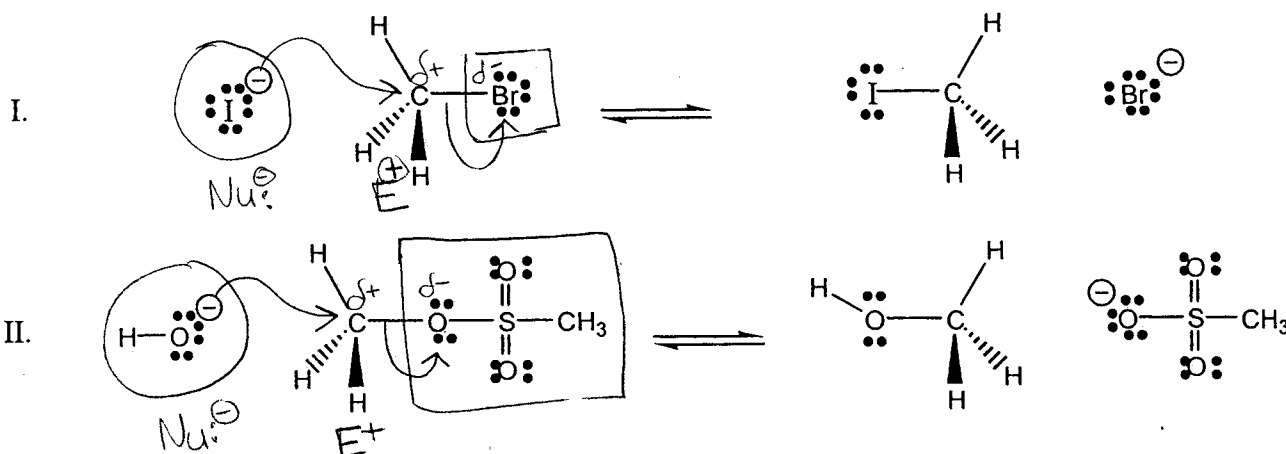


Key
SPTIChemActivity 12**Part A: One-Step Nucleophilic Substitution**

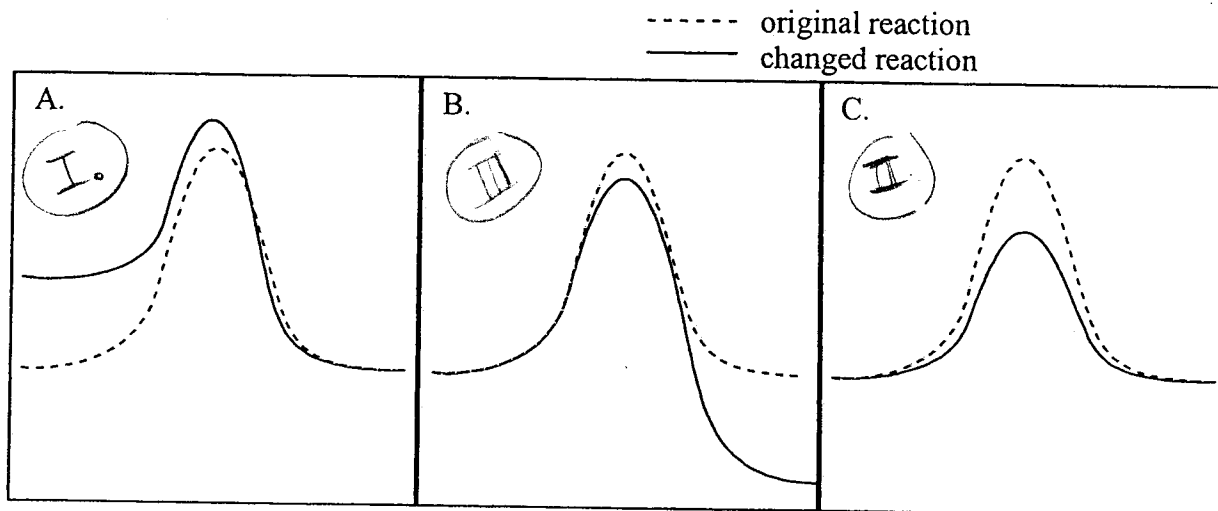
(What are the characteristics of a good leaving group?)

Model 1: One-Step Nucleophilic Substitution Reaction**Critical Thinking Questions**

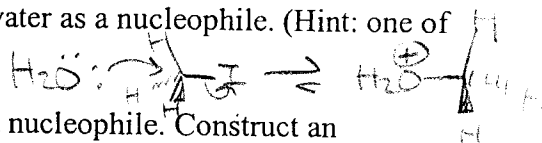
- The two reactions in Model 1 are substitution reactions. In each, an “incoming group” displaces a “leaving group.”
 - Circle each “incoming group” among the reactants in Model 1.
 - Put a box around each leaving group among the reactants in Model 1.
 - Can leaving groups and incoming groups consist of more than one atom? **NO**
- Add a δ^+ and a δ^- to the carbon containing reactants in Model 1 so as to indicate which way the C–LeavingGroup bond is polarized.
- Use curved arrows to illustrate a one-step mechanism that will accomplish each substitution reaction in Model 1. (Hint: you will need to draw more than one arrow for each reaction.)
- “Phile” = “lover of.” (For example: an “anglophile” = a lover of anglo culture).
 - The charge on a nucleus is **(+)** or **(-)** [circle one].
 - A **nucleophile** is an atom that loves to make a bond to another atom with excess **(+ charge)** or **(- charge)** [circle one].
 - For each reaction in Model 1, write the word **nucleophile** below the atom among the reactants that is acting as a nucleophile. **Nu:⊖**
 - Label each atom among the reactants in Model 1 that is acting as an **electrophile** (“electron lover”) and explain your reasoning. **E(+)**

6. Each energy diagram below shows two reaction profiles. The dotted line shows the original reaction, the solid line show the reaction after a change has been made. Match each of the following changes with the correct energy diagram below.

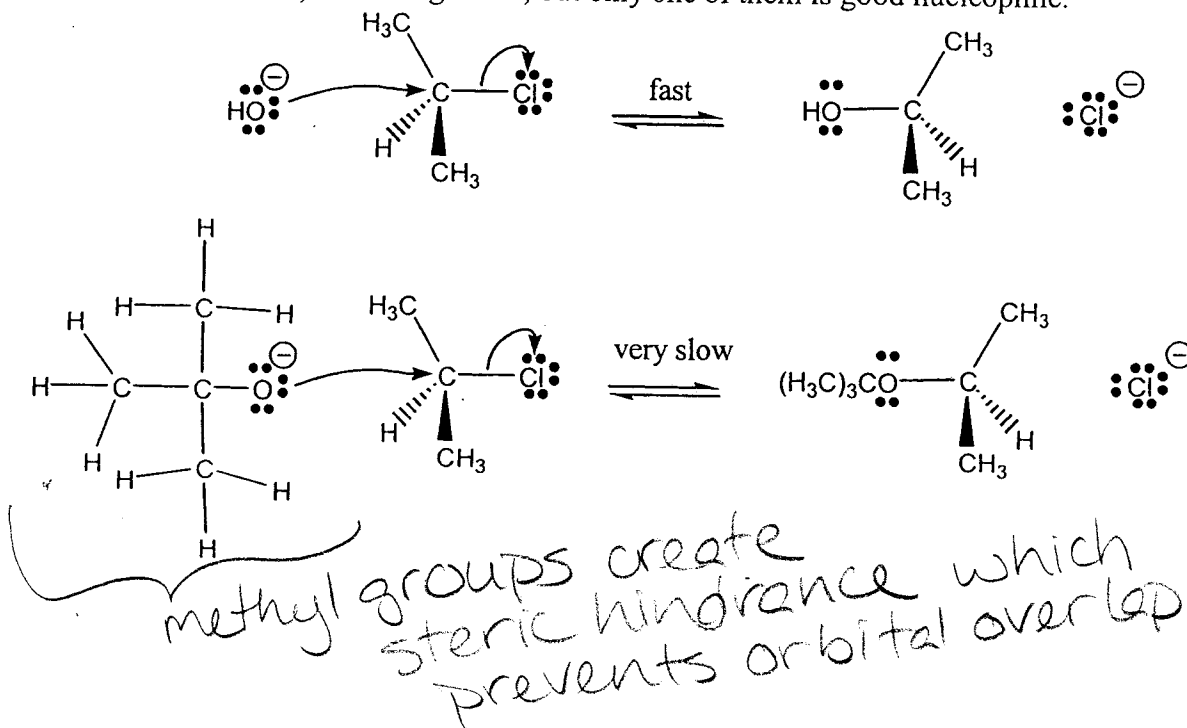
- I. Change to a better nucleophile.
- II. Change from a secondary electrophilic C to a primary electrophilic C.
- III. Change to a better leaving group.



7. Draw the reaction shown in Model 4 using water as a nucleophile. (Hint: one of the products will have a +1 formal charge.)



8. In general a strong base (high P.E.) is a good nucleophile. Construct an explanation for the following exception. Both nucleophiles shown (hydroxide and *tert*-butoxide) are strong bases, but only one of them is good nucleophile.



9. There are also weak bases (low P.E.) that are very good nucleophiles. The explanation for this is mostly beyond the scope of this course. Please know that in each column of the periodic table, nucleophilicity increases as you go DOWN. This means that HS^- is a stronger nucleophile than HO^- , and that I^- is the strongest nucleophile among the halogens. (Interestingly, I^- is also the best leaving group among the halogens!)

In brief, larger atoms have larger orbitals. Nucleophiles with large orbitals are called "soft" bases because they have big fluffy orbitals. Counterexample: A nucleophile like F^- is very small and is a "hard" base. Soft nucleophiles are malleable and tend to make lower energy transition states, thus fast substitution reaction rates.

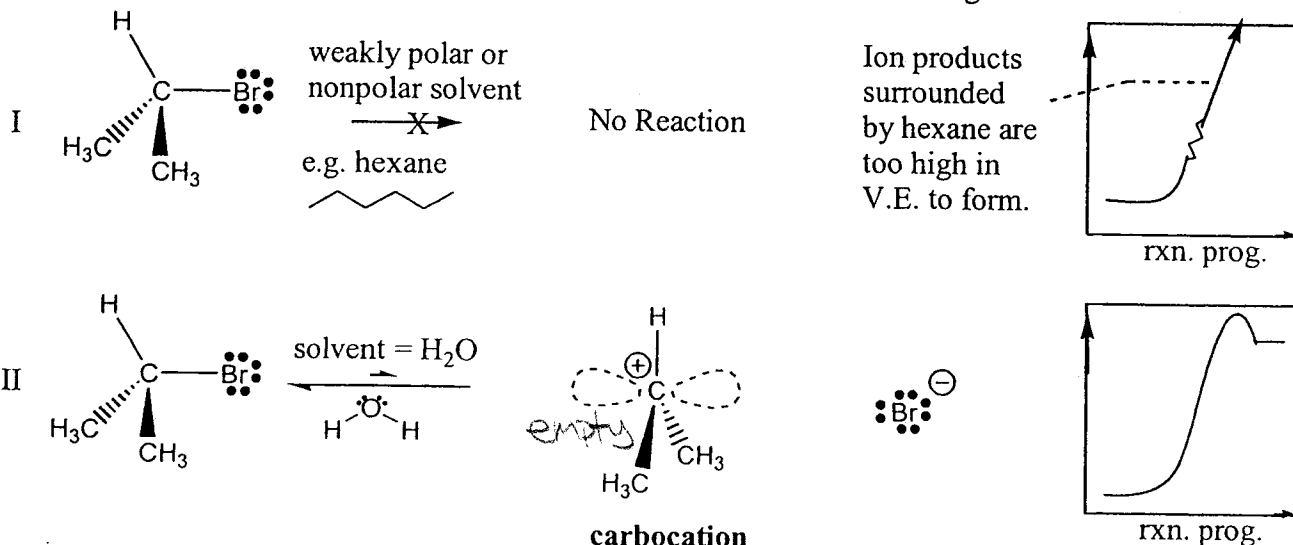
ChemActivity 13

Part A: Carbocations

(Which types of carbocations are most likely to form, and which types never form?)

Model 1: Carbocation Formation

- Polar solvents are very good at stabilizing + and - ions.
- In a polar solvent a good leaving group (X) can spontaneously leave, creating a C^+ ion and an X^- ion.
- Even in a very polar solvent such as water the vast majority of the C—X bonds remain intact because breaking the C—X bond is an uphill process.
- A carbon with a + charge is called a **carbocation**
- A carbocation is reactive and short lived because there is a C lacking an octet.

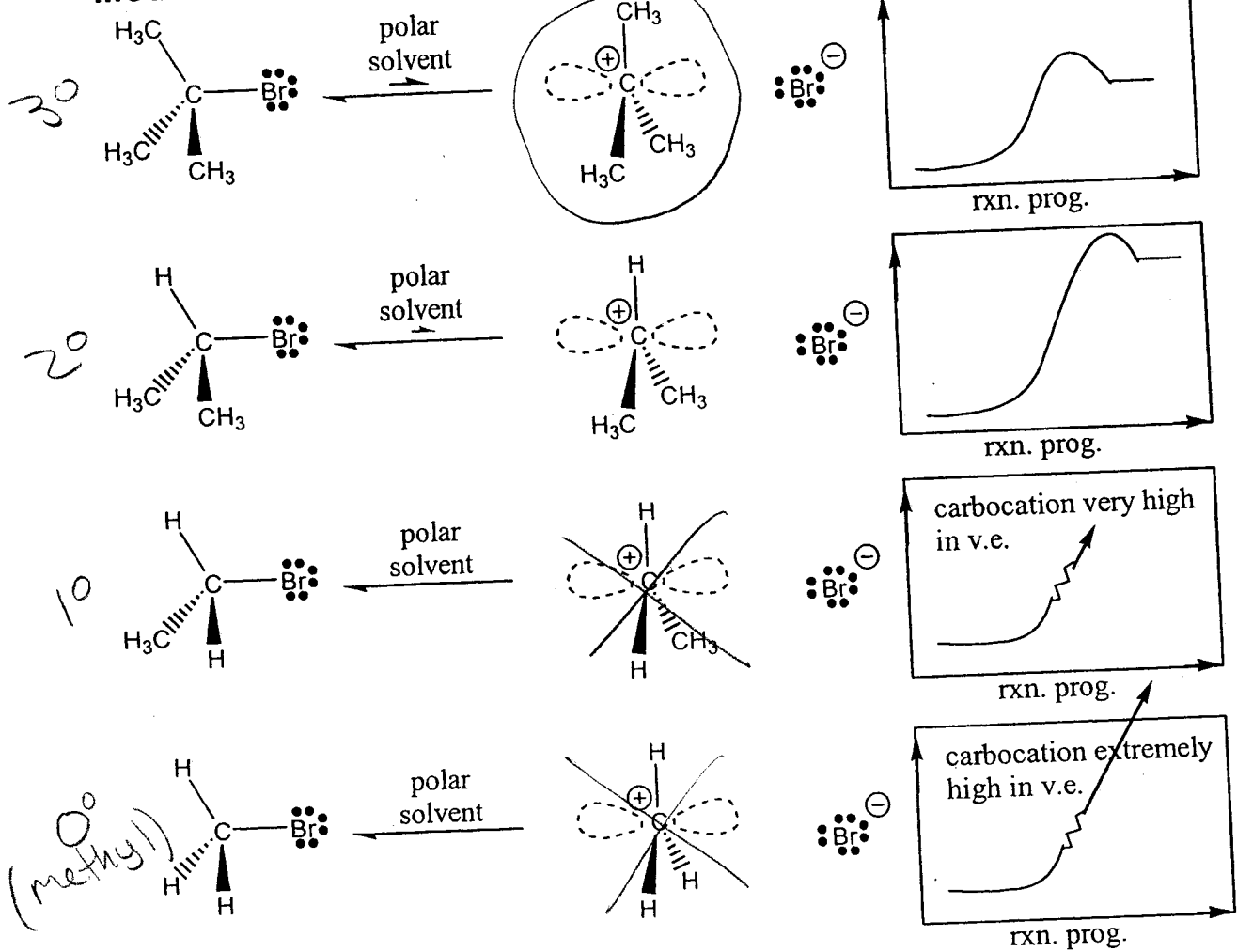


Critical Thinking Questions

- Consider the carbocation in Model 1.
 - Is the $\angle CCC$ bond angle closest to: 109.5° , 120° , or 180° [circle one]?
 - What is the shape of the + charged carbon of a carbocation? *trigonal planar*
 - What is the **hybridization state** of carbon in a carbocation? *sp^2*
 - How many electrons occupy the *p* orbital? Label the *p* orbital shown in Model 1 with the words “full,” “empty,” or “half-full” as appropriate.
 *$0 e^-$ occupy the *p* orbital*
 - Normally, we expect an atom with a + charge to be stable, unreactive and low in potential energy. A carbocation is short lived, reactive and “unhappy”. What does a carbocation lack which might make it “unhappy?”
an octet
- Based on the reaction arrows in Reaction II, there are more reactants or products) [circle one] in the reaction mixture at equilibrium?

Model 2: Carbocation Stability

easiest to form



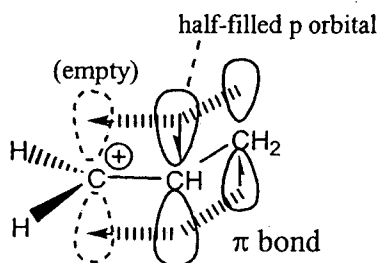
Critical Thinking Questions

- Label each carbocation in Model 2 as 3°, 2°, 1° or methyl (there is one of each).
- Based on the energy diagrams above, circle the carbocation in Model 2 that is easiest to form (requires the smallest input of energy to break the C-Br bond)?
- Based on the reaction arrows above, put an X through the two carbocations in Model 2 that are least likely to form, even in water. (Little convincing evidence for these carbocations has been observed in a chemical reaction.)
- Choose the statement which best explains why the carbocation you circled in CTQ 4 is closest to having an octet.
 - Methyl groups on a carbocation inductively donate electrons to the + charged carbon (**methyl groups are electron donating groups**).
 - Methyl groups on a carbocation inductively withdraw electron density from the + charged carbon (**methyl groups are electron withdrawing groups**).

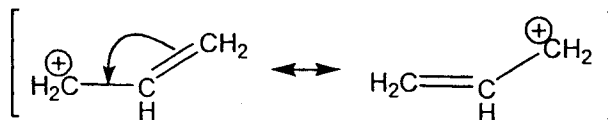
*

Model 3: Conjugation (Resonance Stabilized Carbocations)

- The $\frac{1}{2}$ filled p orbital of a π bond can donate electron density into a neighboring empty p orbital of a carbocation (see below, LEFT).
- This strong orbital overlap is called **conjugation** and can be represented using resonance structures (see below, RIGHT).
- An **allyl carbocation** has a + charge next to a double bond.



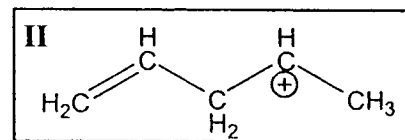
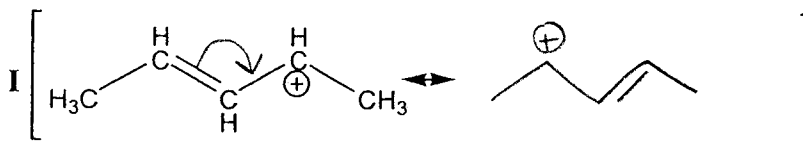
orbital description of
allyl carbocation



resonance description of
allyl carbocation

Critical Thinking Questions

7. Consider the two carbocations below.



- Use a curved arrow to generate a second resonance structure for I.
- Are there other resonance structures for II? *NO*
- In which carbocation (I or II) are the pi electrons more delocalized.
- Is your answer above consistent with the fact that carbocation I is much lower in potential energy than carbocation II? *yes*

Part B: Two-Step Nucleophilic Substitution Reactions

(What molecules are likely to undergo two-step nucleophilic substitution reactions?)

Model 4: Rate Limiting Step

- The higher the concentrations of species involved in a step, the faster that step since the rate of collisions between the reactants is increased.
- A significant increase in the overall rate of reaction is only achieved if you speed up the slow step. (Also known as the "rate limiting step.")

Critical Thinking Questions

8. Consider the following example:

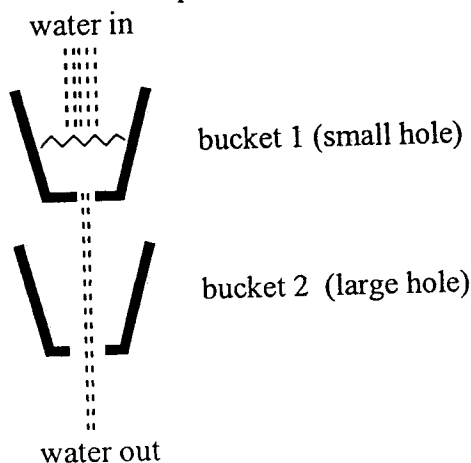
- You have two buckets.
- Each has a hole in the bottom.

a) Which bucket is the "rate limiting step" in this overall process? Explain.

bucket 1

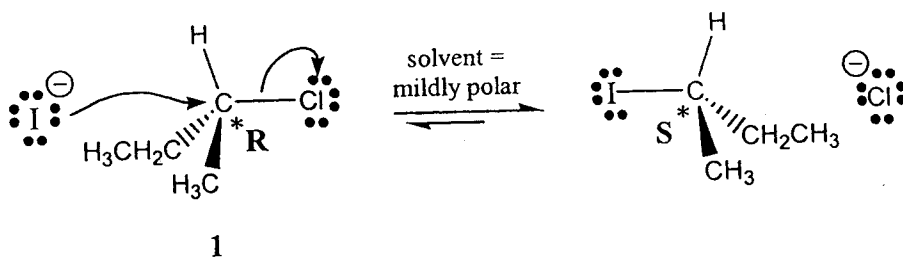
b) Would increasing the size of the hole in the second bucket have a significant impact on the overall rate of water out?

NO

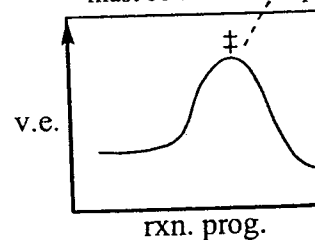


9. If a reaction has only one step, this one step must be the rate-limiting step (the slow step). The data in Table 4a confirms that both the nucleophile and electrophile are involved in this one (slow) step. Explain how the data tell you this.

see below



only one step so it must be the slow step!


Table 4a: Effect of Concentration on Rate for One-Step Substitution

[I ⁻] (nucleophile)	[molecule 1] (electrophile & leaving group)	Relative Rxn. Rate
1 M	1 M	1
2 M	1 M	2
1 M	2 M	2
2 M	2 M	4

Doubling [Nu⁻] Doubles the Rxn Rate
Doubling [E⁺] Doubles the Rxn Rate

10. Consider a **two-step** nucleophilic substitution reaction:

- According to the reaction diagram below, which is the slow step in a two-step nucleophilic substitution reaction: **step 1** or **step 2** [circle one]? (Recall that the slow step is always the step with the higher activation barrier.)
- According to the data in Table 4b which species are involved in the slow step of this reaction? [circle all that apply]: **nucleophile**; **electrophile-L.G.**
- To the box below, add a curved arrow to illustrate how the **S** stereoisomer product could be generated in step 2 of this reaction. Label this arrow "**S forming**."
- Draw a second arrow showing how the **R** stereoisomer is formed and label this arrow "**R forming**."

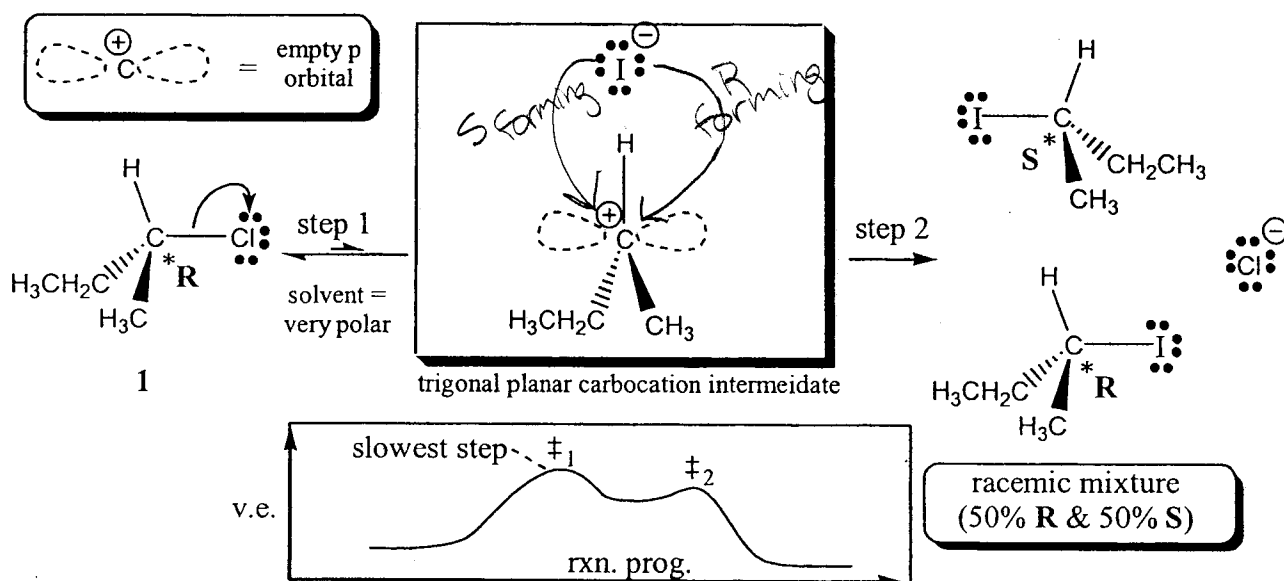


Table 4b: Effect of Concentration on Rate for Two-Step Substitution

$[\text{I}^-]$ (nucleophile)	[molecule 1] (electrophile&leaving group)	Relative Rxn. Rate
1 M	1 M	1
2 M	1 M	1
1 M	2 M	2
2 M	2 M	2

11. The book calls...

a **one-step** substitution reaction a "**S_N2** reaction," and

a **two-step** substitution reaction a "**S_N1** reaction."

The "**S_N**" stands for "**substitution, nucleophilic**," but the 1 and 2 seem to be backwards. To what are the "1" and "2" referring? (Hint: how many species are involved in the slow step of each?)

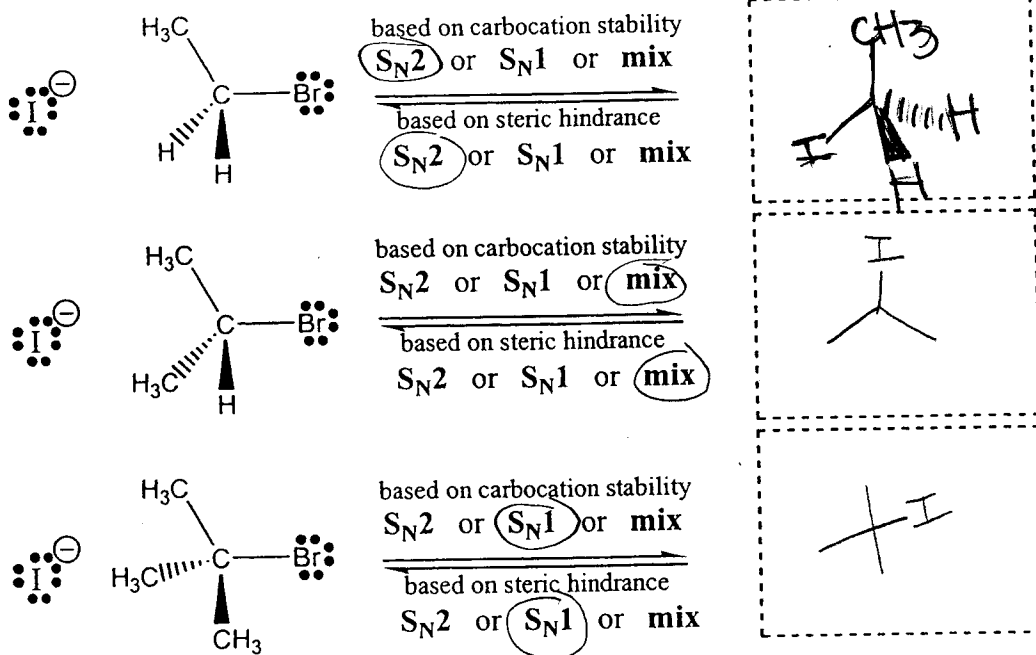
1 = unimolecular transition state in the rate limiting step

2 = bimolecular transition state in the rate limiting step

60

12. A nucleophilic substitution reaction starts with pure R starting material and yields pure S product. Based on this information alone you can tell that the reaction was... one-step or two-step [circle one].
13. A nucleophilic substitution reaction starts with pure R starting material and yields a racemic mixture of R and S products. Based on this information alone you can tell that the reaction was... one-step or two-step [circle one].
14. In a polar solvent, one pair of reactants below...
- goes to products exclusively by a S_N2 mechanism,
 - goes exclusively by a S_N1 mechanism,
 - goes by a mixture of S_N2 and S_N1 mechanisms.

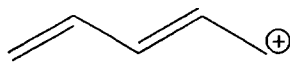
- a) Based on **carbocation stability** (alone), which reaction is least likely to go by an S_N1 mechanism? [circle S_N2 above this reaction arrow]
- b) Based on **carbocation stability** (alone), which reaction is most likely to go by an S_N1 mechanism? [circle S_N1 above this reaction arrow]
- c) Based on **sterics** (alone), which reaction is least likely to go by an S_N1 mechanism? [circle S_N2 below this reaction arrow]
- d) Based on **sterics** (alone), which reaction is most likely to go by an S_N1 mechanism? [circle S_N1 below this reaction arrow]
- e) Based on each factor, which reaction is most likely to be a mix of S_N2 and S_N1 mechanisms? [circle "mix" above/below this reaction arrow]



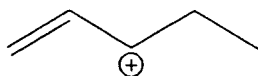
15. Are **carbocation stability factors** and **steric factors** in agreement, or are they in competition? in agreement

Exercises for Part A

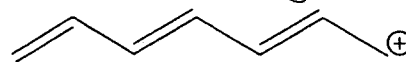
1. Use curved arrows to generate all missing resonance structures for each of the carbocations below. The total number of resonance structure in the set (including the one shown) is given (x) below each structure. *see next page*



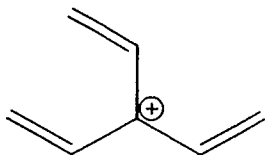
(3)



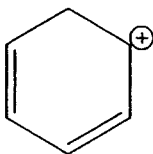
(2)



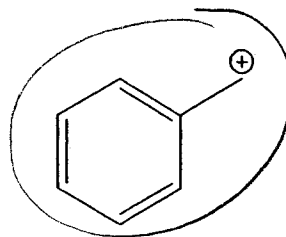
(4)



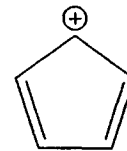
(4)



(3)



(4)



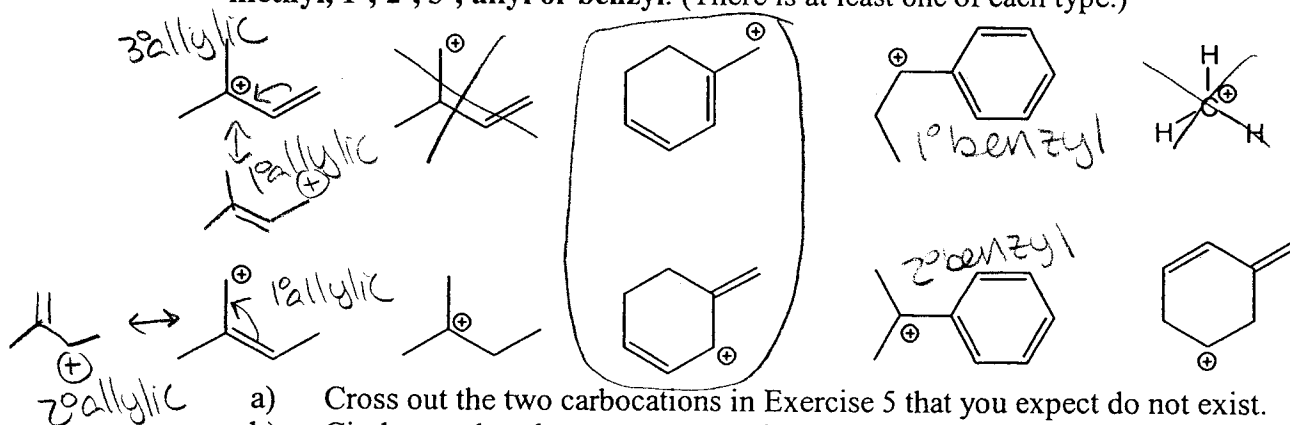
(5)

2. Explain why the following rule works: The more resonance structures you can draw for a carbocation, the lower its potential energy (the "happier" it is).

The \oplus charge is delocalized over more carbons \downarrow PE

4. A **benzene ring** is a six carbon ring with three double bonds. A + charge next to a **benzene ring** is a common occurrence so we give it a name: a **benzyl carbocation**. Circle the benzyl carbocation in Exercise 1.

5. Label each of the carbocations below the most appropriate of the following words: **methyl, 1°, 2°, 3°, allyl or benzyl**. (There is at least one of each type.)

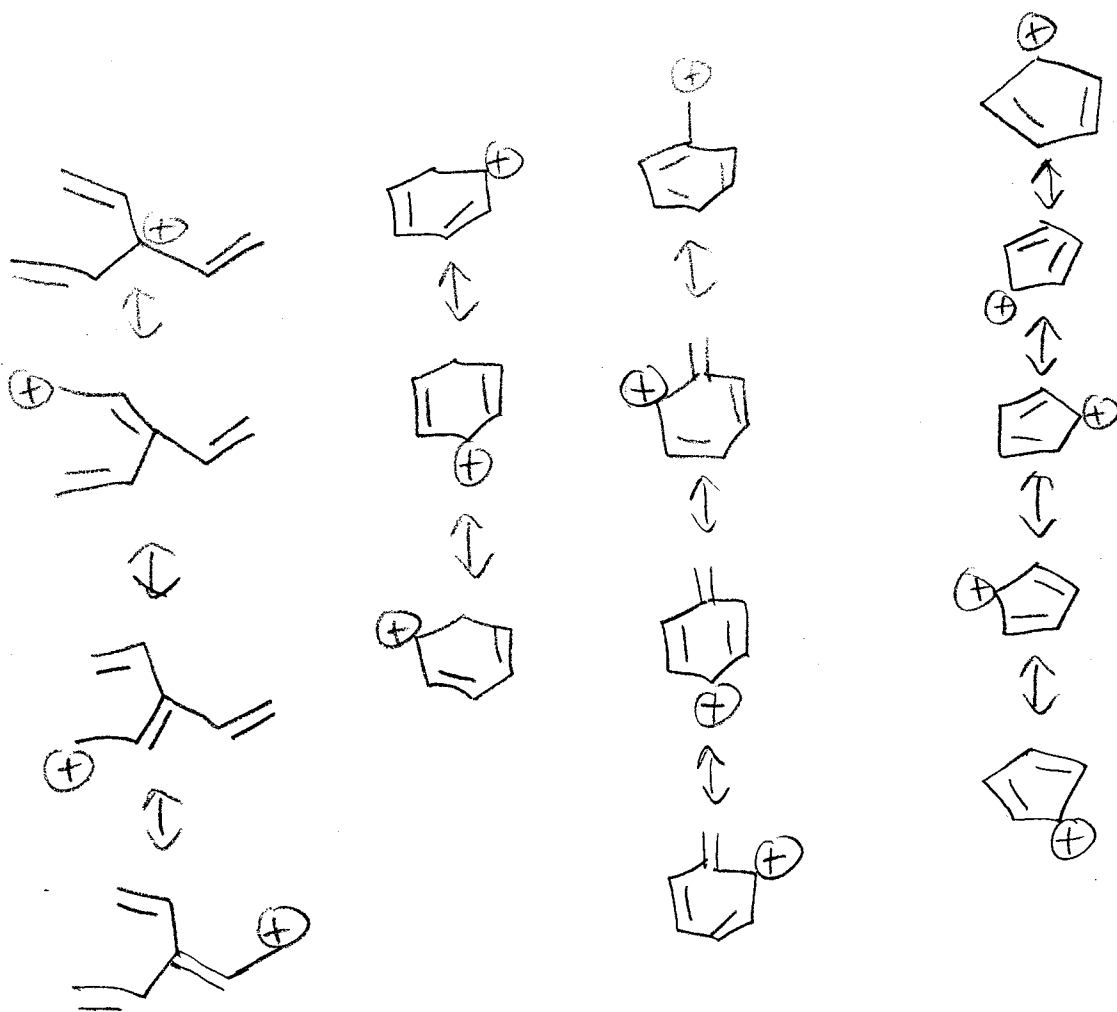
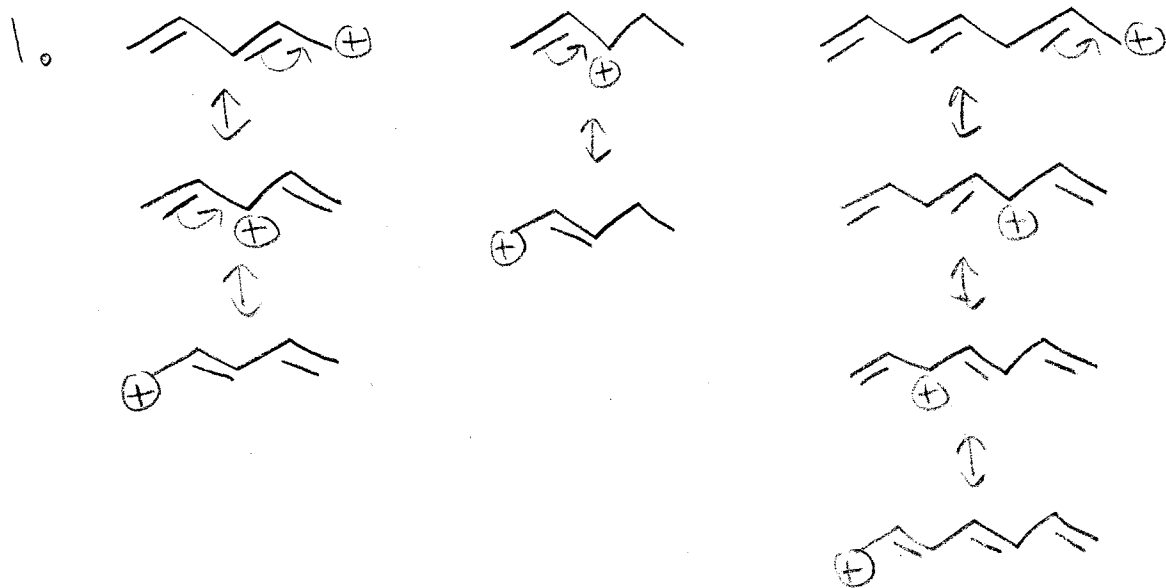


- Cross out the two carbocations in Exercise 5 that you expect do not exist.
- Circle together the two structures in Exercise 5 that are really two resonance structures of the same carbocation.
- Construct an explanation for why the benzyl carbocation in the second row is lower in potential energy than the benzyl carbocation in the first row.
- Explain why the top left structure is lower in potential energy than the one directly below it. (Hint: draw the other resonance structure for each.)

3° allylic character \downarrow PE

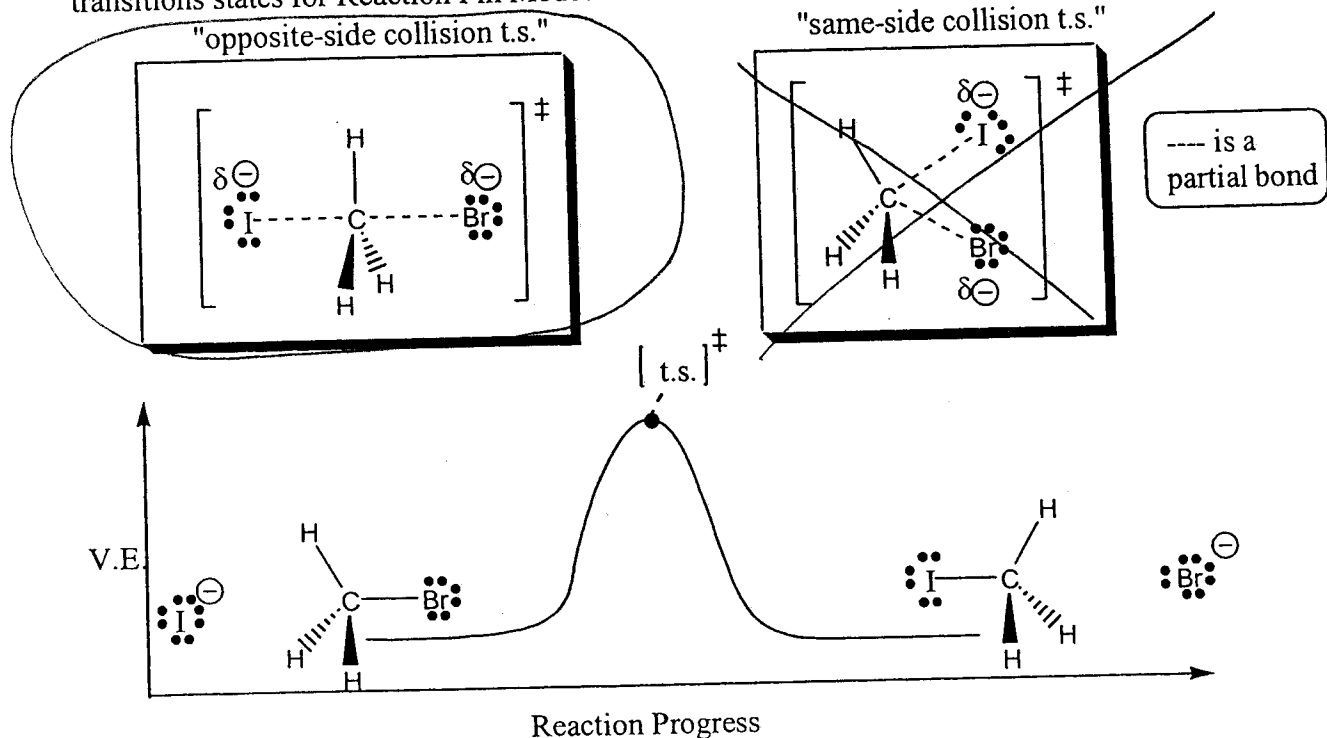
Chem Activity 13 Two-Step Nucleophilic Rxns (S_N²)

Exercises for Part A



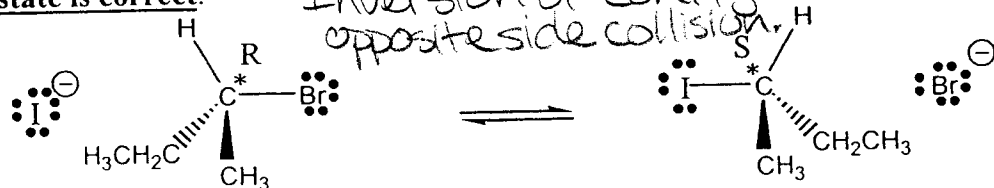
Model 2: Transition State

The **transition state** (t.s.) of a reaction is the highest potential energy species between the reactant (R) and the product (P). The diagram below shows two possible transition states for Reaction I in Model 1. Each is labeled with a "double dagger" (\ddagger).

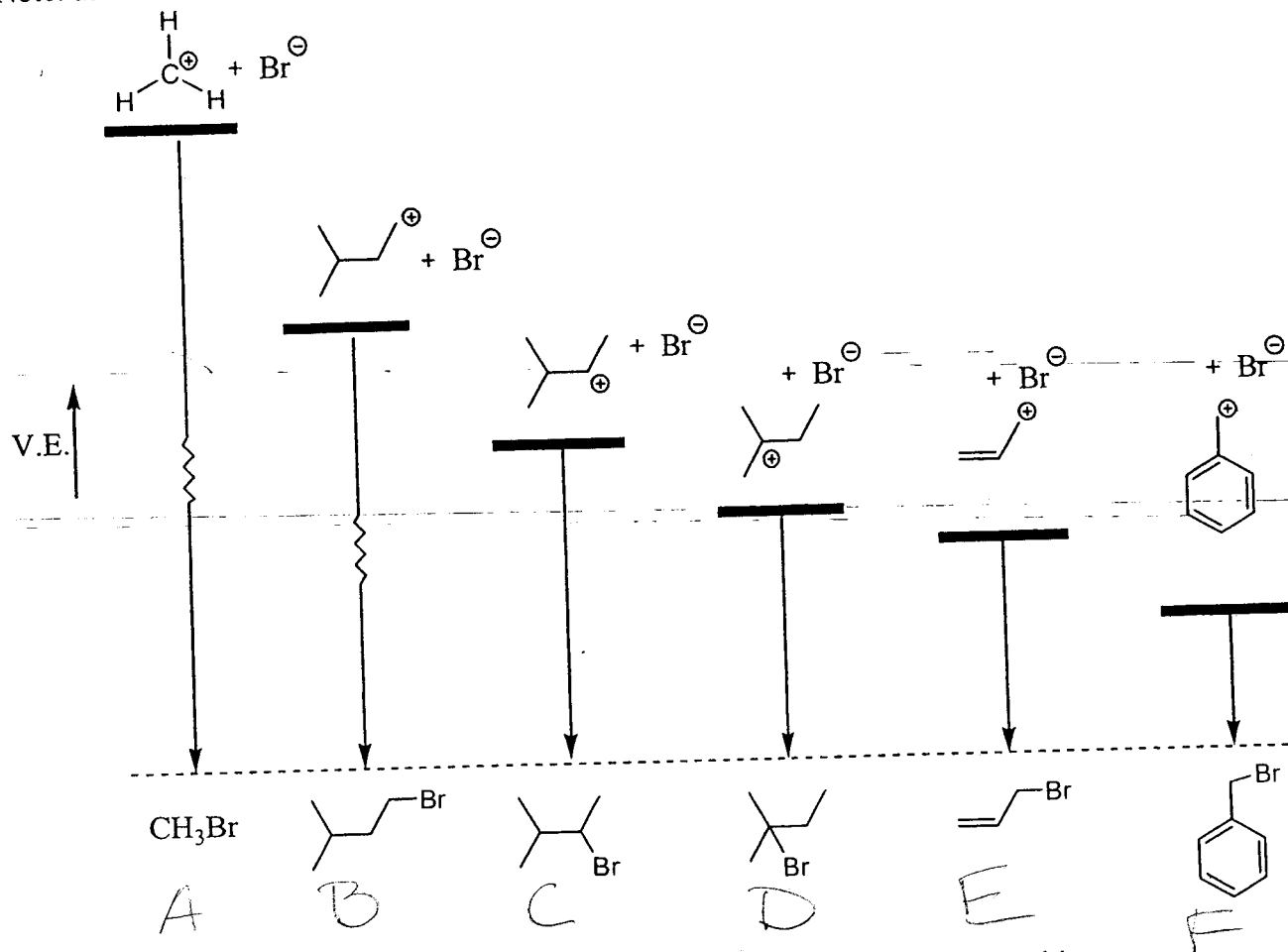


Critical Thinking Questions

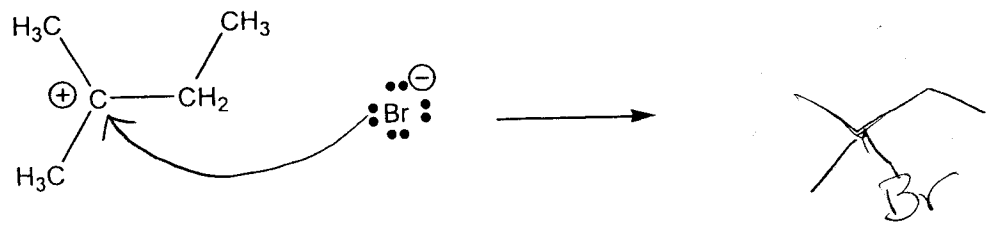
- Both the **nucleophile** and the **leaving group** have a partial negative charge in the transition state. Recall that like charges repel one another. Circle the transition state in Model 2 that minimizes the unfavorable repulsion between these two species.
- You are having holiday dinner at your house, but your parents don't get along with your in-laws. You want to have one set of parents in the house at all times—otherwise it won't feel like a holiday—but never both sets! Which of the following scenarios minimizes unfavorable interactions between the two sets of parents?
 - When the in-laws arrive at the front door, your parents exit out the back.
 - When the in-laws arrive at the front door, your parents exit out the front door, passing the in-laws on the porch.
- The stereochemistry of the product in the following reaction proves that the opposite-side-collision transition state is correct. Cross out the incorrect transition state in Model 2 and **explain how the product below proves which transition state is correct.**



6. Consider the following Figure.
Figure 6: Heats of Reaction for Nucleophilic Addition of Br⁻ to R⁺
 Note: assume that all the neutral products have similar potential energies.



a) Use curved arrows to illustrate the reaction below, and draw the resulting product. (Note: This is one of the reactions from Figure 6)



b) According to Figure 6, which is lower in potential energy: the allyl carbocation shown or the tertiary (3°) carbocation shown?
 c) Based on the information in this chart, rank the carbocations in Exercise 5 from highest potential energy to lowest potential energy.

rel. P.E.

CH_3^+ $\text{R}-\text{CH}_2^+$ $\text{R}-\text{CH}^+$ $\text{R}-\text{C}^+$ $\text{CH}_2=\text{CH}-\text{CH}_2^+$ $\text{C}_6\text{H}_5-\text{CH}_2^+$
A > B > C > D > E > F
 methyl 1° 2° 3° 1° allylic 1° benzylic

Exercises for Part B

8. Place each of the following phrases in the correct box in Table 5.
- Very polar solvent better, but weakly polar ok.
 - Very polar, protic solvent required to stabilize ion intermediates.
 - Must be 2°, 3°, allyl or benzyl
 - Methyl or 1° preferred, 2° ok too.
 - Dependent on identity and concentration of both Nuc and Elec/L.G.
 - Dependent only on identity and concentration of Elect/L.G.
 - Inverted (switch from R to S or vice versa)
 - Racemic mixture produced

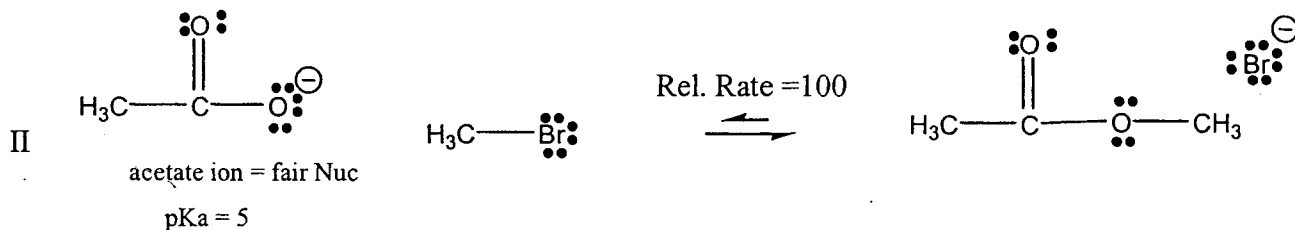
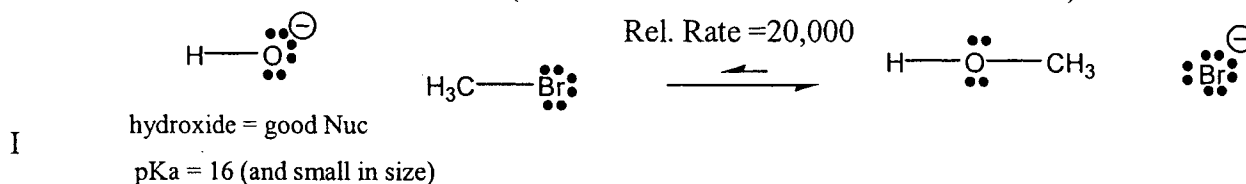
Table 5: Summary of Factors Leading to S_N2 vs. S_N1 Reactions.

Rxn Type	Solvent	Stereochemistry	Electrophile/L.G.	Rate
S _N 2	very polar solvent better, but weakly polar ok	inverted R → S or vice versa	Methyl or 1° preferred 2° ok	dependent on identity of Nuc & E ⁺ & LG
S _N 1	very polar, protic solvent required to stabilize ion intermediates	racemic mixture produced	must be 2°, 3°, allylic or benzylic	dependent only on E ⁺ /LG

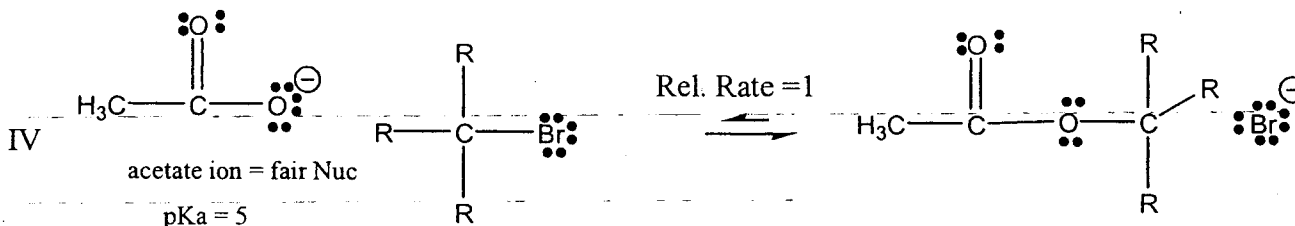
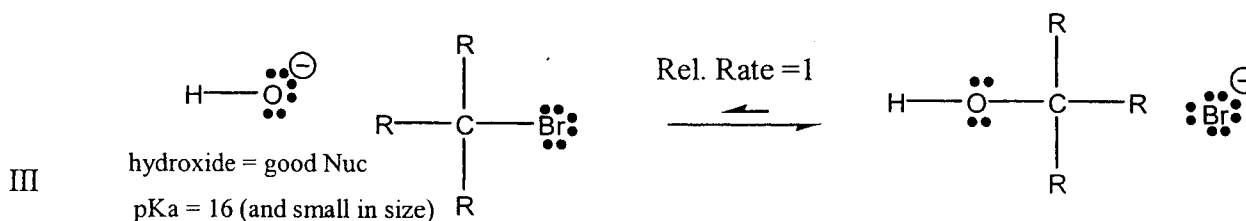
9. The following is an orbital explanation of a S_N1 reaction. Fill in the blanks with appropriate words or phrases and refer to the reaction in CTQ 11.

"In the first step, the leaving group leaves, taking its electrons with it. The resulting carbon changes hybridization state from sp^3 to sp^2 with one empty p orbital and bond angles of 120°. In the second step, the nucleophile enters the picture for the first time and reacts with one or the other lobe of the empty p orbital, filling it with two electrons that were formerly a lone pair on the nucleophile. This creates a new σ bond. The electrons in this new bond are unhappy so close (90° away) to the other bonds. To relieve this steric strain, the carbon atom changes hybridization states from sp^2 to sp^3 . This moves the new σ bond to its proper location 109° away from the other bonds.

10. Hydroxide is a much better nucleophile than acetate ion so it is not surprising that Rxn I is much faster than Rxn II. (Assume solvent = water for reactions I-IV.)



- a) Draw an energy diagram for reactions I and II. Be sure that your energy diagrams reflect the fact that Rxns I and II have different rates and different ΔH_{Rxn} s (one of them is more down hill). *Overlay graphs.*



- b) Explain why Rxn III has exactly the same rate as Rxn IV, even though hydroxide is a much better nucleophile than acetate ion.
- c) Draw an energy diagram for reactions III and IV. Be sure that your energy diagrams reflect the fact that the reactions have the same rate but different ΔH_{Rxn} s (one of them is more down hill).
- d) Draw a mechanism for each reaction.

Handwritten mark

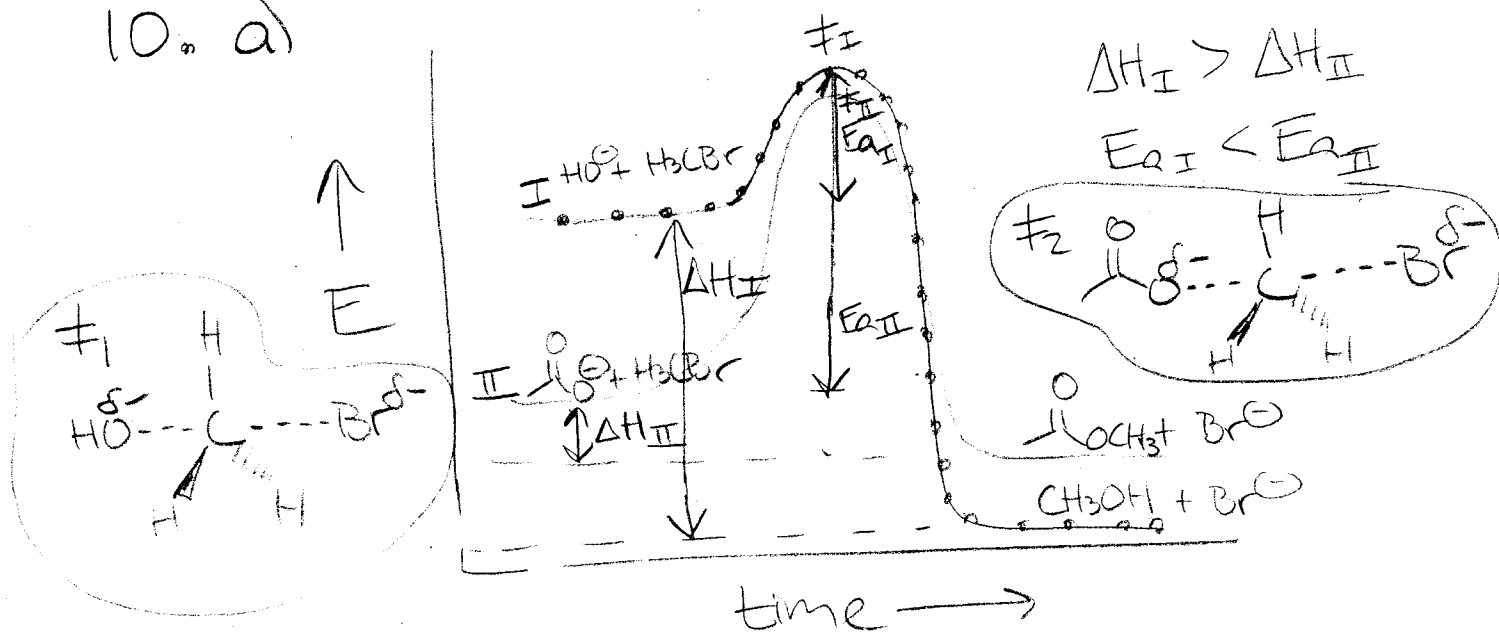
Chem Activity 13

Two-Step Nucleophilic S_N1 Substitution Rxns

Exercises for Part B

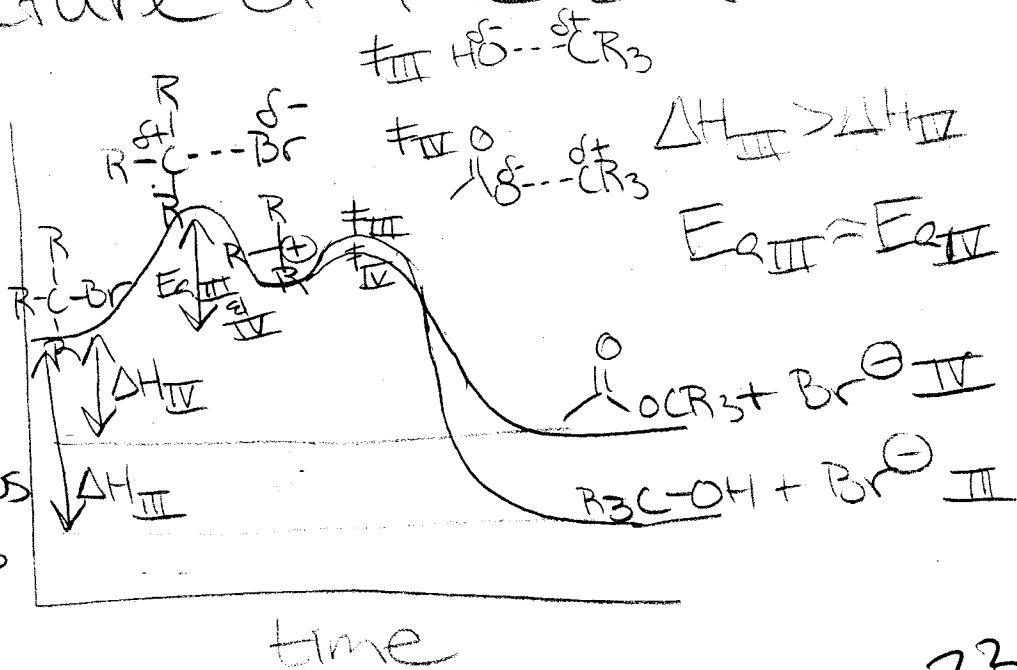
pg 116

10. a)



b) Because the rate limiting step of S_N1 rxns depends only on the structure of the E^+ (R-X)

c)

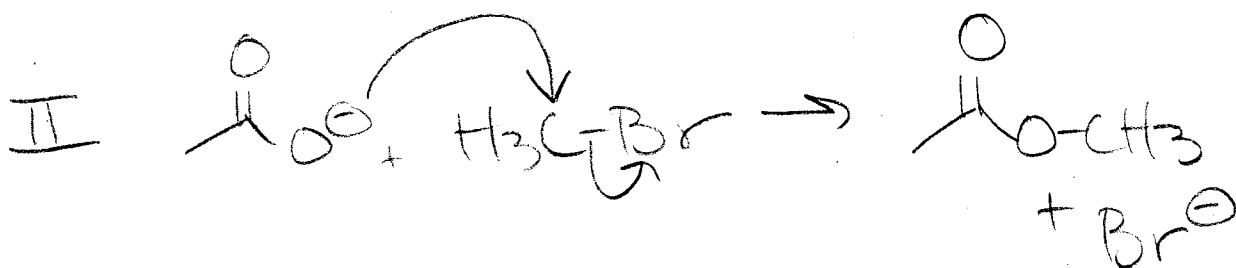
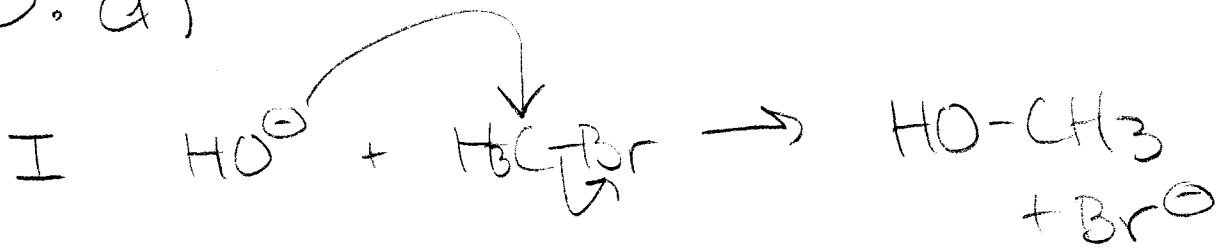


Note: High reactivity of C^+ overshadows differences between Nu's

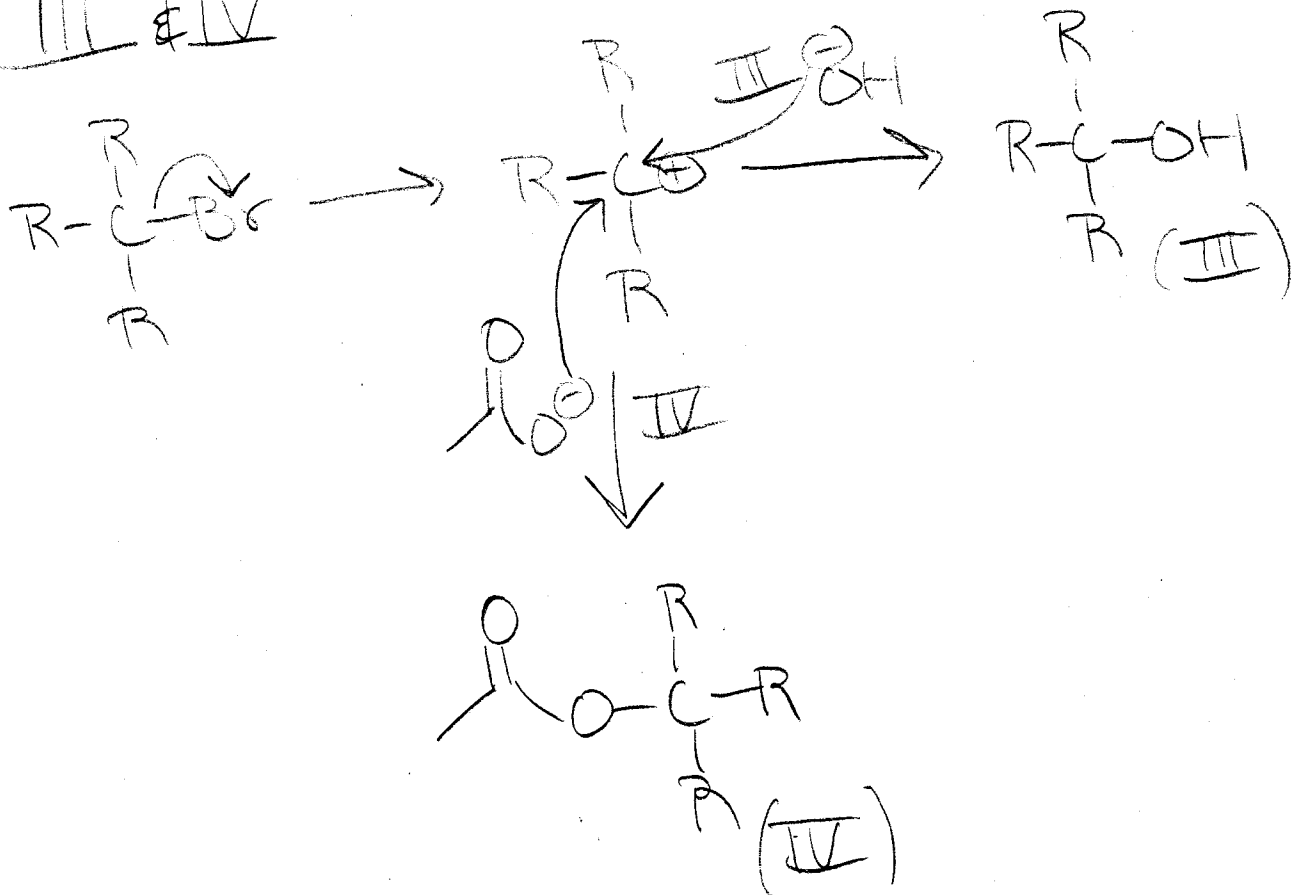
Chem Activity 13 SN1

PS116
(cont'd)

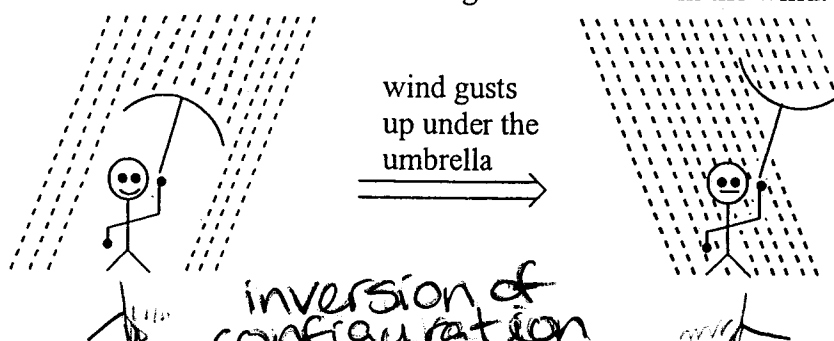
10. d)



III & IV



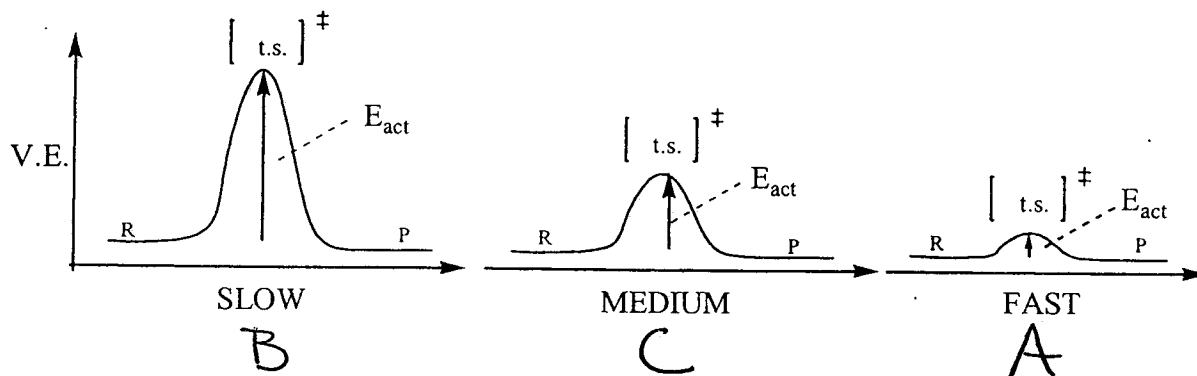
8. Explain how the changes at the electrophilic carbon in a one-step nucleophilic substitution reaction resemble the inverting of an umbrella in the wind.



Model 3: Activation Energy (E_{act})

An acid-base reaction is very fast, partly because the only atom that needs to move is a tiny H^+ . An H^+ can be transferred very quickly. Most other reactions including nucleophilic substitutions are much slower partly because elaborate atom movements are required to get to the transition state. (For example: the flipping of the bonds like an umbrella inverting in the wind). This takes energy and translates into high activation energies.

Reaction rate depends on activation energy (E_{act})



Each of the following lowers the activation barrier (lowers E_{act}) and therefore speeds up the rate of a substitution reaction.

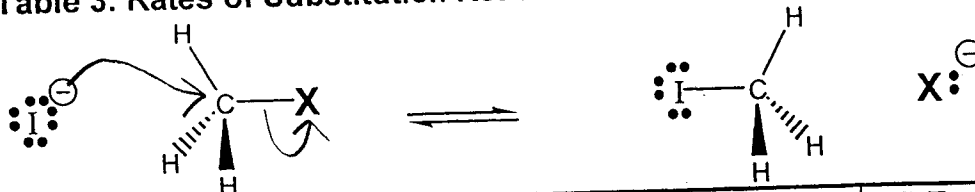
- Use of a good leaving group
- Use of a good nucleophile
- Use of a good electrophile

(The remainder of this activity will be spent identifying the characteristics of each.)

Label the rxn energy diagrams above as

- A) acid-base rxn
 B) intermolecular rxn
 C) intramolecular rxn

Table 3: Rates of Substitution Reactions with Various Leaving Groups (X)



Leaving Group (—X)	Relative Rate of Rxn	pK _a of Conj. Acid (H—X)	Approx. Energy Req. to Break C—X bond (in pKa units)	P.E. of New Lone Pair on X [−] (in pKa units)
best —I	10 ⁷	-5	≈ 0	≈ 0
	10 ⁶	-5	≈ 0	≈ 0
—Br	10 ⁵	-5	≈ 0	≈ 0
—Cl	10 ⁴	-2	≈ 0	≈ 0
	10 ⁴	-2	≈ 0	≈ 0
—F	1	3	3	3
	0.1	5	5	5
NC—	0.001	9	9	9
HO— or RO—	10 ⁻⁵ (v. slow)	16	16	16
H ₂ N—	No reaction	35	35	35
H ₃ C— worst	No reaction	50	50	50

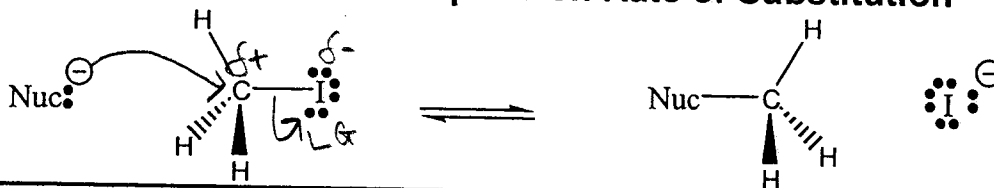
Critical Thinking Questions

- Add curved arrows to the reaction at the top of the page showing one-step nucleophilic substitution.
- Label appropriate species in Table 3 with the words “best leaving group” and “worst leaving group” and explain your reasoning.
- According to the information in Table 3...
 - A good leaving group initially has a strong bond or a weak bond [circle one] to the electrophilic carbon.
 - A good leaving group requires a large or small [circle one] amount of energy to break off from the electrophilic carbon.
 - A good leaving group is stable, happy & low P.E. or unstable, unhappy & high P.E. [circle one] on its own after it leaves the electrophilic carbon.

Part B: One-Step Nucleophilic Substitution

(What are the characteristics of a good nucleophile and electrophile?)

Model 4: Effect of Nucleophile on Rate of Substitution



Nucleophile (Nuc)	Conj. Acid (H-Nuc)	Relative Rate of Rxn	pK _a of Conj. Acid H-Nuc	Approx. P.E. of Nuc	Energy Released (ΔH_{rxn}) When Nuc-C Bond Forms
H_3C^-	$\text{H}_3\text{C}-\text{H}$	10^6	50	50	50
H_2N^-	$\text{H}_2\text{N}-\text{H}$	10^5	35	35	35
HO^- or RO^-	$\text{HO}-\text{H}$ or $\text{RO}-\text{H}$	10^4	16	16	16
$\text{R}-\text{C}(=\text{O})\text{O}^-$	$\text{R}-\text{C}(=\text{O})\text{O}-\text{H}$	100	5	5	5
F^-	$\text{F}-\text{H}$	80	3	3	3
$\text{H}-\ddot{\text{O}}-\text{R}$ or $\text{H}-\ddot{\text{O}}-\text{H}$	RH	1	-2	≈ 0	≈ 0
$\text{O}=\text{S}(\text{R})\text{O}^-$	$\text{O}=\text{S}(\text{R})\text{O}-\text{H}$	0.0001	-5	≈ 0	≈ 0

Critical Thinking Questions

- Fill in Column 2 in Model 4 with the conjugate acids (H-Nuc).
- Add curved arrows to the reaction above the table. Label the electrophilic C with a " δ^+ " and circle and label the "**leaving group**" attached to this electrophilic C.
- Based on the rate data, label appropriate species in Model 4 with the words "**best nucleophile**" and "**worst nucleophile**."
- According to the data in Model 4, which ONE of the following statements is true?
 - A nucleophile must have a free pair of electrons which are available to make a new bond.
 - A nucleophile must have a negative charge and a free pair of electrons which are available to make a new bond.

T I

F

16. According to the information in Model 4...

- a) A good nucleophile is stable, happy & low P.E. or reactive, unhappy & high P.E. [circle one] on its own before it makes a new bond to carbon.
- b) A good nucleophile releases a large amount of energy or a small amount of energy [circle one] when making a new bond to C.
- c) A good nucleophile makes a new bond to carbon that is strong and hard to break or weak and easy to break [circle one].

Model 5: Steric Hindrance

Figure 5a: Substitution Reactions with Different Electrophiles

Steric hindrance = unfavorable electron-electron repulsion that results when molecules or parts of molecules are forced too close together.

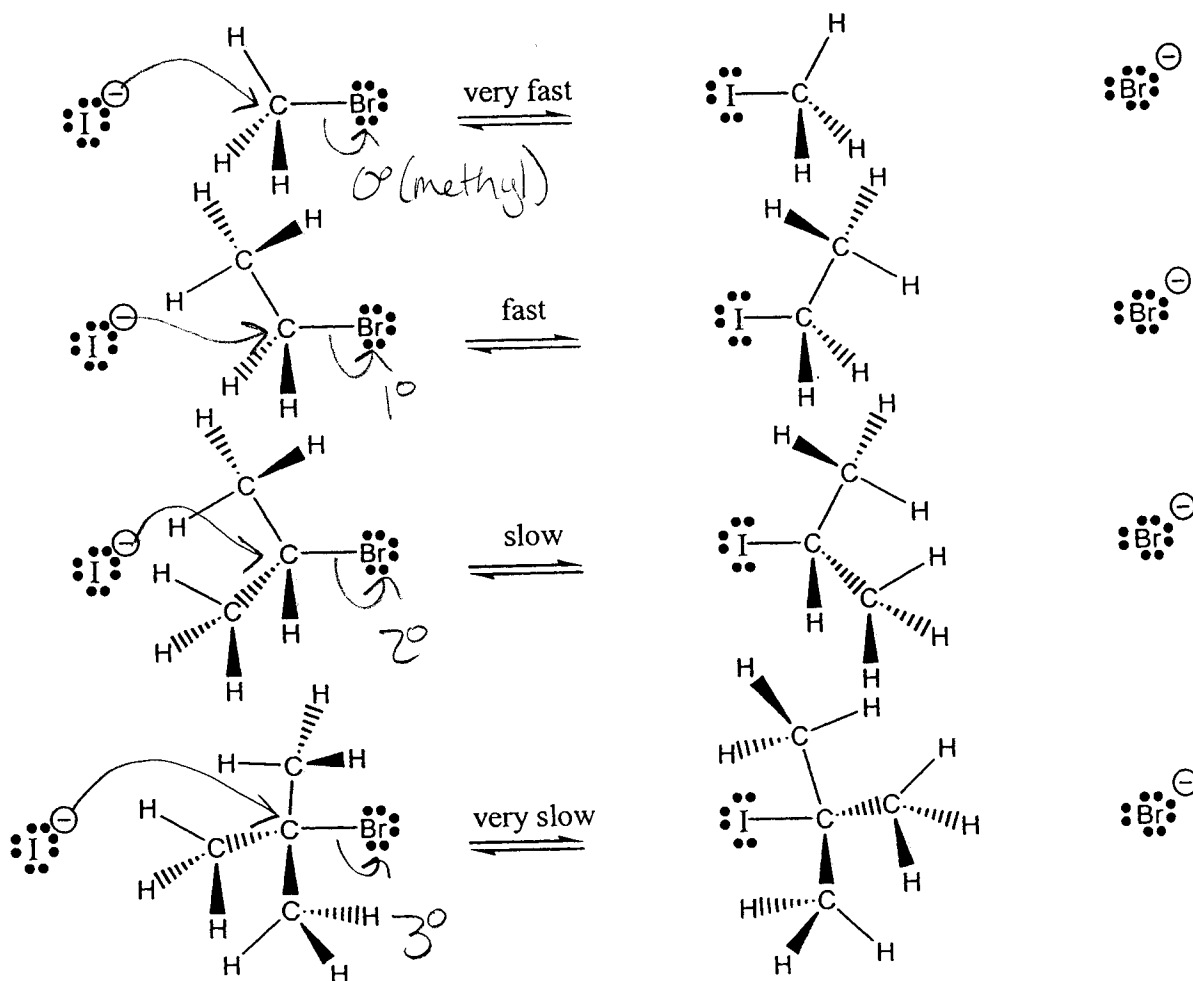
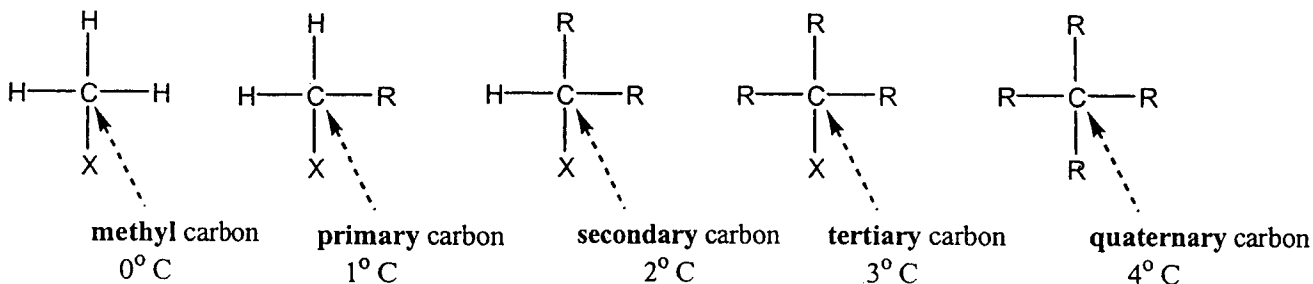


Figure 5b: Methyl, Primary, Secondary, Tertiary and Quaternary Carbons

X = H or halogen such as Br or I

R = alkyl group such as methyl or ethyl



Critical Thinking Questions

17. What is the rule for determining whether a carbon is methyl (0°), primary (1°), secondary (2°), tertiary (3°), or quaternary (4°)?

count the # of carbons bonded to it

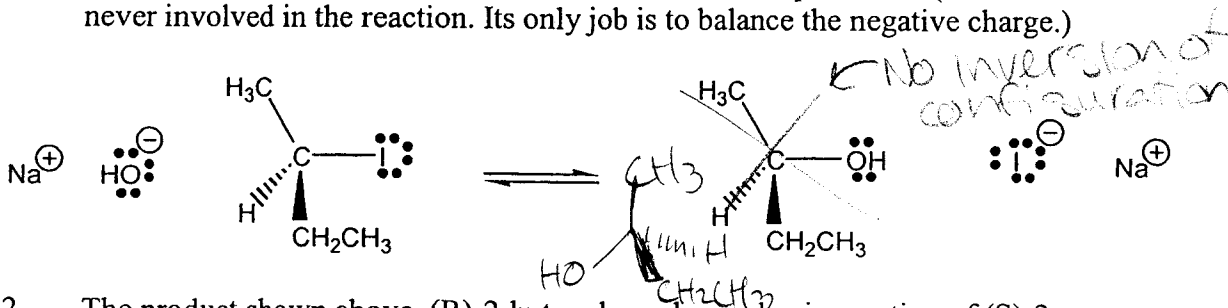
18. Add curved arrows to illustrate each nucleophilic substitution reaction in Figure 5a.
19. Label each C in Figure 5a that is acting as an electrophile with a 0° , 1° , 2° , 3° or 4° .

20. Construct an explanation for the rate data that appears over each arrow in Figure 5a.

rel. SN2 reactivity $0^\circ > 1^\circ > 2^\circ > 3^\circ > 4^\circ$ *fastest* *slowest* *doesn't react by SN2*

Exercises for Part A

1. Explain why the following are NOT the products you would predict for a one-step nucleophilic substitution reaction, and draw the correct product/s. (Note: Na^+ is never involved in the reaction. Its only job is to balance the negative charge.)



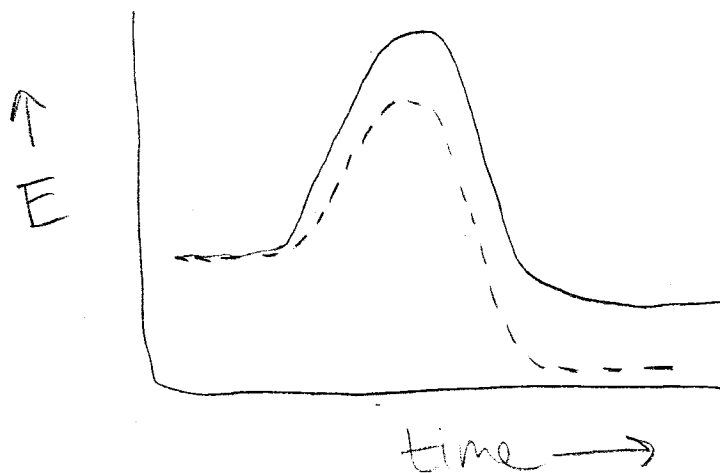
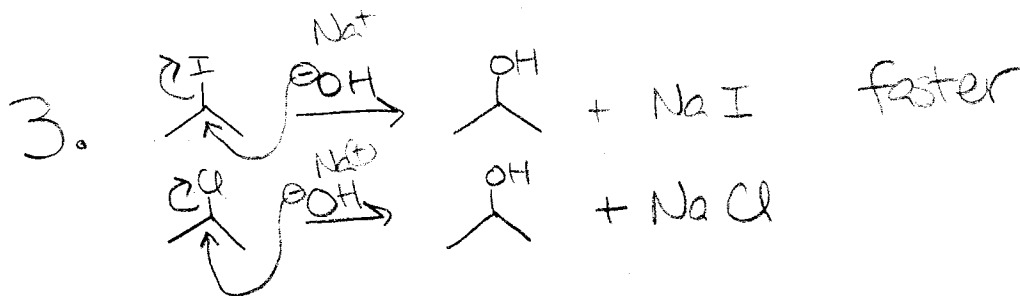
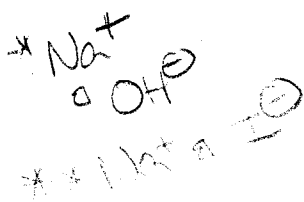
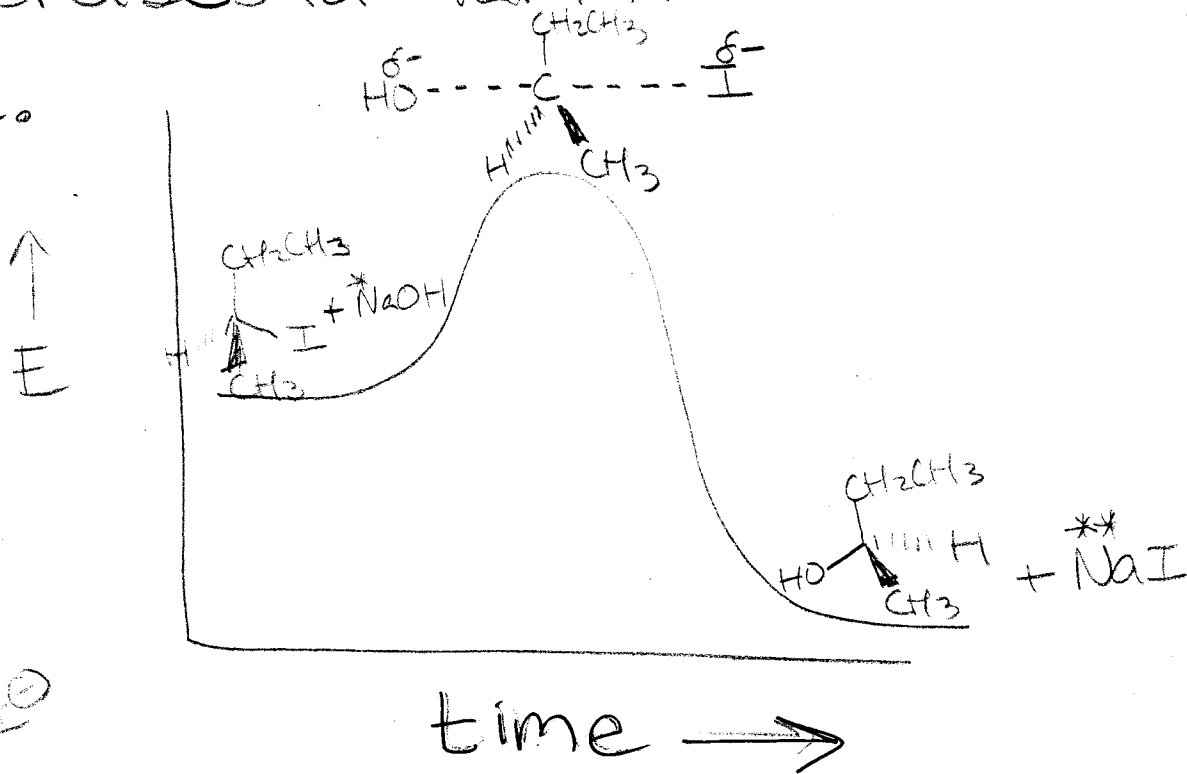
2. The product shown above, (R)-2-butanol, can be made via reaction of (S)-2-iodobutane and NaOH. Draw an energy diagram for this reaction. Include on your energy diagram wedge-and-dash drawings of the reactants, transition state, and products. In your transition state drawing, use a dotted line to indicate a partial bond, and δ^- to indicate partial negative charge on an atom.

see next page

ChemActivity 12 One-Step Nucleophilic Substitution Rxns (S_N2)

Exercises for Part A

2.



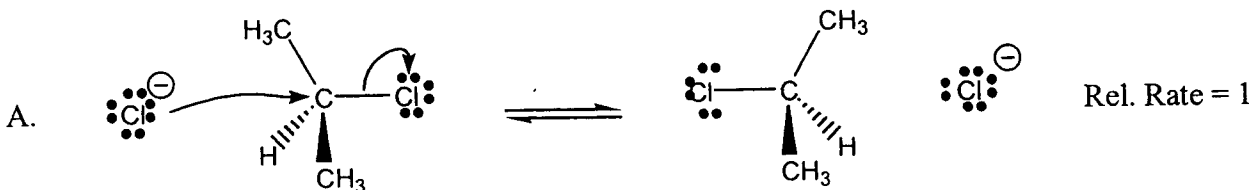
3. Consider a reaction between NaOH and 2-iodopropane and a reaction between NaOH and 2-chloropropane. (Note: Na⁺ is never involved in the reaction. Its only job is to balance the negative charge.) For each reaction...
- Draw the reactants.
 - Add curved arrows to show a one-step nucleophilic substitution reaction.
 - Draw the most likely products of the reaction.
 - Predict, based on the data in Table 3, which reaction will be faster.
 - Draw an energy diagram showing both reactions on the same set of axes. Draw the 2-iodopropane reaction profile with a dotted line and the 2-chloropropane reaction profile with a solid line.

Exercises for Part B

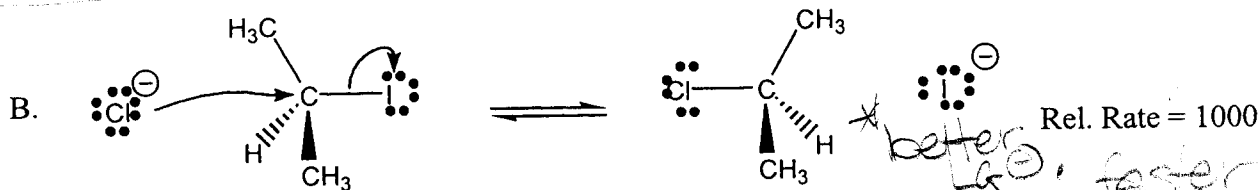
5. Consider the following reactions.

- Construct an explanation for why Rxn A is slower than Rxn B.
- Construct an explanation for why Rxn A is slower than Rxn C.
- Construct an explanation for why Rxn A is slower than Rxn D.

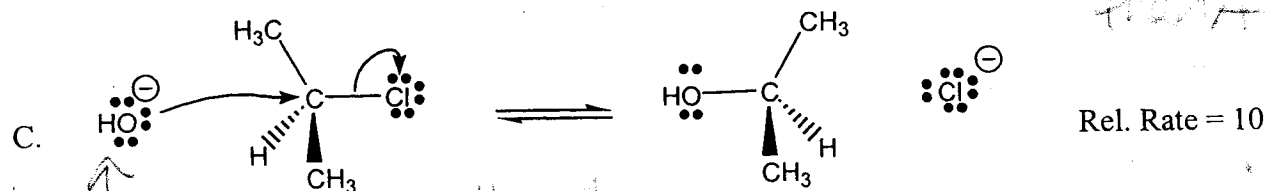
see down



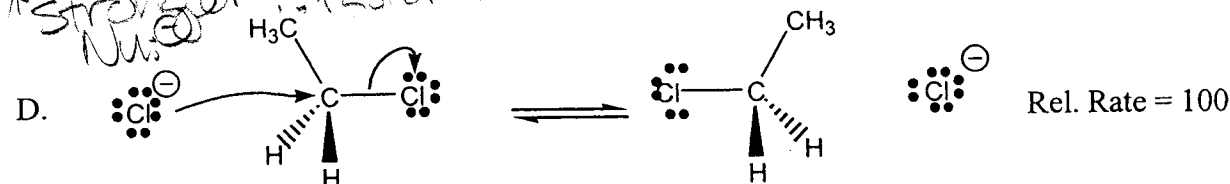
** relative to A*



** better LG, faster than A*



** stronger Nu, faster than A*



less steric hindrance, faster than A