure of the bromide is tertiary with resonance), and polar solvent (water is very polar). Thus  $S_N1$  is a reasonable choice for reaction mechanism.

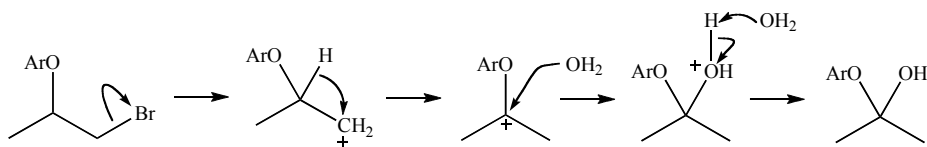
(c) Any other product derived from the intermediate carbocation is reasonable. The most obvious is the benzylic alcohol shown below, derived from capture of water by the carbocation.



- (d) Changing the rate of this reaction means manipulating the rate-determining step. The rate-determining step is ionization of the carbon-bromine bond to form a carbocation. This step does not involve the nucleophile so changing the nature of the nucleophile does not change the reaction rate to any significant extent. Using a better leaving group (iodide ion instead of bromide ion) or a more stable carbocation (one with more resonance) makes the reaction faster. Both of these changes have been incorporated below.

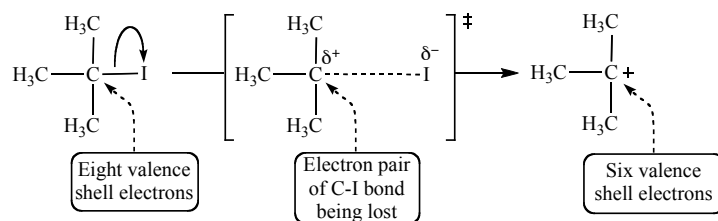


24. The reaction must proceed by either an  $S_N2$  or  $S_N1$  mechanism. We can eliminate  $S_N2$  because water is a poor nucleophile and bromide is simply not a good enough leaving group to overcome this. If the reaction proceeded via the  $S_N1$  mechanism, the primary carbocation quickly rearranges to a carbocation that is secondary with resonance (from the ether oxygen). Capture of water by this carbocation leads to an alcohol as shown below.

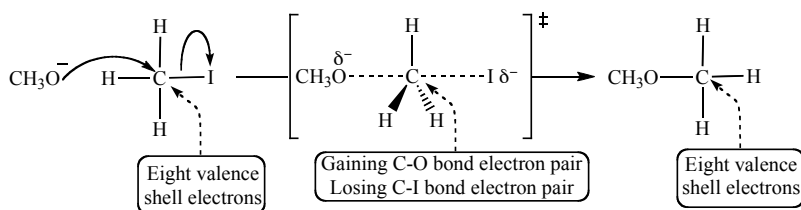


25. A  $\delta^+$  charge indicates the carbon has an electron density that is somewhere between no formal charge and a +1 formal charge. In a transition state, this occurs because the number of valence electrons on the carbon changes.

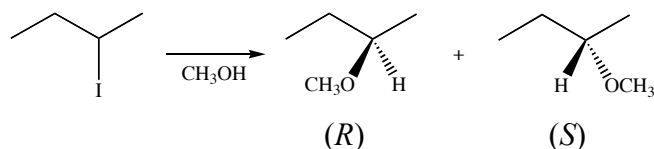
$S_N1$  case: The carbon starts with a full octet (no formal charge) and loses a pair of electrons (because of bond breaking) without gaining them back (by bond formation). It ends up with six valence electrons (a carbocation; formal charge of +1). In this case the carbon has a  $\delta^+$  in the transition state (a point intermediate between a full octet and an open octet).



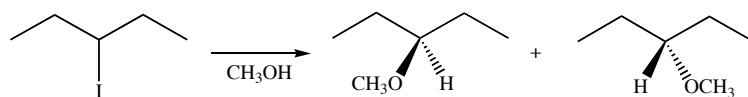
S<sub>N</sub>2 case: The carbon's valence electron count does not change, because it starts with a full octet and ends up with a full octet as well. Therefore we do not draw  $\delta^+$  next to this carbon in the transition state.



26. S<sub>N</sub>1 reaction of 2-iodobutane with methanol gives a mixture of (*R*)-2-methoxybutane and (*S*)-2-methoxybutane. This is true regardless of whether we start with pure (*R*)-2-iodobutane or pure (*S*)-2-iodobutane or a mixture of these.



S<sub>N</sub>1 reaction of 3-iodopentane with methanol gives just one product because methanol attack on either face of the carbocation leads to the same product, 3-methoxypentane. (Verify with models!) This molecule does not have a stereocenter so only one stereoisomer is possible.



These products are identical.

27. The tropylium cation is aromatic. Capture of a nucleophile converts an  $sp^2$  carbon into an  $sp^3$  carbon, thereby breaking the closed  $p$  orbital loop, and destroying aromaticity. Thus tropylium bromide is more stable as an aromatic salt than a nonaromatic, covalent-bonded molecule.