CHEM 344 Fall 2015 Final Exam (100 pts)

Name:

TA Name:

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.

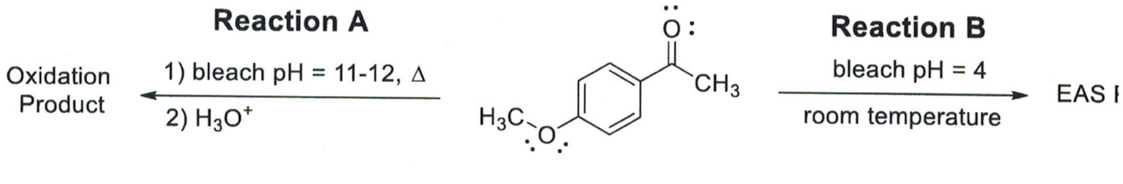
Directions for all calculations:

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)**

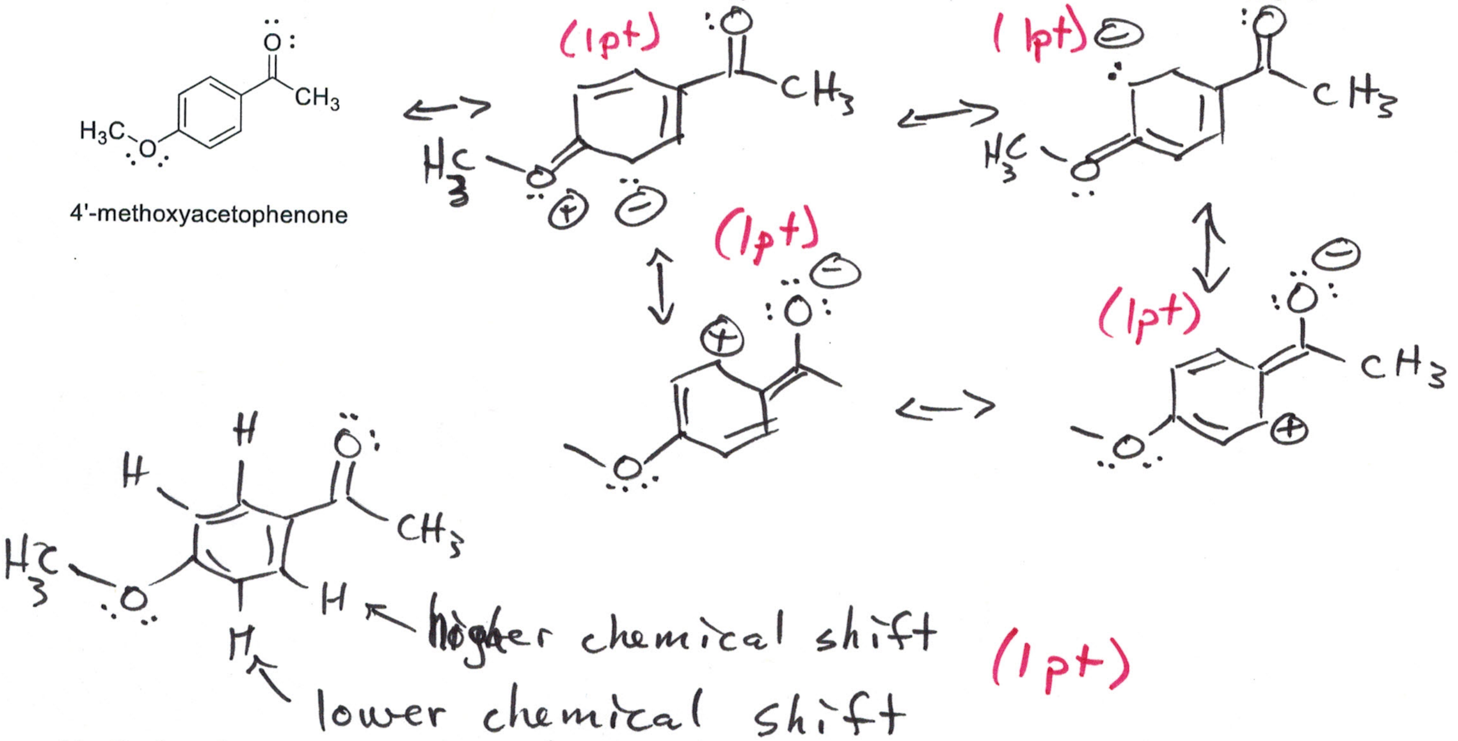


4'-methoxyacetophenone

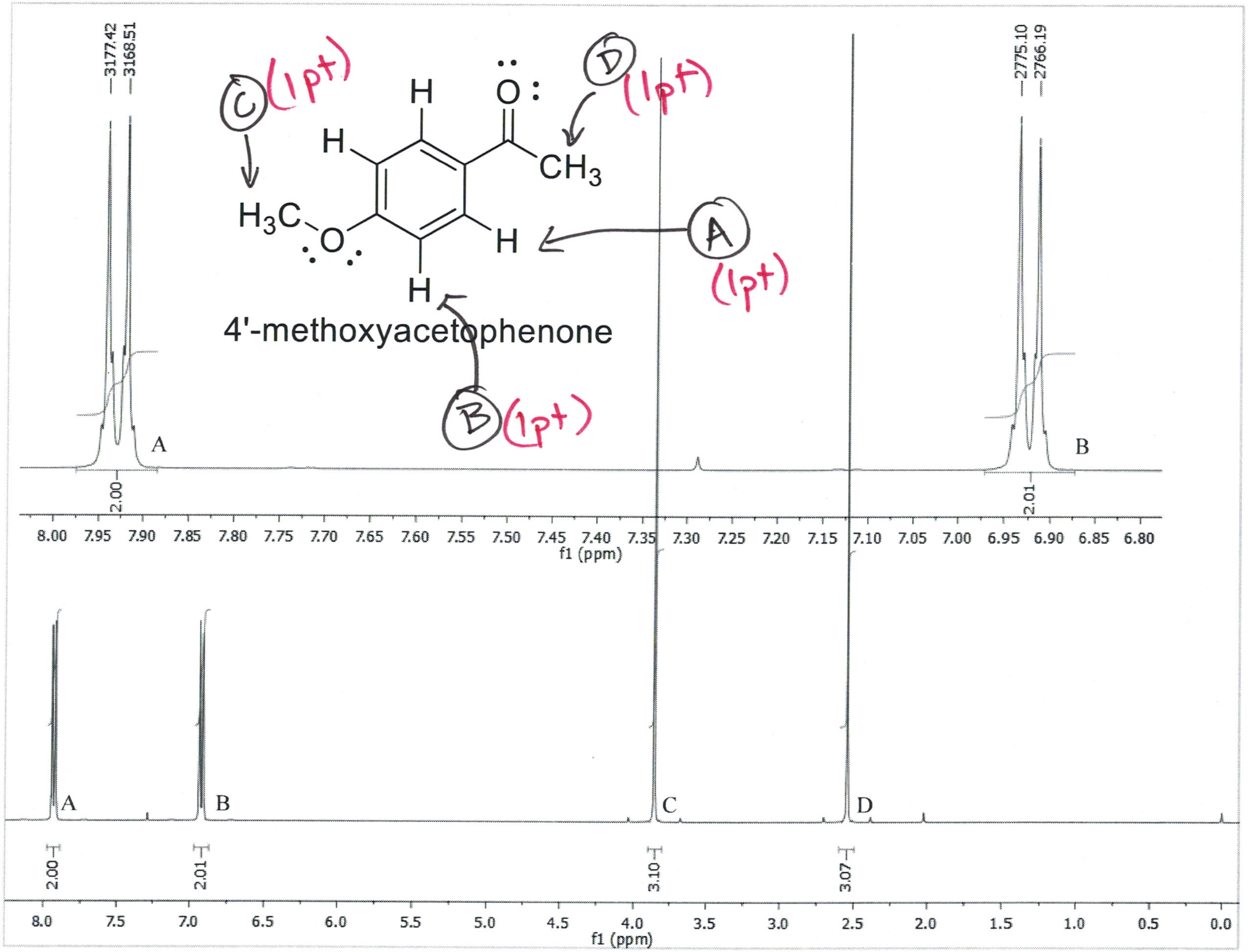
Experimental Procedure for Reaction A at pH = 11 - 12

In a 25 mL round bottom flask, place approximately 0.15 g of 4'-methoxyacetophenone and 6.0 mL of household bleach (nominally 6.0 % sodium hypochlorite, NaClO). Using a fractionating column and condenser, heat the mixture under reflux conditions for 30 minutes. Allow the reaction mixture to cool for 15 minutes and add 2 mL of 3 M aqueous sodium thiosulfate ($Na_2S_2O_3$). Confirm the removal of oxide the oxidizing agent with KI-starch paper. Add 3M aqueous HCl until the solution is neutral and a solid precipitate is formed. Collect the solid by vacuum filtration and dry the solid in an oven at 60 °C for an hour. Prepare a sample for IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR analysis.

a) Use a series of resonance structures to estimate the chemical shift of the ^{1}H-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 ^{1}H-atom in 4'-methoxyacetophenone to its corresponding ^{1}H-NMR signal using the assignments A - D provided. **(4 pts)**


3177.42
3168.51
2775.10
2766.19
C (1pt)
H
Ö:
D (1pt)
H
CH3
H3C
O
H
A (1pt)
H
4'-methoxyacetophenone
B (1pt)
A
B
2.00
2.01
8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85 6.80
f1 (ppm)
A
B
C
D
2.00
2.01
3.10
3.07
8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

c) An aqueous solution of bleach (sodium hypochlorite, NaClO) has a pH greater than 7. Provide a balanced chemical equation for the reaction of hypochlorite ion (ClO^-) with water to justify the basicity of this solution. **(2 pts)**

$$ClO^{\ominus}_{(aq)} + H_2O \rightleftharpoons \underbrace{\overset{\ominus}{O}H_{(aq)}}_{(1pt)} + HClO_{(aq)}$$

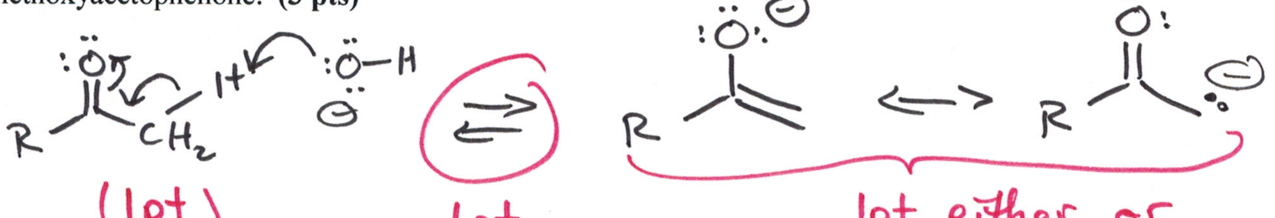
2pts for correct

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)**

$$\underset{\text{oxidized}}{Cl^{\ominus}} + \underset{\text{reduced}}{ClO^{\ominus}} + H_2O \longrightarrow \underbrace{Cl_2 + 2\,OH^{\ominus}_{(aq)}}_{1pt}$$

1 pt

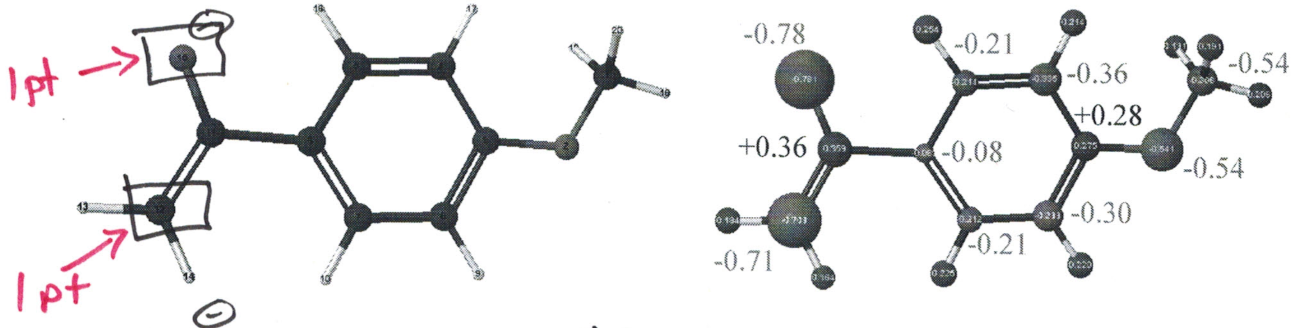
e) The haloform reaction that oxidizes methyl ketones requires the formation of an enolate. Provide an electron pushing mechanism for enolate formation in basic aqueous conditions from 4'-methoxyacetophenone. **(3 pts)**

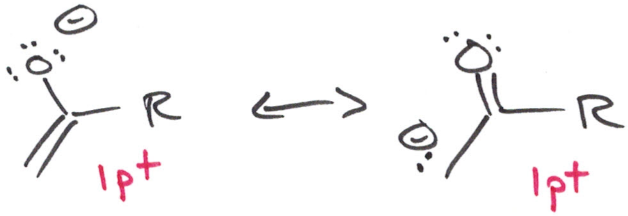


(1pt) 1pt 1pt either or both res. forms.

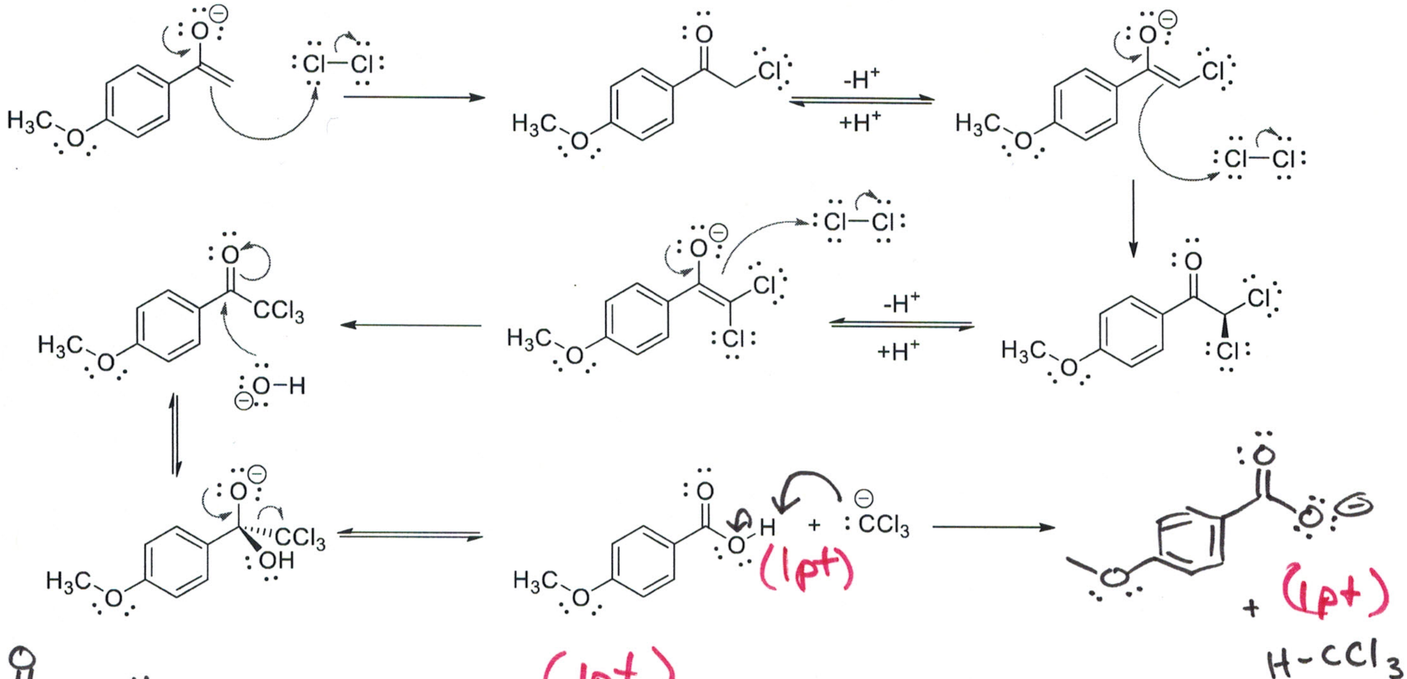
4

f) An NBO calculation on the B3LYP/6-31G(d) optimized enolate anion ($C_9H_9O_2^-$) formed from 4'-methoxyacetophenone has been performed and the results are displayed below. Put a box around the most nucleophilic atoms and provide the resonance structures that justify their nucleophilicity. **(4 pts)**

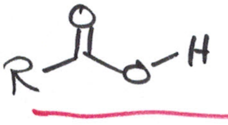




g) The electron pushing mechanism for the remainder of the haloform reaction is provided below. Several of the final steps of the reaction shown are reversible. The final step is irreversible; finish the reaction mechanism and explain what allows the reaction to proceed in relatively high yield. **(4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



(1pt)

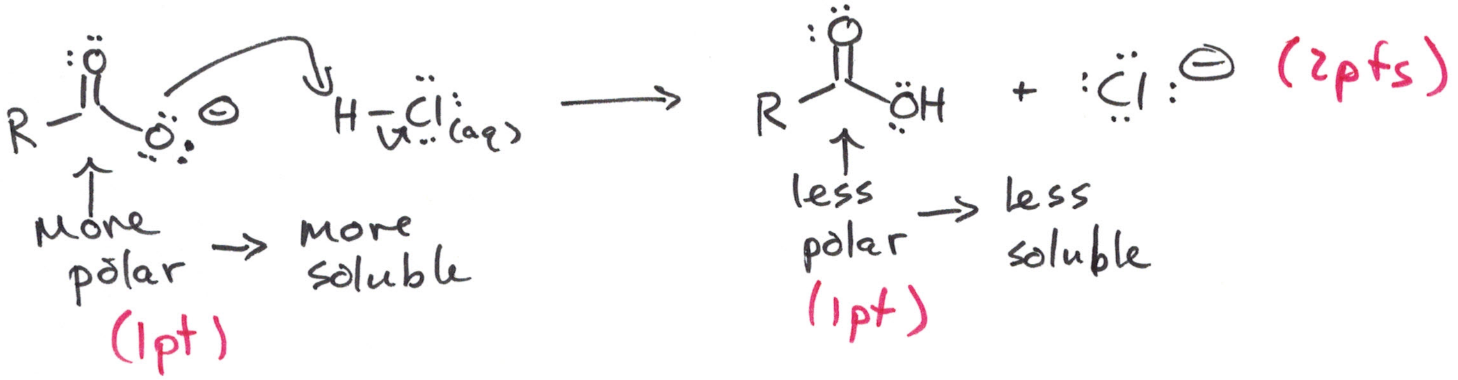
 is much more acidic than H-CCl3, which allows the reaction to progress forward in good yield by LeChâtelier's principle.

(1pt)

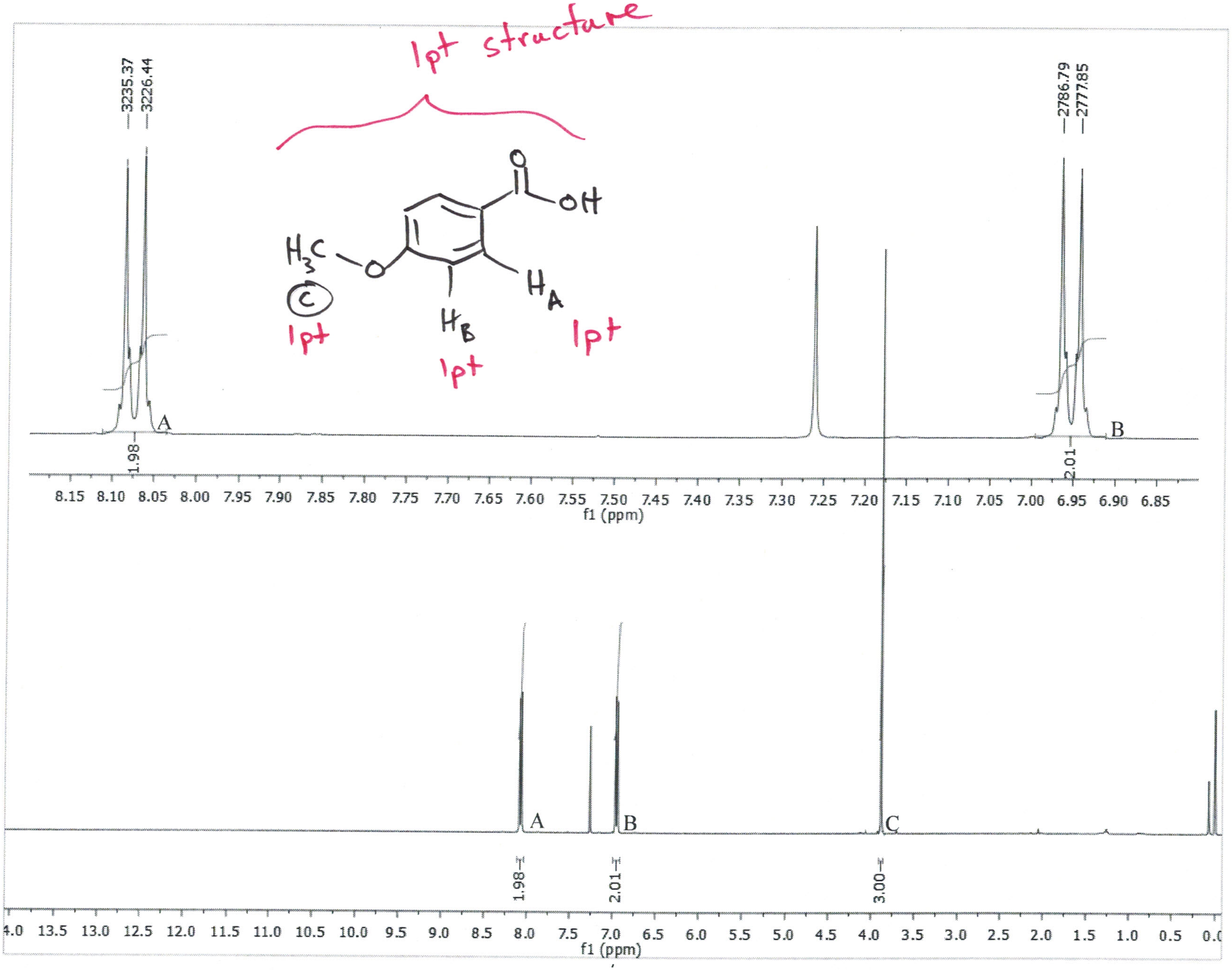
h) In the workup of the reaction, 2 mL of 3 M aqueous sodium thiosulfate ($Na_2S_2O_3$) are added to remove any residual oxidizing agent. If the KI-starch paper turns blue/black when contacted by the mixture after addition of sodium thiosulfate, what does that indicate and what should be done to correct the issue? **(3 pts)**

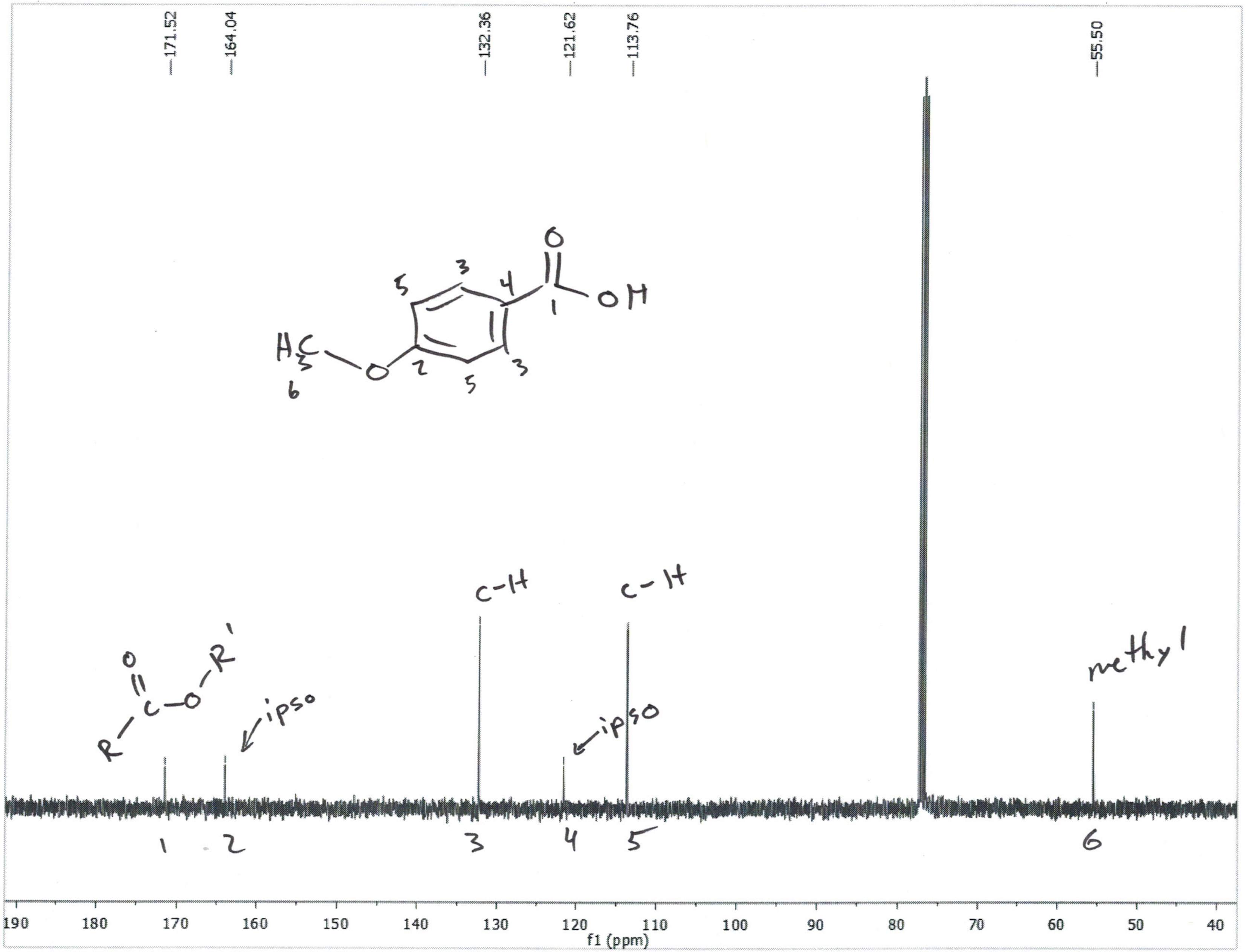
If KI-starch paper turns blue/black then I_2 is being formed by excess $ClO^{\ominus}$. Add more $Na_2S_2O_3$.
(2 pts) (1pt)

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 it forms a precipitate 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 ^{1}H-NMR spectrum on the subsequent page.* **(4 pts)**



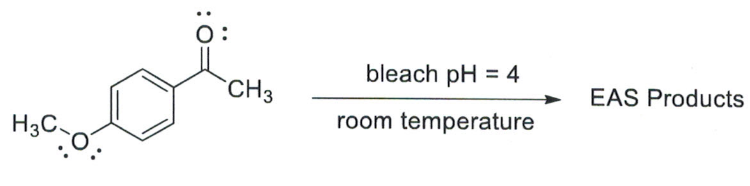
j) Draw the product molecule directly on the ^{1}H-NMR spectrum on page 6 and assign each of its ^{1}H-atoms using the signal labels A-C provided. **(4 pts)** The ^{13}C-NMR spectrum on page 7 is provided for reference only.


1pt structure
H$_3$C
O
OH
H$_A$
H$_B$
Ⓒ
1pt
1pt
1pt
3235.37
3226.44
2786.79
2777.85
A
B
C
1.98
2.01
3.00
8.15 8.10 8.05 8.00 7.95 7.90 7.85 7.80 7.75 7.70 7.65 7.60 7.55 7.50 7.45 7.40 7.35 7.30 7.25 7.20 7.15 7.10 7.05 7.00 6.95 6.90 6.85
f1 (ppm)
4.0 13.5 13.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


171.52
164.04
132.36
121.62
113.76
55.50
O
OH
1
4
3
3
5
5
2
O
H_3C
6
c-H
c-H
ipso
ipso
methyl
R
C
O
O
R'
1
2
3
4
5
6
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
f1 (ppm)

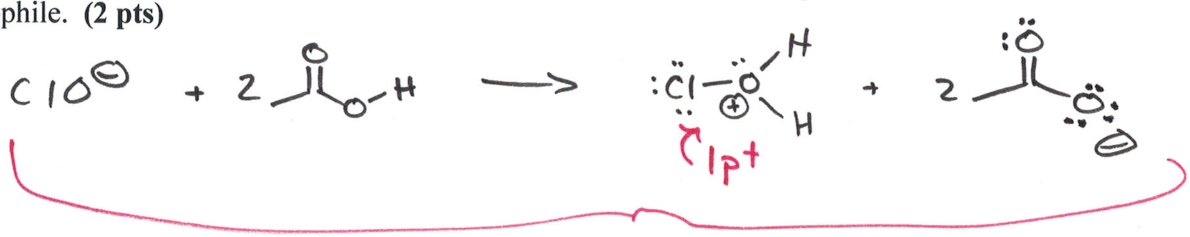
Experimental Procedure for Reaction B at pH = 4

In a 25 mL round bottom flask, place approximately 0.15 g of 4'-methoxyacetophenone and 1.0 mL of glacial acetic acid. Add 2.0 mL of household bleach (nominally 6.0 % sodium hypochlorite, NaClO) and stir the reaction mixture for 30 min. Collect the solid by vacuum filtration and dry the solid in an oven at 60 °C for an hour. Prepare a sample for IR, EI-MS, ^{1}H-NMR and ^{13}C-NMR analysis.



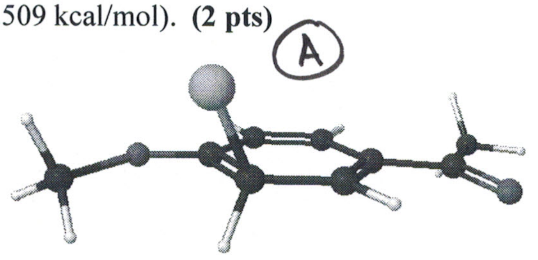
4'-methoxyacetophenone

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_3COOH). Provide a balanced chemical equation and place a box around the active electrophile. **(2 pts)**

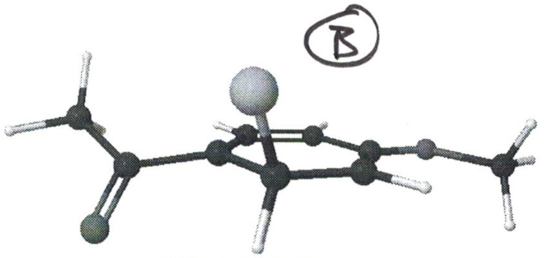


2pts total

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)**



-959.31745 Hartrees

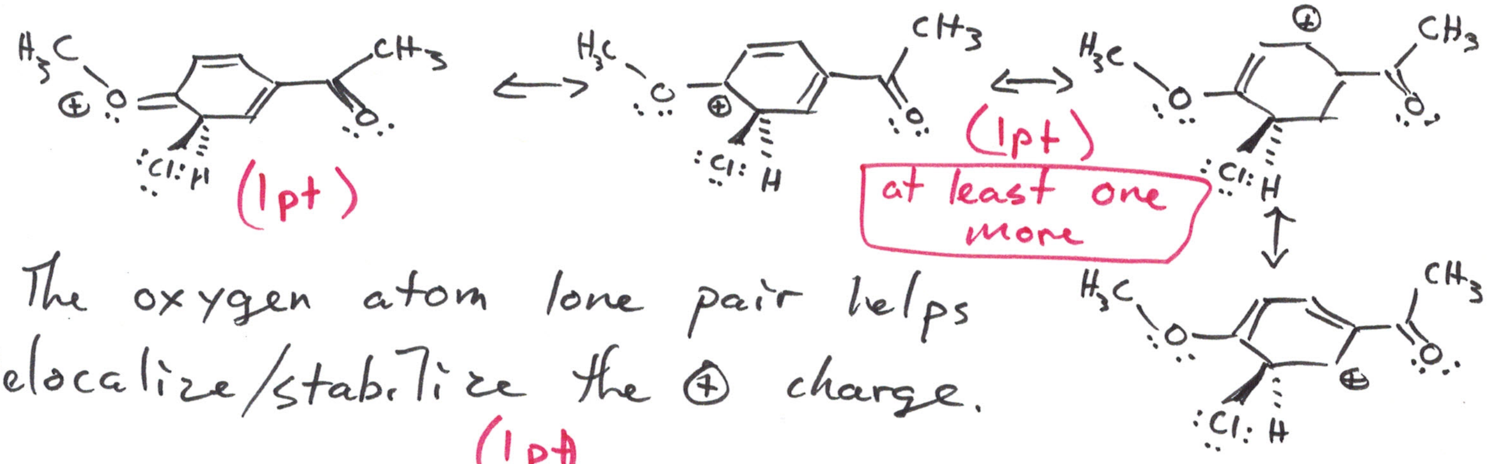


-959.29653 Hartrees

1 pt -601980.334 kcal/mol -601967.283 kcal/mol

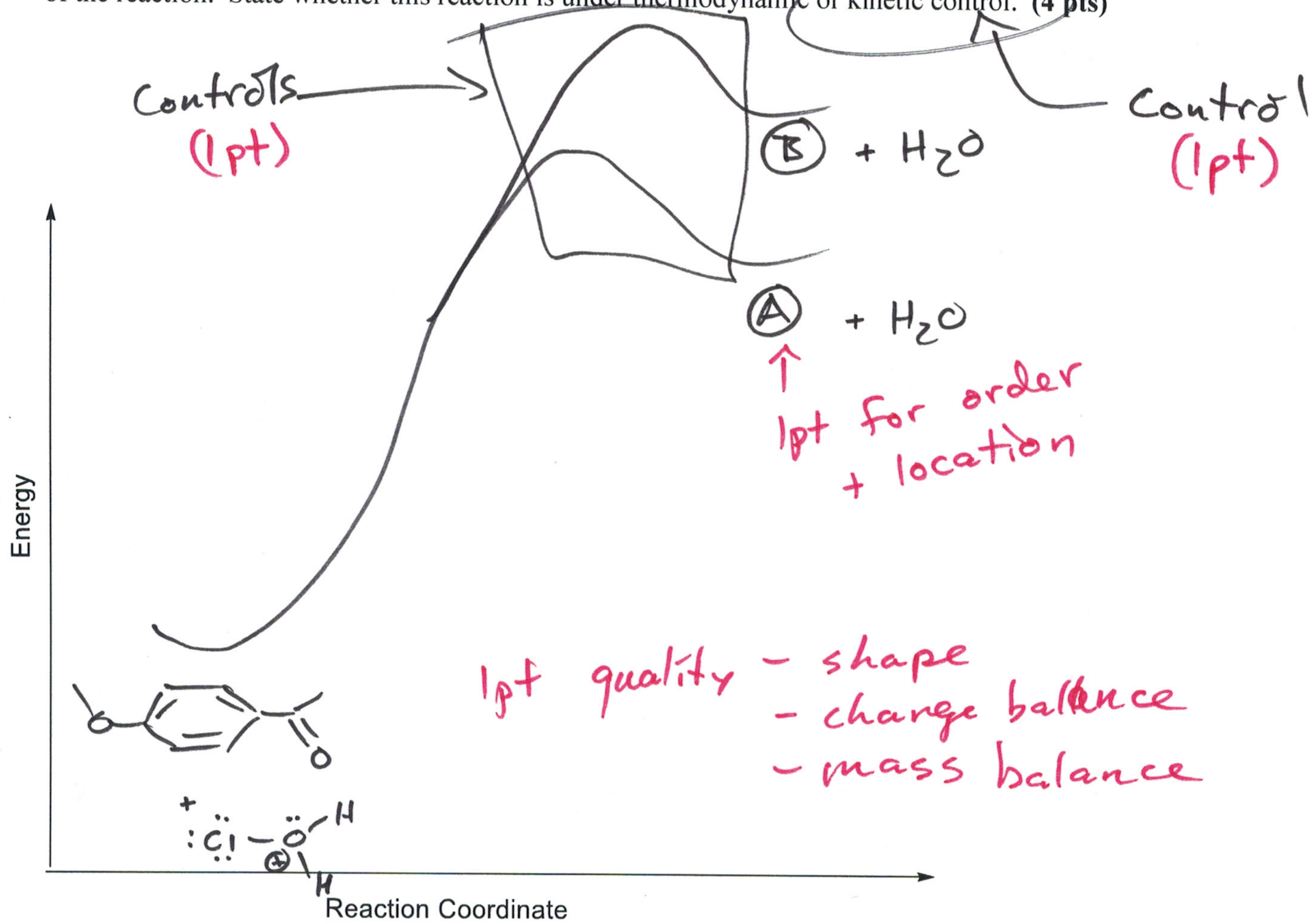
1 pt 0.0 kcal/mol 13.1 kcal/mol

m) Provide a series of resonance structures and a short explanation that justifies the relative stability of the lower energy intermediate. **(3 pts)**



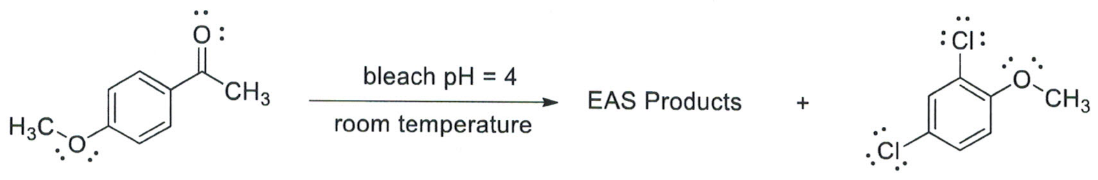
The oxygen atom lone pair helps delocalize/stabilize the ⊕ charge.
(1pt)

n) Draw a 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. State whether this reaction is under thermodynamic or kinetic control. **(4 pts)**



1pt quality – shape
– charge balance
– mass balance

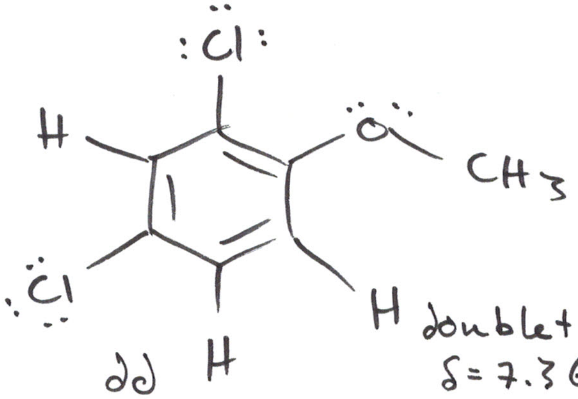
o) Two EAS products and one chlorinated byproduct are identifiable in the GC-Mass and ^{1}H-NMR spectral data. Predict the observed coupling pattern and use empirical (Curphy-Morrison) parameters to predict the ^{1}H-NMR chemical shift for all ^{1}H-NMR atoms for the chlorinated byproduct shown below. **(4 pts)**



4'-methoxyacetophenone

chlorinated byproduct

doublet
$\delta = 7.36 + -0.04 - 0.07$
$= 7.25$ ppm



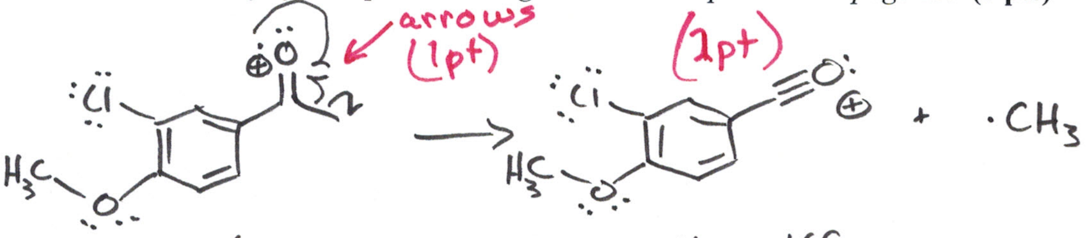
singlet
$\delta = 0.90$
2.95
3.85 ppm

doublet
$\delta = 7.36 + -0.14 + -0.45 = 6.77$ ppm

dd
$\delta = 7.36 + -0.02 + -0.13 + -0.07 = 7.14$ ppm

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)**

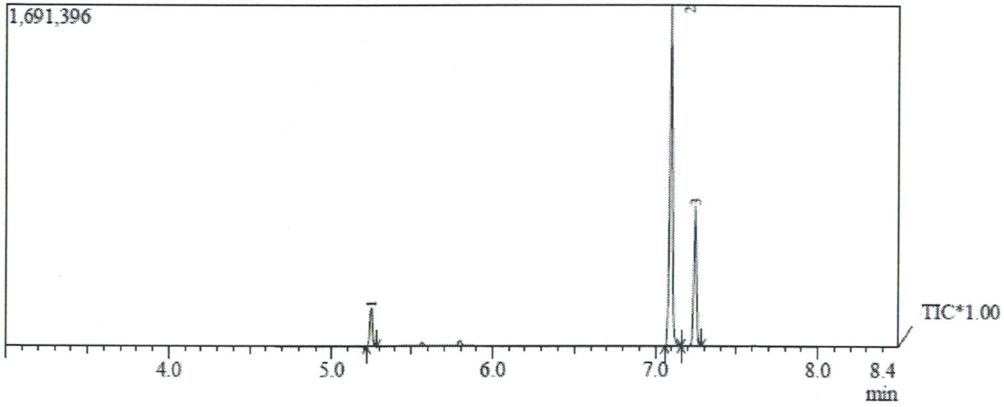
q) For the major component of the mixture, provide an electron pushing mechanism for the formation of the ion responsible for the base peak from the molecular ion in the space below. *It may help to confirm the identity of each product using the ^{1}H-NMR spectrum on page 13.* **(3 pts)**



m/z = 184

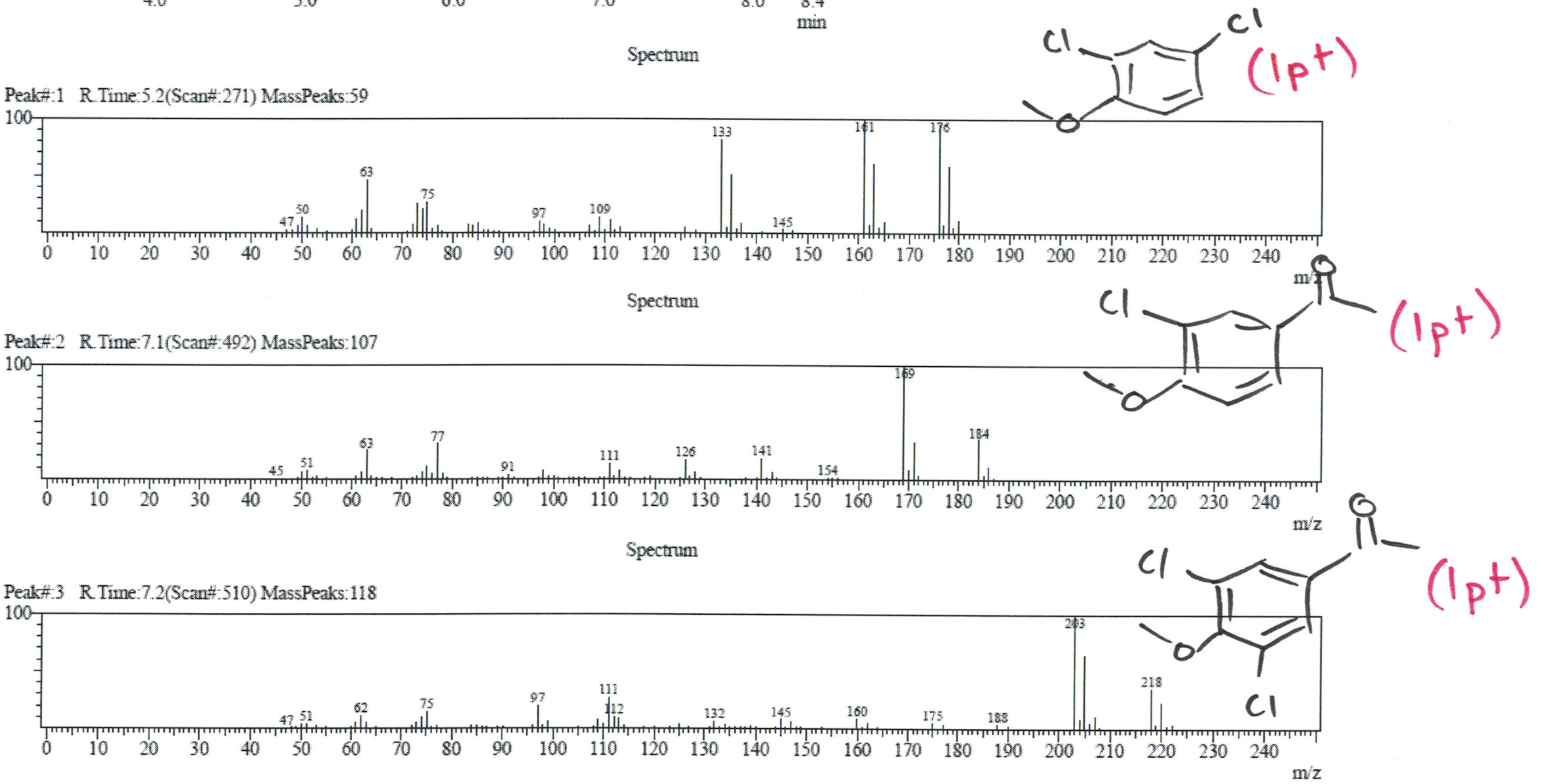
m/z = 169

1pt max for any other m/z = 169 particle



Peak Report TIC

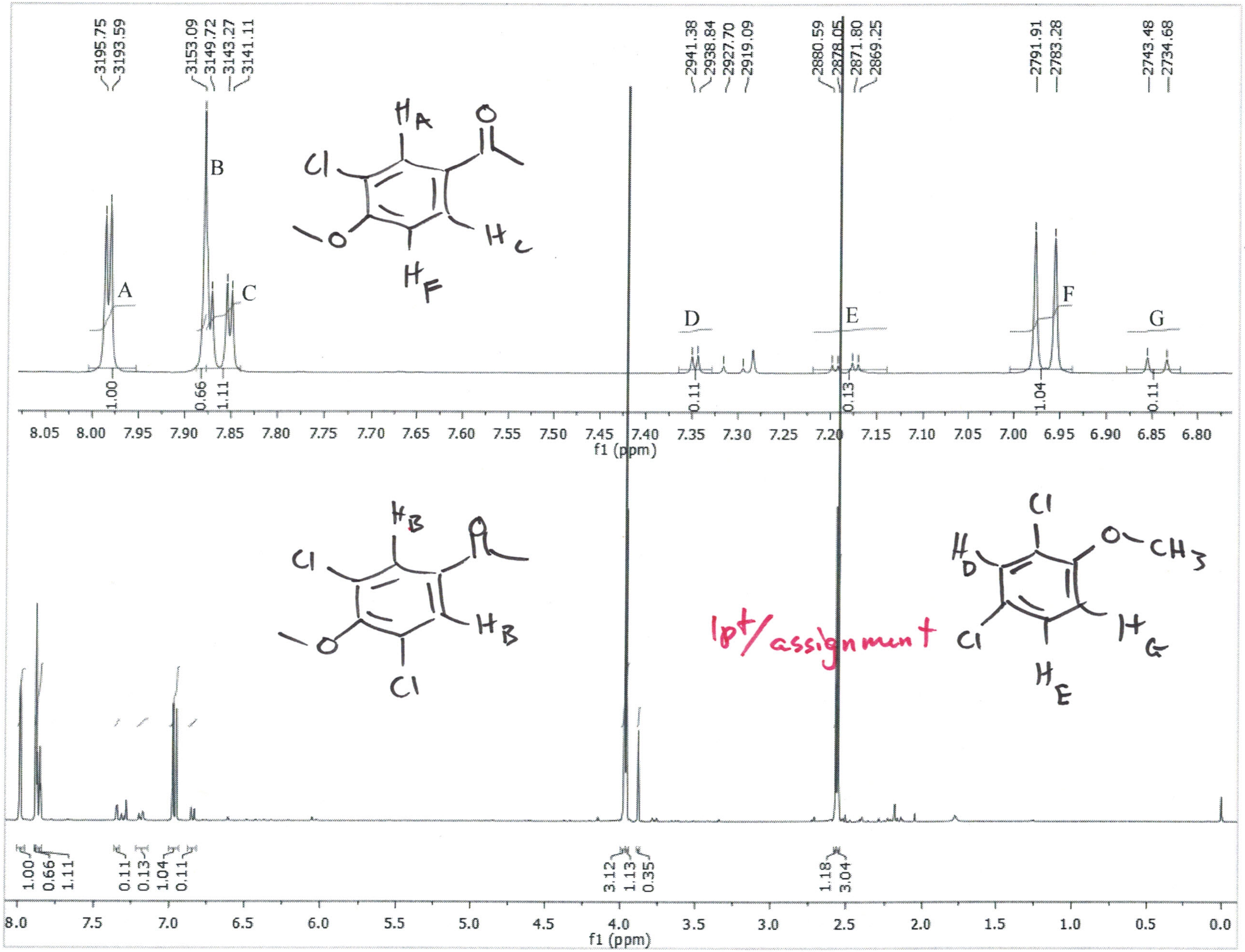
Peak#	R.Time	Area	Area%
1	5.247	240940	7.74
2	7.091	2084032	66.99
3	7.242	786192	25.27
		3111164	100.00



(1pt)

(1pt)

(1pt)



1pt/assignment

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:

Major EAS : Minor EAS : Chlor. byproduct

66.99 : 25.27 : 7.74

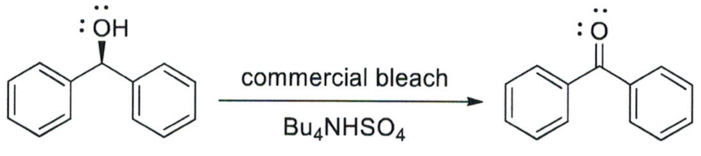
8.66 : 3.26 : 1

^{1}H-NMR Ratio:

$1.00 : \frac{0.66}{2} : 0.11$

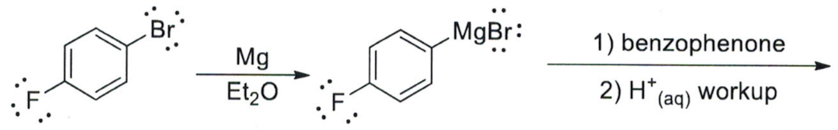
9.09 : 3.00 : 1

2) The reaction of benzophenone with a Grignard reagent derived from 1-bromo-4-fluorobenzne 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)**



benzhydrol

benzophenone



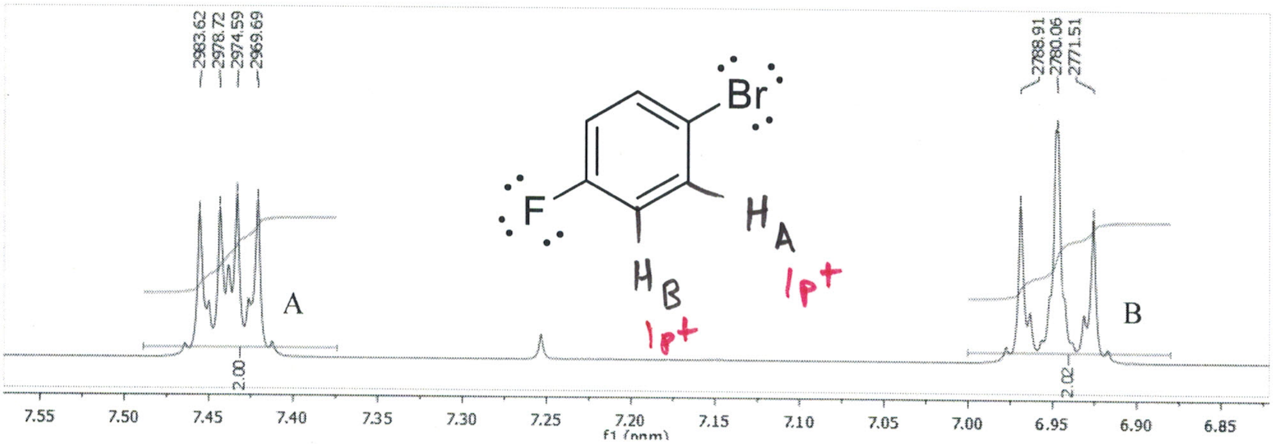
1-bromo-4-fluorobenzene

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.*

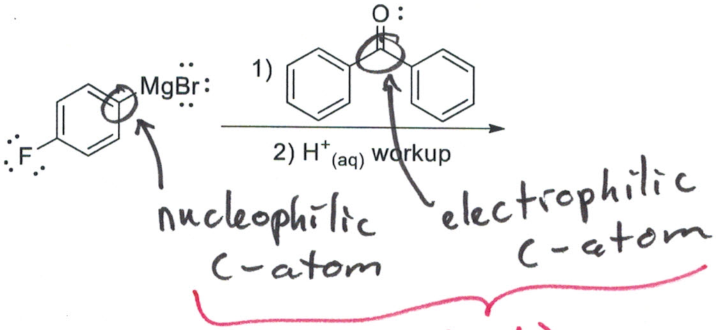
a) The aromatic region of the ^{1}H-NMR sprectrum is provided below. Assign the labeled signals to their corresponding ^{1}H-atoms and determine the values of $^3J_{H\text{-}F}$ and $^4J_{H\text{-}F}$ for this molecule. Show your work. **(4 pts)**



$^4J_{H\text{-}F}$ = 2983.62 Hz − 2978.72 Hz = 4.9 Hz (1pt)

$^3J_{H\text{-}F}$ = 2788.91 − 2780.06 Hz = 8.85 Hz (1pt)

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)**



(1pt)

$$\%\ ionic\ character = \left(\frac{X_C - X_M}{X_C}\right) * 100\ \%$$

$$\% = \frac{2.55 - 1.31}{2.55} * 100 = 48.63\%$$

(1pt)

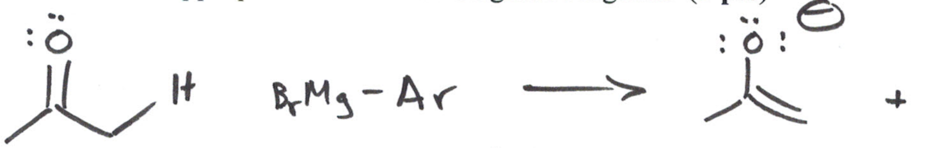
c) During the formation of the Grignard reagent, why is the magnesium broken up, ground, cut, and or scratched? **(3 pts)**

(1pt)

To break through the Mg_2O_1 coating and to reveal Mg^0 which allows the chemical reaction to occur between the Mg^0 and the Ar−X. 2pts

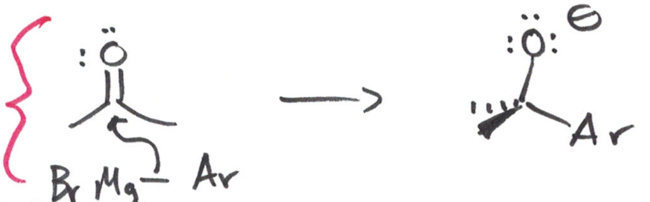
d) Diethyl ether is a common solvent used for the formation of the Grignard reagent as it helps stabilize the Grignard reagent by electron donation. Explain why acetone, which is also an electron donating solvent is not an appropriate solvent for Grignard reagents. **(3 pts)**

3pts



It forms an enolate.

3pts



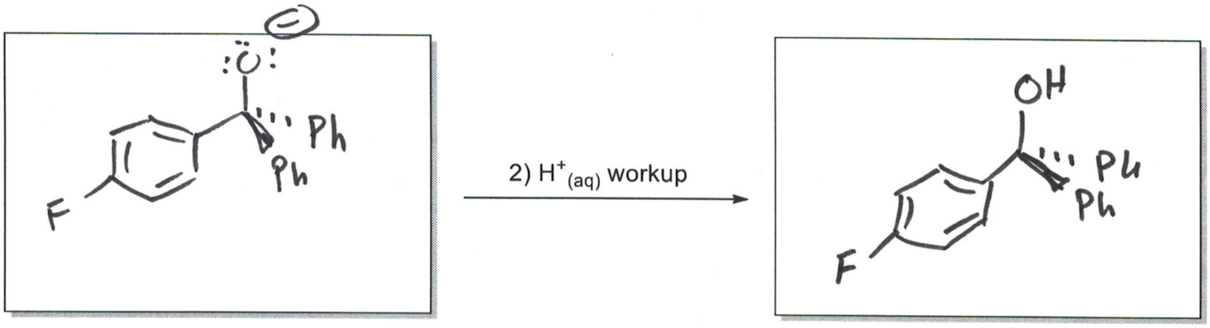
acetone can react with the Grignard

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)**

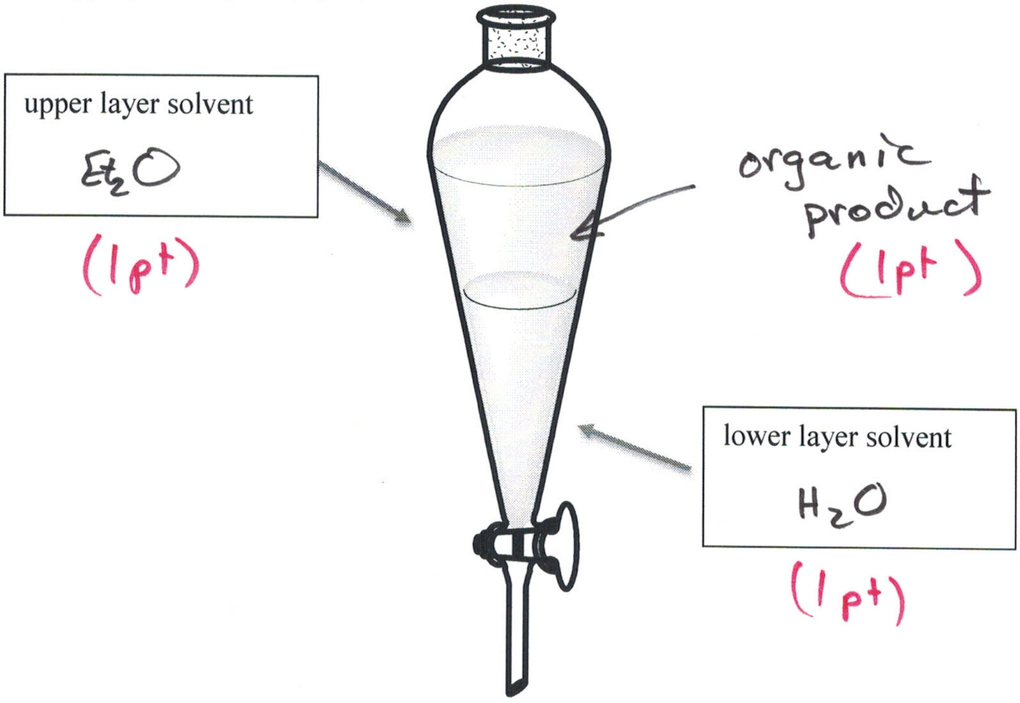
Reflux allows for the heating of a reaction at a constant temperature w/o loss of solvent, reagents or products. (2pts)

It would burn! (1pt)

f) Draw the organic product that is produced after reflux in the box below and show the organic product generated after the 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)**



upper layer solvent

Et_2O

(1pt)

organic product

(1pt)

lower layer solvent

H_2O

(1pt)

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)**

(1pt)

$MgSO_4$ is a drying agent. Enough has been added when it no longer clumps.

(1pt)

i) Determine the percent yield of this reaction given the tabulated quantities of reagents used and the quantity of purified product obtained. *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.* **(3 pts)**

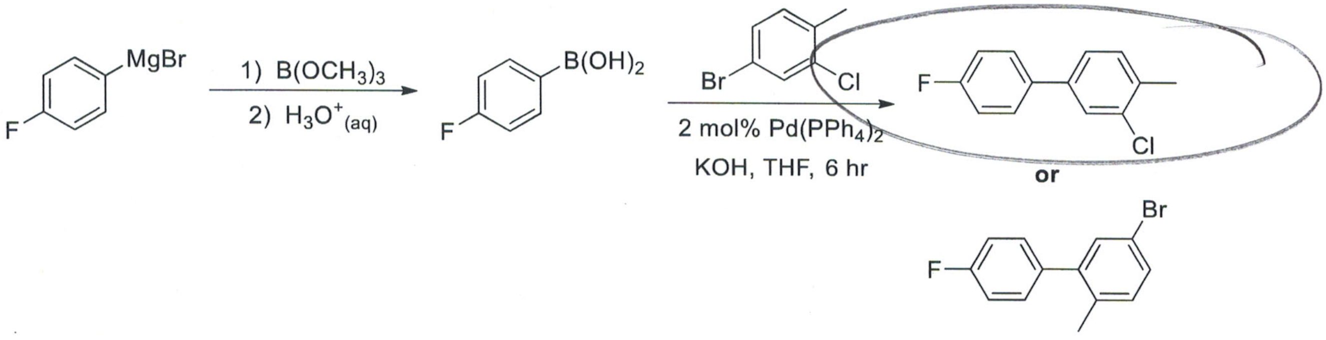
1-bromo-4-fluorobenzene	benzophenone	magnesium	purified product
0.500 mL	1.0 mL	0.135 g	0.607 g
175.00 g/mol	182.22 g/mol	24.305 g/mol	278.11g/mol
$\rho = 1.593\ g/cm^3$	$\rho = 1.11\ g/cm^3$	$\rho = 1.738\ g/cm^3$	

$$\left(1.0\,mL\right)\left(\frac{1.11\,g}{mL}\right)\left(\frac{1}{\frac{182.22\,g}{mol}}\right)\left(\frac{1\,mol}{1\,mol}\right)\left(\frac{278.11\,g}{mol}\right) = 1.694\,g \text{ product}$$

(2pts)

$$\left(\frac{0.607}{1.694}\right)100 = 35.8\,\%$$

j) The Grignard reagent derived from 1-bromo-4-fluorobenzene can also be used to generate the boronic acid derivative necessary for a Pd-catalyzed coupling reaction. Two potential products are depicted below, draw a circle around the most likely product of the coupling reaction. Briefly explain your choice. **(2 pts)**

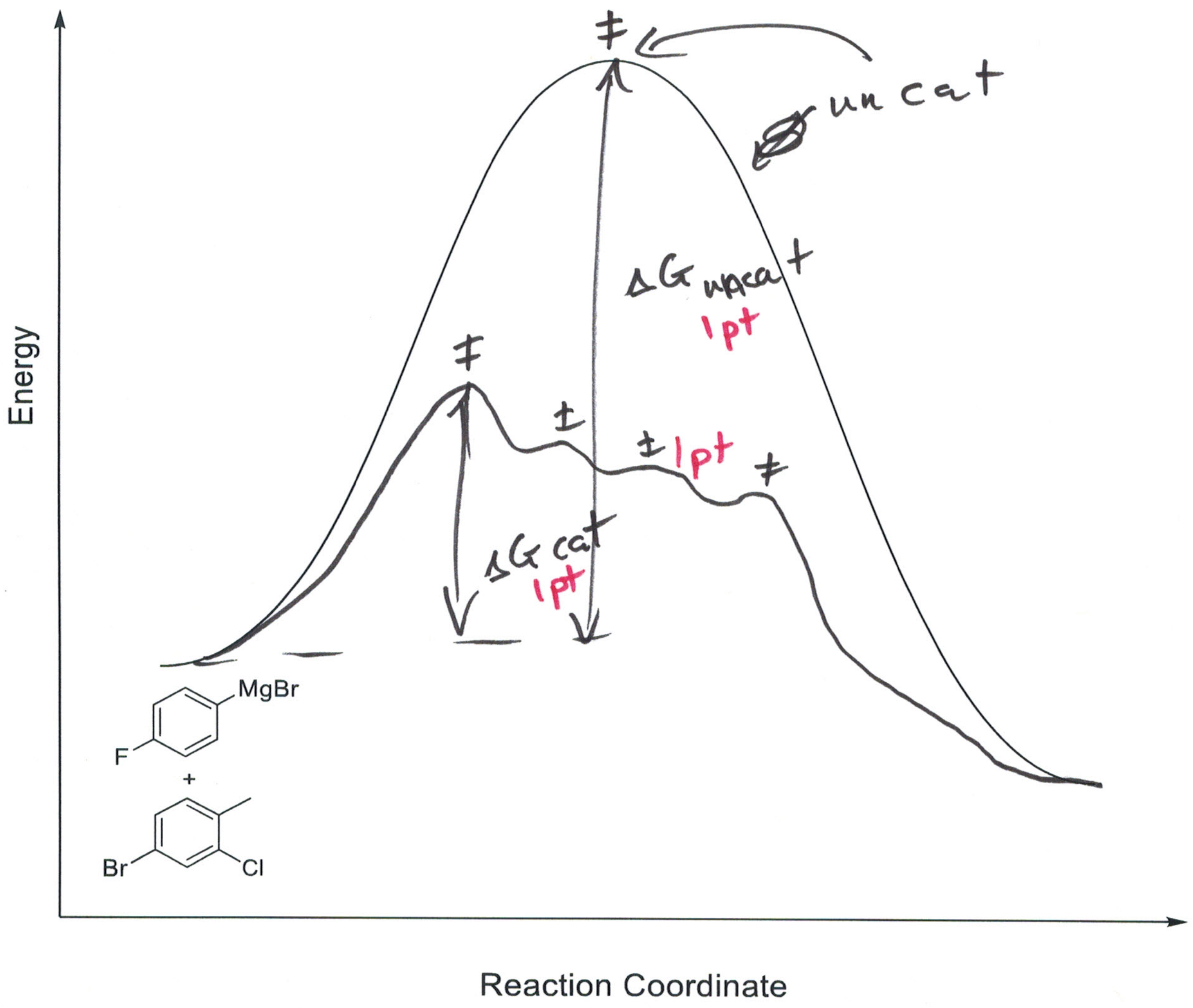


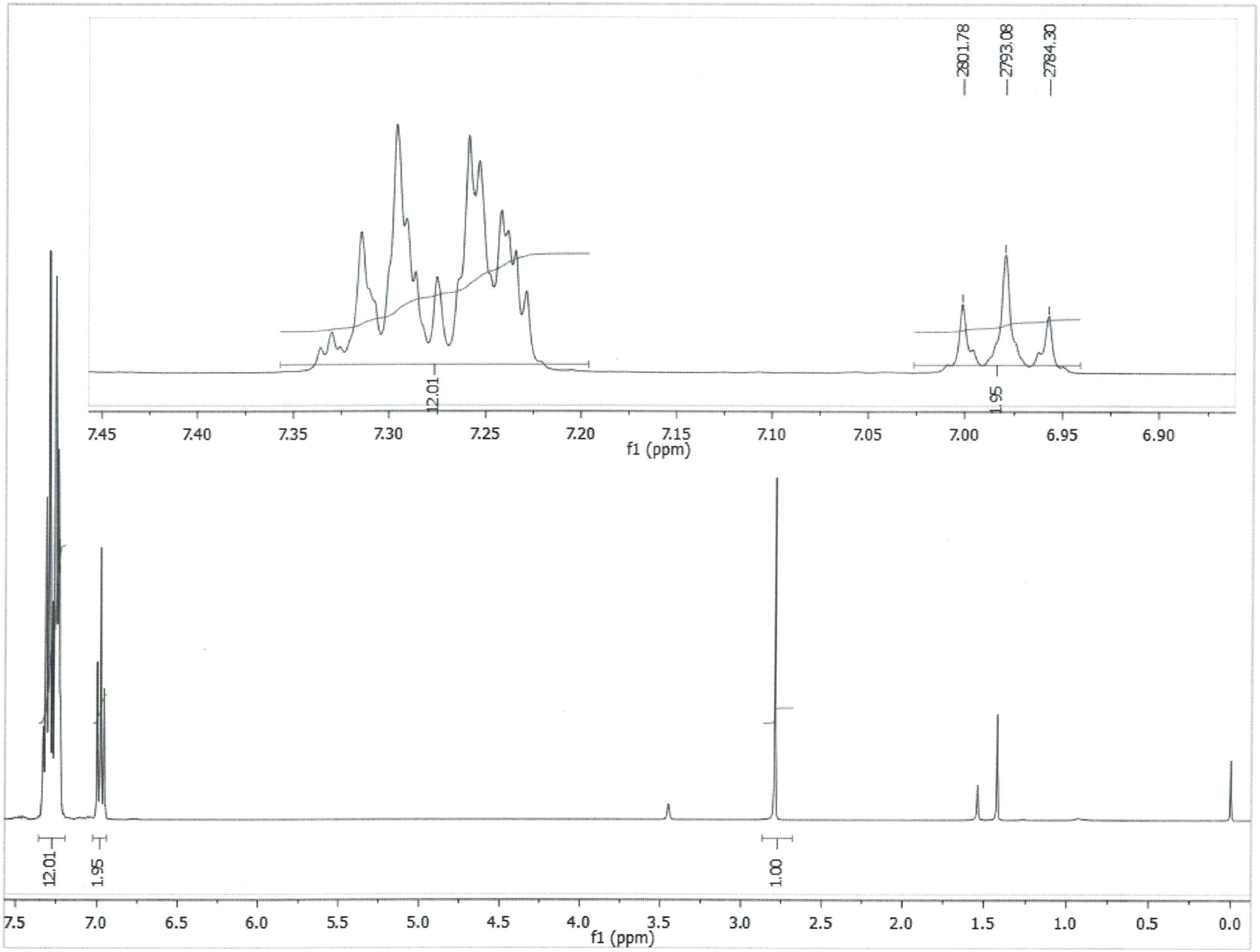
k) Estimate the inter-ring dihedral angle of the biaryl molecule you selected as the product in the previous question (j). Provide a brief explanation for your estimate referring to any important factors that impact the geometry. **(3 pts)**

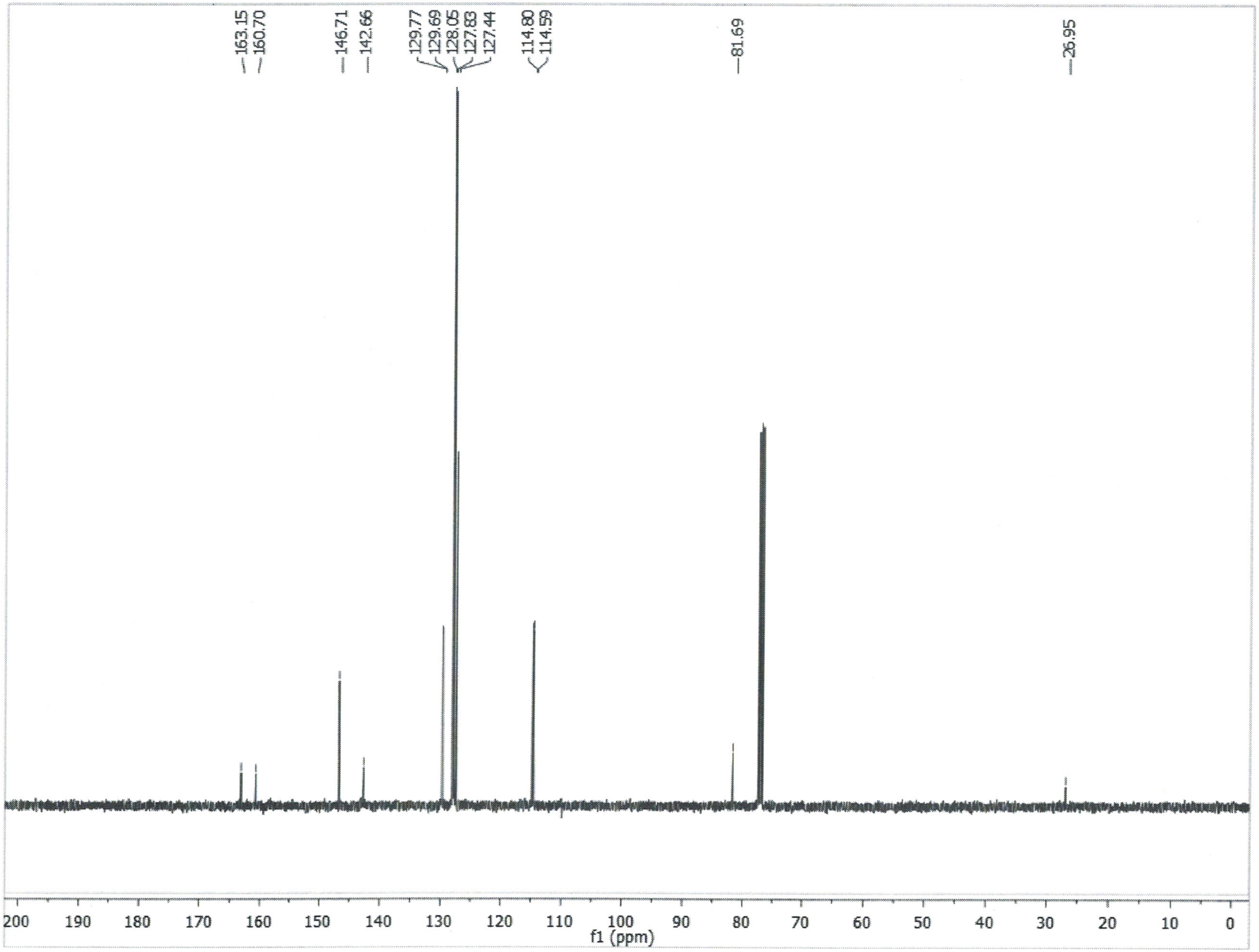
$\simeq 35^\circ$ (1pt)

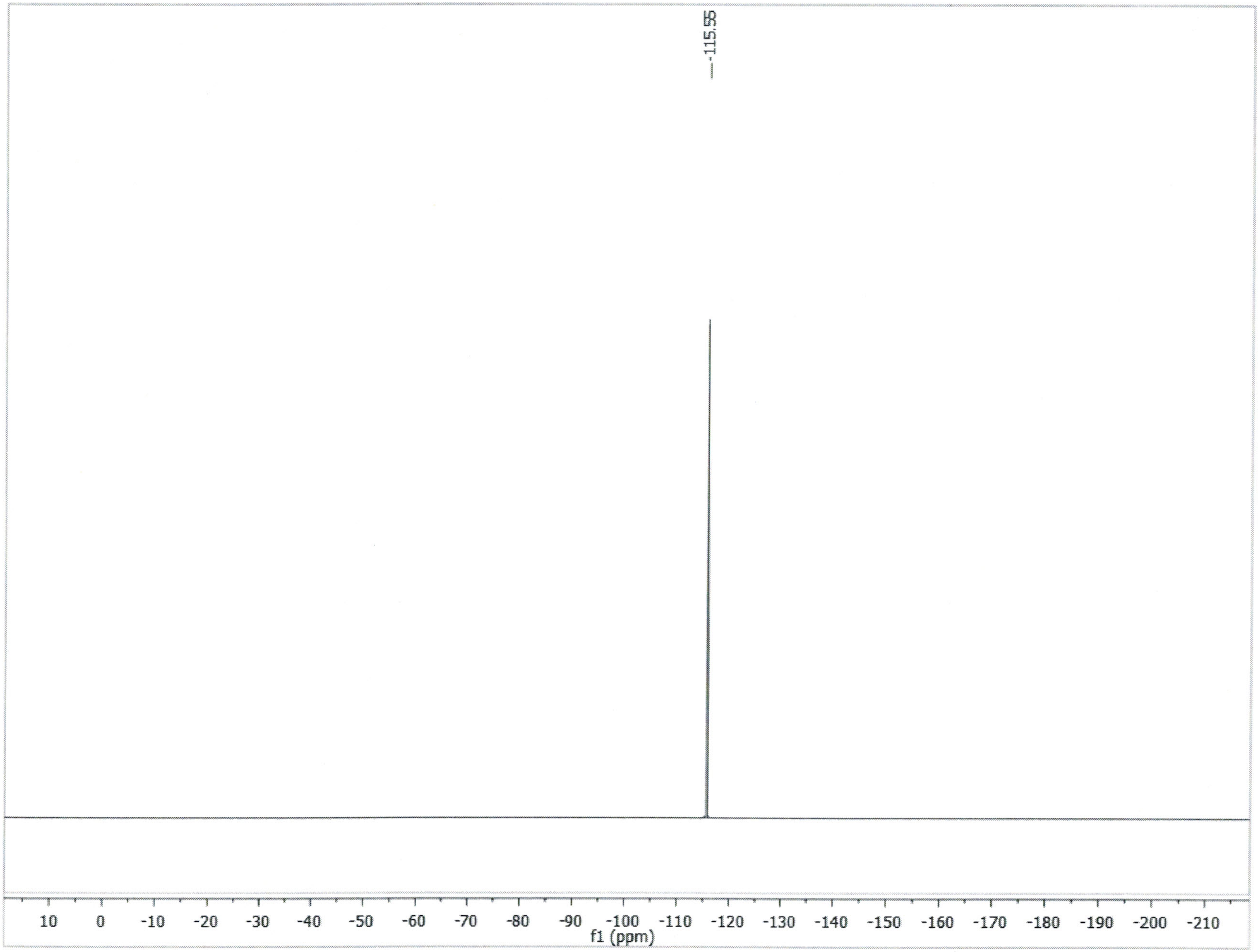
(1pt) π Conjugation favors 0°
(1pt) sterics favors 90°
} compromise → $\simeq 35^\circ$

l) The potential energy surface for an hypothetical uncatalyzed coupling to generate the biaryl molecule you selected as the product in the previous question (j) is shown below. Draw a rough potential energy surface for the Pd-catalyzed reaction assuming that oxidative addition is rate-limiting. Clearly label the activation barrier for the catalyzed and uncatalyzed reactions. **(3 pts)**.




2801.78
2793.08
2784.30
12.01
1.95
7.45
7.40
7.35
7.30
7.25
7.20
7.15
7.10
7.05
7.00
6.95
6.90
f1 (ppm)
12.01
1.95
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


163.15
160.70
146.71
142.66
129.77
129.69
128.05
127.83
127.44
114.80
114.59
81.69
26.95
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


-115.55
10
0
-10
-20
-30
-40
-50
-60
-70
-80
-90
-100
-110
-120
-130
-140
-150
-160
-170
-180
-190
-200
-210
f1 (ppm)

Name:

TA Name:

Problem 1

a) ______ /5

b) ______ /4

c) ______ /2

d) ______ /2

e) ______ /3

f) ______ /4

g) ______ /4

h) ______ /3

i) ______ /4

j) ______ /4

Total______ **/35**

k) ______ /2

l) ______ /2

m) ______ /3

n) ______ /4

o) ______ /4

p) ______ /3

q) ______ /3

r) ______ /7

s) ______ /4

Total______ **/32**

Problem 2

a) ______ /4

b) ______ /2

c) ______ /3

d) ______ /3

e) ______ /3

f) ______ /2

g) ______ /3

h) ______ /2

i) ______ /3

j) ______ /2

k) ______ /3

l) ______ /3

Total______ **/33**

Grand Total = ______ **/100**

Grand Total = ______ **/100** **(math double-check)**