Concepts included:
- Sn1, Sn2 reactions
  - Hammond’s Postulate
- E1, E2 elimination reactions
  - Zaitsev Rule
- Reagents/Solvents favorable for each reaction mechanism

Part 1: SN2 and SN1 Substitution Reactions
1. (7.17) Which nucleophile is needed to convert \((\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Br}\) to each product?

Solution:
First draw out the structure \((\text{CH}_3)_2\text{CHCH}_2\text{CH}_2\text{Br}\) into a skeletal structure:

After this is drawn, we can see that it is a primary alkyl halide. Since this is a primary alkyl halide, it is most fit for SN2 reactions. Having this in mind, we can think about the nucleophile that will attack it.

A.
Remember that primary alkyl halide, which is what we see here, can only undergo SN2 reaction because a primary carbocation is too unstable. Whenever you see primary alkyl halides, rule out SN1 and E1 immediately. SN2 is also a concerted pathway, thus both arrow pushing occurs at the same step.

2. (7.22) What neutral nucleophile is needed to convert C to D? Imatinib, an effective treatment for certain cancers, is prepared in one step from D.

Solution:
Since the question is only asking for the step between C and D, we can ignore the part where the final imatinib is synthesized. From C to D, we can see the addition of a new group with the expulsion of Cl. Thus, this is a substitution reaction. Then, we see that the starting alkyl
halide was primary, thus, we can say that an SN2 reaction occurred that caused the formation of D from C.

Remember that all SN2 reactions follow this general equation.

Don’t be intimidated by the complex structures on the test, remember that all these reactions follow the same trend. Just stay calm and locate the alkyl halides, the leaving group, and the nucleophile. They may be a huge molecule like we saw here in this question.

3. (7.55) Draw the products of each reaction and indicate the stereochemistry where appropriate.
Solution:

- In all of part A-C, we see a strong nucleophile. Then, in part A and part B, we see a primary alkyl halide. Thus, in all 3 parts of the question above, they undergo an SN2 reaction. Then, remember that at the stereocenter of the reaction, a flipped stereochemistry is observed due to backside attack.

A.

Flip of stereochemistry is observed here. A good way to check is to see whether R
becomes S and vice versa after the backside attack. In this case, the starting structure was S configuration, the product was R configuration.

B.

No flipping of stereochemistry occurs here because this is a primary alkyl halide. Remember only the site of attack has a change in configuration.

C.

This is a good example to show which stereocenter is altered and which is not. Remember that only the site of backside attack is flipped, all other stereocenters stay the same.

4. (7.58) Consider the following SN1 reaction:

A. Draw a mechanism for this reaction with arrows
B. Draw the structure of any transition states
C. List out the rate equation for this reaction
D. What happens to the reaction rate if each of the following happens:
   i) Leaving group is changed from I- to Cl-
   ii) Solvent is changed from H2O to DMF
   iii) Alkyl halide is changed from (CH3)2C(I)CH2CH3 to (CH3)2CHCH(I)CH3
   iv) Concentration of H2O increases by a factor of 5
   v) Concentration of both the alkyl halide and H2O are increased by a factor of 5

Solution:
A. The key step is to have a carbocation step here. Remember that only in SN1 do we have a carbocation intermediate, not SN2. First, the leaving group is pushed out to form a carbocation, then, the nucleophile attacks the carbocation, neutralizing the charge.
B. There are 2 transition states for every SN1 reaction. Remember that transition states are the little peaks in energy diagrams. Here is an example of energy diagram of a typical SN1 reaction.

**SN1 energy diagram example**

**SN2 energy diagram example**

Thus, we need to draw 2 transition states.

**TS1:**

![TS1 diagram]

**TS2:**

![TS2 diagram]

C. SN1 is a first order rate kinetics reaction. Hence the name SN1. So we should only have 1
molecule in the rate law equation. 
rate=k[(CH₃)₂C(I)CH₂CH₃], the nucleophile does NOT affect the reaction rate.

D.

i) I- is a better LG than Cl-, thus, if we change the LG from I- to Cl-, the rate of the reaction would be **lowered**. Remember that a good LG is necessary for both SN1 and SN2.

ii) Polar protic solvents favor SN1, H₂O is a polar protic solvent while DMF is a polar aprotic solvent. If we change the solvent from H₂O to DMF, the rate of SN1 would be **lowered**. Remember that tertiary alkyl halides favor SN1 due to a more stable carbocation. Thus, if we change the alkyl halide from a tertiary one to a secondary alkyl halide, the rate of reaction would be **lowered**.

iv) Remember that the rate of SN1 is independent of the nucleophile concentration. Thus, whether increasing or decreasing the concentration of nucleophile **will not affect** the rate of the SN1 reaction.

v) The rate of SN1 is only dependent on the concentration of the alkyl halide. Thus, if we increase both the alkyl halide and the nucleophile 5 fold, the rate will be increased by a factor of 5 as well due to the increased alkyl halide concentration. Here is the rate law for SN1 and SN2 one more time:

SN1 rate = k[R-X]
SN2 rate = k[R-X][Nu⁻]

5. (7.60) Draw the products of each SN1 reaction and indicate the stereochemistry when necessary.

Solution:
A. Remember that in SN1, a racemic mixture would form when there is a stereocenter at the site of the attack. Thus, we should have 2 products here.

Step 1: Formation of Carbocation

Step 2: Nucleophilic attack
B. Similar effect is seen here where a racemic mixture of both stereoisomers will be formed.

Step 1: Formation of carbocation

Step 2: Nucleophilic attack (Both sides)

6. (7.74) Devise a synthesis of each compound from an alkyl halide using any other organic or inorganic reagents.

a.
Part 2: E1 and E2 Elimination Reactions

1. Rank the alkenes in each group in order of increasing stability
Least Stable 

Most stable 

Intermediate

b. \( \text{CH}_2=\text{C(CH}_3\text{)CH}_2\text{CH}_3 \)  
\( \text{CH}_2=\text{CHCH(CH}_3\text{)}_2 \)  
\( (\text{CH}_3\text{)}_2\text{C}=\text{CHCH}_3 \)

Disubstituted 

Monosubstituted 

Trisubstituted

Least stable                             Most stable

To determine stability of alkenes remember the following two facts: The more substituted the alkene the more stable the alkene as R groups are able to donate electron density into the Sp2 hybridized carbons of the alkene. When alkenes are equally substituted it helps to distinguish between cis and trans isomers, the latter being more stable as they have fewer unfavorable steric interactions than the former.

Tip: I highly suggest drawing all condensed structures into skeletal structures just so no point of the molecule goes unnoticed

2. Rank the alkyl halides in each group in order of increasing reactivity in an E2 reaction

a. \( (\text{CH}_3\text{)}_2\text{C(Br)CH}_2\text{CH}_2\text{CH}_3 \)  
\( (\text{CH}_3\text{)}_2\text{CHCH}_2\text{CH}_2\text{CH}_2\text{Br} \)  
\( (\text{CH}_3\text{)}_2\text{CHCH}_2\text{CH(Br)CH}_3 \)

Tertiary alkyl halide 

Primary alkyl halide 

Secondary alkyl Halide

Most reactive 

Least reactive 

Intermediate

b. 

Primary alkyl halide 

Tertiary alkyl halide 

Secondary alkyl halide

Least reactive 

Most reactive 

Intermediate

To determine the most reactive alkyl halide in an E2 reaction it is best to classify the alkyl halide as either a primary, secondary, or tertiary alkyl halide. As the number of R groups on the carbon with the leaving group increases, the rate of an E2 reaction increases. This is because the more
substituted carbon will end up forming a more substituted (thus more stable) alkene after the E2 reaction, lowering transition energy in the process, increasing the halides reactivity.

3. (8.28) Which alkyl halide forms each of the following alkenes as the only product in an elimination reaction?

a. Solution

\[
\begin{align*}
\text{1-bromo-3-methylbutane} & \quad \xrightarrow{\text{E2}} \quad \text{3-methylbut-1-ene} \\
\end{align*}
\]

b. Solution

\[
\begin{align*}
\text{(bromomethyl)cyclohexane} & \quad \xrightarrow{\text{E2}} \quad \text{methylene cyclohexane} \\
\end{align*}
\]
4. Draw all of the substitution and elimination products formed from the following alkyl halide with each reagent. Indicate the stereochemistry around the stereogenic centers present in the products, as well as the mechanism by which each product is formed.

Part A:
Part B:
It is good to break down the problem.

5. Predict the major E2 product formed from each starting material.

a. 

b. 

\[
\begin{align*}
\text{Cl} & \quad \text{Cl} \\
\text{CH(CH}_3)_2 & \quad \text{CH(CH}_3)_2
\end{align*}
\]

c. 

\[
\begin{align*}
\text{Cl} & \quad \text{D} \\
\text{D} & \quad \text{CH(CH}_3)_2
\end{align*}
\]
6. Draw all constitutional isomers formed in each elimination reaction. Label the mechanism as E2 or E1.

a. \( \text{Br} \)\( \xrightarrow{-\text{OCH}_3} \)

b. \( \text{Br} \)\( \xrightarrow{\text{CH}_3\text{OH}} \)

c. \( \text{I} \)\( \xrightarrow{-\text{OC(CH}_3)_3} \)

d. \( \text{ClCH}_2\text{CH}_3\text{CH}_3 \)\( \xrightarrow{\text{H}_2\text{O}} \)

e. \( \text{Cl} \)\( \xrightarrow{-\text{OH}} \)

f. \( \text{Cl} \)\( \xrightarrow{-\text{OH}} \)
Part 3: Cumulative Reaction Mechanisms

<table>
<thead>
<tr>
<th>Alkyl halide type</th>
<th>Reaction with</th>
<th>Mechanism</th>
</tr>
</thead>
</table>
| 1° RCH₂X | • Strong nucleophile  
  • Strong bulky base | → Sₙ₂  
  → E₂ |
| 2° R₂CHX | • Strong base and nucleophile  
  • Strong bulky base  
  • Weak base and nucleophile; | → Sₙ₂ and E₂  
  → E₂  
  → Sₙ₁ and E₁ |
| 3° R₃CX | • Weak base and nucleophile  
  • Strong base | → Sₙ₁ and E₁  
  → E₂ |
1. Determine which reaction mechanism the following conditions favor.
   
a. Primary alkyl halide, NaOCH₃, H₂O
   Sn₂; Primary alkyl halides cannot undergo Sn1 or E1. NaOCH₃ is a strong nucleophile that favors Sn2. The reagent (nucleophile or base) is more important than solvent in determining reaction mech, so even though water prefers Sn1 the strong nucleophile overrides its effects and the reaction undergoes Sn2.

   b. Secondary alkyl halide, DBU, DMSO
   E₂; DBU is a strong, non-nucleophilic base that promotes E2 reaction. DMSO reinforces this as it is a polar aprotic solvent.

   c. Secondary alkyl halide, EtOH, H₂O, heat
   Sn1 AND E1; EtOH is a weak base/nucleophile that cannot enforce Sn2/E2 rxns. H₂O further promotes Sn1 and E1.

   d. Tertiary alkyl halide, KOTBu, acetone
   E₂; KOTBu is a strong bulky (thus non-nucleophilic) base and acetone is polar aprotic.

2. Complete the following reactions by adding appropriate reaction conditions or products. Include the major product.
   
a. 

Since we observe a substitution of a Cl substituent to an I and that inversion and ONLY inversion occurred, this rxn is Sn2. Since I is substituted in, choose a reagent with iodide and a polar aprotic solvent.
b. KOtBu is a strong non-nucleophilic base that facilitates E2. Since there are 2 beta-H’s present, multiple products result, and the more substituted and stable product is the major product (Zaitsev’s Rule). Note that trans is more stable than cis.

\[
\begin{align*}
\text{CH}_3\text{OH} & \quad \text{Br} \\
\text{H}_2\text{O, Heat} & \quad \text{H}_2\text{O, Heat}
\end{align*}
\]

CH$_3$OH is a weak base/nucleophile. On a secondary alkyl halide both E1 and Sn1 may occur. This leads to two Sn1 products (attack from top or bottom face) and two E1 products (from 2 different beta-H’s). The more substituted alkene is the major product. Note that elimination usually predominates substitution when a weak base and nucleophile reacts with a secondary alkyl halide.
3. Draw the product(s) of the following reaction pathways.

In the top rxn, KOH is a strong nucleophile that promotes Sn2 and thus inversion at the chiral center, and ONLY the inverted product emerges. In the bottom rxn, H2O is a weak nucleophile that promotes Sn1 which first undergoes the creation of a carbocation. The carbocation is flat and thus the H2O can attack it from the top or the bottom face, leading to a racemic mixture of enantiomers.

4. Draw the appropriate product(s) for the following reactions. Indicate the major product and stereochemistry, if applicable.
   a.

   DBN is a bulky and strong base that promotes E2. Be careful! There’s only 1 beta-H, resulting in a single product.
b.

With a weak base/nucleophile on a tertiary alkyl halide, the reaction can proceed via Sn1 AND E1. This leads to 2 Sn1 products (Attack from the top or bottom face) and 4 E2 products (because there are 3 different beta-H’s, and for the one not in a ring, cis and trans products can form). The Zaitsev product (major product) is the one that’s most substituted.

c.

This question is kind of tricky! NaOH is a strong base and a strong nucleophile, meaning it can facilitate E2 AND Sn2. However, notice that there are NO beta-hydrogens! Despite being a great base, only Sn2 reaction occurs because elimination cannot occur without beta-H’s. Note that Sn2 leads to inversion, and only the inverted product