Problem Set 3

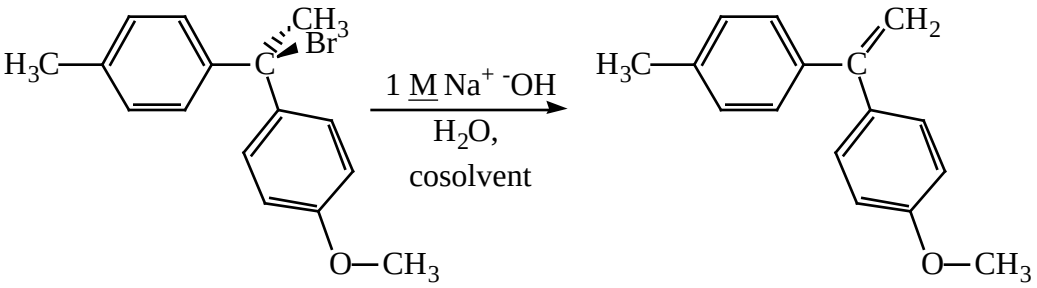
Out: December 3, 1999 Due Back: December 10, 1999

Chemistry 221, 1999

Answers to the following problems should be written, in order and labeled, on 8 1/2 x 11 inch paper. Answers written on the problem set itself will not be graded.

A. For each of the following 2 reactions, provide the mechanism type which best fits the situation and evidence as you see it. Clearly but briefly justify your choice by interpreting the facts given about these reactions. The explanation of the mechanism will be more important than your choice, so try to be clear and complete. Don't forget to read the structures and include the relevant information into your answers.

1)



Questions to Answer for Each Reaction:

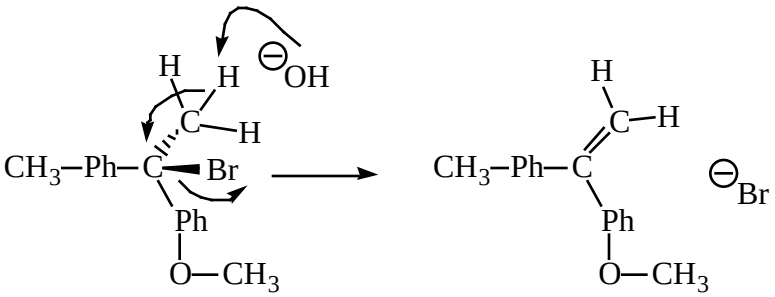
a. **Reaction type** (S_N1, S_N2, E1, E2).

b. Draw the structure of the **major product**. Be sure to specify stereochemistry, if appropriate.

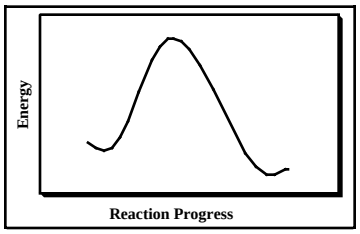
Shown above

c. Show the **stepwise mechanism** of the reaction.

This is a one step mechanism, so drawing an arrow between the two molecules above is theoretically ok. It's nicer with the electron arrows drawn on, and the reagents shown:



d. Draw a **reaction energy diagram** (energy vs. reaction progress). [see box at right]



e. Describe the **stereochemical outcome** of the reaction, using words or structures as needed.

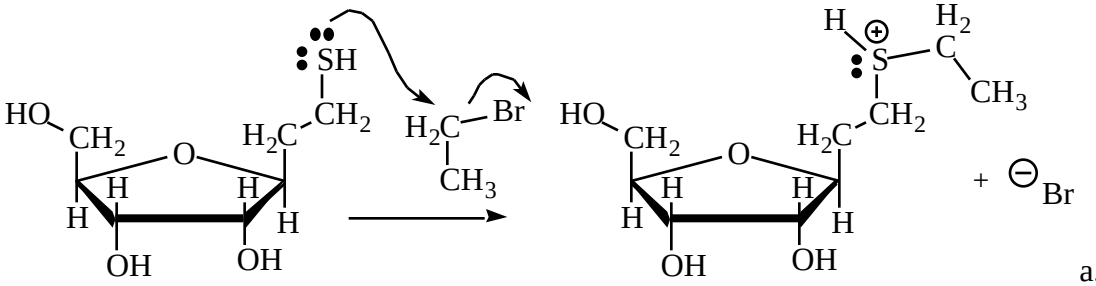
A glance at the product shows that the use of a single enantiomer of the starting material was a bit of a red herring--there are no cis-trans isomers of the product, so we would not be able to determine whether the molecule underwent the expected anti elimination.

f. Describe **one experiment** you could do to prove your idea about the mechanism type. Be sure to include both the description of the experiment **and** what results you

expect to get. Explain how that experiment excludes the alternate mechanisms (the ones you didn't choose).

Many answers are possible. Finding an alkene as the major product rules out any substitution mechanisms; all we have to distinguish after that is the choice between E2 and E1. That could most simply be done by measuring the effect of base concentration on the rate. If it is linear with base concentration, then the mechanism is E2.

2)



a. **Reaction type** (S_N1, $\underline{S_N2}$, E1, E2).

b. Draw the structure of the **major product**. Be sure to specify stereochemistry, if appropriate.

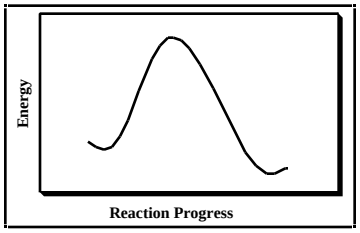
Shown above. Note that there are several choices to be made. Remember the first handouts we saw? They told you to find the leaving group as the first step. Looking at the candidates above, we come up with the semi-reasonable choices of OH^-, SH^-, or Br^-. Of these, pick the best: that would be Br^-, with a pK_a* of -7, vs. 10 for SH^- and 16 for OH^-.

Then, assuming you want a nucleophile (the substrate is 1°), pick the best: the R-SH is near the top of the nucleophile table. Then, you can just work the reaction.

c. Show the **stepwise mechanism** of the reaction.

This is a one step mechanism, so drawing an arrow between the two molecules above is theoretically ok. It's nicer with the electron arrows drawn on, and the reagents shown (see above)

d. Draw a **reaction energy diagram** (energy vs. reaction progress). [see box at right]



e. Describe the **stereochemical outcome** of the reaction, using words or structures as needed.

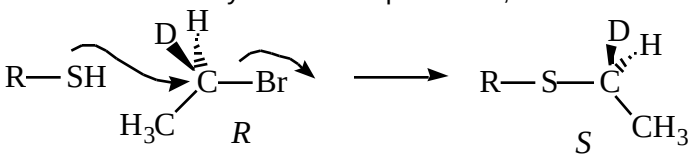
There are lots of stereogenic centers in this molecule. None of them is modified during the reaction, so unless there is a side reaction (which I would not predict), none of the stereogenic centers will change its configuration.

The site of attack is on an achiral carbon, so the predicted inversion could not be seen.

f. Describe **one experiment** you could do to prove your idea about the mechanism type. Be sure to include both the description of the experiment **and** what results you expect to get. Explain how that experiment excludes the alternate mechanisms (the ones you didn't choose).

Many answers are possible. Finding the product shown (called a thioether) as the major product rules out any elimination mechanisms; all we have to distinguish after that is the choice between S_N2 and S_N1. That could most simply be done by measuring the effect of nucleophile concentration on the rate. If it is linear with nucleophile concentration, then the mechanism is S_N2.

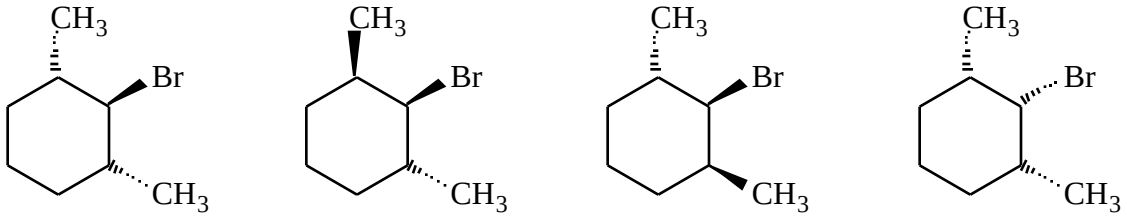
One could propose a stereochemical test for the substitution using a chiral bromoethane, made chiral by the substitution of one deuterium for one hydrogen. Luckily, you don't have to actually do these experiments; that would be a very tricky synthesis.



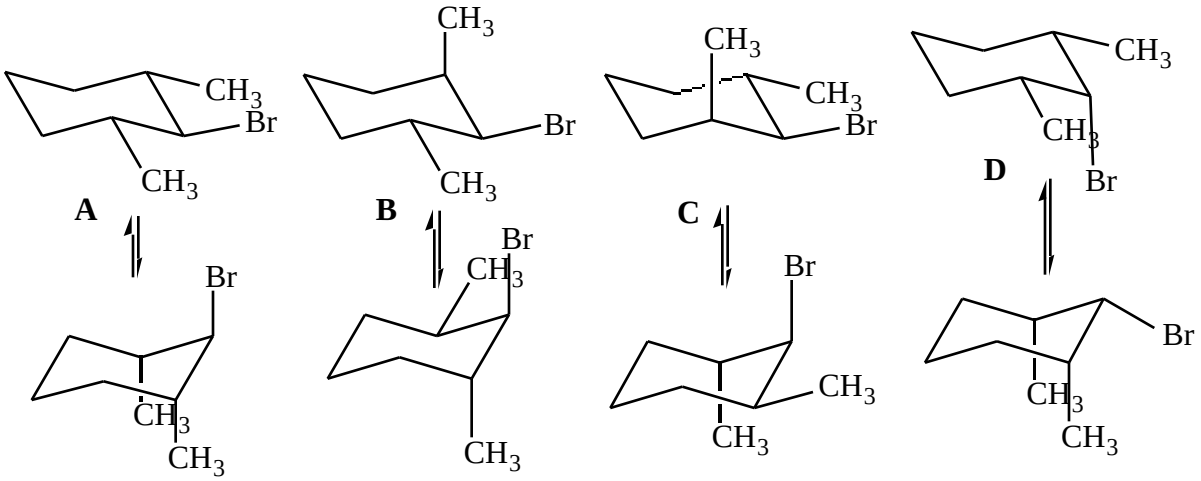
B. Consider the stereoisomers of 2-bromo-1,3-dimethylcyclohexane.

1. Draw all of the stereoisomers of this molecule. [Note the symmetry, and don't draw more than you need to.]

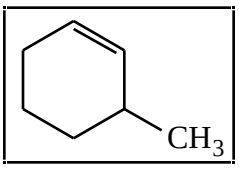
Planar form:



Chair form:



2. Draw the product of an E2 elimination of HBr from one of your isomers (conditions might be 1M $NaOCH_2CH_3$). Are all the products exactly the same?



Shown in the box to the right. Notice that this is a chiral molecule. The products will differ in their stereochemistry. Each enantiomer of the axial methyl form (shown above as B or C), will form a different enantiomer of the product.

3. Rank all of your isomers in order of reactivity in this E2 elimination.

D should be fastest, with B and C having equal and slower rates, leaving A definitely in the dust.

4. Comment on your ranking for each compound. Explain why the fastest should be fastest, etc.

You must draw the chair forms (or examined models) to answer this question. This is a good example of a question in which the way you examine the molecules makes a huge difference in whether or not you can even begin to answer it. Knowing how to look at molecules in order to answer questions is part of the general skill set that we have been working on all semester. You should always consider the view of the molecule when you are having trouble answering questions.

The two structural factors which affect the rate of E2 reactions are the substitution of the C^2 carbons (or the α-carbons, using the textbook's name) and the ability to adopt an anti conformation. Of these two, it must be the conformation, since the substitution of the products is exactly the same in each case!

Once we consider conformation, the most thorough answer will consider both chair forms, as shown above. In all of the structure sets above, the more stable chair is on the top. Interestingly, the differences are not all the same: I guess that the ΔE for A is about 3.7 kcal/mole, while that for B and C (which must be the same, since they are enantiomers) is about 0.5, and that for D is about 5.0 kcal/mole.

Looking at these structures, we find that only for molecule D is the Br axial in the more favored conformation. The Br must be axial for there to be an *anti* relationship between the C^2-hydrogens and the Br. Given the large energy difference between the two forms, we would guess that the Br is in the reactive position nearly all the time, allowing for the fastest reaction.

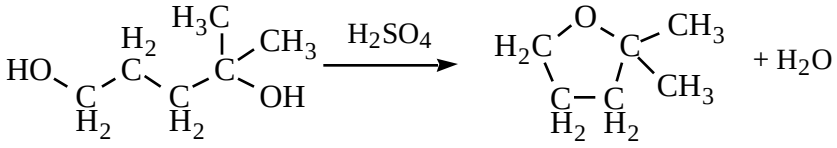
In molecules B and C, the molecules are in their reactive conformations about half the time (the energies of the two forms are quite similar). In addition, there is an *anti*-hydrogen only on one side of the ring; on the other, there is a CH_3 *anti* to the Br. Think about it--the reactive conformation is present less than half the time, so the chances are that the base will encounter a molecule in its reactive conformation in less than 50% of the encounters.

In molecule A, no matter what the conformation, there are never any *anti*-hydrogens next to the Br, and any E2 reaction would have to go through a non-standard pathway, slowing it done considerably, if it even proceeded at all.

5. Would you expect the isomers to have the same order of reactivity for an S_N2 reaction (say, with NaCN)?

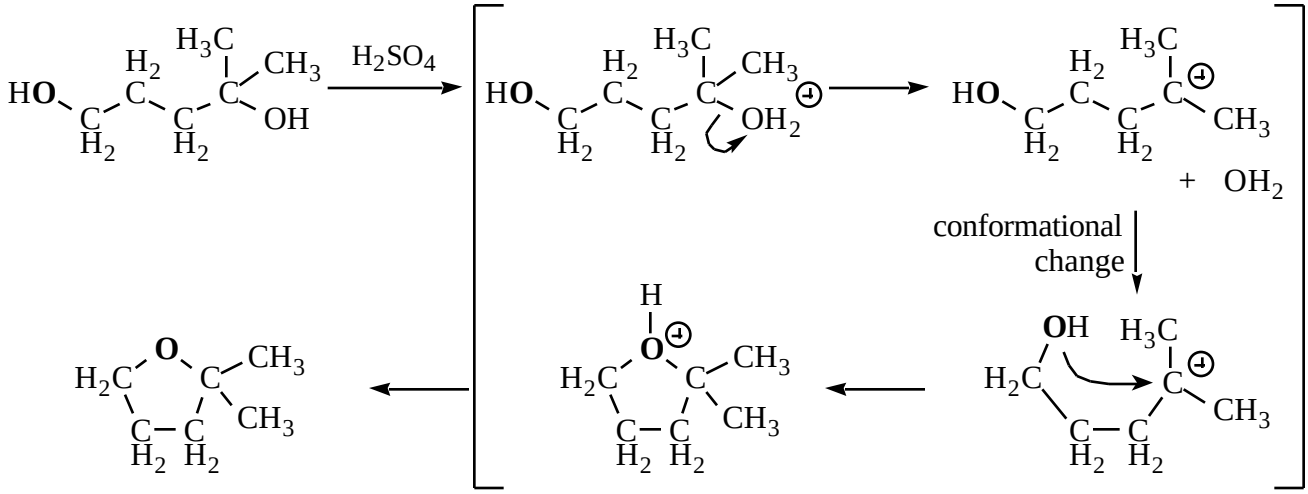
This is not an easy answer to get simply by inspecting the molecules. The fundamental answer to this is "not necessarily", since the two reactions have very different steric requirements. One thing we should know is that isomer A should be much more similar to the other molecules in reactivity. There is no requirement for *anti*-hydrogens for the S_N2 reaction.

C. The following reaction occurs when the diol shown is treated with sulfuric acid.



1

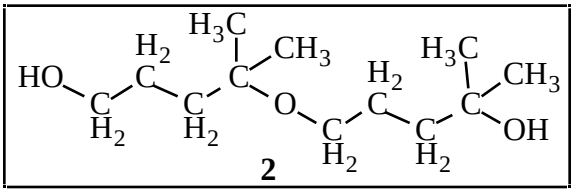
1. Propose a plausible stepwise mechanism for this reaction. It will be helpful to use reaction arrows.



2. Which oxygen remains after the reaction, and which is likely to be lost as water? Explain briefly.

The bolded oxygen above (the primary one) remains with its carbon, and the tertiary OH is removed in the solvolysis reaction. Removal of the tertiary OH makes the more stable carbocation, so it is preferred.

3. Another product, compound **2**, did **not** form in significant amounts. Why did compound **1** form, rather than compound **2**?



2

The reaction shown above gives a cyclization predominantly because it is generally much quicker to cyclize to a 5 or 6 membered ring than it is to bring two molecules together to react. The carbocation is extremely reactive, and the presence of a nucleophile on the end of a flexible tether will cause the two to collide frequently.