CHEM 346 – Organic Chemistry I (for Majors)

Instructor: Paul J. Bracher

Hour Examination #2

Wednesday, October 23rd, 2013
6:30–8:30 p.m.

| Student Name (Printed)	Solutions
Student Signature	

Instructions & Scoring

- You have two hours to complete this exam. The exam will end promptly at 8:30 pm.

- You are allowed access to two (2) letter-sized pages of handwritten notes and a molecular model kit. You may not share these materials.

- Partial credit will be awarded on problems 3, 4, and 5. Try not to leave blank answers.

- You may not access any electronic devices during the examination.

- Your examination may be photocopied.

Question	Points Earned	Points Available
1		15
2		25
3		25
4		20
5		15
TOTAL		100

Original Problems, Required Information in Answers, and Supplementary Explanation

Problem 1. (15 points total, 3 points each) Determine whether the following five statements are true or false. Write out the full word "true" or "false" beside each statement; do <u>not</u> just write "T" or "F". If any part of the statement is false, the entire statement is false.

(i)   TRUE   The proper IUPAC name of compound **A** is (2R,5R)-2-bromo-5-ethoxy-1-heptanol.


A
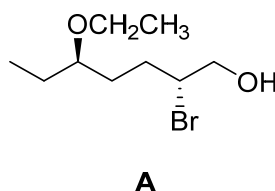
Naming the compound involves following the rules laid down by IUPAC. The longest carbon chain is obvious and you start numbering at the side with the hydroxyl group.

(ii)   TRUE   To conduct a Williamson ether synthesis of isopropyl methyl ether (**B**), route 1 is a better choice than route 2 (see below).
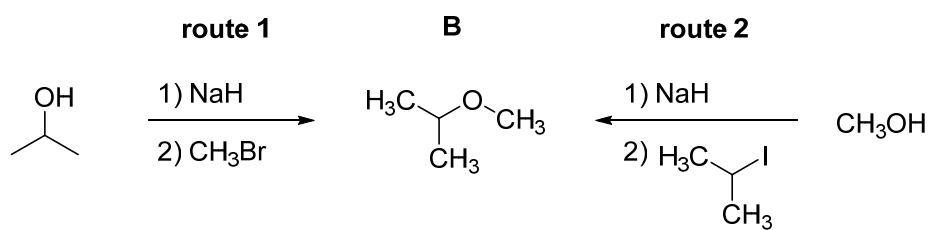
For Williamson ether synthesis, you want to build the molecule such that the more-substituted side of the ether comes from the alkoxide and the less-substituted side comes from the alkyl halide. This is because the mechanism for Williamson ether synthesis is S_N2, and as the alkyl halide becomes more substituted—and hence, hindered—the rate of the substitution reaction will decrease and elimination will become more competitive. Here, route 1 is optimal because it uses a methyl halide (from which elimination is impossible).

(iii) _____TRUE_____   For the following reaction, doubling the concentration of sodium acetate (**C**) in solution will double the rate of the reaction.

C
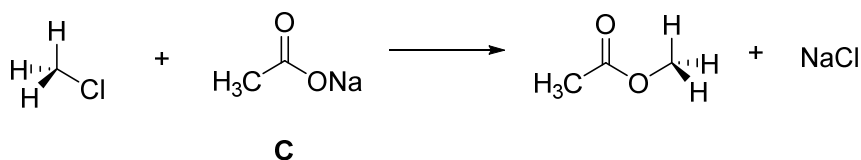
The rate law for an S_N2 reaction (like the one above) is:

rate = k[alkyl halide][nucleophile]

Thus, if you double the concentration of the nucleophile, you can expect for the rate to double as well.

(iv) _____TRUE_____   The boiling point of 1-butanol is higher than the boiling point of diethyl ether.

Size is not a significant issue because these molecules are isomers with the same molecular formula. The key difference is that butanol has a polar hydroxyl group that makes it capable of hydrogen bonding. Diethyl ether has weaker dipole–dipole interactions, and correspondingly, a lower boiling point.
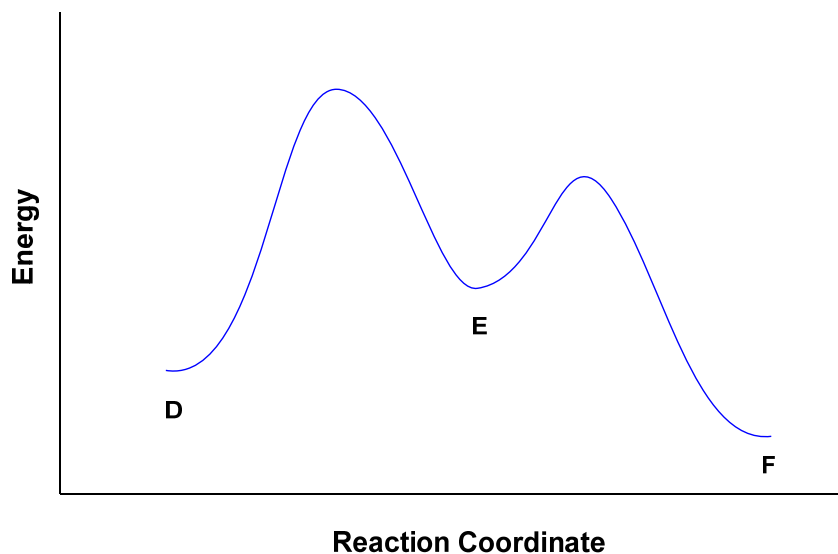
1-butanol

b.p. 118 °C

diethyl ether

b.p. 35 °C

(v)   _____FALSE_____   The energy diagram below depicts the exothermic reaction of **D** to yield the product **F** *via* the transition state **E**.

The reaction from **D** → **F** is exothermic, but **E** is an intermediate along the way (not a transition state). Transition states occur as energy maxima in the diagram (the peaks, not the valleys).

Problem 2. (25 points total, 5 points each) For each question, select the best answer of the choices given. Write the answer, legibly, in the space provided.

(i)   _____C_____   Which reagent and solvent pairing from the choices shown below would make the best selection to favor elimination of HBr from compound **G** to form product **H** and minimize any competing side reactions that would erode the yield?

G   H
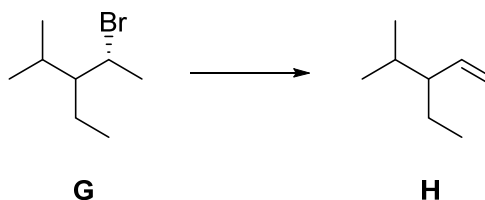
(a) CH_3ONa in ethanol
(b) CH_3ONa in DMSO
(c) *tert*-BuONa in *tert*-butyl alcohol
(d) HCl in methanol
(e) HCl in DMSO

Elimination reactions generally favor generation of the more-substituted alkene product (Zaitsev's Rule). To generate the less-substituted alkene during an elimination, you can use a bulky base like t-BuO¯, which will prefer to access less sterically hindered protons.
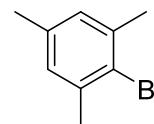
(ii) _____D_____ Which alkyl halide will undergo heterolytic bond dissociation to form a carbocation that is stabilized by both hyperconjugation and a resonance effect as well?
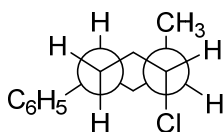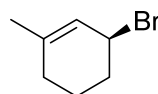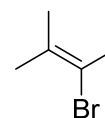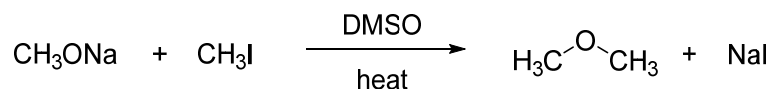

(a)   (b)   (c)

(d)   (e)

Only the carbocation formed by (d) would be stabilized by a resonance effect. By virtue of the alkyl substituents on the carbons that bear the positive charge in the resonance hybrid, the cation is stabilized by hyperconjugation as well. Be careful with (c) and (e)—there would be no resonance stabilization/delocalization of the carbocation for these compounds.

(iii) _____B_____ In the following reaction, what orbital does the nucleophile attack?

$$CH_3ONa \ + \ CH_3I \xrightarrow[\text{heat}]{\text{DMSO}} H_3C{-}O{-}CH_3 \ + \ NaI$$

(a) the empty π bonding orbital of the C–I bond
(b) the σ* antibonding orbital of the C–I bond
(c) the σ* antibonding orbital of the C–O bond
(d) an unhybridized p orbital on carbon
(e) a lone pair on the negatively charged oxygen

S_N2 reactions like this one involve the donation of an electron pair from the nucleophile into the σ^*_{C-X} molecular orbital of the alkyl halide.
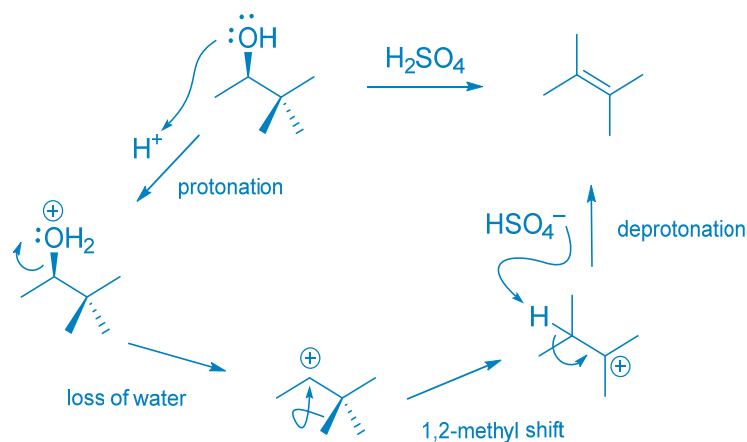
(iv)   E   Which of the following is not a key step in the mechanism for the reaction drawn below.
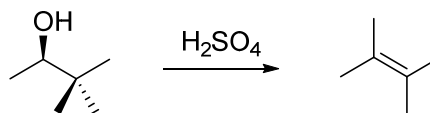
    (a) generation of a carbocation
    (b) protonation of a hydroxyl group
    (c) a 1,2-methyl shift
    (d) deprotonation by a Brønsted–Lowry base
    (e) all of the above are steps in the mechanism

All of the steps are involved in the mechanism, which is shown below:

(v)   D   Consider the following reaction and bond dissociation energies, then select the most correct statement of those given.

$$CH_3I \; + \; H_2O \longrightarrow CH_3OH \; + \; HI$$
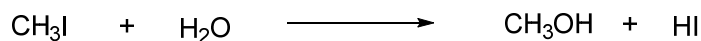
Bond	BDE (kJ/mol)
H–OH	498
CH_3–OH	389
H_3C–I	234
H–I	297

(a) the reaction is endothermic
(b) the reaction occurs in more than one step (i.e., there is more than one transition state along the path from starting materials to products)
(c) the equilibrium constant will increase with the addition of CH_3I
(d) both (a) and (b) are correct
(e) both (b) and (c) are correct

To calculate the enthalpy change for the reaction (ΔH), you add up the bond dissociation energies for the bonds being broken (because you put this energy into the system) and subtract the BDEs for the bonds that are formed (because this energy is released). Here ΔH = 234 + 498 – 389 – 297 = +46 kJ/mol, so the reaction is endothermic. This reaction will also occur in two steps (attack by neutral water, followed by deprotonation). Finally, while the equilibrium of a reaction will shift with the addition of one of the reactants (by Le Chatelier's Principle), the equilibrium constant (K) does not change—it remains constant!

Problem 3. (25 points total, 5 points each) Reactions. The following chemical reactions are missing their starting materials or products. Write the missing compounds into the empty boxes below, as appropriate. For missing products, draw the single organic product that you expect to be produced in the highest yield among all of the possibilities. In some cases, there will be more than one correct answer that will merit full credit.
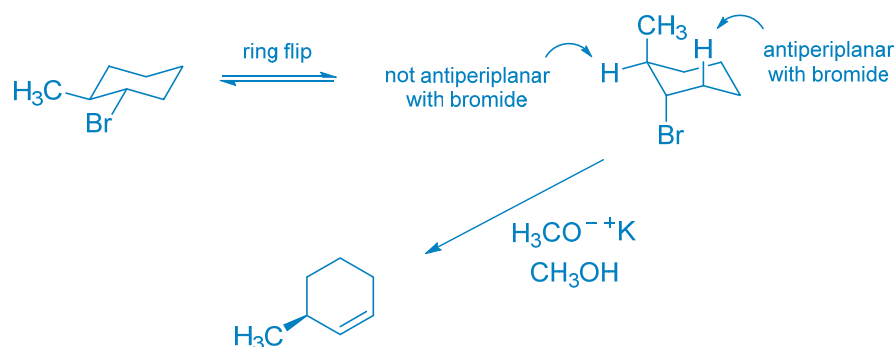
(i) (5 points)
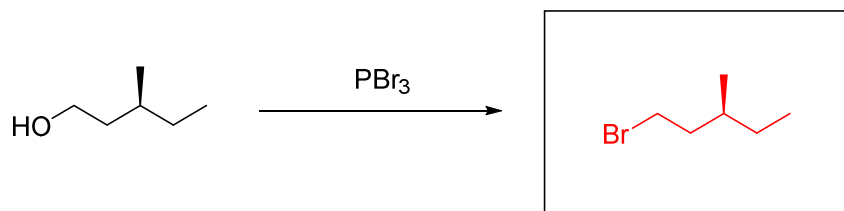
(ii) (5 points)
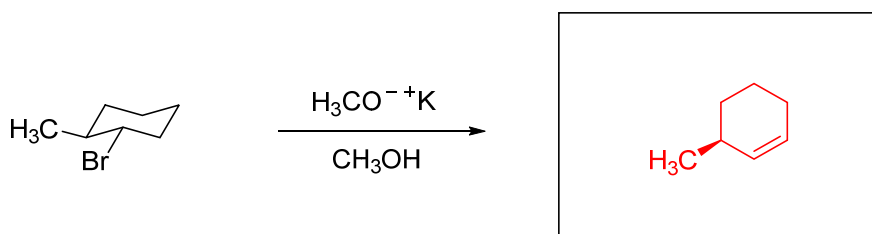
Strong bases generally favor E2 elimination, especially off of secondary centers where both S_N1 and S_N2 would be expected to be sluggish. In the E2 reaction, the proton and halide being eliminated must have an antiperiplanar geometry relative to each other. In a cyclohexane ring, this necessitates the halogen and hydrogen being in axial positions on adjacent carbons. When the conformation of the starting material is flipped to put the bromide in an axial position, there is only one proton capable of being eliminated. So, while it is tempting to draw the trisubstituted alkene product (which would be more thermodynamically stable), the only kinetically accessible product is the disubstituted product shown above.

(iii) (5 points)
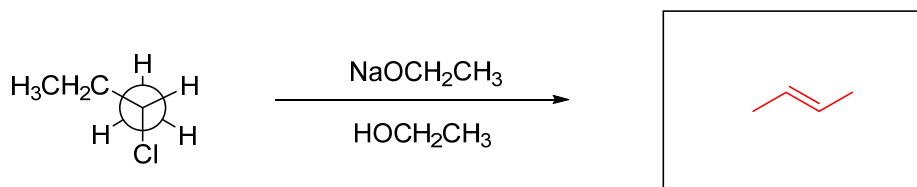
This problem was taken, verbatim, from the practice exam! While the Newman projection shown makes it tempting to eliminate HCl to form the terminal alkene, you must be careful and realize that the molecule can also eliminate HCl to form the more thermodynamically favorable disubstituted *trans* alkene. Perhaps the best way not to miss this possibility is to convert the Newman projection into a Lewis structure before proceeding.

(iv) (5 points)

C_4H_8O
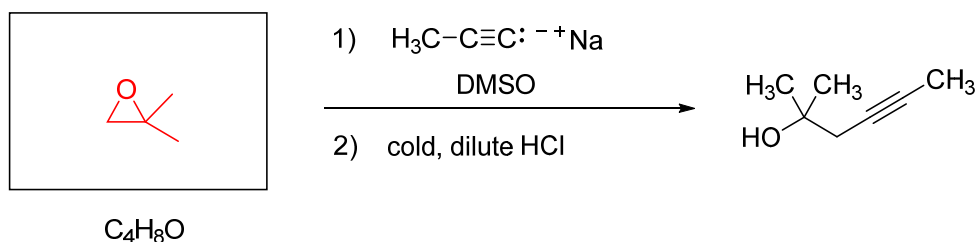
You are given a molecular formula for the mystery starting material, so the first thing to do is to calculate the degree of unsaturation. Here, $\Omega = [2 + 4(2) + 1(0) - 8] / 2 = 1$. By this calculation, we can expect the starting material to have either one ring or one π bond. When asked to determine a mystery starting material, you should work backwards from the product. By inspection, it is easy to see where the $H_3C–C≡C:^-$ group ended up. The triple bond is separated from the hydroxyl group by two carbons, and you should recognize that pattern of atoms as the product when an acetylide anion attacks an epoxide. This attack will occur at the less-hindered carbon of the epoxide electrophile. Epoxides are cyclic compounds, which jives with our calculation of $\Omega = 1$ for this molecular formula.
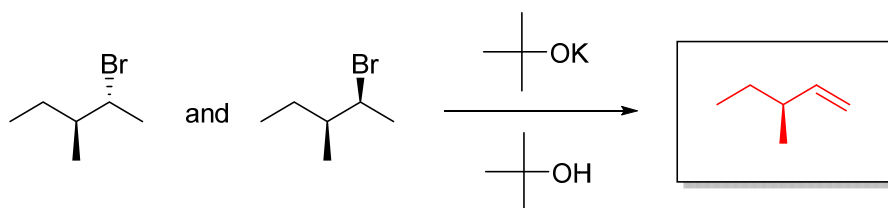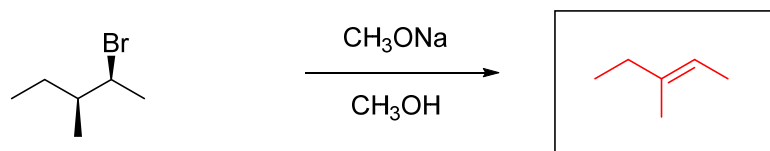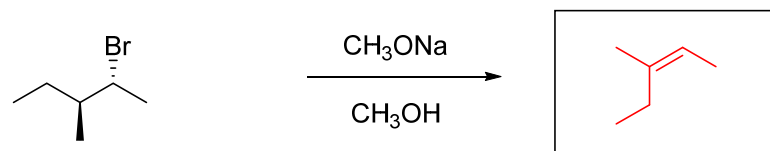
(v) (5 points)
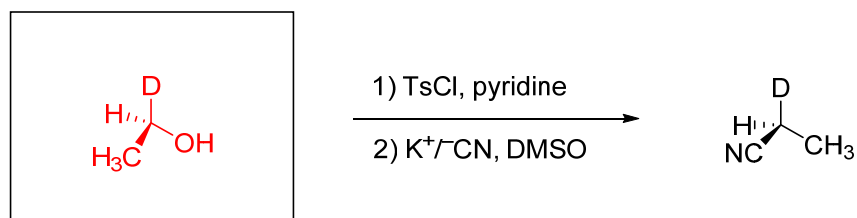
When asked to determine a mystery starting material, you should work backwards. The presence of cyanide (an excellent nucleophile) and DMSO (a polar, aprotic solvent) in the second reaction suggests an S_N2 reaction. This would install the cyano group (–CN) in the product. Now, we need to determine what group left when the cyanide attacked the central carbon. The reagents of the first reaction are those that convert a hydroxyl group (–OH), a poor leaving group, into a tosyl group (–OTs), an excellent leaving group. When we combine this information with the knowledge that S_N2 displacements take place with inversion of stereochemistry, we arrive at the starting material shown above.

Problem 4. (20 points total). Competing reactions of 2-bromo-3-methylpentane.

(i) (4 points) Treatment of both (2R,3S) and (2S,3S)-2-bromo-3-methylpentane with potassium *tert*-butoxide forms the same major product for both compounds. Draw a structure of this product in the box below.


(ii) (6 points) (2R,3S) and (2S,3S)-2-bromo-3-methylpentane react with sodium methoxide in methanol to produce different major products. Both products have the molecular formula C_6H_{12}, and they are diastereomers of each other. In the empty boxes below, draw the major product for each reaction.

(2S,3S)-2-bromo-3-methylpentane

(2R,3S)-2-bromo-3-methylpentane

(iii) (10 points) Explain why (2R,3S)-2-bromo-3-methylpentane forms the product it does versus the other products in parts (i) and (ii). Your explanation must include some form of three-dimensional drawing.

All of the reactions involve strong, alkoxide bases reacting with alkyl halides that have β-hydrogens capable of elimination. These conditions all favor the E2 mechanism. The product in part (i) forms because *t*-BuOK is a bulky base that will favor deprotonation of the less-hindered protons—those on the primary carbon—to generate the less-substituted alkene product shown above.

For part (ii), the methoxide base is smaller (than *t*-butoxide) and can better access the central protons in the two alkyl halide diastereomers. This makes the more thermodynamically stable alkene also accessible kinetically. E2 reactions occur when the halide and the proton being eliminated are in an antiperiplanar geometry. This geometry will control the stereochemistry (*E* vs. *Z*) of the alkene product.
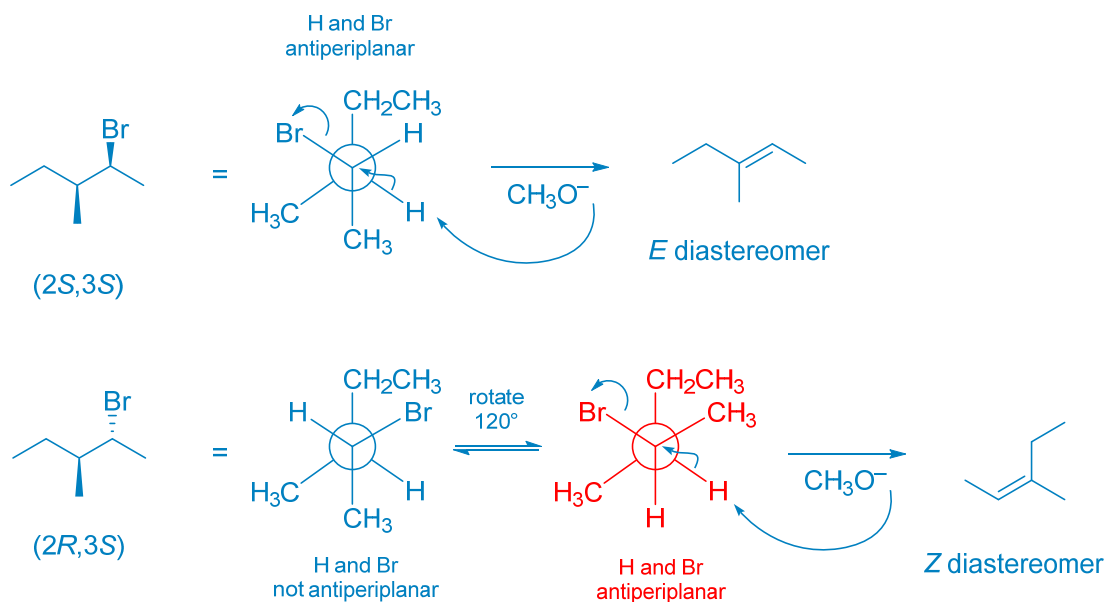
Problem 5. (15 points total) Mustard agents like 2,2'-bis(chloroethyl) sulfide can react to crosslink the DNA in your cells and cause cell death. They were employed extensively in World War I as chemical weapons. These molecules also react quickly with water:
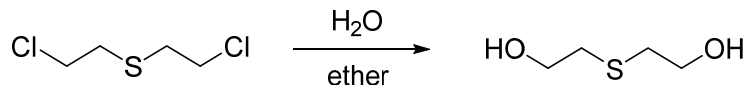
(i) (9 points) If one of the carbons of **J** is isotopically labeled with carbon-13 (*), the following product mixture is observed. The rate of the reaction does not depend on the concentration of water, only on the concentration of **J**. Propose a mechanism for the reaction of **J** with water that is consistent with these observations. Hint: It does not involve the formation of a carbocation.
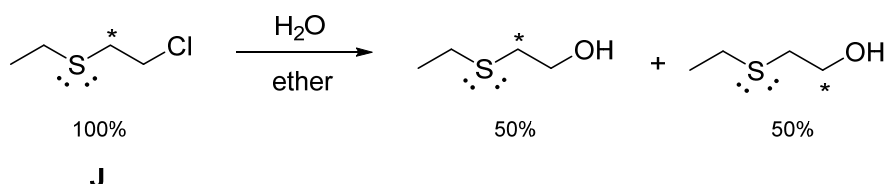

Mechanism
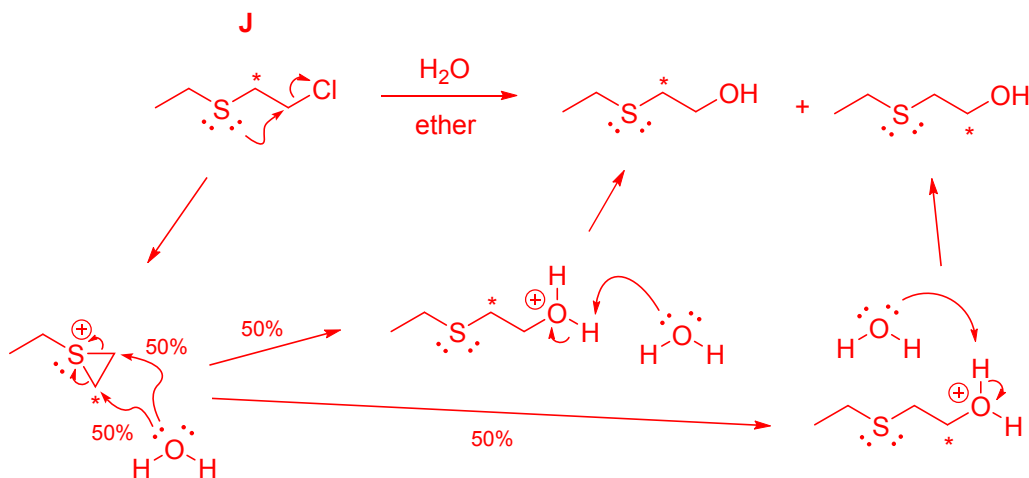
The hint that the mechanism does not involve the formation of a carbocation rules out the standard S_N1 mechanism, while the observation that the rate does not depend on the concentration of water (the nucleophile) rules out a standard S_N2 mechanism. The observation that the rate depends only on the concentration of starting material suggests it alone is involved in the rate-determining step.

You might remember that epoxides can be synthesized by the intramolecular nucleophilic attack of an alkoxide moiety of a molecule on an alkyl halide moiety on the vicinal carbon. Here, we have an analogous situation, where a lone pair on sulfur can displace the chloride anion two carbons away.

This first step generates a cationic intermediate with a three-membered ring and a positive formal charge on carbon. That sulfur cation is an excellent leaving group, and an incoming nucleophile would attack either carbon with no preference, since they are identical. That explains the 50/50 scrambling of the carbon-13 label.

(ii) (3 points) Circle which compound you would expect to react fastest with water.
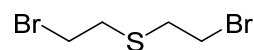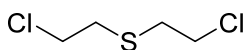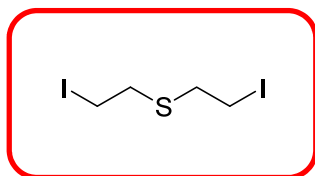
The rate-determining step of the reaction is the intramolecular displacement of the halogen by sulfur. Iodide is a better leaving group than chloride or bromide, so the first compound will react the fastest.

(iii) (3 points) Circle which compound you would expect to react faster with water.
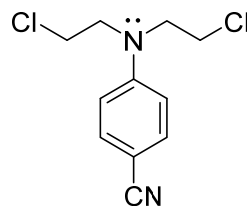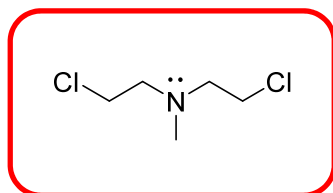
The rate-determining step of the reaction is the intramolecular displacement of the halogen. The nitrogen in the compound on the right is conjugated with an aryl ring with an electron-withdrawing cyano group (resonance effect). Due to this electronic effect, the lone pair on the nitrogen in the compound on the right is less available to serve as a nucleophile (than the lone pair on the nitrogen in the compound on the left). Thus, the compound on the left reacts faster.

Problem 6. (0 points total) Qualitative grumpiness assessment.

(i) _____E_____   Which of the following statements is funny?

> (a) "Organic chemistry is hard; I am having alkynes of problems."
> (b) "Professor S_N1 found the methyl halide hard to impress. She could never get a reaction from him."
> (c) "Why does carbon always return his tuxedo rentals on time? To avoid formal charges"
> (d) "Student #1: Hey man, do you know what reagent I should use to deprotonate an alcohol? Student #2: NaH, sorry, dude."
> (e) All of the above.
> (f) None of the above.
> (g) How can you joke around like this after giving me the hardest orgo exam of my life?!
> (h) Studying for this exam ruined my fall break; I am not in the mood to laugh.
> (i) My beloved Cardinals are in the World Series and I am sitting here taking an orgo exam. =/
> (j) (R)-2-chlorobutane
> (k) (S)-2-chlorobutane

This answer is obvious.