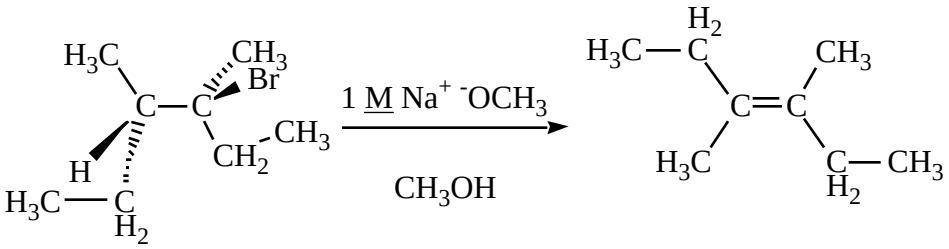
Problem Set 3--Answers

Out: November 23, 1998 Due Back: December 7, 1998

Chemistry 221, 1998

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 discuss those.

1)



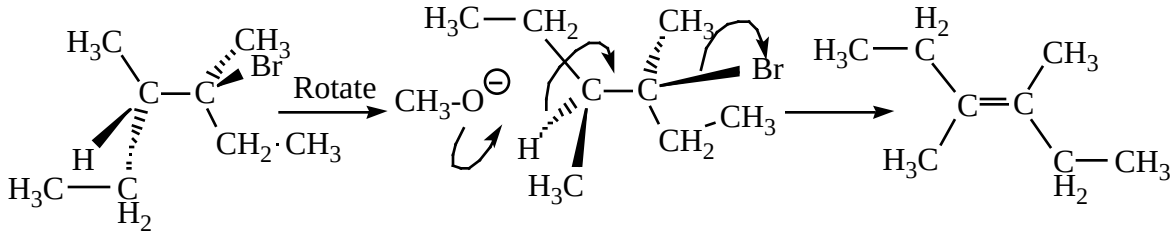
Questions to Answer:

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

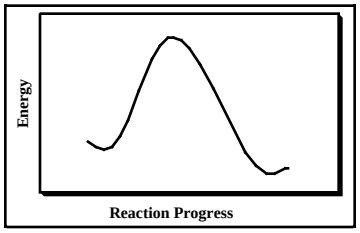
b. Draw the structure of the **major product**. Be sure to specify stereochemistry, if appropriate. Shown above

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. However, as seen below, a single bond rotation is required to bring the H and the Br into the anti position. It's also 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.

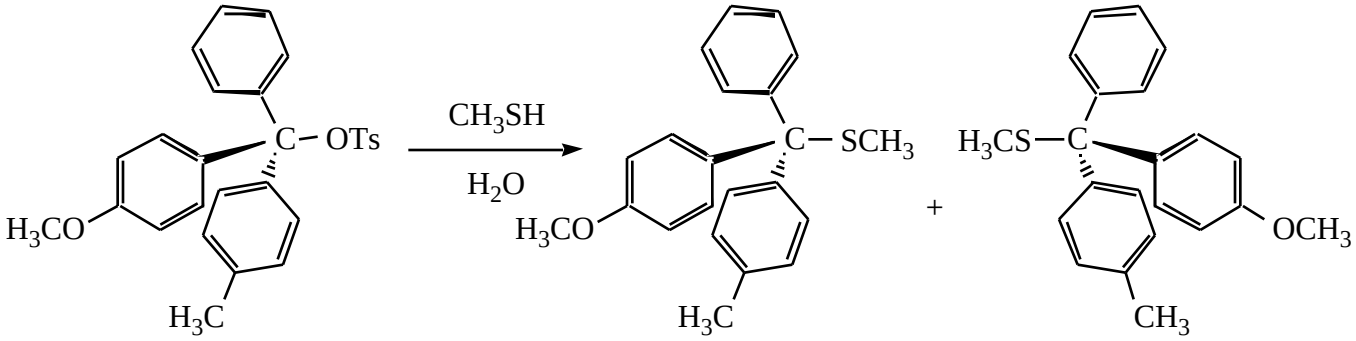
Note that only the *E* product is formed from this starting material. If the mechanism were E1, one would expect to see both the *E* and the *Z*.

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.

There are many possible answers to this question. One experiment that follows from part e., above is to look for the *Z* product. Not finding any, you might conclude that the mechanism is E2, especially if you went to the next step of trying the other diastereomer of the starting material, which should produce only *Z* on dehydrohalogenation. Or, one could measure the kinetic response to base concentration. If the concentration of $NaOCH_3$ were double, one would expect the overall rate to double. There may be quite a few other choices.

2)



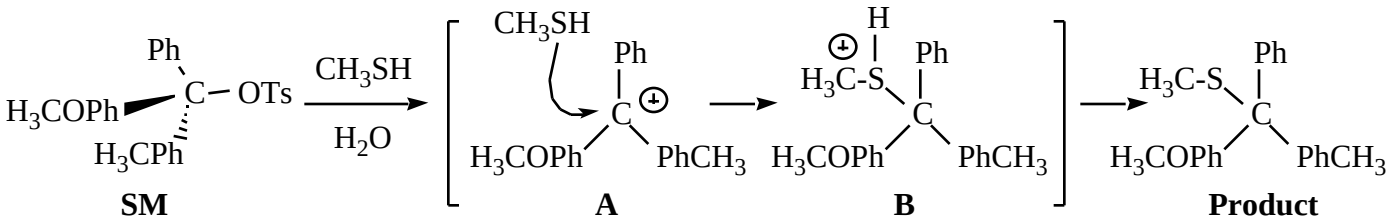
Questions to Answer:

a. **Reaction type** (S_N1, S_N2, E1, E2). $\mathbb{S}_\mathbb{N}\mathbb{1}$.

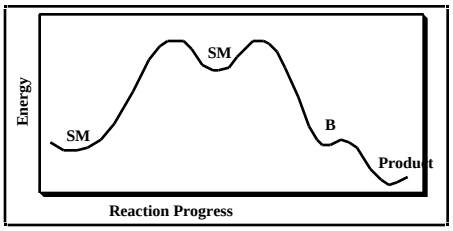
b. Draw the structure of the **major product**. Be sure to specify stereochemistry, if appropriate.

Shown above.

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



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.

The product should be a racemic mixture of the two possible major products. Since the carbocation (**A**) is planar, the attack should be equally probable from either side.,

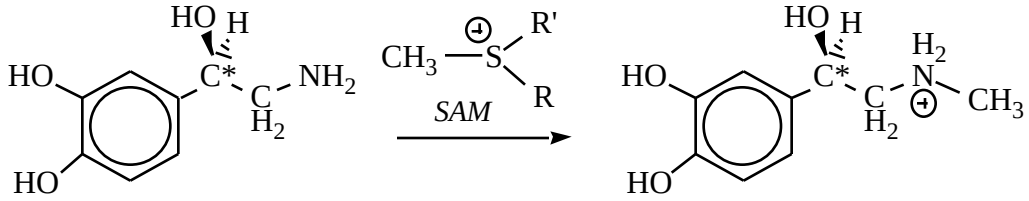
f. Describe **one experiment** you could do to prove your idea about the mechanism type. Be sure to include both the description of the experiment **and** what results you expect to get.

Once again, there are many possible answers. Kinetic analysis should show no effect of the thiol (CH_3SH) on the overall rate of product formation. The stereochemical outcome is also part of the proof: racemic or nearly racemic products would prove this to be S_N1; inverted product (*R*) would show S_N2. Note that we did not have to consider elimination; there are no H's on C^2.

Note that the point of these answers is to provide experimental evidence that your guess about reaction mechanism *for the molecule and reagents you are working with* is correct. Therefore, making radical changes in the molecules or reagent types would make the

work you do irrelevant to the original conditions. The other tricky part about answering these questions correctly is avoiding a result which would come out the same way for more than one reaction type. For example, if you are trying to distinguish between E2 and S_N2, you would not want to run an experiment (like reagent concentration, for example) that would have the same outcome for both reactions. [Of course, the products for E2 and S_N2 should be pretty different....]

B. The chemical neurotransmitter norepinephrine (noradrenaline) is converted in the body to epinephrine (adrenaline) by the molecule *S*-adenosyl methionine (SAM). Answer the following questions about this S_N2 substitution reaction.



Noradrenaline *Adrenaline*

1. What happens to the rest of the SAM molecule after the CH_3 group is transferred? Show a structure, using the R, R' abbreviations. *Hint: the leaving group may be unfamiliar. Use reaction arrows to figure it out, remembering where the new bond is formed.*

The leaving group is R-S-R'. This is a very good, stable leaving group. The pKa for the protonated form (R_2SH^+) is very low: actually about -7, although you don't have that figure. Even if your were to estimate the value as being similar to that of the hydronium ion H_3O^+ at -2, you would see that this is a pretty good leaving group.

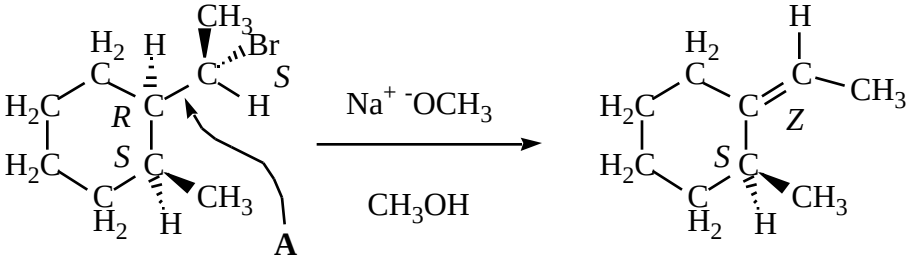
2. Give **two** reasons that the SAM molecule is a good S_N2 substrate [noradrenaline is the nucleophile].

First of all, it has a good leaving group. Secondly, the C^1 is a methyl, which is the least sterically congested possible.

3. What is the absolute configuration of the carbon with the asterisk (*) in adrenaline?

It is ***R***.

C. Consider the reaction of the compound below (a single enantiomer was used) with $NaOCH_3$ in methanol solvent:



1. Identify each chiral center appropriately with *R* or *S*. Mark the alkene with *E* or *Z*.
2. Is the product chiral?

Yes.

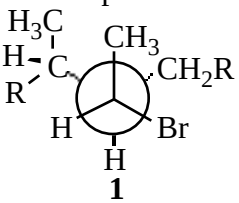
3. Is the solution optically active at the end of the reaction?

Yes.

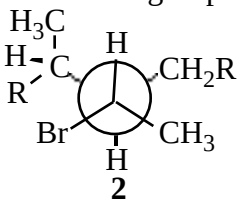
4. Briefly explain your choice for questions 2 and 3.

There is still one stereogenic center, which is still intact (and therefore completely *S*), meaning that the compound should still be optically active.

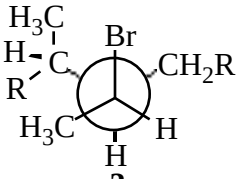
5. Draw a Newman projection of the three staggered conformations about the bond between the ring and the bromoethyl substituent (labeled "**A**" above). You may need to abbreviate part of the structure with "R" groups.



1



2

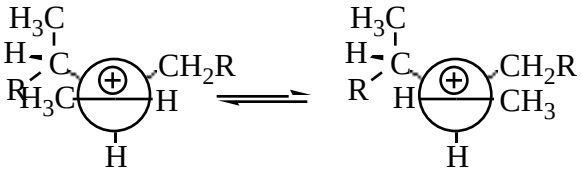


3

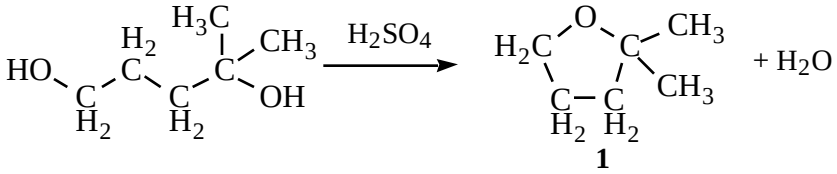
6. Explain, using structures, if necessary, why the double bond isomer shown is the only one to be formed in significant amounts if the concentration of $NaOCH_3$ is about 1M, while both double bond isomers are formed when the concentration of $NaOCH_3$ is about 0.01M.

Only one of the conformers shown above has a productive conformation for E2 elimination: conformer **3**. When the elimination is run under E2 conditions (concentrated base), the major isomer to be formed is the Z isomer as shown.

When the conditions are changed to E1 conditions (dilute base), the relationship between the H and the Br is lost, and the Br can leave at any time. The carbocation formed may have either conformation, interconverted and at equilibrium, and still lead to alkene:

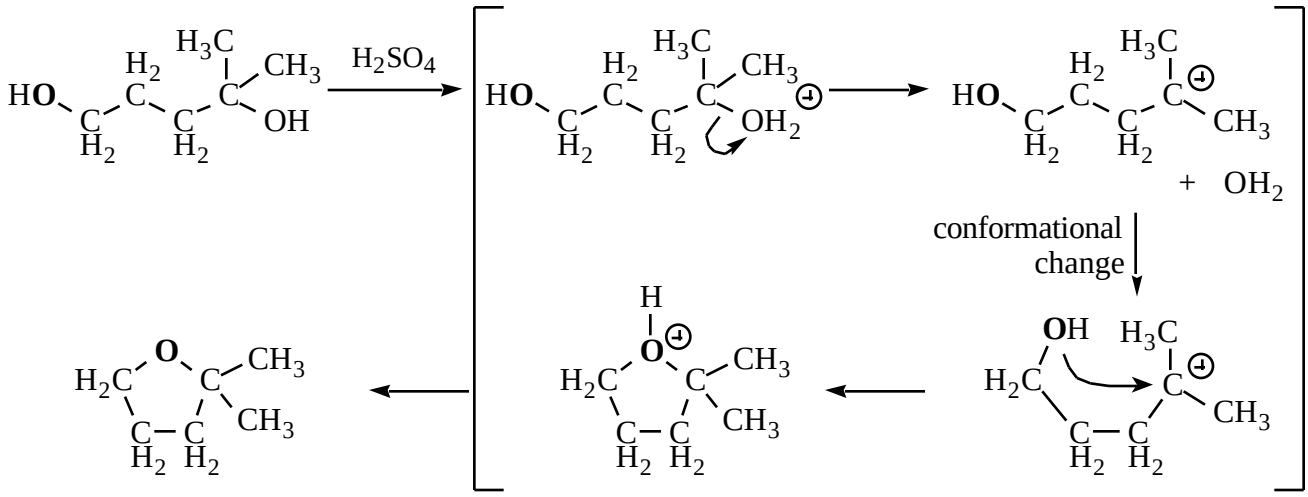


D. The following reaction occurs when the diol shown is treated with sulfuric acid.



1

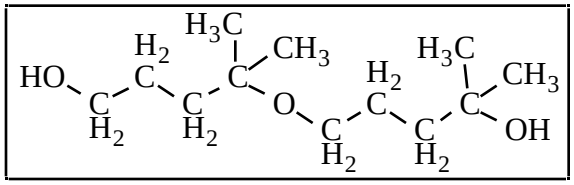
a) Propose a plausible mechanism for this step. It will be helpful to use reaction arrows.



b) 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.

c) Another product, shown to the right, did **not** form in significant amounts. Why did compound **1** form, rather than others?



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.