Instructions/Notes:
- **Bold** numbered questions have appeared on past exams.
- Suggested times are provided in brackets.
- Try the questions without looking at your notes.
- Selected mechanism-type questions will be covered in the tutorial.
- You may email me at ekwan@chem.utoronto.ca if you have any questions.
- Many questions are from Clayden. Good luck!

General Hints (which may or may not apply here):
- Number the atoms in the key starting materials, intermediates, and products.
- Pay attention to any changes in stereochemistry or unexpected retention in stereochemistry.
- Look for sources and sinks for electrons.
- Use all available evidence; be sure your mechanism can explain all the evidence.
- Circle all charges and check for conservation of charge and mass in each step.
- Solvents can play a reactive role.

**Theoretical-Type Questions**

1. Please explain, with the aid of a diagram and an appropriate example, how the magnitude of a primary kinetic isotope effect provides information about the structure of a rate-determining transition state. (10 minutes)

2. Please give the structure of a solvatochromic dye and outline how it can be used to produce a solvent polarity scale. (10 minutes)

3. The IR C-H stretch frequency changes from 3000 cm⁻¹ in iodoform (CHI₃) to approximately 1925 cm⁻¹ when hydrogen is replaced with tritium at 298 K. Please calculate the theoretical maximum PKIE \( \frac{k_H}{k_T} \) for a unimolecular thermal reaction. The following constants may be useful: speed of light: 2.998 x 10¹⁰ cm s⁻¹, Planck’s constant: 6.626 x 10⁻³⁴ J s; Avogadro’s number: 6.022 x 10²³ mol⁻¹. (10 minutes)

4. Please give an example of a reaction where \( \frac{k_H}{k_D} \) might be much greater than the theoretical maximum of approximately 7. Give a brief explanation of why this might be so. (5 minutes)

5. Please give an example of a reaction where the \( r \) parameter in the Yukawa-Tsuno linear free energy relationship is greater than unity. Interpret the meaning of such a value. (5 minutes)
6. (i) What is the purpose of crossover experiments? (5 minutes)
   (ii) Consider the following reaction which the famous Eschenmoser worked on:

   An appealing mechanism is this 6-endo-tet ($S_N2$) process:

   When the starting material is mixed with its hexadeuterated congener in base, the following products were observed:

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1 6-endo-tet is the Baldwin classification for this “cyclizations”. This nomenclature was not covered in class and is not important to this discussion. In the jargon, a 6-endo-tet cyclizations is Baldwin-disfavored.
Think carefully about these results, then please answer the following questions:

(i) Can the leftmost product be explained by the mechanism above? Why or why not? (5 minutes)
(ii) Does the above mechanism require revision? If so, please provide a new mechanism. (5 minutes)

7. This is a very easy review question:

(i) Please give an example of an E1 reaction. (2 minutes)
(ii) Please draw the energy-reaction coordinate diagram for this reaction. (2 minutes)
(iii) Please label the transition state(s) and the intermediate. Are transition state(s) found at energy minima, or energy maxima? Are intermediate(s) found at energy minima or energy maxima? (2 minutes)

Mechanism-Type Questions

NOTE: These questions are roughly arranged in order of increasing difficulty. Please choose a few problems you would like to see taken up during the tutorial.

Easy Questions

1. The Hammett $\rho$ for the following reaction is -2.0:

(i) What is the name of this acid-catalyzed rearrangement? (1 minute)
(ii) Based on this evidence, what is the likely rate-determining step? (5 minutes)

2. The synthesis of peptides on polystyrene beads is called the Merrifield Approach. An important step is the coupling of an amine with a carboxylic acid. The following is a simple exercise in arrow-pushing.

(i) A common coupling agent is called DCC—dicyclohexylcarbodiimide. It is used as follows:

Upon aqueous workup, a urea is produced. Please suggest a plausible mechanism for this transformation. The abbreviation “Cy” indicates a cyclohexane ring. (10 minutes)
(ii) DCC is somewhat problematic because it may racemize the carboxylic acid. An alternative is the use of HOBt, which stands for 1-hydroxybenzotriazole:

![Reaction Equation]

Please suggest a plausible mechanism for this transformation. (Hint: could nucleophilic catalysis be involved?) (10 minutes).

3. Consider the following dehydrohalogenation reactions:

![Relative Rates]

Using the appropriate Newman projections, please explain the difference in reactivities. (Hint: These are elimination reactions which require a specific orbital overlap to occur.) (5 minutes)

**Moderate Questions**

4. The acidic hydrolysis of the below carbodiimide has a Hammett $\rho$ of -0.8. Please suggest a plausible reaction mechanism. (10 minutes)
5. Please consider the isomerization of Z-cinnamic acids under acidic conditions in water:

\[
\begin{align*}
\text{X} & - \text{C} = \text{C} & \text{H}_2\text{O} & \text{H}^+ \\
\text{CO}_2\text{H} & \rightarrow & \text{X} & - \text{C} = \text{C} & \text{CO}_2\text{H}
\end{align*}
\]

The following evidence was obtained:

(a) The rate is faster in H$_2$O than in D$_2$O. ($k_{\text{H}} / k_{\text{D}} = 2.5$)
(b) When the reaction is performed in D$_2$O, the product has approximately 80% D at C-2.
(c) The Hammett $\rho$ for this reaction is -5.

Please combine observations (a)-(c) into a suitable reaction mechanism and provide explanations as to what each observation means. (15 minutes)

6. The ketal is a common protecting group for ketones. Consider the following acid-catalyzed transformation:

\[
\begin{align*}
\text{O} & \text{O} & \text{H} & \text{H}_2\text{O} & \text{O} & \text{O} \\
\text{H} & \text{H}_2\text{O} & \text{O} & \text{O} & \text{O} & \text{O}
\end{align*}
\]

(i) Has the oxidation state changed? (1 minute)
(ii) Please suggest a plausible mechanism for this transformation. (Hint: The mechanism begins with protonation of a ketal oxygen and subsequent attack of water.) (10 minutes)

7. The Wallach rearrangement of N,N'-diphenyl-diazene N-oxide (1) to 4-phenylazo-phenol (2) takes place under acidic conditions and is shown below. (20 minutes)

\[
\begin{align*}
\text{N} & \text{N} & \text{O} & \text{Wallach Rearr.} & \text{N} & \text{N} & \text{O} \\
\text{1} & \text{2} & \text{OH} & \text{OH} & \text{OH}
\end{align*}
\]

Please consider the following observations:

(a) When 1 is placed in a dilute aqueous sulfuric acid solution made from concentrated H$_2$SO$_4$ and water containing 10% H$_2^{18}$O, the product contained 10% $^{18}$O.
(b) Kinetic studies indicate the existence of a diprotonated intermediate.
(c) A $^{14}$N-labelled nitrogen atom in the starting material is totally scrambled in the product.

(i) Combine observations (a)-(c) below into a suitable reaction mechanism, and please give an explanation as to what each observation means.
(ii) Consider observation (a). What further experiment would you perform to confirm that your interpretation of this observation is valid?
(iii) Please propose a possible kinetic study that would lead to observation (ii).
8. Please consider the interesting ester hydrolysis reaction below:

\[
\text{\begin{array}{c}
\begin{array}{c}
\text{CH}_3 \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{CH}_3 \\
\text{H}_2\text{O}
\end{array}
\end{array}
\rightarrow
\text{\begin{array}{c}
\begin{array}{c}
\text{CH}_3 \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O}
\end{array}
\end{array}} + \text{CH}_3\text{COOH}
\]

(a) The rates of ester hydrolysis and hydration of the aldehydes are the same.
(b) If the reaction in carried out in H\textsubscript{2}\textsuperscript{18}O, then half the resulting acetic acid has one \textsuperscript{18}O atom; the other half has none.

Please outline a reasonable reaction mechanism for the above transformation and provide explanations as to what observations (a) and (b) mean.

**Harder Questions**

9. Please consider the following reaction:

\[
\text{tBu} \quad \text{18O} \\
\text{O} \\
\text{H}_2\text{SO}_4 \\
\text{HOAc} \\
\text{\begin{array}{c}
\begin{array}{c}
\text{tBu} \\
\text{18O} \\
\text{CH}_3 \\
\text{O} \\
\text{H}_2\text{SO}_4 \\
\text{HOAc}
\end{array}
\end{array}} + \text{\begin{array}{c}
\begin{array}{c}
\text{tBu} \\
\text{18O} \\
\text{O} \\
\text{CH}_3 \\
\text{H}_2\text{SO}_4 \\
\text{HOAc}
\end{array}
\end{array}
\]

Noting the stereochemical and isotopic labeling evidence, please suggest a plausible mechanism for this transformation. (10 minutes) *Reference: JACS 1964, 86, 1951.*

10. The ring-contraction below is quite similar to the Favorskii rearrangement:

\[
\text{O} \\
\text{1. Br}_2 \\
\text{2. EtO, EtOH}
\]

Please propose a suitable reaction mechanism for this transformation. There may be more than one possible answer. (Hint 1: Step 1 is a standard bromination reaction. Hint 2: Step 2 involves a strained cyclopropanone intermediate.) (15 minutes)