DO NOT REMOVE ANY PAGES FROM THIS EXAM PACKET.

Have a swell winter break. 😊

Directions for drawing molecules, reactions, and electron-pushing mechanisms:
Draw all lone pairs, bonds, arrows, formal charges, and stereochemistry explicitly in all molecular structures.

Directions for all calculations:
Explicitly show all work on all calculations and include all important labels.

Directions for analyzing graded spectra:

- Label each set of equivalent protons using the H_a, H_b, H_c etc. labeling system. Assign each $^1$H-NMR signal and write your assignments directly onto the spectrum. Use the empirical chemical shift parameters (Curphy-Morrison parameters) or chemical shift tables found at the end of the exam to assist your $^1$H-NMR analysis and signal assignments.

- Assign the hybridization of the $^{13}$C-atoms responsible for each $^{13}$C-NMR signal. Identify specific functional group signals; you do not need to assign individual carbon atoms to each signal.

- Assign each key IR absorption band >1500 cm$^{-1}$ to a specific functional group. Draw a part structure responsible for the vibration next to each band.

- Draw fragments for all labeled peaks in the EI-MS directly onto the spectrum (you do not need to show the fragmentation mechanism unless directed to do so).
1) The reaction of household bleach (sodium hypochlorite) and 4'-methoxyacetophenone is highly dependent on the pH of the reaction mixture. At high pH, bleach will oxidize the starting material via a haloform reaction (labeled Reaction A below). At low pH, the bleach will produce an electrophile capable of an EAS reaction (designated Reaction B below). **(67 pts total)**

**Reaction A**

1) bleach pH = 11-12, Δ
2) H₃O⁺

4'-methoxyacetophenone

**Reaction B**

bleach pH = 4

room temperature

EAS Products

**Experimental procedure for reaction A at pH = 11 - 12**

To a 25 mL round bottom flask is added 4'-methoxyacetophenone (0.15 g, 1.0 mmol) and aq. 6% sodium hypochlorite solution (6 mL). The mixture is heated at reflux for 30 min, allowed to cool to room temperature, and aqueous 3 M sodium thiosulfate (Na₂S₂O₃) solution (2 mL) added. The reaction mixture is tested with KI-starch paper to confirm removal of excess oxidizing agent. The mixture is then treated with aq. 3M HCl solution until the solution is neutral and a solid precipitates. The solid is isolated by vacuum filtration, air-dried for 10 min, and analyzed by ¹H-NMR and ¹³C-NMR spectroscopy.

a) Use a series of resonance structures to estimate the chemical shift of the ¹H-atoms attached to the aromatic ring of the starting material (4'-methoxyacetophenone) relative to those of benzene. **(5 pts)**

b) On the subsequent page, assign each ¹H-atom in 4'-methoxyacetophenone to its corresponding ¹H-NMR signal using the assignments A - D provided. **(4 pts)**
4'-methoxyacetophenone
c) An aqueous solution of bleach (sodium hypochlorite, NaClO) has a pH > 7. Provide a balanced chemical equation for the reaction of hypochlorite ion (ClO⁻) with water to justify the basicity of this solution. (2 pts)

\[ \text{Cl}^- + \text{ClO}^- + \text{H}_2\text{O} \rightarrow \]

\[ \text{HClO}_2 + \text{OH}^- \]

(2 pts)

d) The haloform oxidation of a methyl ketone requires the addition of molecular chlorine or its formation in situ. In this experiment, the molecular chlorine is generated from the reaction of ClO⁻ and Cl⁻ in solution. Complete the balanced chemical equation for this reaction. Identify the chlorine atoms that have been oxidized and those that have been reduced. (2 pts)

\[ \text{Cl}^- + \text{ClO}^- + \text{H}_2\text{O} \rightarrow \]

\[ \text{HClO}_2 + \text{OH}^- \]

(2 pts)

e) The haloform reaction that oxidizes methyl ketones requires the formation of an enolate. Provide an electron pushing mechanism for enolate formation in basic aqueous conditions from 4'-methoxyacetophenone. (3 pts)
f) An NBO calculation on the B3LYP/6-31G(d) optimized enolate anion (C₉H₉O₂⁻) formed from 4'-methoxyacetophenone has been performed and the results are displayed below. Put a box around the most nucleophilic atom(s) and provide the resonance structures that justify their nucleophilicity. (4 pts)

![NBO calculation results](image)

-0.78 -0.21 -0.34 -0.31 -0.54
+0.36 -0.08 +0.28 -0.30 -0.71

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g) The electron pushing mechanism for the remainder of the haloform reaction is provided below. Several of the final steps of the reaction shown are reversible. The final step is irreversible; finish the reaction mechanism and explain what allows the reaction to proceed in relatively high yield. (4 pts)

![Haloform reaction mechanism](image)
h) In the workup of the reaction, 3 M aqueous sodium thiosulfate (Na₂S₂O₃) is added to remove any residual oxidizing agent. If the KI-starch paper turns blue/black when contacted by the mixture after addition of sodium thiosulfate, what does that indicate and what should be done to correct the issue? (3 pts)

i) In the workup of the reaction, 3 M aqueous HCl is added to the reaction mixture which results in the formation of a solid product. Provide the chemical reaction that generates the solid product and explain why the product precipitates by referring to its solubility before and after the reaction with HCl. *It may help to confirm the identity of the solid product using the ¹H-NMR spectrum on the subsequent page.* (4 pts)

j) Draw the product molecule directly on the ¹H-NMR spectrum on page 7 and assign each of its ¹H-atoms using the signal labels A-C provided. (4 pts) The ¹³C-NMR spectrum on page 8 is provided for reference only.
Experimental procedure for reaction B at pH = 4

To a 25 mL round bottom flask is added 4'-methoxyacetophenone (0.15 g, 1.0 mmol) glacial acetic acid (1 mL), and aq. 6% sodium hypochlorite solution (2 mL). The mixture is stirred at room temperature for 30 min, during which time a solid precipitates. The solid is isolated by vacuum filtration, air-dried for 10 min, and analyzed by $^1$H-NMR and $^{13}$C-NMR spectroscopy.

\[
\begin{align*}
\text{bleach pH = 4} \\
\text{room temperature} \\
4'\text{-methoxyacetophenone}
\end{align*}
\]

k) Electrophilic aromatic substitution (EAS) reactions require the production of an electrophile. In this reaction, an electrophile capable of chlorination is generated from the reaction of hypochlorite (ClO$^-$) and acetic acid (CH$_3$COOH). Provide a balanced chemical equation and place a box around the active electrophile. (2 pts)

l) Determine the relative B3LYP/6-31G(d) energies of the two regioisomeric arenium cation intermediates for this reaction shown below. Set the lowest energy isomer to 0.0 kcal/mol (1 Hartree/particle = 627.509 kcal/mol). (2 pts)
m) Provide a series of resonance structures and a short explanation that justifies the relative stability of the lower energy arenium intermediate from the previous question. (3 pts)

n) State whether this EAS reaction is under thermodynamic or kinetic control. Draw a correct potential energy surface on the axes below that clearly depicts the formation of the arenium cations and place a box around the portion of the potential energy surface that determines the outcome of the reaction. (4 pts)
o) Two EAS products and one chlorinated byproduct are identifiable in the GC-Mass and $^1$H-NMR spectral data. Predict the observed coupling pattern and use empirical (Curphy-Morrison) parameters to predict the $^1$H-NMR chemical shift for all $^1$H-NMR atoms for the chlorinated byproduct shown below. (4 pts)

\[
\begin{align*}
4'\text{-methoxyacetophenone} & \quad \text{bleach pH = 4} \quad \text{EAS Products} \\
\text{room temperature} & \quad + \\
\text{chlorinated byproduct} &
\end{align*}
\]

p) The GC-Mass spectrum of the crude product obtained from the acidic reaction of bleach with 4'-methoxyacetophenone is provided on the subsequent page. Draw the structure of each component of the crude mixture 1 - 3 directly on their corresponding mass spectra. It may help to confirm the identity of each product using the $^1$H-NMR spectrum on page 13. (3 pts)

q) For the major component of the mixture, provide an electron pushing mechanism for the formation of the ion responsible for the base peak from the molecular ion in the space below. It may help to confirm the identity of each product using the $^1$H-NMR spectrum on page 13. (3 pts)
r) The $^1$H-NMR spectrum of the crude product obtained from the acidic reaction of bleach with 4'-methoxyacetophenone is provided on the previous page. Assign each of the labeled signals (A – G) in the aromatic region to their corresponding $^1$H-atoms directly on the spectrum. (7 pts)

s) Use both the GC-MS and $^1$H-NMR data to determine the ratio of the product ratio. Express the ratio in the form of **major EAS product : minor EAS product : chlorinated byproduct**, setting the relative amount of **chlorinated byproduct** to a value of one. Show your work below including the values selected for each molecule from each spectrum. (4 pts)

**GC-MS Ratio:**

**$^1$H-NMR Ratio:**
2) The reaction of benzophenone with a Grignard reagent derived from 1-bromo-4-fluorobenzene yields a triaryl alcohol product. As described by a reaction on the Chem 344 Fall 2015 midterm exam, benzophenone can be synthesized from benzhydrol using commercial bleach. The use of 1-bromo-4-fluorobenzene to form a Grignard reagent probes the reactivity differences of C–Br and C–F bonds. (33 pts total)

![Reaction Diagram]

**Experimental procedure**

To a dry 25 mL round bottom flask containing a stir bar is added Mg metal (0.135 g), a solution of 1-bromo-4-fluorobenzene (0.50 mL) in anhydrous diethyl ether (8 mL), and 1,2-dibromoethane (3 drops). The flask is equipped with a water condenser and a Drierite tube placed atop the condenser. The reaction mixture is heated at reflux for 30 min, allowed to cool to room temperature, and a solution of benzophenone (1.0 mL) in anhydrous diethyl ether (3 mL) added drop-wise with rapid stirring. The mixture is stirred for 10 min upon complete addition of the benzophenone solution, followed by drop-wise addition of aq. 6M HCl solution (~5 mL) with rapid stirring.

The reaction mixture is then transferred to a separatory funnel, water (10 mL) added, and the mixture extracted with diethyl ether (2 x 3 mL). The combined organic phases are stirred over anhydrous magnesium sulfate, the mixture filtered, and solvent evaporated from the filtrate to leave a yellow residue. A pale yellow solid is obtained upon addition of cold hexane (~5 mL) to the residue. The solid is isolated by filtration, recrystallized from iso-propanol solution, and analyzed by $^1$H-, $^{13}$C-, and $^{19}$F-NMR spectroscopy.
a) The aromatic region of the $^1$H-NMR spectrum of 1-bromo-4-fluorobenzene is provided below. Assign the labeled signals to their corresponding $^1$H-atoms and determine the values of the three- and four-bond coupling constants ($^3J_{HF}$ and $^4J_{HF}$) for this molecule. Show your work. (4 pts)

b) Determine the % ionic character of the C–Mg bond in the Grignard reagent. Identify the nucleophilic and electrophilic atoms in the reaction of the Grignard reagent with benzophenone. (2 pts)

\[
\text{% ionic character} = \left( \frac{X_C - X_M}{X_C} \right) \times 100 \%
\]

\[
\text{1) } \text{MgBr}^+ \quad \text{2) } \text{H}^+ \text{(aq) workup}
\]

F

MgBr

1)

2)

\[
\text{C} \quad \text{O} 
\]

\[
\text{F} 
\]

\[
\text{H}^+ \text{(aq) workup}
\]

\[
\text{benzophenone}
\]

c) During the formation of the Grignard reagent, why is the magnesium broken up, ground, cut, and/or scratched? (3 pts)
d) Diethyl ether is commonly used as a solvent for the formation of Grignard reagents as it helps stabilize the Grignard reagent by electron donation. Explain why acetone, which is also an electron donating solvent, is not an appropriate solvent for Grignard reagents including any necessary balanced chemical equations. (3 pts)

e) The reaction mixture of benzophenone and the Grignard reagent was heated using a reflux condenser for 45 minutes. Explain the purpose of reflux and what would happen to this reaction if heated without a reflux condenser. (3 pts)

f) In the box below, draw the organic product that is produced after addition of benzophenone solution to the reaction mixture and the organic product generated after subsequent addition of HCl\(_{(aq)}\). (2 pts)
g) After the acidic workup, the mixture is transferred to a separatory funnel a depiction of which is shown below. Clearly label each solvent layer on the image provided below. Place the organic product of the reaction in the appropriate layer. (3 pts)

h) After the organic layers are combined anhydrous MgSO$_4$(s) is added to the container. What is its purpose and how can you tell when sufficient anhydrous MgSO$_4$(s) has been added? (2 pts)
i) Determine the percent yield of this reaction given the tabulated quantities of reagents used and the quantity of purified product obtained. (3 pts) It may help to confirm the identity of the product using the $^1$H-NMR, $^{13}$C-NMR, and $^{19}$F-NMR spectra on pages 21 - 23. You do not need to assign the NMR spectra for credit.

<table>
<thead>
<tr>
<th>1-bromo-4-fluorobenzene</th>
<th>benzophenone</th>
<th>magnesium</th>
<th>purified product</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.500 mL</td>
<td>1.0 mL</td>
<td>0.135 g</td>
<td>0.607 g</td>
</tr>
<tr>
<td>175.00 g/mol</td>
<td>182.22 g/mol</td>
<td>24.305 g/mol</td>
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<tr>
<td>$\rho = 1.593 \text{ g/cm}^3$</td>
<td>$\rho = 1.11 \text{ g/cm}^3$</td>
<td>$\rho = 1.738 \text{ g/cm}^3$</td>
<td></td>
</tr>
</tbody>
</table>

j) The Grignard reagent derived from 1-bromo-4-fluorobenzene can also be used as a substrate for a Pd-catalyzed coupling reaction to form a biaryl compound. Two potential coupling products are depicted below. Draw a circle around the most likely product of the coupling reaction and briefly explain your choice. (2 pts)
k) Estimate the inter-ring dihedral angle of the biaryl molecule you selected as the product in part (j). Provide a brief explanation for your estimate referring to any important factors that impact the geometry. (3 pts)

l) The potential energy surface for a hypothetical uncatalyzed coupling to generate the biaryl molecule you selected as the product in part (j) is shown below. Draw an approximate potential energy surface for the Pd-catalyzed reaction assuming that oxidative addition is the rate-limiting step. Clearly label the activation barrier for the catalyzed and uncatalyzed reactions. (3 pts).
Interpretation not required for credit.
Interpretation not required for credit.
Interpretation not required for credit.
Name:

TA Name:

<table>
<thead>
<tr>
<th>Problem 1</th>
<th>Problem 2</th>
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<tbody>
<tr>
<td>a) ____/5</td>
<td>a) ____/4</td>
</tr>
<tr>
<td>b) ____/4</td>
<td>b) ____/2</td>
</tr>
<tr>
<td>c) ____/2</td>
<td>c) ____/3</td>
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<tr>
<td>d) ____/2</td>
<td>d) ____/3</td>
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<tr>
<td>j) ____/4</td>
<td>j) ____/2</td>
</tr>
</tbody>
</table>

| Total_____ /35 | Total_____ /32 | Total_____ /33 |

Grand Total = _____ /100

Grand Total = _____ /100 (math double-check)