Chem 633: Advanced Organic Chemistry 2013 · Midterm

Please answer the following questions *clearly and concisely*. In general, use pictures and less than 10 words in your answers.

Write your answers in the space provided.

Write your initials on each page you want graded.

There are 12 total pages to this exam. The last 2 pages were intentionally left blank and may be used for scratch paper. Please be sure your copy has 12 pages before you begin.

Molecular models are allowed.

Calculators are unnecessary and prohibited.

<table>
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<tr>
<th>Problem</th>
<th>Points</th>
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<tbody>
<tr>
<td>1</td>
<td>8/20</td>
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<tr>
<td>2</td>
<td>18/30</td>
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<tr>
<td>3</td>
<td>3/15</td>
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<td>4</td>
<td>4/20</td>
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<tr>
<td>5</td>
<td>2/15</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td><strong>34/100</strong></td>
</tr>
</tbody>
</table>
1. (20 points) Please explain the following observations. (Use pictures and few words.)

(a) The $pK_a$ of 1a and 2a are the same, but the $pK_a$ of 1b is much lower than that of 2b.

Consider conjugate base...

Me's do not affect stability of conj base in later 2a.

N(1,3) strain prevents NO₂ from being in conj

(b) The gauche conformation of the following molecule is favored over the anti conformation.

ANTI
Looking down C1-C2 bond:

$lp_0 \leftrightarrow \sigma_{C-H}$ x 2
cross overlap with unfilled orbitals

Looking down C2-O3 bond:

$lp_0 \leftrightarrow \sigma_{C-H}$ x 2

GAUCHE:
C2-O3:

$lp_0 \leftrightarrow \sigma_{C-H}$ x 2

$lp_0 \leftrightarrow \sigma_{C-O}$

$lp_0 \leftrightarrow \sigma_{C-H}$

+3 if w/o picture.
(1 – continued)
(c) The more stable conformation of this tetraaza-cyclohexane has the methyls arranged as shown in 3b.

![Chemical structures]

3a: Me,

Me's are all equatorial, but 1pN's are not able to overlap w/ any unfilled orbitals.

3b: Me,

*NO/1,3-diaxial interactions in either chair conformation (only Me, H)
*Equatorial + axial 1pN's overlap w/ \( \sigma^*_{C-N} \) (x 4).

(d) The following equilibrium lies to the right.

![Chemical structures]

Me,

>99% at equilibrium

Me,

vs.

Me,

\( \sigma^*_{C-C} \)

\( \sigma^*_{C-C} \)

H 1pN

+1 for steric hindrance

Better energetic overlap -> more stabilization
2. (30 points) The reaction of carbene 1 and aldehyde A leads to epoxide 2. This reaction is rapid and reversible.

\[ \text{MesN} \overset{\text{Me}}{\text{N Mes}} + \overset{\text{H}}{\text{O}} \overset{\text{R}}{\text{R}} \rightleftharpoons \overset{\text{MesN}}{\text{Me}} \overset{\text{Me}}{\text{N Mes}} \]

1 \hspace{1cm} 2a, R = p-(NO_2)C_6H_4 \hspace{1cm} 2b, R = t-Bu

Aa, R = p-(NO_2)C_6H_4
Ab, R = t-Bu

(a) The reaction of aldehyde Aa leads to quantitative conversion of the starting materials to the product. Estimate \( K_{eq} \) and \( \Delta G^\circ \) for this reaction.

Quantitative conversion... \( K_{eq} \geq \frac{100}{1} \left( = \frac{127}{118} \right) \)

\( \Delta G^\circ \geq -2.8 \text{ kcal/mol} \)

(Recall: 1 order of magnitude in \( K_{eq} \) => 1.4 kcal/mol in \( \Delta G^\circ \))

+4 if sign is wrong, but clear that pdt is favored.

+2 for \( K_{eq} \) only.
(2 - continued)
(b) The reaction of aldehyde \textbf{Ab} proceeds to less than 85% conversion. To study this reaction, researchers performed experiments and obtained the following data. Please show how you would determine $\Delta G^\circ$ from this data. (Note: You do not need to calculate $\Delta G^\circ$. Just show the equations and how you would plug in the numbers.)

![Graph showing ln(K_eq) vs 1/T](image)

\textbf{Figure S1.} Plot of ln K\textsubscript{eq} vs 1/T for the reaction 1 + pivaldehyde $\rightarrow$ 2h. The equation for the best fit line shown in red is as follows: $y = mx + b$, where $m = 5650 \pm 60$ K and $b = -16.8 \pm 0.2$.

$$\ln K_{eq} = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R}$$

\begin{align*}
m &= \text{slope of the line} = \frac{-\Delta H^\circ}{R} \\
R &= \frac{1.984 \text{ cal}}{k\cdot\text{mol}} \\
\Delta H^\circ &= -5650 \text{ K} \times \frac{1.984 \text{ cal}}{k\cdot\text{mol}} \times \frac{1000 \text{ cal}}{1 \text{ kcal}} = 8.31 \frac{y}{k\cdot\text{mol}} \\
\Delta H^\circ &= -11.2 \text{ kcal/mol} \\
y-\text{int} &= \frac{\Delta S^\circ}{R} \\
\Delta S^\circ &= (R)x(y-\text{int}) = (1.984 \frac{\text{cal}}{k\cdot\text{mol}})(-16.8) = -33.3 \frac{\text{cal}}{\text{mol} \cdot \text{K}} \\
3 \text{ if doesn't use plot given} \Rightarrow \text{divide by } R.
\end{align*}

$$\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ$$
(2 – continued)
(c) Researchers also wanted to determine $\Delta G^\dagger$, but the reaction was too fast. Instead, they studied the rate of exchange of aldehyde with epoxide 2a. For these experiments, they used a labeled aldehyde Aa$^\ast$ (labeled at H$^\ast$) and observed the decay of [Aa$^\ast$] and growth of [2a$^\ast$]. They hypothesize that this exchange reaction proceeds via 1.

What do the following data tell you?

<table>
<thead>
<tr>
<th>Entry</th>
<th>Equiv of Aa$^\ast$</th>
<th>$k_{obs}$ (s$^{-1}$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>4.4 ± 0.5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>4.3 ± 0.4</td>
</tr>
</tbody>
</table>

$\emptyset$ order in [Aa$^\ast$]

(d) What do the following data tell you?

$\Delta H^\dagger = 23.9 \pm 1.9$ kcal/mol
$\Delta S^\dagger = 8 \pm 5$ cal/mol·K

$\Delta S^\dagger > 0 \rightarrow$ Transition state is more disordered than starting material (ground state).
(2 – continued)
(e) Based on the above data, which step is rate determining (Step 1 or Step 2)?

Step 1

(f) Please draw a reaction coordinate diagram for the exchange reaction.

\[
\text{\begin{tabular}{c}
2a + Aa_+ \\
$\Rightarrow$ \\
1 + Aa_+ \\
$\Rightarrow$ \\
2a_+ + Aa
\end{tabular}}
\]

(RxN coordinate)

(Also ok to draw barriers the same height)
3. (15 points) Hydroxyl groups (OH) can be used to direct epoxidations with m-CPBA, as shown in transition state A below. The epoxidation step is irreversible.

(a) Please explain the observed stereochemistry of intermediate B. In other words, why is the epoxide “up”? Include clear, 3-dimensional depictions of transition state A in your answer.

(b) Draw a reasonable arrow-pushing mechanism for the transformation of intermediate B to product 2 that is consistent with the observed stereochemistry of product 2.

(Cannot be Sn2 -> Retention of Stereochem)
4. (20 points) The identity of $R$ has a large effect on the rate of the rearrangement shown below. When $R = t$-Bu, the reaction is 370 times faster than when $R = H$.

\[
\begin{array}{c}
\text{HO-} \text{CF}_3 \\
\text{R} \\
\text{A} \\
\text{R} \\
\text{R} \\
\text{R} \\
\text{R} \\
\end{array}
\xrightarrow{\text{HO-} \text{CF}_3} \begin{array}{c}
\text{R} \\
\text{R} \\
\text{A} \\
\text{R} \\
\text{R} \\
\text{R} \\
\text{R} \\
\end{array} \rightarrow \begin{array}{c}
\text{R} \\
\text{R} \\
\text{A} \\
\text{R} \\
\end{array}
\]

(a) Please explain this rate difference.

(b) Please draw a reasonable arrow-pushing mechanism for the conversion of intermediate $A$ to 2. For each step, please name the HOMO-LUMO interaction(s). You do not need to draw the HOMO or LUMO.

Mech: +4 if draw all transition states in multiple steps as conceived.
5. (15 points) Please draw a reasonable arrow-pushing mechanism for the following reaction (Grossman, Chapter 2, #2h).

Note: $^3\text{OAc}$ is not a great base... you can only deprotonate fairly acidic H's.

4 - forming mixed anhydride
4 - closing ring
4 - attacking aldehyde
3 - elim. to put in dbl bond.