Exercise 8

Mechanisms of Reactions

Fig. X8-1

Svante August Arrhenius (1859- 1927). Predicted climate change.
http://nobelprize.org/nobel_prizes/chemistry/laureates/1903/arrhenius-bio.html

An understanding of the mechanisms of organic reactions provides valuable insight that immensely contributes to progress in organic chemistry. From an experimental and practical perspective, mechanistic information helps improve yields by enabling chemists to optimize reaction conditions. Mechanisms also provide very important predictive power that enables chemists to apply reactions to additional substrates and to modify the reaction pathway by varying and controlling the conditions. As humans, we are fortunately very curious beings and mechanisms help answer the question "how does this reaction occur". Ideally, we would like to be able to take a motion picture of the reaction as it occurs but at least currently, this is not possible. Despite lacking this ability, considerable useful information can be obtained about the mechanism of a reaction from:

product structure
kinetic studies (concentration and temperature effects on reaction rates)
reactant structural changes on rates and product structures
stereochemistry of the reaction
kinetic isotope effects
isotope labeling
solvent effects

The problems below have been designed to provide mechanistic experience and insight in organic reactions. For additional problems on the mechanisms of organic reactions, see ***Exercise 16.***

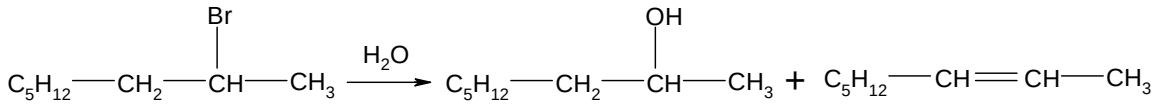
1. The mechanisms of nucleophilic substitution reactions (S_N1, S_N2) are usually extensively studied in organic chemistry courses.

   a. Write the reaction of *(R)*-2-bromobutane with hydroxide to give a 2-butanol in a stepwise fashion twice. Assume first that it follows an S_N1 mechanism and second an S_N2 mechanism. Use arrows to show bond and electron pair movement that play an important role during the conversion of stating material to product.

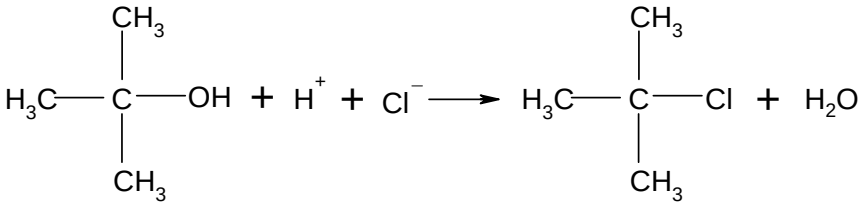
   b. Draw energy vs reaction coordinate diagrams for the two mechanisms in *a* above.

   c. List the variables above that might help to determine the operative mechanism. Explain how you would use the variable and give limitations of the method. [For example, consider changing from *(R)*-2-bromobutane to 2-methyl-2-bromobutane. A change from a 2^o reaction center to a 3^o center should result in a faster reaction for an S_N1 mechanism (increased carbocation stability and less steric crowding in the transition state going to the intermediate) and a slower reaction for an S_N2 mechanism (steric inhibition of attack by nucleophile). However, the structural change could change the mechanism from S_N2 to S_N1. If a reaction rate increase is observed, the conclusion should be that *(R)*-2-bromobutane reacts via an S_N1 reaction or the structural difference changed the reaction mechanism and evidence is needed from experimentation with a better control of variables.]

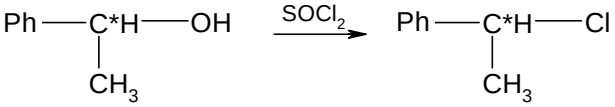
2. For the reaction illustrated below, the bromide reacts about 30 times faster than the corresponding chloride. However, the product ratio of olefin to alcohol is the same for the bromide and chloride. Discuss the mechanistic implications of this observation.



3. When the concentration of *t*-butyl alcohol is tripled in the following reaction, the reaction rate triples. However, when the chloride concentration is increased, the reaction rate remains unchanged. When the hydrogen ion concentration is doubled, the reaction rate doubles. Give a mechanism and an energy vs reaction coordinates diagram that are consistent with these experimental results.



4.. The reaction to the right proceeds with retention of configuration. Suggest a mechanism that is consistent with this observation.



5. a. The addition of bromine to *E*-2-butene yields the meso 2,3-dibromobutane [equal mixture of *(2S,3R)*-2,3-dibromobutane and *(2R,3S)*-2,3-dibromobutane]. Give the conclusions you can make about the mechanism from this information and write a detailed mechanism for the reaction.

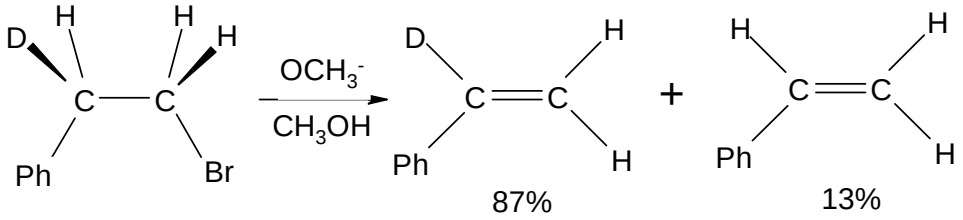
   b. If sodium chloride is present when the reaction above is run, what additional product(s) would you expect to obtain? Explain your answer.

   c. For Part b, should the amount of sodium chloride affect the reaction rate and/or the amount(s) of additional products? Explain your answer.

6. When Ph-CH=CD_2 is hydrated in the presence of acid to partial completion, the remaining recovered starting material does not show any loss of deuterium. What conclusions can you make about the mechanism from this result? Draw possible energy vs reaction coordinate diagrams for the possible operative mechanisms. Does the result allow you to rule out any mechanisms? Explain your answer.

7. a. Kinetic isotope effects provide a powerful technique for the investigation of reaction mechanisms. Suffice it to say that if the breaking of a C-H bond is important in the rate determining step, the reaction will be considerably slower (often as much as 7 times slower) if a deuterium (hydrogen-2) is present instead of hydrogen-1. On the other hand, if the a C-H bond does not break during the reaction or breaking of the C-H bond occurs in a fast step, approximately equal rates should be observed for C-H as for C-D containing compounds. When the elimination reaction of 1-bromo-2-phenylethane is run in the presence of hydroxide, the reaction rate for Ph-CH_2-CH_2Br is about seven times faster than for Ph-CD_2-CH_2Br. What does this observation allow you to conclude about the mechanism of the elimination for 1-bromo-2-phenylethane in base solution? Does this observation allow you to distinguish between E_1 and E_2 mechanisms.

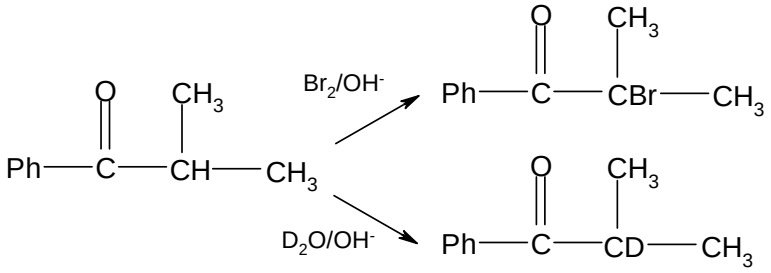
b. An alternative method to exploit isotope effects is illustrated in the reaction below:



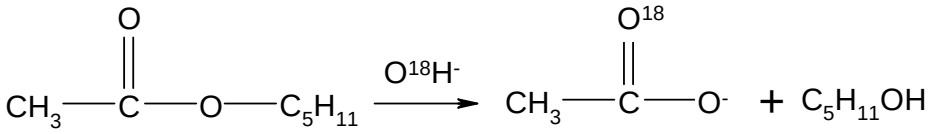
Are the results given above consistent with *part a* of this problem? Explain your answer.

8. In most electrophilic aromatic substitution reactions, the rates of reaction of benzene and perdeuterobenzene (hexadeuterobenzene) are within experimental error of each other. Write a plausible mechanism for electrophilic aromatic substitution that is consistent with the lack of an isotope effect. Based on your mechanism, explain why an isotope effect is not observed.

9. 2-methylpropiophenone undergoes bromination (Br_2/OH^-) or deuterium exchange D_2O/OH^-) at the α carbon at the same rate (to give 2-bromo-2-methylpropiophenone or 2-deutero-2-methylpropiophenone respectively). Discuss the mechanistic conclusions that can be drawn from these observations.

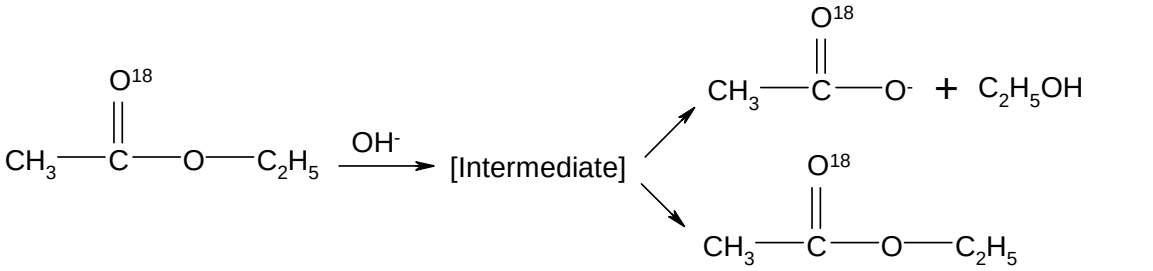


10. The reaction of hydroxide labeled with oxygen-18 with most esters results in incorporation of the label into the salt of the resulting acid and the absence of any labeled oxygen in the alcohol.



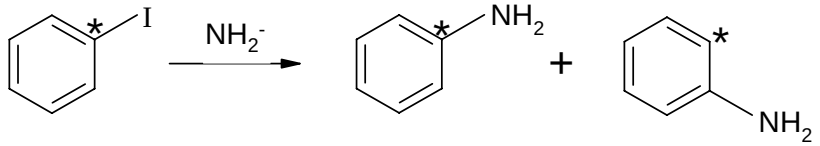
Discuss the mechanistic implications of this result. Be sure to discuss which bonds are broken and formed.

11. Additional information concerning the mechanism of ester saponification is derivable from the results obtained when the carbonyl oxygen in the starting ester is labeled with oxygen-18. After the reaction is run to partial completion, recovered starting material shows that the oxygen-18 content of the ester has decreased. Discuss the implications of this observation especially with regard to the reversibility of any steps in the reaction and the structure of a reaction intermediate.



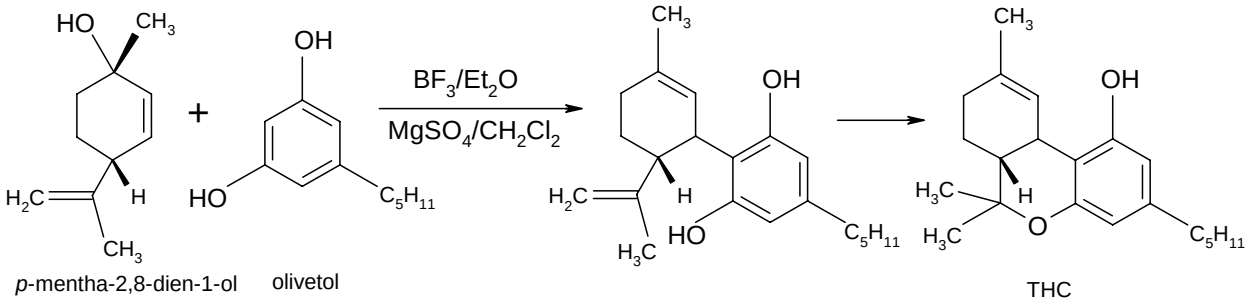
recovered "unreacted" ester has a lower percentage of oxygen-18 than in starting ester.

12. Propose a mechanism consistent with the following observation and suggest an experiment that could support or refute your proposed mechanism.



* = labeled carbon-14 50% 50%

13. A one-step synthesis of THC from *p*-mentha-2,8-dien-1-ol and olivetol was reported by Razdan et. al. [Razdan, R. K.; Daizell, C.; Handrick, G. R. *J. Am. Chem. Soc.*, **1974**, *96*, 5860-5865. "Hashish. A Simple One-Step Synthesis of (-)-Δ^1 -Tetrahydrocannabinol (THC) from *p*-Mentha-2,8-dien-1-ol and Olivetol"]. At first glance, the synthesis looks complex but more careful inspection reveals that the synthesis can be broken down into two reactions, a Friedel-Crafts like attack of a carbocation on an activated aromatic ring followed by electrophilic addition to a double bond.. Each of these reactions should be understandable in terms of mechanisms studied in the organic chemistry course. Write a detailed step by step mechanism for the overall reaction.



p-mentha-2,8-dien-1-ol olivetol THC